

Pioneers in Personalized Medicine

Agendia and Genomic Health Are Changing the Way Patients with Breast Cancer Are Treated

By Don Sharpe and John McCleery

It is not news that genomic diagnostics—the ability to use a patient's genomic profile to help determine the best therapeutic approach to breast cancer—have been used successfully. As this field grows in the United States, as evidenced by the emergence of another breast cancer genetic profiling test, we look into the mechanisms behind these diagnostic products and examine the unique approaches of two different companies marketing these tests.

Many are predicting that personalized medicine is going to transform the way diseases are diagnosed and treated, but it is not yet known what exact effect this new technology will have in oncology. Currently, its greatest potential appears to be in enhancing physicians' ability to stratify patients to appropriate risk categories according to their unique genetic profile. However, as novel targeted therapies continue to overtake chemotherapy as standard of care, the ability provided by this

technology to pinpoint specific genes within tumors could become an invaluable asset in the drive towards individualized care. It is with these considerations in mind that some have proclaimed personalized medicine the next game-changer for the business of oncology, and one in which a relatively wide-open field could give a company with the right data and timing a market all to themselves.

Two respective pioneers in the field of personalized medicine—Agendia and Genomic Health—have rapidly carved out their story in this emerging field. Each has developed robust technologies that are changing the way treatments are discovered and how they are being used. A recipient of *Time* magazine's 2007 Invention of the Year award, Agendia's MammaPrint™ is currently the only FDA-cleared breast cancer diagnostic test, while Genomic Health's Oncotype DX®, which hit the market in 2004, is buoyed by an impres-





sive reimbursement profile and exceptional commercial success. Both companies are moving swiftly to further develop their genetic testing capabilities and are expanding beyond their first tumor type as they blaze the trail for genetic profiling and cancer treatment.

A Look inside Agendia

The original research on which Agendia was founded took place at the Netherlands Cancer Institute, where co-founders Dr. Laura van't Veer and Professor Dr. René Bernards developed an mRNA-based method for genomic profiling that was able to predict outcomes in breast cancer. Dr. Bernard Sixt, a former director of global strategic marketing at Amersham Health (now part of GE Healthcare), joined Dr. van't Veer and Bernards in 2003

and officially formed Agendia. In 2004, based on Dr. Bernards' and van't Veer's original work on gene signature, Agendia launched its first clinically validated product, MammaPrint.

MammaPrint is an in vitro diagnostic test that relies on fresh tumor samples. A US physician can request a [cont. on pg 16 >>](#)



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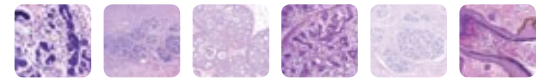
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Companies/Products at a Glance

	Agendia	Genomic Health
CEO	Bernard Sixt	Randy Scott
Location	Amsterdam, The Netherlands	Redwood City, CA
Key Diagnostic Product	MammaPrint™	Oncotype DX®
How It Works	Using fresh tumor specimens, this system analyzes the expression of a panel of 70 genes. The results of this analysis provide an estimate of metastasis free survival. It allocates patients into high- and low-risk category and is always informative.	Using formalin-fixed, paraffin-embedded tumor specimens, this system analyzes the expression of a panel of 21 genes. The results of this analysis provide an estimate of the likelihood of disease recurrence, as well as the likelihood that a patient will benefit from chemotherapy.
Patient Type	<ul style="list-style-type: none"> • Age <61 years old • Tumor size < 5.0 cm • Stage I or II • Lymph node negative • ER+ or ER— • Tamoxifen independent 	<ul style="list-style-type: none"> • Newly diagnosed • Stage I or II • Lymph node negative • ER+ • Tamoxifen dependent
After Tissue Sample Is Received, Results Are Delivered Within...	10 Working Days	10–14 Days
FDA Clearance	Yes	No (not required at this time)
Payer Reimbursement	No	Yes (more than 80% of U.S. insured lives covered)
Key Validation Study	Buyse M, et al. Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. <i>J Natl Cancer Inst.</i> 2006;98:1183-92.	Paik S, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. <i>N Engl J Med.</i> 2004;351:2817-26. Paik S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. <i>J Clin Oncol.</i> 2006;24(23):3726-3734.
Web Address	www.agendia.com	www.genomichealth.com

MammaPrint Specimen Collection and Transportation kit from Agendia at least four working days before surgery. The tumor sample is sent to pathology labs in Amsterdam, where it undergoes gene expression profiling to determine whether a patient's tumor has a predetermined 70-gene sequence, thus enabling a physician to more accurately

establish a patient's risk of breast cancer recurrence within a certain time by defining it clearly as "high" or "low." MammaPrint has the additional benefit of cutting down on the number of patients improperly diagnosed as "high-risk." Test results are made available within 10 days after the arrival of the specimen.



