

## Gene-Expression Profile Testing

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The problem of determining with some level of scientific assurance which women don't need these treatments is one that research is just beginning to address with newly available technologies. Finding reliable and accurate ways to help determine which patients will benefit from each breast cancer treatment is extremely important.

Much current cancer research focuses on finding ways to understand the specific characteristics of the cells of individual tumors. This would allow doctors to recognize which cancers don't need certain treatments, and to tailor treatments for those that do. Because every living cell contains genes that control the production of specific proteins, one approach is to identify sets of genes in cancer cells that cause either too much or too little production of the proteins that they control. Such under- or over-production of proteins is typical of cells that are malfunctioning - like cancer cells.

New understanding of the human genome (all the genes in the human cell), together with the development of new scientific technologies, has provided various ways to compare the activity of the genes in normal cells with their activity in cancer cells. Such comparisons allow researchers to pick out genes that reliably distinguish between the two. Once a distinct pattern has been identified that differentiates the cancer cells from the normal cells, it is hoped that further refinements of the methodologies may be helpful in predicting, for example, how quickly and aggressively the cancer cells will grow and divide.

### Tumor Measurement Technologies

Research is underway in a number of laboratories to identify genes associated with breast cancer and to measure their activity in tumor cells. Such measurements are known as gene expression profiles. Several techniques for measuring gene expression are available. One method, known as microarray analysis, measures gene activity in "fresh" (or "unpreserved") frozen tissue samples. Tumor samples are frequently preserved in this way in Europe. In the United States, on the other hand, tumor samples are more commonly preserved in formalin and embedded in paraffin blocks. Microarray analysis cannot be done on tissue that has been preserved in this way. Instead, a method known as reverse transcriptase-polymerase chain reaction (RT-PCR) can be used to measure gene expression. This difference in common methods of tissue processing has led to the development of tests on each side of the Atlantic that are quite different from one another, and that are based on measurements of the activity of different sets of genes.

### Available Tests

In Europe, using microarray analysis, researchers are studying the usefulness of at least two different groups, or "panels", of genes in studies on early stage tumors from node negative patients. One is a 70-gene panel, and another is a 76-gene panel. 1,2 Only three genes are common to both panels, while all the others are unique to one test or the other. In spite of this difference, both panels have yielded results that appear to be promising, 3 and a commercial test based on the 70-gene panel is already available in the United States under the name MammaPrint®.

Gene expression profiling using RT-PCR has led researchers in the United States to investigate several other panels of genes that produce too much or too little protein in early stage, node-negative, and estrogen receptor-positive breast cancer cells. One of these is a 21-gene panel known commercially as Oncotype DX, which is also available in the United States. 4 (See NBCCF Fact Sheet: Prediction of Recurrence Using the Oncotype DX Test .) This panel has a single gene overlap with the 70-gene MammaPrint® panel.

The reasons for the very low levels of overlap between the various gene panels under investigation can include such things as differences in tissue preparation, differences in laboratory methodologies, and differences in measurement techniques. Whether one of the existing panels will prove to be significantly superior to others, or whether newer panels will emerge that have better predictive power remains to be seen. It is clear that additional validation studies and more clinical experience are needed to establish the reliability of gene expression profiling for predicting tumor recurrence and response to specific treatments. At present, these gene-expression profile tests have only been validated on stored sample tissue.

NBCCF has partnered with the Eastern Cooperative Oncology Group on the first prospective, Phase III trial to utilize Oncotype DX, known as TAILORx (Trial for Assigning Individualized Options for Treatment (Rx)). This study seeks to

determine whether adjuvant hormonal therapy alone is as effective as adjuvant hormonal therapy plus chemotherapy for certain women with early-stage breast cancer. For more information on this study, visit NBCCF's TAILORx Trial page .

#### Regulation of Gene-Expression Profile Tests

Although test developers may opt to apply for FDA approval, this is not a prerequisite for marketing this type of tissue test. Oncotype DX has not been FDA approved at this time, but the safety and performance standards of the labs where it is performed are regulated under the Clinical Laboratory Improvements Act (CLIA). At a practical level, this means that the extensive, prospective clinical trials required by the FDA to establish the clinical importance of the tests may not have been done. Without FDA approval, consumers must rely on examination of the data in published studies to reach conclusions about the usefulness of these tests.<sup>5</sup>

MammaPrint® has only recently been approved by the FDA, and continued regulation is needed to ensure its consistency and accuracy.

