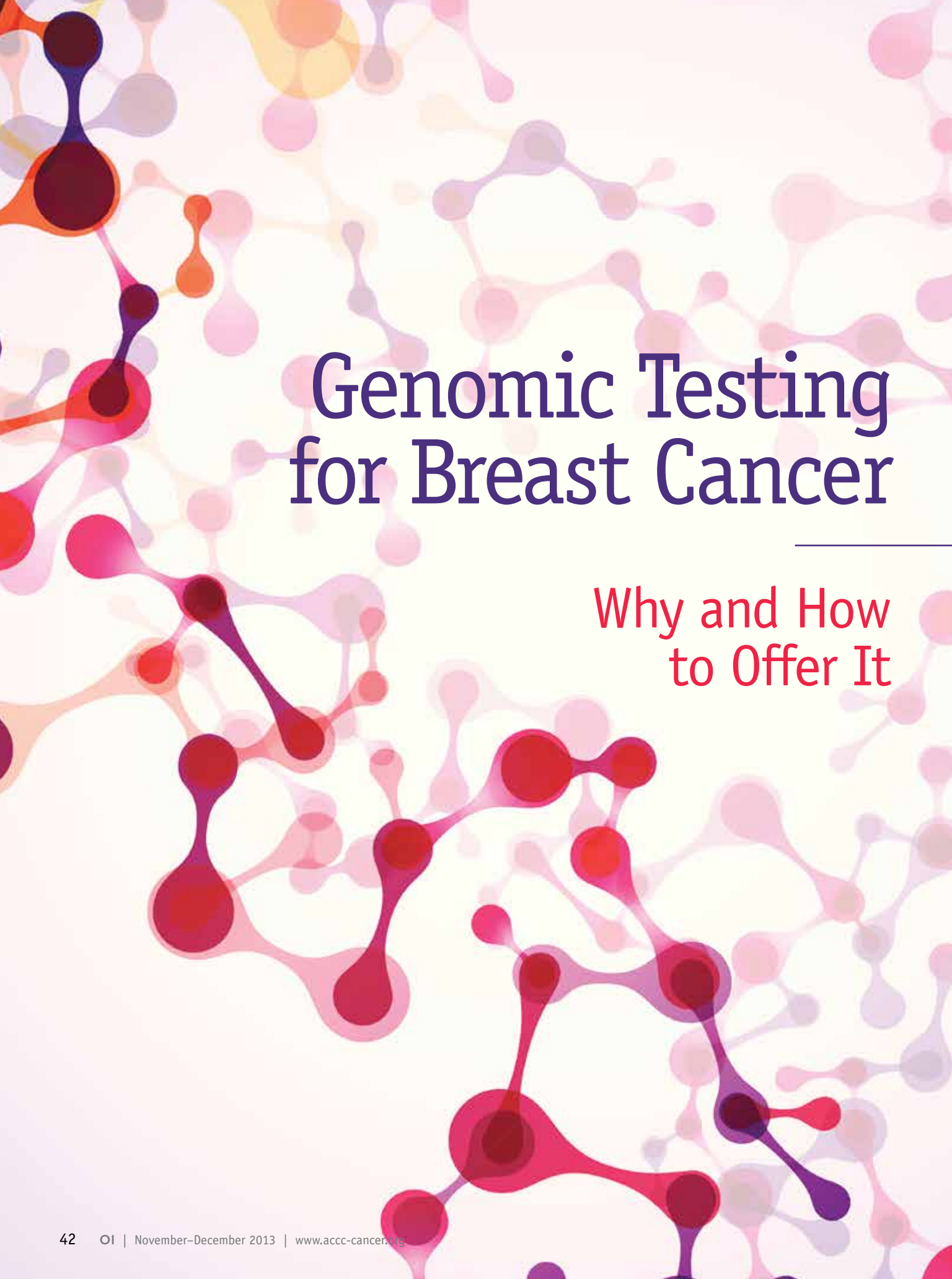

Genomic Testing for Breast Cancer

Why and How to Offer It

BY JAMES V. PELLICANE, MD, FACS

New technologies spread in medicine roughly the same way they do in other parts of society. There are early adopters, followed by the early majority, the late majority, and then everyone else. Genomic testing for breast cancer treatment is following this predictable pattern. The approach is now established enough that both a first-generation test and a significantly more evolved second-generation test are available. Neither test is experimental; their results are well accepted in the field.[1,2] Today these tests are transforming the approach to breast cancer treatment taken by oncologists, surgeons, and multidisciplinary breast care teams.

