Genetic Testing and De-escalation of Contralateral Prophylactic Mastectomy

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The American Society of Breast Surgeons (ASBrS) published two important and related clinical practice guidelines within the past 5 years. In 2016, the ASBrS concluded that contralateral prophylactic mastectomy (CPM) should be “discouraged” for women with an average risk of contralateral breast cancer.¹ In 2019, the ASBrS recommended that genetic testing be made available to *all* women with breast cancer.² These two recommendations are synergistic, as demonstrated by the accompanying article by Metcalfe et al.³ To date, the impact of these ASBrS recommendations on breast cancer practice in the United States is not known.

Metcalfe et al. designed a multicenter prospective cohort study in Ontario to determine whether the results of genetic counseling and testing influenced CPM decisions for women with unilateral breast cancer.³ They found that about one third of women leaning toward CPM changed their minds after genetic counseling and receipt of negative BRCA1/2 testing results. In the overall cohort of patients who tested negative for BRCA, only 15% elected to undergo CPM. Despite the encouraging results from this prospective study, it is not clear whether genetic testing will successfully de-escalate CPM in all settings. For example, in a retrospective single-center study from the MD Anderson Cancer Center, Yi et al. reported that pre-operative genetic testing for BRCA 1/2 was independently associated with a higher rate of CPM.⁴

The use of CPM has been increasing for more than two decades in the United States, and surgeons still are performing too many CPMs currently.^{5,6} This trend has been observed in all cancer stages, races, and geographic regions of the United States, as well as among all age groups, even the elderly.⁶ Similar trends have been observed in Canada.⁷ Surprisingly, these practices have continued despite increasing evidence that CPM provides no survival advantage for average-risk patients.⁸

One challenge for patients with newly diagnosed breast cancer when making surgical decisions is their perception of this “average” risk. The most common reason cited by patients for CPM is worry about contralateral breast cancer.⁹ Previous survey studies indicate that many women with unilateral breast cancer substantially overestimate their risk for the development of contralateral breast cancer.^{10,11} In a meta-analysis from the Early Breast Cancer Trialists’ Collaborative Group, the 10-year risk of contralateral breast cancer was only 4% to 5%. Most of the patients in this meta-analysis were treated in the 1970s and 1980s.¹²

In the United States, the rates of metachronous contralateral breast cancer began declining around 1985 and still were decreasing in the early 2000s.¹³ In the recent Trial Assigning Individualized Options for Treatment (TAILORx) study, the 9-year cumulative risk for contralateral breast cancer was only 1.4%.¹⁴ The use of adjuvant chemotherapy and endocrine therapy significantly reduces the risk of metachronous contralateral breast cancer.¹⁵ In comparison, the 10-year risk of contralateral breast cancer for patients with unilateral breast cancer and BRCA mutation is about 30%.¹⁶ The ASBrS guidelines conclude that “CPM *should* be considered” for selected groups at significant risk for contralateral breast cancer (including carriers of deleterious BRCA1/2 mutations).¹

Nevertheless, previous studies have demonstrated that most patients who undergo CPM do not have strong genetic or familial risk factors for the development of contralateral breast cancer.¹⁷

Multigene panel testing is one of the most impactful tools available for physicians to use in counseling patients with newly diagnosed breast cancer. It informs about the risks of associated malignancies, identifies patients who may be candidates for specific systemic therapies (e.g., PARP inhibitors), and provides potentially life-saving information for family members. Additionally, the results of multigene panel testing can provide patients with accurate information about the risk of contralateral breast cancer and may de-escalate the use of CPM for patients with average risk, as demonstrated by Metcalfe et al.³

The cost of multigene panel testing dropped dramatically during the past decade and currently is substantially lower than the cost of other breast cancer testing, such as magnetic resonance imaging (MRI). A cost-effectiveness microsimulation modeling study found that multigene panel testing for unselected patients with breast cancer was extremely cost-effective compared with testing based on family history or clinical criteria.¹⁸

The current National Cancer Comprehensive Network guidelines regarding testing criteria for high-penetrance breast and/or ovarian cancer susceptibility genes are unnecessarily complex and confusing. As a result, genetic testing is grossly underused in the United States. Childers et al.¹⁹ reported that more than 70 % of eligible breast cancer patients never have discussions regarding genetic testing. Even among those tested, Armstrong et al.²⁰ reported that 23 % of the patients did not receive the results of genetic testing until after surgery. Additionally, Armstrong et al.²⁰ found that women older than 50 years who were unaware of their negative BRCA1/2 tests were more likely to choose CPM than those who were aware of their negative results. For these reasons, we agree with the ASBrS recommendation that genetic testing for all patients with breast cancer at diagnosis can increase access and allow for tailored treatments and surveillance strategies based on genetic risk.