The use of fresh samples is a key distinction between MammaPrint and Oncotype DX, which utilizes formalin-fixed, paraffin-embedded tissue samples. Predictably, both companies have positioned their sampling methods as an advantage, while questioning the utility of the methods employed by their competitor. Agendia claims that fresh sampling is an easier process, which was proven safe to ship at ambient temperatures by the FDA with their June '07 clearance of RNARetain® (the RNA preserving solution that maintains the integrity of the sample).

Agendia has also shared its belief that paraffin embedding, which dates back to the 19th century, is a technique destined to be overtaken by fresh sampling as genomic testing comes into its own. Genomic Health has countered that preparing tumor blocks in paraffin is a considerably more common practice in most institutions, many of which are also not yet equipped to properly obtain fresh samples. Additionally, they have pointed to data such as those appearing in the journals *American Journal of Pathology* in 2004 and *Clinical Chemistry* in 2007, which indicate that Oncotype DX effectively accounts for variations in tumor samples, including sample preparation and fixation, as evidence supporting the rationale of paraffin-based sampling.

The Road to Commercialization

Research published in a 2002 study in *Nature*, in which microarray analysis was performed on the primary breast tumors of 117 young patients with lymph node negative disease, revealed the 70-gene panel that would eventually form the basis of MammaPrint. In the study, researchers concluded the gene expression profile would “outperform

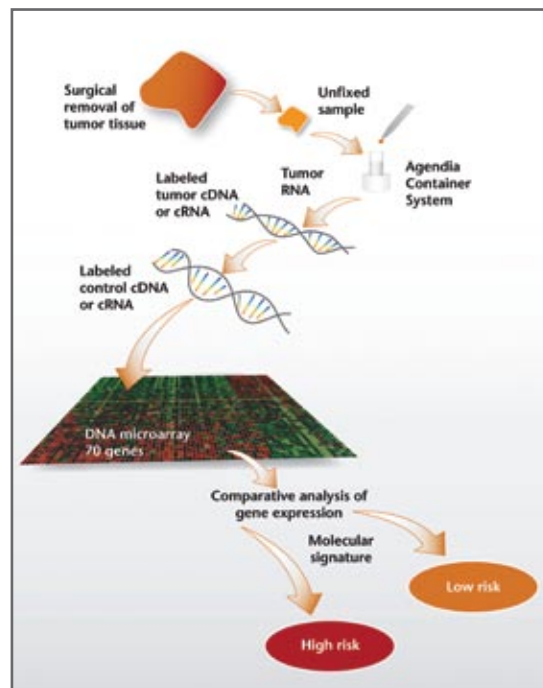
all currently used clinical parameters in predicting disease outcome.”

They had a chance to test that theory in a study appearing later that year in the *New England Journal of Medicine*, and the results backed up their claim. The 70-gene prognosis profile was applied to 295 consecutive patients with stage I/II primary breast carcinomas who were then placed into either poor prognosis or good prognosis groups accordingly. Using a multi-variable Cox regression analysis, the researchers discovered that the prognosis profile was a strong independent factor in predicting disease outcome, and was more precise than the National Institutes of Health criteria based on clinical and histological data alone.

Validation of these early findings came in a 2006 multicenter study of 307 patients with breast cancer conducted by an independent international consortium whose results appeared in the *Journal of the National Cancer Institute* in which MammaPrint clearly outperformed conventional clinico-pathological assessment as determined by the Adjuvant!® software [Adjuvant Inc.]. The study found that the

MammaPrint gene signature led to improved predictions in all study outcomes, including time to distant metastases (HR = 2.32 vs. HR = 1.68, respectively) and overall survival (HR = 2.79 vs. HR = 1.67, respectively). The authors concluded that MammaPrint added independent prognostic information to clinico-pathological risk analysis in early breast cancer.

Results such as these were enough to convince the FDA to approve MammaPrint in February 2007. “FDA approval was comforting in that it came out of [cont. on pg 18](#) >>>



Source: www.agendia.com

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rigorous peer review of the literature (i.e. safety and effectiveness) and showed that all practicalities of clinical testing are under control (i.e. sampling and logistics).”

MammaPrint has a broad indication for all stage I and stage II patients with up to three positive nodes and, importantly, it is independent of ER status and treatment. “This is nice because the ER test has been proven unreliable, so physicians do not have to worry about the ER test confounding the MammaPrint test results,” explains Sixt.

