510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:
k081092

B. Purpose for Submission:
Modifications of the cleared device intended use with addition of 5 year prognostic information for breast cancer patients ≥ 61 years.

C. Measurand:
70 gene expression profile

D. Type of Test:
Expression microarray
Test service performed in a single laboratory in Agendia's Amsterdam facility.

E. Applicant:
Agendia BV

F. Proprietary and Established Names:
MammaPrint®

G. Regulatory Information:
1. Regulation section:
   21 CFR 866.6040 Gene expression profiling test system for breast cancer prognosis
2. Classification:
   Class II
3. Product code:
   NYI, Classifier, prognostic, recurrence risk assessment, RNA gene expression, breast cancer
4. Panel:
   Immunology (82)

H. Intended Use:
1. Intended use(s):
   MammaPrint® is a qualitative in vitro diagnostic test service, performed in a single laboratory, using the gene expression profile of fresh breast cancer tissue samples to assess a patients' risk for distant metastasis (up to 10 years for patients less than 61 years old, up to 5 years for patients ≥ 61 years).

   The test is performed for breast cancer patients, with Stage I or Stage II disease, with tumor size ≤ 5.0 cm and lymph node negative. The MammaPrint® result is indicated for use by physicians as a prognostic marker only, along with other clinicopathological factors.
2. Indication(s) for use:
   Same as intended use
3. Special conditions for use statement(s):
   For prescription use only
   MammaPrint® is not intended for diagnosis, or to predict or detect response to therapy, or to help select the optimal therapy for patients.
4. Special instrument requirements:

Agilent 2100 Bioanalyzer: Serial number DE54700497 and DE24802382
Agilent DNA microarray scanner: Serial numbers US22502555 and US45103019

Note: The scanner and bioanalyzer are components of this assay and are cleared only for this assay and not for any other application. In addition, clearance is only limited to the bioanalyzer and scanners with the serial numbers as specified above.

I. Device Description:

The MammaPrint® test is performed and provided as a service by Agendia Laboratory. The test is a microarray based gene expression analysis of RNA extracted from breast tumor tissue. The test is a custom-designed array chip manufactured by Agilent Technologies using the Agilent oligonucleotide microarray platform which assesses the mRNA expression of the 70 genes in triplicate. The MammaPrint® microarray features eight 1900-feature subarrays per glass slide which can each be individually hybridized. Per subarray, 232 reporter genes are printed in triplicate, including the 70 genes which make up the MammaPrint® prognostic profile.

The analysis is based on several processes: isolation of RNA from fresh tumor tissue sections, DNAse treatment of isolated RNA, linear amplification and labeling of DNAse treated RNA, cRNA purification, hybridization of the cRNA to the MammaPrint® microarray, scanning the MammaPrint® microarray and data acquisition (feature extraction), calculation and determination of the risk of recurrence in breast cancer patients.

The MammaPrint® analysis is designed to determine the gene activity of specific genes in a tissue sample compared to a reference standard. The result is an expression profile, or fingerprint, of the sample. The correlation of the sample expression profile to a template (the mean expression profile of 44 tumors with a known good clinical outcome) is calculated and the molecular profile of the sample is determined (Low Risk, High Risk, Low Risk Borderline, High Risk Borderline).

J. Substantial Equivalence Information:

1. <u>Predicate device name(s)</u>:
   Agendia BV's MammaPrint®
2. <u>Predicate 510(k) number(s)</u>:
   k062694, k070675 and k080252
3. <u>Comparison with predicate:</u>
   The device is the same as the predicate, except for the modification in the intended use.

K. Standard/Guidance Document Referenced (if applicable):

None

L. Test Principle:

The MammaPrint® service is a microarray based gene expression analysis of a tumor. Refer to k062694 for detailed description.

M. Performance Characteristics (if/when applicable):

1. <u>Analytical performance:</u>
   Since the device is the same as the predicate device, please see the analytical performance data from k062694, k070675 and k080252.
   a. *Precision/Reproducibility:*

Same as previous submission.
b. *Linearity/assay reportable range:*
Not applicable.
c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
Same as previous submission.
d. *Detection limit:*
Same as previous submission.
e. *Analytical specificity:*
Same as previous submission.
f. *Assay cut-off:*
Same as previous submission.
2. Comparison studies:
There are no method comparison studies. The new study was compared to clinical outcome data.
a. *Method comparison with predicate device:*
Not applicable
b. *Matrix comparison:*
Not applicable.
3. Clinical studies:
A consecutive series of patients treated at NKI-AVL (Netherlands cancer Institute) between 1984 and 2000 were selected according to the following criteria: female, unilateral T1 or T2 primary invasive carcinoma, negative nodal status, older than 55 years at diagnosis, no adjuvant therapy and frozen tumor material available in the NKI-AVL tissue bank.