With genomic testing, one-size-fits-all medicine is giving way to personalized medicine—diagnoses and treatments that are tailored to the individual characteristics of each patient's cancer. Cancer centers that provide genomic testing can offer many patients the choice of forgoing chemotherapy without increasing the risk of recurrence. That in itself can be an advantage for a cancer center in a competitive environment. More importantly, it is the appropriate way to provide patient care. Recent statements from a task force of the National Cancer Institute (NCI) and an international panel of breast oncology experts have underlined the growing value of genomic testing to determine both recurrence risk and molecular subtype to guide personalized treatment.

These tests are simple to adopt. They require no capital outlay and no major disruption to a cancer center's ordinary administrative processes, and yet, genomic testing for eligible patients has not reached even the "early majority" phase of adoption. This article explores the reasons for its slow diffusion in the field; details the multiple advantages of the tests for patients, providers, and the healthcare system at large; and describes the simple practical steps to provide the tests.

How Genomic Testing Changes Diagnosis & Treatment

The advantages of genomic testing for breast cancer are profound—clinically, economically and, for patients, experientially. Those advantages are available right now in certain applications, and expanded applications may be just around the corner.

The most noteworthy clinical advantage today is the ability to predict with a high degree of reliability how aggressive a tumor is—that is, how likely the cancer is to recur or metastasize. If there is a low risk of recurrence and no overwhelming factors where more aggressive therapy would be supported by the literature, the medical oncologist may offer the patient the option of not undergoing adjuvant chemotherapy and the potential side effects. Women generally find the prospect of those side effects disturbing and often for good reason.

Relatively common complications of adjuvant chemotherapy for breast cancer include nausea and hair loss, as well as compromising of memory, concentration, and motor function (in one-quarter to one-third of women).[3,4] The latter may persist long term.[3] Other potential complications include mouth sores, diarrhea, weight loss or weight gain, depression, and low blood cell counts leading to fatigue, vulnerability to infections, and easy bruising or bleeding.[3,4]

Long-term complications of adjuvant chemotherapy can include anemia, thrombocytopenia (abnormal blood clotting), liver and kidney damage, neuropathy, allergic reactions, heart muscle damage and heart failure, other heart and nervous system problems, severe joint and muscle pain, menstrual abnormalities, sexual dysfunction, and infertility.[3,4] Serious secondary cancers, such as leukemia, are a rare long-term complication.[3,4]

These complications are not a secret. Women have heard of them and dread them. With genomic testing, many patients can now choose to safely avoid all of these complications without an impact on their chances of survival.[5]

The financial impact of avoiding chemotherapy is considerable. While it is not possible to state an average cost of adjuvant chemotherapy due to the number of factors involved, costs range from tens to hundreds of thousands of dollars. The savings to the healthcare system, if genomic testing were more widely adopted, could be substantial.

The value of genomic tests is underlined in new clinical practice guidelines, published in the August 2013 edition of *Annals of Oncology* and provided by the St. Gallen panel of international breast cancer experts along with European and Japanese Oncology societies.[6] The St. Gallen guidelines emphasize the need to use genomic assays that can provide molecular subtyping to determine which patients need to undergo chemotherapy.[6]

In the U.S., an NCI taskforce has recently pointed toward the value of molecular diagnostics to reduce overtreatment such as unnecessary chemotherapy for breast cancer.[7] The taskforce noted that many patients are overdiagnosed and overtreated today. Overtreatment can have serious side effects that could be avoided,

for certain patients identified by molecular testing. "Molecular diagnostic tools that identify indolent or low-risk lesions need to be adopted and validated," the authors said, adding that "understanding the biology of individual cancers is necessary to optimize early detection programs and tailor treatments accordingly."[7]

Why is Genomic Testing Not More Widely Used?

According to Google, breast cancer patients are the number-one seeker of healthcare information on the Internet, as evidenced by almost 2 million monthly hits searching the key words "breast cancer." Breast cancer patients often arrive at the doctor's office already informed about genomic tests. In fact, both companies making genomic breast cancer tests offer patient education websites for this purpose. Should physicians be uninformed about these tests, they risk losing informed patients to cancer centers that offer these tests routinely.

While genomic testing is established enough to be covered in general practice guidelines, a significant number of clinicians have not even heard of the concept. Even among physicians who are aware of genomic testing, many have serious misunderstandings about molecular diagnostics, as revealed in "Molecular Testing the Community Setting," an education program conducted by the Association of Community Cancer Centers (ACCC).[8]

For this project ACCC conducted two informal online surveys, one of multidisciplinary team members and one of pathologists. Survey findings, along with focus group discussion and follow-up interviews, identified several barriers that stood in the way of molecular testing adoption. One of those barriers was, in the words of the ACCC survey report, "need for significant upfront capital investment and competing capital priorities."[8]

While this barrier may affect other forms of molecular testing, there is no upfront capital investment to stratify breast cancer patients with genomic testing. The tests are simply ordered online from either of the two companies that offer testing. The companies then bill the patient's insurer(s) for the cost and design an individual payment plan for the patient for any uncovered fees.