“More than 70% of patients who have node-negative breast cancer are successfully treated without chemotherapy. Identifying which patients with breast cancer [that] will most likely require adjuvant chemotherapy is an important step in personalizing a patient’s treatment regimen, and [will] ensure that patients aren’t receiving unnecessary treatment,” said Dr. van’t Veer.

Building an Economic Case

According to Dr. Sixt, “Demand is high, but we need to demonstrate sustainability.” The next step is commercialization. “While we don’t have payer reimbursement, it is intuitive that the test will save on total cost of therapy,” said Dr. Sixt.

Agendia reports that it receives multiple kit requests per week from US-based physicians. At the last San Antonio Breast Cancer Consortium, the company’s release of data generated huge curiosity about MammaPrint. “We have received great initial traction in the US,” reports Dr. Sixt, much of which stems from a grassroots communications effort.

Genomic Health Blazes the Trail

In some ways, Genomic Health’s multigene diagnostic assay, Oncotype DX, laid the foundation for Agendia’s MammaPrint. While Dr. Randall Scott was working at the genomics company InCyte, he noticed that the cost of DNA sequencing and micro-array technology was dropping, making it more accessible for development. Steve Shak came from Genentech where he was involved in the development of Herceptin. Scott’s and Shak’s concepts came together and Genomic Health was formed as a company that would apply genomics to develop personalized medicine. Dr. Scott noted that they made the decision to focus on oncology because, “We knew that the Herceptin approach was opening the door to personalized medicine in oncology.”

Oncotype DX was cleared by the Clinical Laboratory Improvements Act of 1988 (CLIA) and became available commercially in the US in 2004. Like MammaPrint, it takes a sample of tumor tissue and runs a series of tests to check the tumor’s genetic profile to establish the expression of the tumor’s mRNA for their predetermined panel of 21 genes. The test determines the likelihood of distant breast cancer recurrence as well as the likelihood an individual patient will benefit from chemotherapy. The test is validated for use in newly-diagnosed, stage I or stage II, node-negative, ER positive patients with breast cancer and reports clinical experience for those treated with tamoxifen.

Gauging Potential Risk and Benefit

The physician orders the assay and then sends a tumor sample from the formalin-fixed paraffin embedded tissue biopsy to Genomic Health’s labs in Redwood City, California. Upon specimen receipt, results are generally available about 10 to 14 days later. When the lab gets the sample, a quality control analysis of the pathology of the tumor is performed to ensure that sufficient tumor is present and, if necessary, to dissect out significant areas of non-tumor tissue or biopsy cavities. RNA is extracted



and analyzed for the 21 genes. The physician then receives a report showing the patient's Recurrence Score between 0 and 100, illustrating where that patient fits in the context of those enrolled in the NEJM validation clinical trial in terms of distant recurrence rates and their benefit from chemotherapy. Studies demonstrate that women with higher Recurrence Scores are more likely to benefit from chemotherapy, whereas women with lower Recurrence Scores derive minimal if any benefit from chemotherapy.

Dr. Scott notes, "We feel that the significant accomplishment with Oncotype DX is to correlate with chemotherapy benefit, because this is the clinical utility information at the heart of the treatment decision. At the same time, this is the information most useful to payers."

There has been some press recently that the HER2 test has a larger-than-expected error level, begging the question, is the Oncotype DX HER2 assessment more reliable than HER2 or similar? "We think that our technology, called quantitative RT-PCR, allows us to create a quantitative score for each gene so in the 16-gene panel we include information on HER2, ER, and PR. Because we don't rely on immunohistochemistry, which can be subjective, we think we can improve the quality of the tests for patients. Physicians will also receive an ER and PR score (a quantitative level) as part of our report which has the potential to be a predictor of response to tamoxifen. We are moving in the direction of offering quantitative single gene testing for HER2," explains Dr. Scott.

