Revised Guidelines Signal That Gene Expression Profiles Are Coming of Age

By Steve Benowitz

When the National Comprehensive Cancer Network (NCCN), a consortium of 21 comprehensive cancer centers, released its most recent breast cancer treatment guidelines in January, they included for the first time the option to use gene expression profiles in the treatment decision-making process.

For many of those who watch the field closely, this addition was a milestone for the burgeoning discipline of molecular diagnostics and a sign of changing times in the practice of medicine.

“This reflects what has occurred in clinical practice,” said Eric Winer, M.D., director of the breast oncology center at Dana-Farber Cancer Institute in Boston and a member of the NCCN expert panel charged with reviewing and updating the guidelines. “Gene expression profiles have the potential to be a huge advance.”

Although the new guidelines note that several gene expression tests are still in development, they point to only one option for now: Oncotype DX, made by the Redwood City, Calif–based Genomic Health. In the United States, it is the most readily available and widely used of such diagnostic tests. Oncotype DX measures the activity of 21 cancer-related genes to generate a recurrence score that can help predict the risk of a cancer returning in women with estrogen receptor–positive, lymph node–negative breast cancer, as well as their response to chemotherapy. The higher the recurrence score, the more likely it is that the cancer will recur. The score is used in combination with other, more traditional factors such as age, tumor size, levels of hormone receptor protein, and tumor grade.

Acceptance of Oncotype DX stems from retrospective analyses of the results of two trials studying estrogen receptor–positive, node-negative breast cancer. The test was able to quantify the risk of recurrence and predict an individual’s response to tamoxifen and chemotherapy.

“People have always known that the benefits of chemotherapy were not uniform. Some got a lot of gain, some very little, but it was hard to figure out who these individuals were,” said Harold Burstein, M.D., Ph.D., associate professor of medicine at Harvard Medical School and another NCCN panel member. “Over the past several years, there’s been a lot of talk about how to determine which estrogen receptor–positive breast cancer patients merit chemotherapy in the adjuvant setting. It became clear from the dialogue that our institutions were using this test. In a large way, it was really [from this use] that the guidelines formally added it as part of the algorithm to consider for determining therapy for these breast cancer patients.”

He noted that there are other molecular diagnostic assays under development, such as the 70-gene assay, Mammaprint, aimed at determining which patients with estrogen receptor–positive, node-negative breast cancer are more likely to develop distant metastases.

“The clinical research that has led to the development of these tests allows us to make much more informed decisions that are tailored to the needs of the individual on the basis of the biology of the tumor,” Burstein said. “That’s a fundamental goal for this kind of work. The guidelines are really following the lead of what is happening at major academic medical centers, rather than the other way around.”

Controversy Remains
But not everyone agrees that Oncotype DX is ready for widespread use. According to NCCN panel chair Robert Carlson, M.D., professor of medicine at the Stanford University Medical Center, “The single place that the current guidelines are controversial and have been criticized is in the inclusion of the 21-gene [Oncotype DX] assay in treatment decision making. It’s a recommendation that has been criticized particularly by our international colleagues mainly because of the lack of prospective data and the fact that we are looking at a relatively short time in validating its use.” Others are concerned that decades of experience in cancer histopathology are being discounted.

Carlson said that its incorporation into the NCCN guidelines should not be overinterpreted. “It means that there is a substantial amount of data that support its use in a select subset of patients with invasive breast cancer in terms of whether chemotherapy should be used as part of treatment. The guidelines don’t say that the 21-gene assay must or should be used but that it can be considered by physicians in the treatment decision discussion. It should be used only if it can make a difference in the treatment decision.”

An ongoing randomized trial might resolve some of the questions involving the test’s use. The NCI-supported TAILORx trial uses Oncotype DX to stratify patients into three groups—those who will receive chemotherapy, those who will receive hormone therapy (tamoxifen), and a large intermediate group who are randomized to hormone therapy or hormone therapy and chemotherapy. This intermediate group has recurrence scores in the middle range, in which the treatment decision is uncertain. The goal of the trial (with survival as an endpoint) is to determine whether hormone therapy and chemotherapy are better than chemotherapy alone for women with early-stage breast cancer. The trial is intended to also serve as a way to validate Oncotype DX prospectively.

In Practice
But even as research continues, “in community practices, many oncologists are ordering these tests,” Winer said, “and Oncotype DX can guide decisions. But it’s
like a new drug on the market—doctors begin to use it but don’t know how to use it optimally as yet. We’re implementing the tests in practice but still have a long way to go to understand how best to use them.”

Oncotype DX helps most in clinical decision making for women who have recurrence scores at the extremes (high recurrence scores indicate that chemotherapy might be beneficial, whereas low means that chemotherapy would probably not be of substantial benefit), but its value is less than clear for the group of women whose scores land somewhere in the middle range.

“I think that there is a subset of patients for whom you would choose to change therapy on the basis of the Oncotype DX results,” said Charles Shapiro, M.D., director of breast medical oncology at Ohio State University Medical Center in Columbus.

But how does a physician decide who belongs to that subset? Uncertainty plays a big part. “When the oncologist and patient, who has early-stage, estrogen receptor–positive, node-negative breast cancer, are uncertain whether chemotherapy would add enough benefit, that’s when I recommend the test,” Shapiro said. “Most of us use it for patients when we are on the fence about a treatment choice.”

He noted that historically, treatment choice was based on tumor characteristics, such as size and nodal status. But, Shapiro said, “Our clinical experience shows us that small tumors can be bad actors and can recur. Large tumors don’t necessarily have to recur. This is a more biologically based way of deciding treatment.”

Combining conventional techniques with the newer molecular tests will take some time. “Oncotype DX and its cousins are direct challenges to what traditional pathologists have done as their jobs,” Burstein noted. “There are still questions about how to integrate these tests with traditional pathology.

“You’re talking about a fundamental shift in the way people think about treating breast cancer,” he said. “We’re trying to graft our traditional criteria onto the new molecular criteria. It’s not unique to breast cancer—this will happen in other cancers as well.”

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