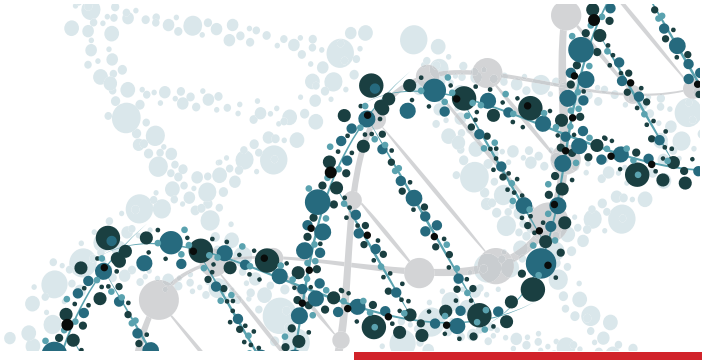
RGA

Global Health Brief



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Prognostic Genomics and Breast Cancer

Up to 70% of breast cancer patients prescribed chemotherapy after their surgeries might not need it. But how can clinicians make that decision, and insurers determine whether to cover the determining tests? Help today is coming from a growing portfolio of increasingly sophisticated genomic tests that can assess recurrence risk for early-stage breast cancer patients and guide both clinicians and insurers. This informative Global Health Brief discusses breast cancer genomic testing (including the increasingly utilized MammaPrint® test) and how to effectively assess claims for these tests.

Sincerely,
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Personalized Medicine

Since their emergence soon after the completion of the mapping of the human genome (2003), genomic tests for breast cancer tumors have become an effective tool in medicine's cancer-fighting arsenal.

These personalized tests, which are generally ordered right after a tumor's post-surgery pathology report, are not intended to diagnose a patient or assess their therapy response. Rather, they are to examine the genetic makeup of the breast tumor to get a sense of the risk that the cancer might recur, whether in the breast or elsewhere, and from there, determine if chemotherapy would be the most effective post-surgery therapy option.

Knowing a patient's potential recurrence risk for breast cancer, the most common type of cancer worldwide, can have a substantial direct impact on patient mortality and convey high benefits both to patient and insurer.

About the Tests

Guidelines provided by groups such as the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the European Society of Medical Oncology (ESMO) recommend the use of clinical and pathological factors, including results of genomic tests, to establish patient risk of breast cancer recurrence and to guide treatment.

Currently, four genomic tests (see Table 1, next page) are available for assessing breast cancer risk and the likelihood a patient might need chemotherapy.

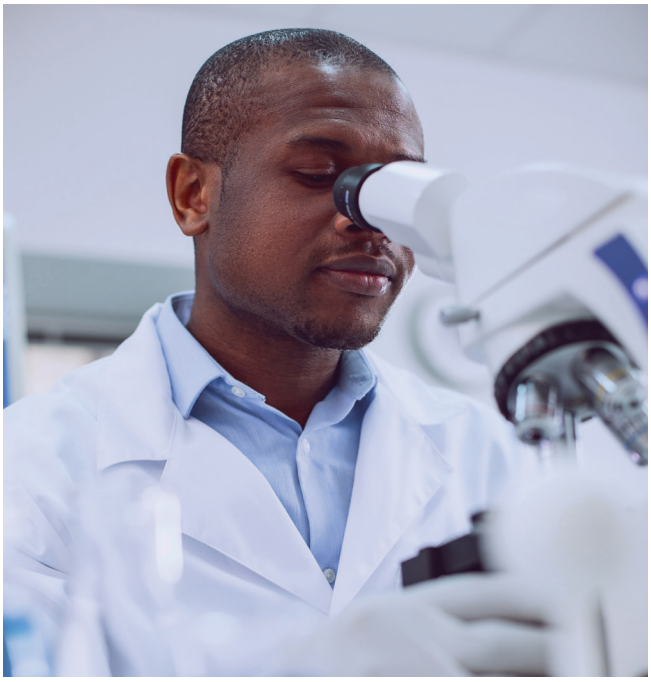


TABLE 1: GENOMIC BREAST CANCER TESTS			
Test	Year Introduced	# Tumor Genes Assessed	Clinical Application
MammaPrint®	2004 (2017 U.S.)	70	Determines candidates for chemotherapy after breast cancer surgery and who can safely avoid it without subsequent negative impact on health and survival. Patient risks are classified as either high or low.
EndoPredict	2011 (2017 U.S.)	12	Predicts risk of distant recurrence and metastasis within 10 years.
Oncotype DX	2004	21	Generates a recurrence score between 1 and 100. Risk results for women over 50 are segmented as low (0-25 points) and high (26-100). For women under 50, risk results are segmented as low (0-15), low to medium (16-20), medium (20-25), and high (26-100). For those with high risk scores, the benefits of chemotherapy are considered to outweigh the potential side effects.
Prosigna (formerly PAM50)	2015	58	Predicts risk for postmenopausal women of distant recurrence of early-stage hormone receptor positive breast cancer with up to three positive lymph nodes within 10 years of diagnosis and after five years of hormone therapy.

