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Point of View

Best Practices for Genomic Assay Testing in Early-Stage Breast Cancer: Clinical and Medicolegal Perspectives

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Many patients with early-stage invasive breast cancer (ESBC) do not benefit from adjuvant chemotherapy, a fact that has fueled research into the development of practical applied genomic tests for clinical decision making. The Oncotype DX Breast Recurrence Score, available since 2004, provides prognostic information beyond traditional clinicopathologic factors and is the only test proven to predict adjuvant chemotherapy benefit in ESBC.[1] Breast Recurrence Score testing produces a continuous Recurrence Score (RS) result ranging from 0–100. Higher numbers reflect greater recurrence risk and greater potential chemotherapy benefit. Results also can be subdivided into 3 risk categories: low (RS <18), intermediate (RS 18–30), and high (RS ≥31).

Just as estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) testing personalize treatment with hormonal and HER2-targeted therapy, respectively, an RS result personalizes chemotherapy decision making for patients with ER-positive, HER2-negative, node-negative disease and select patients with 1–3 positive axillary lymph nodes, changing treatment decisions in approximately 36% of cases, primarily related to the avoidance of chemotherapy.[2]

Despite proven clinical utility, Breast Recurrence Score testing is inconsistent and varies by clinicopathologic factors and geographic location.[3] As a result, chemotherapy overtreatment and undertreatment continue to occur, a reality that should concern all clinicians involved in breast cancer workup and subsequent management. In November 2015, our group met to discuss the clinical and legal implications of genomic testing and provide practical tools to foster multidisciplinary collaboration around implementing standard-of-care genomic testing for patients with ESBC.

Determining Clinical Utility

Appropriate validation and testing are crucial before the routine clinical use of a genomic assay for clinical decision making.[4] A genomic assay should guide therapy only when it has demonstrated analytic validity and clinical utility. Analytic validity refers to its accuracy, reliability, and reproducibility, while clinical utility refers to high-level evidence demonstrating its ability to improve outcomes or, if outcomes are similar, reduce costs or toxicity relative to when the assay is not used. Clinical validity, a third critical concept, indicates that an assay accurately and reliably divides a population into 2 or more distinct clinical or biologic groups; however, such prognostic information is insufficient on its own to guide treatment decisions.[5]

The clinical utility of the Breast Recurrence Score has been demonstrated with archived tumor specimens collected in practice-changing clinical trials conducted by several cancer cooperative groups.[6,7] Pivotal studies demonstrate that the Breast Recurrence Score predicts chemotherapy benefit in node-negative disease[6] and in patients with 1–3 positive nodes.[7] It is the only multigene breast cancer assay with Level 1 evidence for determining the risk of distant recurrence and prediction of chemotherapy benefit.

Currently, the American Society of Clinical Oncology (ASCO) strongly recommends its use to guide adjuvant chemotherapy decisions in ER-positive, HER2-negative, node-negative breast cancer, and the National Comprehensive Cancer Network (NCCN) recognizes it as the only genomic assay proven to predict chemotherapy benefit, incorporating it into its guidelines for use in patients with ER-positive, HER2-negative tumors greater than 0.5 cm and pathologic node-negative or micrometastatic nodal disease.[1,5] The NCCN also supports consideration of its use in select patients with 1–3 positive nodes.

Ongoing prospective clinical trials will further validate its clinical utility with respect to adjuvant treatment decisions in node-negative (TAILORx) and node-positive (RxPONDER) disease.[8] Results for the nonrandomized, low-range result stratum from TAILORx (RS <11, n = 1626) confirm that the Breast Recurrence Score identifies ESBC patients who may

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be spared chemotherapy safely.[8] With endocrine therapy alone, these patients had 5-year disease-free survival and distant-recurrence free survival rates of 93.8% and 99.3%, respectively. Results are not yet available for the primary study group, the intermediate-range stratum (RS 11–25), which comprises patients randomized to endocrine therapy with or without chemotherapy, or the high-range stratum (RS >25), who received chemotherapy as standard practice.

Medical Oncologist Perspective

The decision to administer chemotherapy to an individual patient, as well as the decision to avoid it, should not be made lightly. Breast cancer patients frequently come to their first appointment armed with information, and misinformation, about chemotherapy risks and benefits. Some, fearing side effects, hope to avoid chemotherapy at all costs, while others so fear cancer recurrence and death that they pursue all treatments that they perceive will reduce those risks, regardless of the expected toxicity. Genomic test results can help improve a patient's understanding of her individual recurrence risk, and the benefit of chemotherapy, such that she can make a more informed treatment decision. Several genomic assays are now available for prognostic use in ESBC, but they are not necessarily interchangeable.

For example, ASCO indicates that the Prosigna Breast Cancer Prognostic Gene Signature Assay (PAM50) also can be used for adjuvant chemotherapy decision making in ER-positive, HER2-negative, node-negative ESBC.[5] However, comparative studies find poor correlation between PAM50 and the Breast Recurrence Score.[9,10] The 2 tests classified patients similarly less than 60% of the time, and in one study, more than half of the patients classified as high risk by PAM50 were classified as low risk by the RS result.[9] Based on TAILORx, these patients would receive no clinical benefit from chemotherapy; however, chemotherapy likely would have been recommended based on PAM50, highlighting the significant clinical impact of poor test correlation. Given this background, it is prudent to choose the test with the strongest evidence of clinical utility and predictive ability, which remains the Breast Recurrence Score.[1]

Pathologist Perspective

Genomic testing is now as relevant and necessary as ER and HER2 testing, and routine or reflex testing for appropriate patients provides multiple benefits for all stakeholders. Because an RS result changes adjuvant treatment recommendations for approximately 1 out of 3 patients, having that information as soon as possible increases the utility of the initial pathology report, expedites time to treatment plan finalization, and minimizes patient confusion that can arise when treatment recommendations change. For example, in a large Nevada community practice setting, the average time from surgery to treatment plan finalization was 90 days in 2010. After implementation of Breast Recurrence Score reflex testing, the average time was reduced to 12.6 days, a remarkable improvement.

