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EDITORIAL – BREAST ONCOLOGY

Updated Guidelines on When to Consider Germline Testing for Patients with Breast Cancer

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INTRODUCTION AND SUMMARY OF THE ASCO-SSO GUIDELINES

Since the mid-1990s, the American Society of Clinical Oncology (ASCO) has offered guidelines on germline genetic testing for patients affected by breast cancer.[1] Historically, genetic testing had been reserved for patients with strong family histories or other high-risk features of breast cancer (e.g., young age at diagnosis or synchronous bilateral breast cancers). In contemporary practice, the use of multigene panel testing (MGPT) has allowed for comprehensive genetic testing. Additionally, increased accessibility and decreased cost have expanded testing to broader patient populations.

In this editorial, we summarize and comment on the recently published ASCO and Society of Surgical Oncology (SSO) Guidelines on Germline Testing in Patients With Breast Cancer.[1] The guidelines recommend that patients age 65 years or younger with newly diagnosed or prior breast cancer and select patients older than 65 years with a concerning family history should be offered *BRCA1/2* testing, that patients with a recurrent, second primary or other breast cancer eligible for poly (ADP-ribose) polymerase (PARP) inhibitor therapy should be offered *BRCA1/2* testing regardless of age, and that testing for other high- or moderate-penetrance genes might ordered if there is a concerning family history of breast cancer or if the results will inform the patient's personal or familial risk. Other aspects of the guidelines consider that a variant of uncertain significance (VUS) should not have an impact on management, that patients should receive an appropriate level of pre-test information in order to consent to testing, and that patients with pathogenic variants (PVs) should receive individualized post-test counseling.[1]

OTHER PROFESSIONAL SOCIETY GUIDELINES AND KEY DATA SUPPORTING THE ASCO-SSO UPDATE

Many professional societies have developed guidelines for genetic testing in breast cancer (Table 1). Each society varies slightly in its recommendations, specifically regarding age at breast cancer diagnosis and type of testing.[1–3] In 2019, the American Society of Breast Surgeons (ASBrS) issued a statement recommending that germline genetic testing be made available to all patients with a personal history of breast cancer regardless of age at diagnosis.[2] The 2024 National Comprehensive Cancer Network (NCCN) Guidelines advocates testing for all patients age 50 years and younger with breast cancer, those age 65 years and younger with a triple-negative breast cancer (TNBC), and multiple other subgroups suggestive of a hereditary predisposition.[3] The Cancer Care Ontario presents similar guidance, recommending testing for all patients age 45 years and younger, age 50 years and younger with a significant family history of breast cancer, or age 60 years and younger with TNBC.[4]

The ASCO-SSO expert panel concluded that the ideal balance of sensitivity and specificity was reached at an age-testing threshold of 65 years regardless of tumor characteristics or other factors.[1] This recommendation is likely due to the higher prevalence of PVs in this age cohort.[6] Furthermore, the potential benefits of surgical risk reduction, specifically

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TABLE 1 Overview of the current professional society recommendations on genetic testing

Professional society	Recommended age	Recommended panel
ASBrS[2]	All ages	Testing should include *BRCA1/BRCA2* and *PALB2*, with other genes as appropriate for the clinical scenario and family history.
NCCN[3]	≤50 years (all comers) &/or ≤65 years (TNBC)	High-penetrance breast cancer-susceptibility genes
ASCO[1]	≤65 years	*BRCA1/2,* testing for other high- or moderate-penetrance genes may be ordered if there is concerning family history or it will inform the patient's personal or family cancer risk.
ESMO[5]	All ages "in high-risk groups"	*BRCA1/2* testing
CCO (Ontario, Canada)[4]	≤45 years (all comers) &/or ≤50 years (with significant family history) &/or ≤60 years (TNBC)	Based on patient's personal and family history

ASBrS American Society of Breast Surgeons; *NCCN* National Comprehensive Cancer Network; *TNBC* triple-negative breast cancer; *ASCO* American Society of Clinical Oncology; *ESMO* European Society for Medical Oncology, *CCO* Cancer Care Ontario

contralateral risk-reducing mastectomy (CRRM), appear to be greatest for patients age 65 years or younger because secondary malignancies are less frequent in patients older than this with a primary breast cancer.[7]