Source: BreastCancer.org

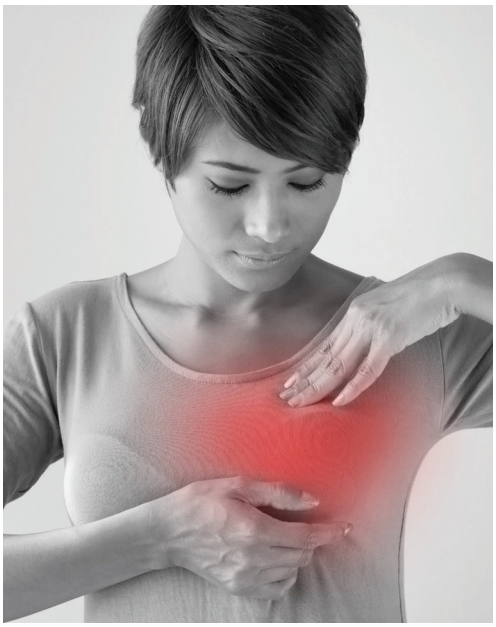
Indications for each test also vary. Table 2, below, summarizes indications for each.

TABLE 2: TEST ADMINISTRATION INDICATIONS				
	MammaPrint®	Prosigna	EndoPredict	Oncotype DX
Stage	Stage I or II, or operable Stage III	Stage I or II, invasive, and has been treated with surgery and hormonal therapy	Stage I or II	Stage I, II, or IIIa invasive
Ages	All ages	Post menopause	All ages	All ages
Tumor size	<5 cm	<5 cm	--	--
Lymph node involvement	Either node negative or 1-3 positive nodes	If Stage I, node negative. If Stage II, node negative or 1-3 positive nodes	Node negative or 1-3 positive nodes	Node negative or positive
HER2 status	Negative	Negative	Negative	Negative
ER/PR status	Positive	Positive	ER Positive	ER Positive

There are three additional prognostic genomic breast cancer tests, but they are not chemotherapy-focused. The Breast Cancer Index (BCI) test assays seven genes to predict recurrence risk of certain breast cancers within five to 10 years and is also used to determine at the five year mark whether to extend hormone therapy up to 10 years. The Oncotype DX Breast DCIS test, examines 12 genes in a patient's ductal carcinoma in situ to determine recurrence risk and whether the patient might benefit from radiation.

BluePrint®, a breast cancer genomic test from the developers of MammaPrint®, is intended for assaying a tumor before its removal. This test analyzes 80 genes to determine the cancer's subtype – luminal A or B, HER2 type, or basal (also known as triple negative). From there, the results are used together with results of the MammaPrint® test to determine the cancer patient's long-term risk prognosis and, depending on the type of cancer, which therapy is most suitable and if therapy might be needed at all.

Are They Reliable?



Genomic testing for breast cancer tumors is recommended in cases where prognostic uncertainty persists. These tests should not be confused with predictive genetic tests for breast cancer, which indicate a patient's risk for certain inherited cancers by looking for mutations in specific genes. Currently, approximately 110 genes are known to be associated with breast cancer.

These genomic tests examine genes isolated from a patient's tumor after its excision to determine the risk of future medium to long-term probability of recurrence, and from that, especially in high-risk cases, whether antineoplastic therapy to reduce that probability would be appropriate.

Clinicians generally base their chemotherapy recommendations on their assessment of whether a patient's cancer is at risk of recurring within the next five years. Before the development of genomic tests, the assessment was traditionally based on tumor features such as stage (tumor size, regional nodal involvement), grade, expression of estrogen and progesterone receptors and of human epidermal growth factor receptor-2 (HER2), and patient features such as age and menopausal status. Interestingly, many of these traditional risk assessment items are the same ones used today to determine whether a genomic test might be appropriate.

The test results can (and have) substantially reduced indications of recurrence risk for many breast cancer survivors, and with it the need for chemotherapy.

At the point, genomic breast cancer tests are still being assessed. Two five-year clinical validation studies, the MINDACT trial for the MammaPrint® test and the Trial Assigning Individualized Options for Treatment (Rx) (TAILORx) trial for Oncotype DX, have thus far generated positive results. MINDACT determined that 94.7% of patients surveyed with high clinical and low genomic risk (as determined by the test) had, at the end of five years, distant metastasis-free results. TAILORx's results, published in 2018, found that 70% of women with high clinical risks could forego chemotherapy.

Considerations

Breast cancer is normally a covered diagnosis under health insurance. As clinical guidelines are currently recommending (but not requiring) these genomic tests, most companies now cover them as long as they are used as stipulated in the guidelines. Many insurers also authorize chemotherapy treatments even if the genomic tests indicate low recurrence risk. It is important for claims assessors to evaluate if the tests are necessary.

Insurers that cover the tests should consider using these guidelines:

- Tests should only be administered in cases where there is still uncertainty about the risk of recurrence or the benefit of chemotherapy.
- They must be requested and supported only by clinical oncologists.
- Only tests performed at the time of tumor removal should be authorized

Ensure there is clinical follow-up for each case where the test was administered. Insurers that exclude coverage of genomic testing for breast cancer risk must state it in their terms and conditions.

Conclusion

The entire field of genomic medicine is moving quite fast, making it imperative that insurers stay current with the latest developments. What's important right now is that the availability of these tests does not necessarily mean they are always useful or indicated. Rather, these tests need to be used only when medically necessary and appropriate and where they will add value. ■