Patients without complete axillary staging and patients with prior malignancies (except for non-melanoma skin cancer), bilateral synchronous breast tumors or patients treated with neoadjuvant therapy were not included. All patients had been treated by modified radical mastectomy or breast conserving surgery, including axillary lymph node dissection, followed by local radiotherapy if indicated. Clinical data were retrieved from medical records, blinded to MammaPrint. Follow-up was completed till May 2009.

Mammaprint analysis of the 131 patients resulted in 87 patients that were classified as good prognosis and 44 as poor prognosis for developing metastases. Main endpoints for the Kaplan-Meier analyses were: time to distant metastases as first event, time to any recurrence and time to breast cancer specific death.

Metastatic disease within 5 yrs for patients ≥ 61 years
PPV = 0.22 (0.12-0.38)
NPV = 0.93 (0.85-0.97)

Positive predictive value (PPV) is the probability that a condition occurs (e.g. metastatic disease occurs within a given time frame) given the device output for that patient is high risk. Negative predictive value (NPV) is the probability that a condition does not occur (i.e. metastatic disease does not occur within a given time frame) given the device output for that patient is low risk.

Time to Distant Metastases (years)

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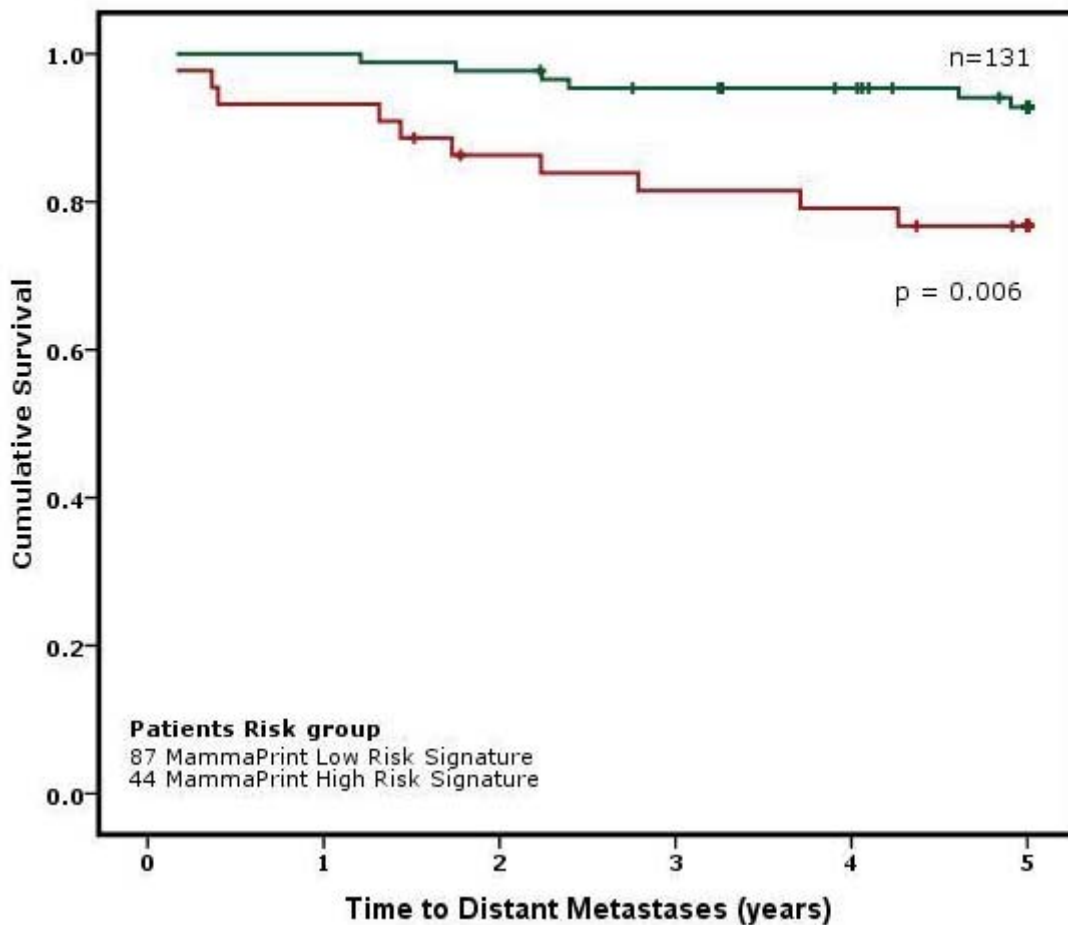
      a. *Clinical Sensitivity:*
         Same as previous submission.
      b. *Clinical specificity:*
         Same as previous submission.
      c. *Other clinical supportive data (when a. and b. are not applicable):*
         Same as previous submission.
   4. Clinical cut-off**:**
     Same as Assay cut-off.
   5. Expected values/Reference range:
     Same as previous submission.

N. Proposed Labeling:
The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:
The submitted information in this premarket notification is complete and supports a substantial equivalence decision.