Moreover, reflex testing allows the pathologist to resolve any biomarker discordances before a treatment plan is finalized. The Breast Recurrence Score assay includes single-gene reverse-transcriptase polymerase chain reaction testing for ER, progesterone receptor, and HER2 expression. This second set of biomarkers provides additional quality control on the existing immunostain panels that pathologists routinely perform for ESBC. A discordant result can identify problems with in-house staining related to technical or preanalytic problems. It also can lead to secondary review and/or repeat testing that elucidates previously unrecognized features about a breast cancer that can lead to a change in treatment.

One such example was presented at a recent tumor board involving a young patient whose tumor was classified as HER2-negative based on initial core biopsy testing with HER2 immunohistochemistry and fluorescent in situ hybridization; however, the Breast Recurrence Score assay showed increased HER2 mRNA transcript levels on the subsequent resection specimen. The pathologist performed additional staining on the resection specimen and found significant intratumoral heterogeneity with respect to HER2 expression. Although the Breast Recurrence Score result itself is not validated for treatment decisions in HER2+ breast cancer, use of the assay ultimately led to the inclusion of trastuzumab in the treatment regimen, which one would expect to significantly lower the patient's recurrence risk.

Because there is poor correlation between clinicopathologic factors and the Breast Recurrence Score, universal testing of appropriate candidates is preferable to a ''pick-and-choose'' approach. Clinical practice guidelines such as those from ASCO and NCCN provide direction to support the implementation of reflex testing or development of standard testing protocols for patients who meet specified selection criteria.

This approach is efficient and prevents patients from missing out on the potential benefits of early genomic results. Another presented case involved a patient deemed at low risk of recurrence based on clinicopathologic factors who was found to be at high risk based on an RS result of 30. Without early genomic testing, this patient might have received tamoxifen alone or started tamoxifen only to undergo treatment interruption and chemotherapy initiation at a later time. Reflex testing avoided this situation and aided in the initiation of timely, appropriate treatment. Of course, because a test result has the potential to impact management, the test should only be ordered on patients deemed potential candidates for chemotherapy based on guideline-driven criteria and/or criteria agreed on by the multidisciplinary treatment team. Such criteria may include age, comorbidities, and patient willingness to receive chemotherapy.

Surgical Perspective

Early genomic assay results also can help with surgical treatment planning. The decision to refer a patient to a medical oncologist before surgery is relatively straightforward when the core biopsy identifies triple-negative or HER2-positive disease, scenarios wherein the benefits of preoperative systemic therapy have been well demonstrated, but are less clear for ER-positive, HER2-negative disease. In the latter scenario, knowing up front whether a patient is likely to benefit from chemotherapy is useful. Surgeons must consider multiple factors, ranging from the anatomic to the social, emotional, and logistical for the patient, and the RS result can impact each of these domains.

For example, for a patient with ER-positive breast cancer who strongly wishes to avoid mastectomy but is not a candidate for breast-conserving therapy (BCT), a high RS result can motivate preoperative chemotherapy, which may

facilitate BCT. Conversely, a low RS could motivate preoperative endocrine therapy.[11] For a patient struggling with her surgery decision, an RS result that justifies chemotherapy allows for surgery to be deferred, providing more time for the patient to investigate and learn more about reconstruction and radiation therapy options. For others, the RS result may justify avoiding chemotherapy entirely, whether given preoperatively or postoperatively. In addition, patients with a low RS result sometimes feel more emboldened about survival, and body image becomes more important to their surgery choice. Clearly, the RS result is valuable for shared and informed surgical decision making.

Medicolegal Perspective

Another perspective to consider is whether, given the extent and strength of the evidence, there is a legal obligation to test. The underpinnings for a medical malpractice suit include: (1) the existence of a duty of care, (2) deviation from standard of care, and (3) a resulting injury. In the United States, more than half of all medical malpractice suits are because of failure to order a diagnostic test. It is generally assumed that the test, whether genomic, radiographic, or laboratory-based, would have been informative and actionable in the patient's case.

The US legal system has not yet considered a case in which a genomic assay was not ordered for a patient with ESBC and injury occurred as a result. However, the underpinnings for such a case are increasingly apparent. There is a duty of care, and injury is plausible. For example, liability may exist if a patient develops debilitating or other injurious side effects from chemotherapy that was later found to be unnecessary. Similarly, a patient whose disease recurs could conceivably pursue litigation if chemotherapy was not recommended based on clinicopathologic factors and a genomic assay was never performed or performed later and found to show a high recurrence risk. The key today is whether or not genomic testing is considered the legal standard of care and represents the minimal level of competence to expect from practitioners in the field.

Conclusions

Clinical practice guidelines increasingly recognize the value of genomic testing in ER-positive, HER2-negative ESBC, but testing remains underutilized across the United States.[3] Efforts to increase testing rates to ensure that treatment decisions are made on validated, personalized data are needed and must involve all members of the multidisciplinary team. Organizations and individual physicians need to consider which team member is best suited to order the test so that all team members have the results when they need them. Implementing standard-of-care testing improves patient care by personalizing chemotherapy decisions, minimizes time from diagnosis to treatment, avoids patient confusion caused by changing recommendations, and may reduce medicolegal risk. Currently, the Breast Recurrence Score is the best-validated genomic assay and only test proven to predict adjuvant chemotherapy benefit in patients with node-negative or node-positive (1–3 nodes), ER-positive, HER2-negative ESBC.

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