The education project also identified another financial barrier to adopting the tests: "Unwillingness on the part of administration to take risks and invest time…and staff upfront."[8] But as I will describe in more detail in the following section, it is becoming increasingly risky *not* to offer genomic testing. The staff commitments for a cancer center are also minimal.

Genomic testing is used to determine the nature of a diagnosed breast cancer patient's breast tumor. Genomic testing provides information on how that specific tumor is behaving and what is driving the growth of the tumor. With this information, a more specific treatment plan can be developed for each patient. If the genomic test shows the tumor to be at low risk for recurrence, a patient can with good confidence elect to forgo chemotherapy, because further therapy to reduce recurrence risk is unnecessary.[5]

There are two more reasons that genomic tests have not been more widely adopted: inertia and outright resistance to change. Sometimes, it is more comfortable for physicians to continue doing things as they have in the past because those things seem to work well for them in their practices. In addition, some physicians may be more cautious than others in accepting new technologies and processes.

That said, reluctance or delay in adopting genomic testing is perfectly understandable. Genomic testing is a significant paradigm shift in the way we think about breast cancer growth and metastasis and requires an equally significant shift in thinking. Physicians are also pulled in many directions at once, with constant change in all fields. They can certainly be forgiven for not having the time to review all the new literature about genomic profiling—particularly if breast cancer therapy is not their main focus. This fact alone explains why many physicians will continue with their traditional approach to the disease.

Advantages of Incorporating Genomic Testing

There are many advantages to offering genomic testing at your breast cancer treatment center or community cancer center.

Ease and benign nature of testing. Genomic testing is not an invasive test. It is performed on tissue previously removed by surgery or biopsy. It has no side effects. Genomic testing simply provides information on which to base treatment decisions. It means those decisions can be made more wisely than they could have been before the advent of genomic testing. In short, there is no clinical downside.

Improved patient care. This is of course the most important factor. Genomic testing provides the information upon which more accurate and more personalized treatment decisions can be based. Patients who are found to be at low risk of recurrence have the option of avoiding the side effects and lifestyle disruption of chemotherapy. Patients shown to be at high risk of recurrence can choose a therapy regimen, likely including chemotherapy, which is personalized to their tumor biology.

Cancer centers that do not offer genomic testing run the risk of over- or under-treating their patients. These programs are operating on information that, while necessary and helpful in the current environment, can only be described as insufficient and outdated if considered alone. Clinicians are effectively assuming that all patients have the same need for and will get the same benefit from chemotherapy. But that's not the state of objective medical knowledge today. These cancer centers may be needlessly recommending chemotherapy to some of their patients. Those patients will be exposed to risk and side effects but receive no treatment benefit because the decision to treat was based on outdated parameters.

How your cancer center is perceived. Genomic testing is well on its way to becoming the standard of care. Cancer centers that do not soon incorporate genomic testing will fall behind the mainstream, and may be viewed as such by the public and medical professionals alike. The positive side of this scenario is that if your cancer center offers genomic testing, prospective patients will perceive it as providing state-of-the-art diagnoses and treatment in a circumstance that affects their daily experience of life as well as their long-term survival. In short, it can be a strong market differentiator.

Cost. The only conceivable objection to genomic testing then could be cost: that it is not a cost-effective use of personal or healthcare system dollars. But the cost per patient to the healthcare system is about $4,000. That's far less than the typical lifetime cost of adjuvant chemotherapy, resulting in a net savings to society. Government and most private payers cover genomic testing. Both testing companies also have financial assistance programs for patients based on financial need.

As noted previously, there are no capital costs to adding genomic testing. No new medical or administrative staff need be added because the testing companies handle the billing. Because genomic testing is different from genetic testing, no genetic counselor is needed. The primary investment is brief training time for a medical oncologist or breast surgeon and a nurse or nurse navigator to better understand the test so they can knowledgeably interface with patients.

Deciding Which Test to Offer

Here are two genomic tests for breast cancer:

- A "first-generation" test, Onco*type* DX® Breast Cancer Assay, from Genomic Health, Inc.
- A "second-generation" panel called Symphony, from Agendia, Inc., which encompasses MammaPrint® and two other, closely related tests.

