Applying the approach of personalized medicine to cancer care is gradually becoming crucial for ensuring the correct use of targeted therapies and individualizing the management of patient care. The role of genetics in breast cancer is not new, but the ever-increasing numbers of new molecular diagnostics and targeted therapies are making this disease a growing focus of personalized medicine.

Several studies reported at the 2012 CTRC-AACR San Antonio Breast Cancer Symposium focused on the role of personalized medicine in breast cancer management.

BluePrint and MammaPrint Molecular Assays Reclassify Many Primary Breast Cancers

In a retrospective study of 208 patients with breast cancer, the use of molecular subtyping revealed that 25% of these tumors had been misclassified when diagnosed clinically, and therefore these patients should have been receiving different treatments if these molecular tests had been applied prospectively.

Specifically, 39% of the breast cancers that had been classified clinically as HER2 disease should have instead been managed with therapies for luminal-type breast cancer, such as endocrine therapy, and 20% of cancers that had been classified clinically as triple-negative breast cancer should have received therapies for luminal and HER2 disease (eg, endocrine therapy and trastuzumab-based regimens).

The investigators used frozen tumor samples from 208 patients (median age, 56 years) who were managed at 2 American institutions, following the National Comprehensive Cancer Network guidelines between 1992 and 2010. The median follow-up was 11.3 years.

The majority (59%) of patients had estrogen receptor-positive (ER+) or progesterone receptor-positive (PR+) cancer; 20% had HER2 phenotype, and 24% had triple-negative breast cancer, as assessed by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). All patients had undergone lumpectomy or mastectomy with axillary staging.

In this study, 2 microarray-based assays—BluePrint and MammaPrint—were used retrospectively to evaluate the clinical diagnosis performed with IHC and FISH. The assays showed that 13 of 188 tumors that had been classified as ER+, PR+, or HER2-negative were not luminal-type cancer by BluePrint; 24 of 41 cancers clinically identified as HER2 were not shown to be so by BluePrint; and 10 of 49 triple-negative tumors were not confirmed as basal-type cancer by BluePrint.

Overall, 51 patients had to be reclassified based on these molecular tests. Of these, 28 patients were reassessed for ER, PR, and HER2 status.

The patients with luminal-type early breast cancer that was identified by BluePrint have excellent relapse-free survival rates of 97% for those with luminal A cancer, and 98% for patients with luminal B cancer.

These findings have important clinical implications for the accurate identification of women with a specific type of breast cancer and the selection of appropriate therapy.

According to lead investigator Massimo Cristofanilli, MD, FACP, Chair, Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA, and colleagues, “The use of MammaPrint and BluePrint should be implemented in the management of primary breast cancer for the selection of adjuvant therapy in the era of personalized care.”

EndoPredict Identifies Women with ER+ Breast Cancer at Risk for Late Metastases

Another multigene test, EndoPredict, can help to identify women with ER+/HER2-negative breast cancer who are likely to develop metastatic disease in the long-term. EndoPredict, which is not yet available for use in the United States, is different from other molecular assays in its ability to predict later, rather than earlier, metastases, according to lead investigator Peter C. Dubsky, MD, Associate Professor, Department of Surgery, Medical University of Vienna, Austria.

“OncoType DX and other predictive tests that rely on genetic signatures are used to predict earlier recurrence within the first 5 years,” Dr Dubsky said. “It is important to be able to predict risk of late recurrence for ER-positive breast cancer, because after 5 to 10 years of follow-up, mortality rates are higher for ER-positive than for ER-negative breast cancer.”

If these results are validated, then a low EndoPredict score would suggest a lower risk of recurrence and a higher chance for cure with standard treatment. EndoPredict would be available as a routine test for all breast cancer patients, in combination with standard treatment, Dr Dubsky said.
score could identify the women with breast cancer who could forego extended antihormonal therapy.

Unlike other multigene tests that are based solely on the molecular fingerprint of a tumor, the EndoPredict score factors in tumor biology data that are derived from tumor size and nodal status along with gene expression for 8 genes (3 proliferation genes and 5 ER-dependent genes) and 3 reference genes, similar to the techniques used in the Oncotype DX assay.

This study was conducted on tumor tissue from 1702 postmenopausal women (median age, 64 years) with ER+/HER2-negative breast cancer who participated in 2 randomized trials—the Austrian Breast Cancer Study Group (ABCSG)-6 and ABCSG-8.

Overall, 33% had node-positive disease. None of the women received adjuvant chemotherapy, but all of them received some form of hormonal therapy for 5 years, including tamoxifen alone or as a sequence of tamoxifen and an aromatase inhibitor. All the women had low-to-intermediate clinical risk.

Based on a predefined EndoPredict clinical score that combined the EndoPredict with nodal status and tumor size, 64% of the patients were determined to be at low risk for distant metastases; 98.2% of these women were free of late metastases at 10 years and were 5 times more likely to remain free of late metastases at 10 years than the 33% of women with a high EndoPredict score.

Further analysis showed that the genes associated with ER signaling added independent prognostic information for late recurrence.

Discussing the importance of these findings, Dr Dubsky noted that current clinical trials are not providing the type of data needed to predict late metastases. “We currently have around 20,000 women in ongoing extended/late endocrine therapy clinical trials….We see very low rates, and the efficacy data of these trials is unchanged after adjusting for age, stage at diagnosis, and race or ethnicity. Triple-negative cancer was not associated with ER-negative, PR-negative, HER2-negative and non–triple-negative breast cancer (luminal A, luminal B, and HER2-enriched).

The association between triple-negative breast cancer and non–triple-negative breast cancer and BRCA1 or BRCA2 mutation status was then examined.

The triple-negative subtype was strongly correlated with BRCA status (P < .001). Women with triple-negative tumors were 5 times more likely to be BRCA carriers than women with non–triple-negative tumors (odds ratio [OR], 5.6; 95% confidence interval [CI], 4.1-7.5). The association between triple-negative breast cancer and BRCA1 was more robust (OR, 12.2; 95% CI, 8.3-17.9) and was unchanged after adjusting for age, stage at diagnosis, and race or ethnicity. Triple-negative cancer was not associated with BRCA2 status (OR, 1.6; 95% CI, 0.9-2.7).

Conclusion

These data, taken together, point to the increasing importance of personalized medicine in the daily management of patients with breast cancer. Consequently, research is needed to evaluate the cost impact of incorporating these molecular tests into clinical practice, and to compare the cost-effectiveness of these various tools, considering that more accurate diagnosis is associated with improved health outcomes and therefore often with reduced overall costs, despite the extra costs associated with the administration of the test itself.