February 27, 2013

Dear,

There has been significant progress made in the evolution of second generation gene profiles for breast cancer that may be of interest to you and your patients. Limitations of the first generation 21-gene assay with regards to accuracy and narrow range of clinico-pathologic features are being addressed by newer technologies. As a leader in the diagnosis and management of breast cancer patients, you have the opportunity to familiarize yourself with several of the more important aspects of this emerging paradigm change. Newer concepts in tumor biology, defined by genomic profiling, are providing exciting insights about the way you can optimize the advances in therapeutic options for early stage breast cancer. As the Chief Medical Officer of Agendia, I appreciate this opportunity to share with you several brief **Agendia** updates and news about our *Symphony* breast cancer offering.

We have been pleased by the very positive response to the publication of the RASTER[1] prospective outcome-based study in January 2013. This landmark study demonstrated that newly diagnosed breast cancer patients, in a community setting, could be accurately stratified by the MammaPrint 70-gene signature such that 51% of patients could safely forgo chemotherapy with excellent outcomes. This study significantly adds to the body of more than sixty peer-reviewed publications related to the clinical validation of MammaPrint in a wide variety of patient sub-groups. If you would like more information about the RASTER study or a copy of the manuscript, please go to our website at Agendia.com to download the full manuscript.

In order to understand how this remarkable second generation gene profile was able to achieve this performance, I encourage you to read further.

Background:

As cancer specialists, we are all aware of the contribution to our field that was made by the 21-gene assay. This first-generation genomic profile assisted us to predict chemotherapy response in high risk, node negative, ER positive, Her-2-neu negative patients. Furthermore, this early technology introduced the potential role of genomic profiling and personalized medicine to the oncology community, by providing a tool to assess some basic biology of breast cancer in a finite subset of patients and in turn guide therapy decisions. However, as in all things science, discovery and innovation continue to move forward.

MammaPrint Development:

In 2002, technology and scientific discovery combined to facilitate the development of a second generation gene profiling test for breast cancer, MammaPrint. This 70-gene expression profile now

further expands our understanding of the critical genomic pathways that drive the clinical behavior of breast cancer. The MammaPrint genomic profile was developed without the constraints of 250 pre-selected genes that were presumed to be critical to the behavior of breast cancer. Rather, the developers of MammaPrint interrogated an **unbiased hierarchal ranking of the entire genome (25,000 genes)** using mRNA in untreated, node negative patients who were either in remission or had relapsed at 5 years. The assay was subsequently validated at 10 years follow-up in an independent patient cohort[2]. As previously stated, MammaPrint has been validated in a much broader range of patients than its 21-gene assay predecessor. MammaPrint is validated in ER negative as well as ER positive, and HER-2 positive and HER-2 negative as well as in patients with up to 3 positive nodes. Moreover because MammaPrint was developed in untreated patients, the prognostic outcome does not have to be "earned" by obligatory treatment with Tamoxifen as is the case with the 21-gene assay

Second Generation Profile Results:

MammaPrint produces a very clear binary result of either “High risk” or “Low risk” and eliminates the ambiguity of either an intermediate risk category or overlapping 95% confidence limits between the low and intermediate categories. Moreover the binary result more accurately reflects the dichotomous medical decision making of recommending chemotherapy or not in early stage breast cancer. The elimination of the ambiguous "intermediate risk" result with the use of MammaPrint has provided clinicians with an actionable result 100% of the time. If routine clinico-pathologic guidelines are utilized to resolve the ambiguity of the "intermediate risk" category, a substantial majority of those patients are vulnerable to a “consider chemotherapy” recommendation without the requisite assurance of personal benefit to be derived from that choice. Furthermore, since the initial report of the 21-gene assay, the "intermediate risk" group has nearly doubled in size to 39% in 2012[3].

