NIH/NCI Press Release: Molecular Test Can Predict Both the Risk of Breast Cancer Recurrence and Who Will Benefit From Chemotherapy

A new test can predict both the risk of breast cancer recurrence and may identify women who will benefit most from chemotherapy, according to research supported by the National Cancer Institute (NCI), part of the National Institutes of Health, and performed in collaboration with the National Surgical Adjuvant Breast and Bowel Project (NSABP) and Genomic Health Inc. These results suggest that almost half of over 50,000 U.S. women diagnosed with estrogen-dependent, lymph-node negative breast cancer* every year are at low risk for recurrence and may not need to go through the discomfort and side effects of chemotherapy.

The test is based on levels of expression (increased or decreased) of a panel of cancer-related genes. This panel is used to predict whether estrogen-dependent breast cancer will come back, according to a study that will be published online in the New England Journal of Medicine on Friday, December 10, 2004**. Scientists on this study also will present new results on that day at San Antonio Breast Cancer Symposium indicating that the same test can predict which women benefit most from chemotherapy. Women with low risk of breast cancer recurrence--about half of the women in the recent study--do not appear to derive much benefit from chemotherapy.

The researchers used tissue samples and medical records from women enrolled in clinical trials of the cancer drug tamoxifen, which blocks the effect of estrogen on breast cancer cells. These women had a kind of breast cancer defined as estrogen receptor-positive, lymph node-negative. Each year, over 50,000 women are diagnosed with this kind of breast cancer, which needs estrogen to grow but has not spread to the lymph nodes. Currently, many women with this type of breast cancer in the United States do receive chemotherapy in addition to hormonal therapy.

Using samples from 447 patients and a collection of 250 genes in three independent preliminary studies, 16 cancer-related genes were found that worked best. The scientists created a formula that generates a "recurrence score" based on the expression patterns of these genes in a tumor sample. Ranging from 1 to 100, the recurrence score is a measure of the risk that a given cancer will recur***.

Prior to this research, analysis of the expression of genes was performed on tumor specimens that were frozen rather than on tissue prepared for routine pathologic evaluation (fixed and embedded). The expression analysis depended on measurement of RNA (the molecule necessary for the translation of a gene into a protein), and RNA is altered when tissues are fixed and embedded. Frozen tissues are generally not readily available in routine practice. Researchers at Genomic Health Inc. developed a method for performing these analyses on tissues embedded in paraffin wax. Their method allows them to use the altered RNA that is found in fixed tissue.

The results published in the New England Journal of Medicine validate the ability of the recurrence score to predict risk of recurrence. Using biopsy tissue and medical records from another NSABP tamoxifen trial, researchers divided 668 women into low, intermediate, and high risk of recurrence groups. Fifty-one percent were in the low risk group (with a score of less than 18); 22 percent were at intermediate risk (recurrence score 18 or higher but less than 31); 27 percent were at high risk (a score of 31 or higher).

These risk group divisions correlated well with the actual rates of recurrence of breast cancer after 10 years. There was a significant difference in recurrence rates between women in the low and high risk groups. In the low risk group, there was a 6.8 percent rate of recurrence at 10 years; in the intermediate and high risk categories these rates were 14.3 and 30.5 percent, respectively. Up to a recurrence score of 50, rates of recurrence increased continuously as the recurrence score increased. These trends held across age groups and tumor size.

"These results were generated perhaps a decade earlier than would have been possible if the researchers had not had access to biopsy tissue from the NSABP trials," notes Sheila E. Taube, Ph.D., associate director of NCI's Cancer Diagnosis Program.

The same 21-gene test has also been used to predict how beneficial chemotherapy will be for women with estrogen receptor-positive, lymph node-negative breast cancer for women on tamoxifen in NSABP trials. These results will be presented at the San Antonio Breast Cancer Symposium on December 10, 2004.

"NCI staff worked with the company, NSABP and experts from other NCI Cooperative Groups to develop an overall strategy to validate the test; this plan was fruitful and may lead to providing an important tool for physicians and women to use in

considering breast cancer treatment decisions," said Taube.

In the treatment study, women with high recurrence scores, who are representative of about 25 percent of patients with this kind of breast cancer, had a large benefit from chemotherapy in terms of 10 year recurrence-free rates. Women with low recurrence scores, who represent about 50 percent of these patients, derived minimal benefits from chemotherapy. The group under study was not large enough to determine whether chemotherapy is detrimental to the low risk group.

"The test has the potential to change medical practice by sparing thousands of women each year from the harmful short- and long-term side effects associated with chemotherapy," said JoAnne Zujewski, M.D., senior investigator in NCI's Cancer Therapy Evaluation Program.

For more information about cancer, visit the NCI Web site at http://www.cancer.gov or call NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237).

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*Tumor size can affect the estimate of the number of women diagnosed with this type of cancer. This estimate is based on tumors larger than 1 centimeter and smaller than 5 centimeters.
**Print version: Paik S, Shak S, Wolmark N, et al. A Multigene Assay to Predict Recurrence of Tamoxifen-Treated, Node-Negative Breast Cancer. New England Journal of Medicine, 351(27). December 30, 2004.
***This technology is called the Oncotype DXTM.