#### Limitations of Gene-Expression Profile Testing

There are a number of important issues around this type of testing that consumers need to be aware of. For example:

- Gene-expression profile tests for breast cancer prognosis have been used only for specific tumor types. For example, MammaPrint® has been developed for early stage (Stage I or II) breast cancer tumors that have not metastasized to the axillary nodes, and Oncotype DX has been developed for early stage, ER+ tumors that have not metastasized to the nodes. Also, studies have not included women whose tumors were node-positive (in the case of MammaPrint®), or either hormone receptor-negative or node-positive (in the case of Oncotype DX), so data are not available on the utility of these tests in those populations.
- Published research to date is very limited, and further clinical research will be needed to determine whether such tests will be useful in helping women make treatment decisions that are clinically sound.
- Prospective, randomized clinical trials are needed to determine the clinical relevance of these tests and their value relative to traditional prognostic and predictive methods.<sup>C</sup> One good example of a study that has been developed to address this issue is the Phase III trial known as MINDACT (Microarray for Node negative Disease may Avoid ChemoTherapy). MINDACT is a study which will compare the risk assessment profiles of MammaPrint® and Adjuvant! Online (clinical-pathological criteria) in selecting node-negative breast cancer patients for adjuvant chemotherapy. The first interim results from MINDACT will be presented in 2010.
- Gene-expression tests are expensive, and insurance coverage cannot be assumed.

#### Conclusion

NBCCF does not endorse specific drugs, devices, or procedures for breast cancer care. We are nonetheless excited by the prospect of the development of tests that can help characterize individual tumors and provide tools for tailoring treatments to match those characteristics. NBCCF believes that any gene expression profile tests must be appropriately validated and studies replicated before they are used in the clinic outside of research protocols. For this reason, we support continued research on these and other such tests, and we continue to encourage women to consider participation in well-designed clinical trials to help reach that goal.

#### About NBCCF

The National Breast Cancer Coalition Fund is a grassroots organization dedicated to ending breast cancer through the power of action and advocacy. The Coalition's main goals are to increase federal funding for breast cancer research and collaborate with the scientific community to implement new models of research; improve access to high quality health care and breast cancer clinical trials for all women; and expand the influence of breast cancer advocates in all aspects of the breast cancer decision making process.

#### Notes

A. Treatment decisions are typically based on variables such as age and general health status, tumor size, tumor stage and grade, the degree of lymph node involvement, whether or not the tumor tests positive for estrogen and/or progesterone receptors, and whether it is positive for the HER2/neu protein. More subtle information will be needed, however, to allow doctors to tailor individual treatments to the exact molecular characteristics of the individual tumor in all cases.

B. Both gene signatures include Cyclin E2, origin recognition complex, and TNF superfamily protein.

C. For example, more research comparing the results of complex laboratory tests such as the MammaPrint® and Oncotype DX tests to simpler and more accessible tests such as the ADJUVANT! on-line test is needed. ADJUVANT! is based on a computer-generated algorithm that computes a probability of tumor recurrence based on age and general health along with clinical indicators such as ER and HER2 status, tumor grade, tumor size, and number of positive axillary nodes.

## References

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2. Wang, Y, Klijn, J, Zhang, Y, et al. Gene-Expression Profiles to Predict Distant Metastasis of Lymph-Node-Negative Primary Breast Cancer. *Lancet*, 2005, 365:671-679.
3. Foekens JA, Atkins D, Zhang Y, et al. Multicenter validation of a gene expression-based prognostic signature in lymph node-negative primary breast cancer. *J Clin Oncol*, 2006 Apr 10;24(11):1665-71.
4. Paik, S, Shak, S, Tang, G, et al. A Multigene Assay to Predict Recurrence of Tamoxifen-Treated, Node-Negative Breast Cancer. *N Engl J Med*, 2004, 351:2817-2826.
5. On September 7, 2006, the FDA issued draft regulatory guidance and rules for tests that measure and analyze multiple genes, proteins, or other pieces of clinical information taken from a patient. The regulation is meant to ensure that patients and providers are using accurate and reliable tests.