Approval Status

Oncotype DX currently lacks FDA approval. All laboratory-developed genetic tests are regulated under the Clinical Laboratory Improvement Amendment (CLIA), but recently the FDA discussed changing that policy and regulating laboratory-developed tests starting with IVDIMA assays like Oncotype DX. "We're getting geared up for FDA regulation right now," says Scott. "The CLIA path allows us to bring products to market more quickly, and allows us to make more rapid improvements in the process. Our concern is that if the FDA moves into regulating this field,

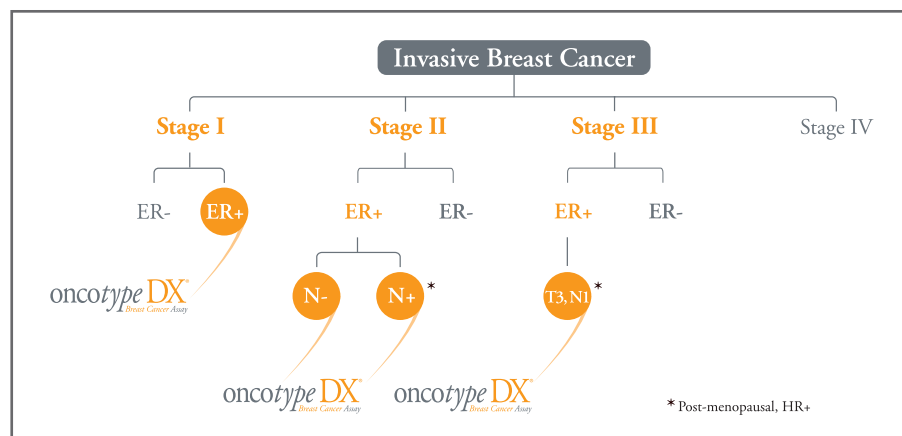
it will probably slow the pace of innovation. A 510(k) or PMA from the FDA, for example, can delay or limit the indication and therefore use of the test by physicians and patients."

Development and Patient Population

The identification of the gene panel began with an extensive analysis of the human genome. Three retrospective studies were conducted to discover a set of biomarkers that became their 21-gene assay panel. At the time of initial diagnosis, 250 genes in patient tumor samples were obtained. "We found genes that consistently predicted clinical outcomes in all three studies," says Scott.

Following the identification of a large set of genes associated with breast cancer, the 21-gene assay panel incorporated the genes which consistently correlated with distant recurrence-free survival. This assay was then validated, using prospectively-defined endpoints, in a large, randomized, double-blind study known as the NSABP

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Source: www.genomichealth.com

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Study B-14. Over 650 tumor samples were studied. “This was the first major validation study which began to lend credibility to our story,” says Scott. It was also the pivotal study that determined the use of tamoxifen as a standard of care for the treatment of early stage breast cancer. A second validation study with Northern California Kaiser Permanente showed the same results.

The third large study, called the NSABP B-20 study, looked at whether Oncotype DX results could predict chemotherapy benefit. Again, the laboratory analyzed samples in a blinded fashion; when the results were matched by an honest broker to the clinical data and then unblinded for analysis, the results indicated that patients with low Recurrence Score results had minimal, if any,

benefit from chemotherapy. Dr. Scott believes the results of this study are the most compelling because physicians feel confident that they can identify patients who won’t benefit from chemotherapy.

Building an Economic Case

“We estimate that more than 80% of insured lives are now covered for the test,” says Scott. In addition, Genomic Health has published two health economic studies that demonstrate the cost effectiveness of the assay. According to Scott, “Oncotype DX can save on the total cost of therapy, but also all the supportive care that goes with chemotherapy.” **DS JM**

Corporate Milestones

Year	Agendia	Genomic Health
2007	<ul style="list-style-type: none"> • FDA clears MammaPrint for In Vitro Diagnostic Multivariate Index Assay for use in breast cancer prognosis • Wins <i>Time</i> magazine’s “Innovator of the Year” award 	<ul style="list-style-type: none"> • Aetna and UnitedHealth establish coverage • Initiates clinical development program in colon cancer • Oncotype DX meets BCBS TEC Assessment • ASCO adds Oncotype DX test to recommendations • NCCN adds Oncotype DX to guidelines pathway • Reports positive data in node-positive population • 46,500 Oncotype DX tests ordered since commercial launch
2006	<ul style="list-style-type: none"> • MammaPrint distributed to South Africa and the U.K. • Gains exclusive rights to a genetic profile developed by Erasmus MC that predicts resistance to tamoxifen • Translational Research Breast International Group validates MammaPrint “clinical utility” 	<ul style="list-style-type: none"> • Chemotherapy benefit study published in <i>JCO</i> • Medicare establishes coverage • Reports positive early results in colon cancer gene identification study
2005	<ul style="list-style-type: none"> • First company worldwide to receive ISO accreditation for microarray-based test (MammaPrint) 	<ul style="list-style-type: none"> • Kaiser Permanente begins coverage • Genomic Health goes public • Economic Analysis published in <i>AJMC</i> • Oncotype DX approved by CLIA, becomes commercially available • Validation study published in <i>NEJM</i> • Reports positive chemo benefit data