Another area of variability among professional societies is when to consider testing genes beyond *BRCA1/2*. The current ASCO-SSO guidelines recommend *BRCA1/2* testing at a minimum for those specified in the guidelines because the results may have an impact on systemic therapy recommendations, surgical decision-making, or both. Furthermore, the guidelines state that testing for other high-penetrance cancer susceptibility genes should be offered to appropriate patients based on family history. Broader testing with MGPT also may be considered, particularly when it may inform risk of a second primary cancer or family risk assessment.

In comparison, the European Society for Medical Oncology (ESMO) recommends *BRCA1/2* testing only.[5] Currently, the evidence driving tailored systemic therapy decision-making based on genetic test results for breast cancer patients primarily stems from those afflicted with PVs in *BRCA1/2*.[7,8] Therefore, it is particularly important to identify these patients early given the known clinical benefit of PARP inhibitors in this setting.[8]

Future studies will continue to investigate the potential benefits of targeting other germline PVs with systemic therapies because other disease sites have begun to have such subgroups identified. Meanwhile, most results from MGPT will have a limited impact on systemic therapy recommendations for breast cancer patients, although there may be potential implications related to surgical decision-making and/or informing familial risk.

The detection of high-penetrance PVs (including *PALB2*, *TP53*, *PTEN*, *STK11*, and *CDH1*) could influence surgical decision-making, refine risk estimates of a second primary cancer, and inform familial risk assessment, and thus should be offered to appropriately selected patients. At the time of this writing, however, testing for moderate-penetrance breast cancer genes offers no actionable systemic treatment options for the index breast cancer. From a surgical perspective, the evidence currently is insufficient to recommend for or against risk-reducing mastectomy (RRM) for moderate-penetrance PVs. The 2024 NCCN guidelines recommend management based on family history.[3] Testing may, however, inform risks of second primary cancers or familial risk, and thus may be offered to appropriate patients undergoing *BRCA1/2* testing, similar to what is seen with the high-penetrance PVs.

COMMENTARY

The ASCO-SSO guidelines reflect a thoughtful approach to genetic testing for breast cancer patients, with the recommendations landing between the all-inclusive ASBrS and the stricter NCCN guidelines. These new guidelines may permit more patients to be tested and could potentially identify those eligible for PARP inhibitors, subsequently improving outcomes. Testing may have surgical implications depending on patient age, age at diagnosis, family history, and patient preferences.

Despite these benefits, there are, of course, potential challenges associated with implementation. Although the differing society recommendations have created slight ambiguity concerning who should be tested and how, it is clear that MGPT has largely replaced *BRCA1/2*-only testing during the last decade.[9] Support of MGPT for patients with breast cancer is primarily centered around the concern for underdiagnosis of PVs. In a 2019 study of almost 1000 breast cancer patients undergoing testing via an 80-gene panel, 9.4 % of those meeting the NCCN criteria and 7.9 % of those not meeting the criteria carried PVs ($p = 0.42$), implying that strict adherence to the NCCN guidelines may miss patients with actionable mutations.[10] More than half of the PVs detected were in genes other than *BRCA1/2*.[10] Although valuable, this may create uncertainty in management. For

example, the potential survival benefits of RRM for patients with PVs in genes other than *BRCA1/2* (and *TP53*) are unclear. Conflicting evidence exists regarding the influence of broadening genetic testing practices on surgical decisions (Table 2). Surgeons should be thoughtful when considering both the risks and benefits of testing. They should weigh patients' personal and family histories, presenting what information is known versus unknown, and use shared decision-making principles when discussing options.