A cancer center must decide whether to offer both tests or just one—and if the latter, which test it wants to offer.

In my view, the wisest strategy is to offer the second-generation panel of tests alone. This decision makes sense from both a clinical and a cost-effectiveness standpoint. The three tests in the panel, which are done at the same time on one tissue sample, are the most advanced scientifically; yield the most definitive results; and are applicable to many more breast cancer patients than is the first-generation test.

The case for offering both tests does not hold up to scrutiny, in my opinion. That decision is better understood after examining the differences between the tests in detail (see "Actionable Results," at right). Those differences come down to several factors:

Foundation science. The first-generation test was developed by studying 250 genes that breast cancer experts at the time (more than a decade ago) thought might affect cancer recurrence and which genes performed well in their assay.[1] The research resulted in a 21-gene "signature."

In contrast, the second-generation test was developed using a scientific method based on the Human Genome Project. That is, the second-generation test was based on the examination of the approximately 25,000 genes mapped by the project.[2] The methodology made clear to researchers which genes were relevant to recurrence based on the difference between signatures of cancers that recurred versus cancers that did not recur, resulting in a 70-gene signature giving a dichotomous result.[2]

Prospective outcome studies. The first-generation test has been more widely used, with more than 300,000 patients tested. However, I am not aware of the publication of any peer-reviewed study in which actual treatment decisions were prospectively based on the test and reported the patients' outcomes.

The second-generation test does have prospective data validating it. A study published this year in the *International Journal of Cancer* showed that among women who were identified by MammaPrint as having a low risk for recurrence—the majority of whom chose not to receive chemotherapy—97 percent were cancer-free five years later.[5] The study also found that among women identified by the test as being at high risk—who then chose to undergo chemotherapy—91 percent were cancer-free five years later.[5] The results, which apply to women with early-stage breast cancer who are lymph-node-negative, further validated the second-generation test. They show that the second-generation test accurately stratifies patients into low-risk and high-risk groups for purposes of personalizing their cancer treatment.[5]

Applicability. While both tests are for early-stage breast cancer patients, the first-generation test is only applicable to women who are estrogen-receptor (ER) positive and HER2/Neu-negative.[9,10] The second-generation test has no such limitation. It can be used for all early-stage breast cancers.[11,12]

It is also important to understand that the first-generation test is based on research with women who had completed five years of tamoxifen therapy. Its validity is unclear if women have not completed a full course of tamoxifen.[1] That is important to note, because studies show about half of women who begin taking tamoxifen quit before the five-year point.[13] Again, there is no such limitation with the second-generation test because the test was developed and subsequently validated on untreated patients.[2]

Actionable results. The first-generation test stratifies women into three groups: low-risk, intermediate, and high-risk. Women in the low-risk group may choose to avoid chemotherapy and those in the high-risk group are advised to pursue a more aggressive approach. But those in the intermediate group, encompassing about 37 percent of results, are in treatment limbo.[14] The first-

generation test does not indicate any particular action and those patients are no better off than if they had not had the test at all. This test does not appear sophisticated enough to stratify all women. It may be helpful at either end of the spectrum, but for the significant number of patients in the middle, the test provides no help.

In contrast, all results of the second-generation test are "actionable." The test stratifies women into low- and high-risk groups only, and the implications regarding chemotherapy are clear for everyone. This difference is most likely related to the objective way in which the genomic signatures were derived. Again, the second-generation test began with 25,000 candidate genes as opposed to 250. Plus, the study design lets the tumor itself guide the gene selection, instead of researchers adding bias to the test by choosing the genes that scientists thought were relevant at the time the first-generation test was developed.

The issue of actionable results gets to the crux of whether a cancer center should offer two tests or one. Some cancer centers test women with the first-generation test, and if a woman gets an intermediate result, they then test her with the second test to determine definitively if she is at low- or high-risk for recurrence. If clinicians had simply started with the second-generation test, they would have had a definitive result to begin with and could have begun treatment earlier.

Cost-effectiveness. While both tests cost about the same ($4,000), more than one-third of women who take the first-generation test will get an intermediate, non-actionable result—meaning the test did not help with treatment decision making and insurance still must be billed. The second-generation test has no such drawback. Offering both tests potentially doubles the cost for patients in terms of co-payments, co-insurance, deductibles, and other out-of-pocket-expenses.

