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DRUG DISCOVERY

## Novel Tests Based on Genomic Markers

**Assay Tutorial:** Improving the Clinical Utility of Testing for Breast Cancer Recurrence

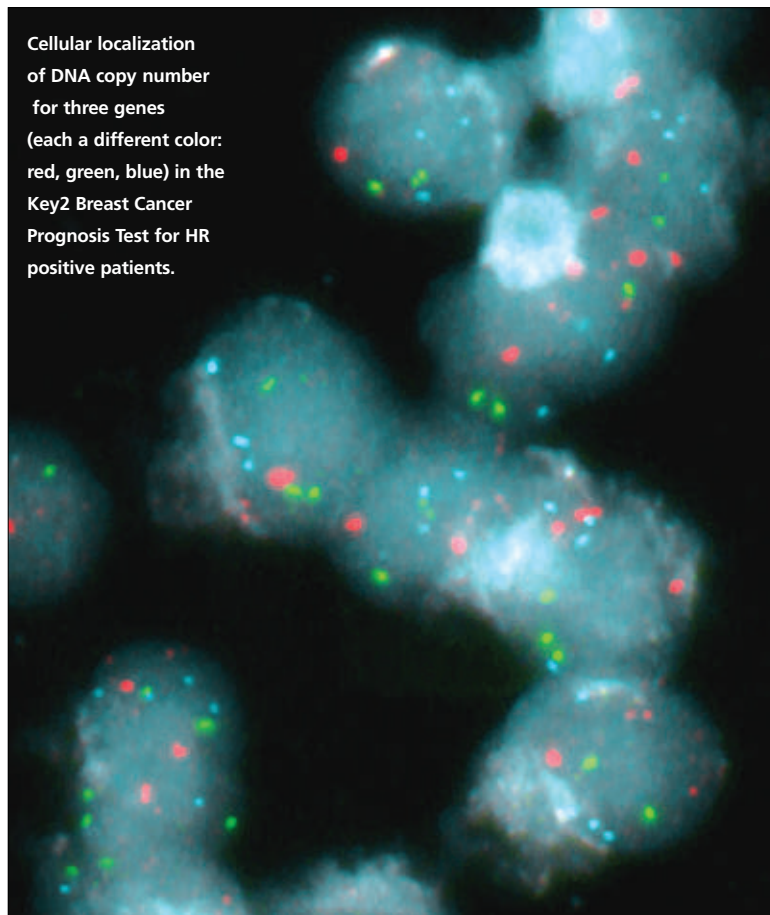
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**D**iscovery of small combinations of DNA or RNA markers to develop predictive tests poses a significant challenge. And yet, there is a growing need to address both the discovery of markers and deployment of new genomic tests to gain solid acceptance for use in clinical trials and clinical testing laboratories.

If a marker set has less than five genes, a variety of assay formats can be used, including fluorescent in situ hybridization (FISH), a method commonly used by both oncology testing laboratories and laboratories supporting clinical trials.

During a roundtable at the "Molecular Medicine Tri-Conference" held recently in San Francisco, fifteen industry professionals validated this need, agreeing that multiple markers will be required to develop an accurate test. But how many markers are enough remains the active question.

Interviews with leading experts in the pharmaceutical industry confirmed that multiple markers are



required to develop biomarkers in conjunction with new drugs. These efforts are showing good return, both technically and clinically.

**Exagen Diagnostics** ([www.exagendiagnosics.com](http://www.exagendiagnosics.com)) has a computational approach to marker discovery that identifies combinations of genomic markers to accurately categorize patient groups. This “pure discovery” approach consistently yields small marker sets of three to five genes and has been proven in more than ten projects in various indications.

The first area for commercialization of marker tests is to predict recurrence in breast cancer patients. The second area of focus is marker discovery to develop a blood test that predicts which hepatitis C patients are likely to respond to standard treatment with interferon and ribavirin.

### **Innovative Marker Discovery**

Unlike conventional deductive methods that rely on knowledge of the function and pathway for specific genes, Exagen’s approach relies on “pure” inductive, data-driven discovery.