Less information exists regarding the implications of infrequent genetic variants for genes other than *BRCA1/2*. This has led to the identification of a large number of VUSs and, with that, confusion about how to manage patients found to harbor a VUS. The detection of VUSs, which are not actionable, may add burden to providers. The interpretation of a VUS finding can be nuanced, and discussions with patients can be lengthy. In the absence of clear guidelines for a specific VUS, providers may offer supplemental screening, risk-reducing options, or both based on other factors such as a strong family history and early-onset breast cancers. Standard yearly follow-up assessment should be encouraged, as would be recommended for any other patient without a VUS. In addition to these management considerations, patients should check in periodically to assess whether the VUS has been reclassified. Notably, most VUSs are reclassified as benign or likely benign.[18] However, if a VUS is reclassified as pathogenic, the patient should be offered updated recommendations. Surgeons who order genetic testing themselves need to develop systems for continual follow-up evaluation of these reclassifications, which may be challenging.

Resource constraints are another potential challenge to implementation of increased genetic testing. Both the ASCO-SSO and ASBrS guidelines support pre-test counseling by a breast surgical oncologist, genetic counselor, or other knowledgeable medical professional.[1,2] Although some surgeons are certainly comfortable discussing and ordering their own genetic testing, others may not feel that they are sufficiently well-versed in these evolving and complicated topics. Consequently, increases in multi-disciplinary care resources (e.g., an institution's hereditary cancer team) may be needed. Pre-test counseling has traditionally included detailed conversations impregnated with nuances. These conventional pre- and post-test counseling models are not sustainable if tests are performed for all breast cancer patients age 65 years or younger. With challenge sometimes comes innovation, which has led to numerous studies demonstrating the feasibility and acceptability of streamlined counseling with comprehensive discussion occurring after results demonstrate a VUS or PV.[19] As these models improve, future work should build on these principles and shift the focus to expanding cascade-testing for family members of mutation carriers.

In summary, the ASCO-SSO updated guideline recommends that *BRCA1/2* testing be offered to all patients age 65 years or younger with a with a breast cancer diagnosis. Although MGPT has largely replaced *BRCA1/2*-only testing

TABLE 2 A non-exhaustive list of studies that reported on the potential association between the act of genetic testing and performance of contralateral risk-reducing mastectomy (CRRM)

References	Year	Study type	*n*	Testing	Findings	CRRM rates
Murphy[11]	2010	Single-institution retrospective	301	*BRCA1/2*	Patients who underwent testing were 9 times more likely to undergo CRRM	Increased
Welsh[12]	2017	Single-institution retrospective	97	*BRCA1/2*	CRRM rates 22 % with VUS versus 25 % without VUS	No impact
Kurian[9]	2018	Population-based retrospective	5026	*BRCA1/2* versus MGPT	No difference in CRRM rates between *BRCA1/2* and MGPT@@CRRM rates for VUS were 30.2 % versus negative results 35.3 %.	No impact
Pederson[13]	2018	Single-institution retrospective	477	MGPT	CRRM rates for VUS were 21.4 % versus negative results 20.1 %.	No impact
Murphy[20]	2020	Single-institution retrospective	1613	MGPT	OR to undergo CRRM 3.9 (2.7–5.8) for non-BRCA PV OR 1.8 (1.3–2.6) for VUS	Increased
Bagwell[14]	2021	Multi-institution retrospective	838	MGPT	CRRM rates for VUS were 32.6 % versus negative results 31 %.	No impact
Metcalfe[15]	2021	Single-institution prospective	766	*BRCA1/2*	Patients receiving negative results had decreased CRRM rates (37 % → 15 %).	Decreased
Ro[16]	2021	Multi-institution retrospective	707	MGPT	CRRM rates for VUS were 25.8 % versus negative results 25.9 %.	No impact
Weiss[17]	2023	Single-institution retrospective	6064	MGPT	OR to undergo CRRM 24.4 (16.7–36.23) for high-risk breast cancer-related PVs OR 1.52 (1.25–1.86) for testing with negative results	Increased

VUS variant of uncertain significance; *MGPT* multigene panel testing; *PV* pathogenic variant; *CRRM* contralateral risk reducing mastectomy; *OR* odds ratio

during the past decade, more studies are needed to further clarify the potential implications (or lack thereof) of such testing, and the genes included on such panels likely will continue to evolve as more data accumulate.

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