Increasingly, surgeons currently are initiating multigene panel testing before formal genetic counseling to facilitate timely receipt of testing results that guide surgical decision-making. We think this trend will reduce barriers and improve access to genetic testing that improves patient-centered care. However, surgeon-initiated genetic testing cannot be performed in a vacuum but must be a component of an overall team approach with certified genetic counselors in order to provide access to timely and appropriate care for patients with newly diagnosed breast cancer.

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REFERENCES

1. Boughey JC, Attai DJ, Chen SL, et al. Contralateral prophylactic mastectomy (CPM) consensus statement from the American Society of Breast Surgeons: data on CPM outcomes and risks. *Ann Surg Oncol*. 2016;23:3100–5.
2. Manahan ER, Kuerer HM, Sebastian M, et al. Consensus guidelines on genetic testing for hereditary breast cancer from the American Society of Breast Surgeons. *Ann Surg Oncol*. 2019;26:3025–31.
3. Metcalfe K, Eisen A, Poll A, et al. Frequency of contralateral prophylactic mastectomy in breast cancer patients with a negative BRCA 1 and BRCA 2 rapid genetic test result. *Ann Surg Oncol*. 2021. <https://doi.org/10.1245/s10434-021-09855-6>.
4. Yi M, Hunt KK, Arun BK, et al. Factors affecting the decision of breast cancer patients to undergo contralateral prophylactic mastectomy. *Cancer Prev Res*. 2010;3:1026–34.
5. Tuttle TM, Habermann EB, Grund EH, et al. Increasing use of contralateral prophylactic mastectomy for breast cancer patients: a trend toward more aggressive surgical treatment. *J Clin Oncol*. 2007;25:5203–9.
6. Marmor S, Altman AM, Mayleben WT, et al. The use of contralateral prophylactic mastectomy among elderly patients in the United States. *Breast Cancer Res Treat*. 2019;177:175–83.
7. Findlay-Shirras L, Lima I, Smith G, Clemons M, Arnout A. Canada follows the U.S. in the rise of bilateral mastectomies for unilateral breast cancer: a 23-year population cohort study. *Breast Cancer Res Treat*. 2021;185:517–25.
8. Portschy PR, Kuntz KM, Tuttle TM. Survival outcomes after contralateral prophylactic mastectomy: a decision analysis. *J Natl Cancer Inst*. 2014;106:dju160.
9. Han E, Johnson N, Glissmeyer M, et al. Increasing incidence of bilateral mastectomies: the patient perspective. *Am J Surg*. 2011;201:615–8.
10. Abbott A, Rueth N, Pappas-Varco S, et al. Perceptions of contralateral breast cancer: an overestimation of risk. *Ann Surg Oncol*. 2011;18:3129–36.
11. Rosenberg SM, Tracy MS, Meyer ME, et al. Perceptions, knowledge, and satisfaction with contralateral prophylactic mastectomy among young women with breast cancer: a cross-sectional survey. *Ann Intern Med*. 2013;159:373–81.
12. Early Breast Cancer Trialists' Collaborative G, Davies C, Godwin J, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet*. 2011;378:771–84.
13. Nichols HB, de Gonzalez AB, 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;29:1564–9.
14. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med*. 2018;379:111–21.
15. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;365:1687–1717.
16. Metcalfe K, Lynch HT, Ghadirian P, et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. *J Clin Oncol*. 2004;22:2328–35.
17. Hawley ST, Jagsi R, Morrow M, et al. Social and clinical determinants of contralateral prophylactic mastectomy. *JAMA Surg*. 2014;149:582–9.
18. Sun L, Brentnall A, Patel S, et al. A cost-effectiveness analysis of multigene testing for all patients with breast cancer. *JAMA Oncol*. 2019;5:1718–30.

19. Childers CP, Childers KK, Maggard-Gibbons M, Macinko J. National estimates of genetic testing in women with a history of breast or ovarian cancer. *J Clin Oncol*. 2017;35:3800–6.
20. Armstrong J, Lynch K, Virgo KS, et al. Utilization, timing, and outcomes of BRCA genetic testing among women with newly diagnosed breast cancer from a national commercially insured population: the ABOARD study. *JCO Oncol Pract*. 2021;17:e226–35.

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