The technology mines genome-wide data in a global search to discover the best combinations of genes, without respect to gene function. Combinations are then ranked. Thus, unbiased selection across all genes is assured, and each gene has an equal chance of being in the final combination.

To discover prognostic DNA copy number markers for breast cancer, Exagen concurrently mined gene expression data and DNA copy number data to discover sets of genes that separate patients who have a low risk of recurrence from patients with a higher risk.

Seventeen genes were identified that were consistently found in top combina-

tions, and all seventeen were taken into a retrospective validation study of formalin fixed, paraffin embedded (FFPE) tumor specimens from 229 patients with invasive ductal carcinoma of the breast (Stages I, II, and III).

Seventeen BACs (bacterial artificial chromosomes), each containing one of the seventeen genes, were used as FISH probes to determine the optimal combination of genes to accurately separate low risk from high risk patients.

This study, conducted at the University of New Mexico Cancer Research and Treatment Center, confirmed the validity of the discovery approach and demonstrated that two different sets of three genes each were sufficient—one set for hormone receptor<sup>1</sup> (HR) positive patients and one set for HR negative patients.

In independent test sets, the HR positive marker set had a 93.8% NPV in lymph node negative patients, and the HR negative set had a 100% NPV in lymph node negative patients. Each marker set had a 91% NPV in patient populations that are both node positive and node negative, exceeding the performance of current criteria used to determine low risk of recurrence.

These two genomic tests, named the Key2 Breast Cancer Prognosis Tests™, dovetail with existing patient stratification by HR status and improve the ability to predict those patients who are at low risk of recurrence.

Using these tests, both HR positive and HR negative breast cancer patients can be tested at the point of tumor removal to predict which patients are at low risk of recurrence and who, therefore, may not benefit from additional treatment (after surgical resection and local irradiation).

### **Gaining Solid Clinical Laboratory Acceptance**

To enhance acceptance and laboratory use of small sets of markers for breast cancer and other indications, Exagen also developed a practical FISH format, referred to as patterns of genomic amplification (PGA) FISH. These tests detect DNA copy number changes, and gene signals are specifically localized within tumor cells and counted. PGA FISH™ tests have a shorter procedure and provide results the same/next day.

After copy number counts are tallied for each gene, the final result is expressed as a Prognostic Index, which places each individual patient in a category of low, medium, or high risk of recurrence. These tests detect the fundamental changes that define cancer, providing a portrait of each person’s individual cancer.

### **In Vitro Diagnostic Test Kits**

After further validation in a prospectively designed study in archived tissues from multiple sites and upon clearance by the FDA, Exagen anticipates offering in vitro diagnostic (IVD) kits to clinical laboratories under the brand name Key2 Breast Cancer.

Anticipated for launch early in 2006, these tests will be used at the point of testing for HR status and Her2/neu by the same laboratories that currently perform these tests. The Key2 tests are practical and cost-effective for clinical testing.

As a FISH procedure, pathologists continue to be involved in offering new genomic marker tests with associated improvements. Additionally, each of these tests may be used to advantage in Phase IV trials of new breast cancer drugs to enrich patient populations for those at higher risk of recurrence.

In the future, standard genomic testing procedures will likely employ a panel of tests to predict recurrence and treatment response at the point of tumor removal. A full panel may consist of the Key2 Breast Cancer Prognosis Tests plus treatment response tests for drugs like Femara®, Arimidex®, Alimta®, Aromasin®, or other new, emerging drugs for breast cancer.

Using proprietary technologies, Exagen has developed multiple solutions

and a strong pipeline of tests. The company's marker discovery approach provides high accuracy in categorizing groups of patients. The PGA FISH technology offers a more rapid test either for clinical trial use or for use by existing clinical testing laboratories that offer FISH-based oncology testing.

By offering IVD kits that provide critical information to physicians/patients, genomic markers will have a powerful impact when used in conjunction with

standard clinical, pathologic, and histological data to guide decisions about an individual patient's disease. **GEN**

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Note

1. Positive either for estrogen receptor (ER) and/or progesterone receptor (PR)



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