Looking at cost-effectiveness in a larger framework, a paper published last year in the journal *Cancer* found the second-generation test to be significantly more cost-effective for the healthcare system at-large.[15] The researchers compared "the costs and quality-adjusted life-years (QALYs) of treatment decisions guided by" the tests. In this scenario, patients who used the first-generation test to guide treatment decisions spent $27,882 and gained 7.364 QALYs. Those who based their treatment decisions on the second-generation test spent substantially less—$21,598—and gained 7.461 QALYs. Both differences were statistically significant.[15]

Patient relationships. Patients seek definitive answers from clinicians and tests. Ambiguity is upsetting to them. Yet, cancer centers that offer the first-generation test will frequently have to report ambiguous intermediate results to their patients. If clinicians then use routine clinico-pathologic guidelines to "split the difference," they may end up recommending that a majority of those patients consider chemotherapy—when in fact as many as half of patients may not benefit from it.

Molecular subtyping. The second-generation test provides quantitatively more information for treatment decision making. That's because it is actually part of a three-assay suite of tests. For instance, one of the assays (BluePrint™) classifies breast cancer into basal, luminal, and ERBB2 (HER2/Neu dominant) molecular subtypes. Each subtype is known to have a different prognosis and to respond differently to various therapies. This additional layer of information goes beyond the basic stratification of patients into low-risk and high-risk groups and can help guide—and personalize—treatment decisions.

The value of molecular subtyping will increase over time as more data is accumulated. For example, paradigm-shifting findings continue to emerge about clinically HER2-positive patients and the different subtypes they express. Studies are also revealing substantial findings about basal subtype patients. The first-generation test does not provide molecular subtyping and is therefore not really sophisticated enough to tease out these potentially relevant differences.

No need for more personnel. With both of the genomic tests, staffing considerations are quite straightforward. Administrative and office staff, plus clinicians, including nurse navigators, need to be aware that the test is being offered. The cancer center will need a relationship with a pathologist and the breast surgeon who will obtain the tumor sample, either surgically or with a core biopsy. The sample is then typically sent to the testing company as formalin-fixed, paraffin-embedded (FFPE) tissue. The medical oncologist will use the test results to help patients decide on an appropriate treatment strategy. The two main companies that offer these tests handle the billing to Medicare, Medicaid, and insurance companies.

Going Forward

Genomic testing that stratifies breast cancer patients with regard to their risk of cancer recurrence is now beginning to figuratively stratify breast cancer treatment centers, as well. Those that offer genomic testing will be seen as providing the most advanced care available. Those that do not offer genomic testing will increasingly be perceived as behind the curve.

This is particularly true when it comes to the decision process about whether or not a patient should undergo chemotherapy. The consequences of that decision are so significant that informed patients will seek the most sophisticated advice they can find. Today, that means genomic testing. OI

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GENOMIC TESTING FOR BREAST CANCER: A PATIENT'S STORY

E.L., a physical therapist in Richmond, Va., wasn't expecting any surprises when she received the results from her first-ever mammogram in November 2011. But she got one. The radiologist found what looked like breast cancer.

Among the many fears racing through her head was the possibility that she would have to undergo chemotherapy after her surgery, to prevent a cancer recurrence. "You always hear about people being really sick, throwing up, losing all their hair," said E.L. "Then I researched it on my own and read about having long-term heart problems, getting 'chemo brain,' and other serious issues. I have a friend who had an intestinal cancer. She had chemo and got neuropathy, including numbness, in her hands. That would have been a real problem in my profession."

Before her surgery, E.L. met with her breast surgeon, who recommended that her tumor be evaluated with the second-generation genomic test. Following her January 2012 operation, her medical oncologist advised that the first-generation test be ordered, as well.

The results for both tests arrived in mid-March 2012. The first-generation test result was confusing. It was right on the border between the test's low-risk and intermediate categories, which meant there was no clear direction about whether chemotherapy would be helpful. The second-generation test result left no such questions. It placed her squarely in the low-risk category. But how should she weigh that score against her first-generation test reading?

E.L. consulted with her breast surgeon, who had first told her about the second-generation test. He said that he could not make the decision for her but made it clear that in her situation, he would not choose chemotherapy. He also assured E.L. that the second-generation test, besides providing more straightforward results, was more sophisticated than the first-generation instrument. E.L. decided she could safely choose to avoid chemotherapy and not look back.

Today, E.L. is in the midst of tamoxifen therapy, a normal recommendation for her hormone receptor-positive form of the disease. It affected her mood at first but other than that, the therapy has gone smoothly. Because there's no chemotherapy in the picture, she's back to the life she enjoys—playing tennis, taking exercise classes, and working a full schedule. She's a big believer in the benefits of genomic testing.

"It just makes sense to look at what's driving the tumor," E.L. said. "And no one should have to do chemo if they don't really have to. If a woman has breast cancer and her doctor doesn't do genomic testing, I would definitely recommend that she find another doctor who does."