Submitted by: William Audeh M.D.
Company: Agendia, Inc.
Address: 22 Morgan, Irvine, CA 92618
Email: william.audeh@agendia.com
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NCCN Guideline Panel: Breast Cancer

On behalf of Agendia Inc, I respectfully request the NCCN Breast Cancer Guideline Panel to review new data on the clinical utility of the **70 gene MammaPrint assay** for prognosis and prediction of chemotherapy benefit in early stage breast cancer, in support of inclusion in the Guidelines (BINV6) as a **recommended** test.

Since the 2016 NCCN Breast Cancer Panel review of MammaPrint, which undertook review of data as of July 2016, there has been a significant development, as of August 2016, with Level IA data which support this submission: **70-gene signature as an Aid to Treatment Decisions in Early Breast Cancer** [1]

Specific Changes:

1) On BINV-6, move N1mic to Node+ branch, 1-3 LN+, and classify tumors by pT size and LN status.
2) For **LN – tumors >0.5cm**, replace "consider 21-gene RT-PCR assay" with **"recommend 70-gene MammaPrint gene expression assay**" with retention of the "ff" footnote. The algorithm may then split into two branches: 70 gene Low Risk – adjuvant endocrine therapy alone and 70 gene High Risk – adjuvant chemotherapy + endocrine therapy.
3) The language in the "ff" footnote should be amended to "Other multigene assays may be considered to help assess risk of recurrence but have not been validated with **prospective randomized evidence to predict the lack of clinically meaningful benefit of chemotherapy"**
4) For **LN +, 1-3 nodes**, **add "recommend 70-gene MammaPrint gene expression assay"** with addition of the "ff" footnote. The algorithm may then split into two branches: 70 gene Low Risk – adjuvant endocrine therapy alone and 70 gene High Risk – adjuvant chemotherapy + endocrine therapy.

Rationale: The current guideline (BINV6) for ER+, HER2- breast cancer advises the consideration of chemotherapy based on clinical factors such as T $\geq$ 0 .5cm or pN1mic, pN1a (1-3+ LN). The utility of genomic assays in this setting is to identify tumors with gene expression patterns which accurately predict the lack of clinically meaningful benefit from chemotherapy. The MINDACT trial [1] enrolled 6,693 subjects and provided **5 Year prospectively randomized evidence indicating the low risk of recurrence for tumors classified as Genomically Low Risk by the 70 gene MammaPrint assay and treated without chemotherapy: 5 year DMFS ranged from 94.7% to 97.6%, depending on associated clinical risk**. In the MINDACT trial, 75% of ER+HER2- patients were MammaPrint Low Risk and 25% were MammaPrint High Risk.

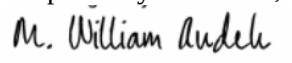
Additional supportive Evidence –
The long term prognostic performance of MammaPrint has been extensively validated and recently also in the randomized Stockholm Low Risk Trial[2]. The identification of MammaPrint Low Risk patients as baseline good prognosis patients with very low chemotherapy response rates (~0-5% pCR) was earlier shown by studies of MammaPrint in the neo-adjuvant setting[3,4].

Analytical and Clinical Validity FDA Clearances: Since its initial 510(k) clearance in 2007, MammaPrint has received a total of six FDA 501(k) clearances. The data of the clearances confirming analytical and clinical validity is summarized and published[5]. Analytical validity of MammaPrint over 10 year time frame in clinical trials and routine diagnostics was recently published by Beumer et al[6].

Medicare Coverage: MammaPrint received Medicare coverage in November 2009 for the management of women with T1-T3, N0-N1, M0, ER independent (i.e. ER+/-) breast cancer. This LCD was reestablished in 2012. LCD Title and ID Number: MammaPrint Test - Breast Cancer Prognosis L30376. The LCD states "MammaPrint enables a more accurate prognosis of breast cancer recurrence to assist physicians in dealing with their patients with breast cancer."

Clinical Implementation: Agendia expects to perform between 8,000 and 15,000 test in the US in 2017.

Respectfully submitted,



William Audeh M.D.
Chief Medical Officer
Agendia Inc.

The following papers from peer-reviewed publications are submitted in support of the proposed changes:

1. Cardoso F, van't Veer L, Bogaerts J, Slaets L, et al. 70-gene Signature as an Aid to Treatment Decisions in Early Stage Breast Cancer. *New England Journal of Medicine* (2016) 375:717-729
2. Esserman LJ, Thompson CK, Yau C, et al. Identification of tumors with an indolent disease course: MammaPrint ultralow signature validation in a retrospective analysis of a Swedish randomized tamoxifen trial. *Cancer Research.* 2015;76:P6-09-01.
3. Esserman LJ, Berry DA, Cheang MC, et al. Chemotherapy response and recurrence-free survival in neoadjuvant breast cancer depends on biomarker profiles: results from the I-SPY 1 TRIAL (CALGB 150007/150012; ACRIN 6657). *Breast Cancer Research and Treatment.* 2012;132(3):1049-1062.
4. Whitworth P, Stork-Sloots L, de Snoo FA, Richards P, Rotkis M, Beatty J, Mislowsky A, Pellicane JV, Nguyen B, Lee L, Nash C, Gittleman M, Akbari S, Beitsch PD: Chemosensitivity Predicted by BluePrint 80-Gene Functional Subtype and MammaPrint in the Prospective Neoadjuvant Breast Registry Symphony Trial (NBRST). *Ann Surg Oncol* 2014.
5. Delahaye LJMJ, Wehkamp D, Floore AN, Bernards R, van 't Veer LJ, Glas AM: Performance characteristics of the MammaPrint breast cancer diagnostic gene signature. *Personalized Medicine* 2013, 10:801–811.
6. Beumer I, Witteveen A, Delahaye L, et al. Equivalence of MammaPrint array types in clinical trials and diagnostics. *Breast Cancer Research and Treatment*. 2016;156:279-287. doi:10.1007/s10549-016-3764-5.