Clinical Utility:

With the fundamental differences in assay development firmly in mind, the key take-away message from this discussion is: MammaPrint has facilitated a patient-centric paradigm shift in thinking about how we can stratify our early stage breast cancer patients. Historically, we have been conditioned to think in terms of how to predict which patients should be treated with chemotherapy. The body of data that has been amassed for this second generation tool has demonstrated that MammaPrint can accurately predict which patients can ***safely forgo chemotherapy and still have excellent outcomes***. The RASTER study of 427 patients treated in a community setting with T1-3, N0-1 tumors demonstrated that when the MammaPrint result was prospectively included in the decision to use chemotherapy; 85% of the MammaPrint "Low Risk" patients who declined chemotherapy enjoyed a 97% DMFS at 5 years. The vast majority of those patients were completely untreated with either endocrine or chemotherapy! Conversely 81% of the MammaPrint "High Risk" patients appropriately chose to receive modern chemotherapy +/- endocrine therapy selected by their oncologist and went on to achieve a 91% DMFS at 5 years.

This first-of-its-kind prospective observational trial with five year outcomes has no comparable data set in the first generation 21-gene test repertoire. In fact, despite the fact that more than 300,000 patients have been tested by the first generation test, to date there is still not a single published trial in which the 21-gene assay was employed prospectively to drive treatment decisions and where patients outcomes were reported!

MammaPrint, like its predecessor, also has addressed the question of which patients will benefit from chemotherapy. Multiple neo-adjuvant and retrospective adjuvant trials have demonstrated the ability of clinicians to improve upon patient outcomes by their appropriate selection of "best of breed" chemotherapy and targeted endocrine/immunotherapy in the MammaPrint "High Risk" signature patients. Knowledgeable clinicians applying their understanding of therapeutics in "High Risk" patients have demonstrated a progressively improving track record of 5 and 10 year survivals

in the treated "High Risk" patients compared with untreated "High Risk" patients.

The reliability of MammaPrint to deliver the test results discussed above has been substantially demonstrated by 5 consecutive FDA clearances beginning in 2007. Furthermore, MammaPrint has been included in the St. Gallen guidelines.

Equally important, since January 2012 MammaPrint has been available for formalin fixed, paraffin embedded (FFPE) tissue specimens as well as fresh tissue thereby facilitating critical patient answers in both the adjuvant and neoadjuvant settings.

Given the fundamental differences between these two generational tests, one would logically expect that discordant results might be observed when the two tests are applied in patient populations. The issue however, is not whether there is a discordancy in the results. The issue is which gene profile is capable of most accurately predicting patient outcomes and defining the sub-populations of patients who will or will not benefit from chemotherapy. Only when those results are appropriately compared can any inference be made with regard to the issue of discordancy. If retrospective studies of the 21-gene test's accuracy are any indication, three studies demonstrate 10 year recurrence rates of 14% to 25% in "low" risk patient populations, LN- untreated, LN+ on Tamoxifen or LN+ Tamoxifen and Chemotherapy[4,5,6]. In none of the MammaPrint validation studies have we observed these recurrence rates in Low Risk patients.

The Future:

MammaPrint is only one part of a unique trilogy of gene signature tests (Symphony Suite) that provide clinicians with the most complete and advanced analysis of a patient's breast cancer today. With the appreciation that molecular subtypes are increasingly important in defining the optimal therapy, Agendia has matured the performance of both BluePrint and TargetPrint. BluePrint is an 80-gene mRNA analysis that stratifies tumors into Basal, Luminal, ERBB2 subtypes. In combination with MammaPrint, BluePrint offers the greatest degree of accuracy to stratify patients and optimize their treatment options. TargetPrint provides a uniquely accurate and quantifiable profile of the tumor's receptor status. Utilization of the full Symphony suite assists physicians in refining complex treatment decisions for their patients.

As with any new technology reliability and performance are key elements in clinical adoption. The MammaPrint test is the only FDA cleared test of this kind available in the market. There is US reimbursement coverage for MammaPrint in excess of 200 million lives and the number of tests ordered by oncologists grew 140% this past year. Clinicians are voting with their feet and the movement to second-generation genomic profiling methods is rapidly taking place.

Our clinical team is available to discuss the Agendia Symphony Suite of tests with you. We wish you and your patients all the best and we will continue to provide innovative tools for managing cancer treatment.

Sincerely,

Neil Barth M.D., F.A.C.P

Chief Medical Officer

Agendia, Inc.

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