

Section 5: 510(k) Summary

1. Assigned 510(k) number

The assigned 510(k) number is K070675

JUN 22 2007

2. Company

Agendia BV  
Slotervaart Medical Center 9D  
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The Netherlands  
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3. Contact

Guido Brink, Director Quality Management and Regulatory Affairs

4. Date Prepared

March 1<sup>st</sup> 2007

5. Proprietary Name

MammaPrint<sup>®</sup>

6. Classification Name

Gene expression profiling test system, for breast cancer prognosis.

7. Common Name

Multivariate device for cancer prognosis

8. Classification

Class II, regulated under 21 CFR 866.6040, product code NYI

9. Predicate Device

Agendia BV's MammaPrint (k062694)

### 10. Device Description

The MammaPrint service is a microarray based gene expression analysis of a tumor. The analysis is based on several processes: using fresh tissue stored in RNAlater, isolation of RNA from frozen tumor tissue sections, DNA'se treatment of isolated RNA, linear amplification and labeling of DNA'se 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).

### 11. Intended Use

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 patient's risk for distant metastasis.

The test is performed for breast cancer patients who are less than 61 years old, with Stage I or Stage II disease, with tumor size  $\leq 5.0$  cm and who are lymph node negative. The MammaPrint result is indicated for use by physicians as a prognostic marker only, along with other clinicopathological factors.

### 12. Performance Data (non-clinical)

#### **Analytical performance**

MammaPrint analytical (i.e., non-clinical) performance characteristics investigated comprise Precision, Reproducibility, Cutoff, Sensitivity, Specificity, Accuracy, Robustness and Ruggedness.

The technical validity of MammaPrint is determined on multiple individual validation experiments; a comprehensive three-way inter-laboratory comparison study between three independent laboratories in three different countries (Dutch, French and U.S.); data of about 200 analyses of two reference samples over a period of 12 months, used to

monitor experiment-to-experiment quality; and quality controls for which the cut-off for all QCs is based on over 5000 hybridizations (2500 samples) performed at Agendia.

Comparison validation experiments performed on over 50 human tissue tumor pairs and 6 mice xenografts, preserved using two different tissue preservation methods (fresh frozen and fresh RNA later preservation at room temperature), show similar analytical results (MammaPrint Index) and prognostic outcome (High Risk/Low Risk) of the MammaPrint device.

Based on 12 month repeated experiments of a Low Risk and High Risk control sample (i.e., more than 190 independent analyses), the Analytical Accuracy of the measurement is 98,5%.

#### ***Classification performance***

Based on the analytical performance of MammaPrint, the accuracy of classifying a sample as High Risk or Low Risk, is 97.7% (i.e., 1.1% false negative classification).

#### ***Borderline Sample***

As a result of the technical inaccuracy, analytical measurements (i.e., MammaPrint Index) can fall within a pre-defined area around the classification cut-off between the High Risk and Low Risk profile (i.e., "Borderline Sample").

Based on the analyses results of independent MammaPrint analyses over a time period of over 2 years, it has been shown that less than 5% of the analyzed samples are considered to be "Borderline Samples".

"Borderline Samples" have a less than 90% classification accuracy (i.e. >10% chance of false classification).

Looking at all generated data it is concluded that the MammaPrint analysis is considered to be Precise, Reproducible, Sensitive, Specific, Accurate and Robust and valid for the Intended Use.

### 13. Clinical Data

Clinical performance testing is based on the following studies:

<b>Study</b>	<b>Purpose</b>	<b>Time Frame</b>	<b>Comments</b>
Nature Paper (1) Type: Training	Development of breast cancer prognosis 70-gene profile (LNO, <55)	2002, 78 patients, 6.4% adjuvant treatment	Within 5 year metastasis risk by profile multivariate OR 18
NEJM Paper (2) Type: Training and Validation	Validation of the 70-gene profile in consecutive series of breast cancer patients (LNO, <53)	2002, 151 patients, 5.2% adjuvant treatment	Metastasis-free survival by profile at 10 yrs: low risk profile 87%, high risk profile 44% (at 5 yrs: 93% and 56% respectively)
MammaPrint Paper (3) Type: Training and Validation	Development of MammaPrint	2006, reproducibility of (1) and (2) on MammaPrint	Highly reproducible MammaPrint as diagnostic tool
Transbig Paper (4) Type: Validation	Independent European validation of 70-gene signature (LNO, <61)	2006, 302 patients, no adjuvant treatment	Metastasis-free survival by profile at 10 yrs: low risk profile 88%, high risk profile 71% (at 5 yrs: 96% and 83% respectively)

### 14. Conclusion

The MammaPrint device subject of this 510(k) using fresh tissue is substantially equivalent to the original MammaPrint under k062694

(1) Gene expression profiling predicts clinical outcome of breast cancer;

Laura J. Van 't Veer et al; Nature (2002) 415, p530-536.

(2) A Gene-Expression Signature as a Predictor of Survival in Breast Cancer;

Marc J. Van de Vijver et al;. New Engl J Med (2002) 347, p1999-2009.

(3) Converting a breast cancer microarray signature into a high-throughput diagnostic test; Annuska M. Glas et al; BMC Genomics (2006) accepted.

(4) Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer; Marc Buyse et al; J Natl Cancer Inst (2006), 98, p1183-1192.



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2098 Gaither Road  
Rockville MD 20850

Agendia BV  
c/o Mr. Guido Brink  
Director Regulatory Affairs  
Slotervaart Medical Center, Floor 9D  
Louwesweg 6, 1066 EC Amsterdam  
The Netherlands

JUN 22 2007

Re: k070675

Trade/Device Name: MammaPrint®  
Regulation Number: 21 CFR 866.6040  
Regulation Name: Gene expression profiling test system for breast cancer prognosis  
Regulatory Class: Class II  
Product Code: NYI  
Dated: May 31, 2007  
Received: June 4, 2007

Dear Mr. Brink:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820). This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The

Page 2 –

FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific information about the application of labeling requirements to your device, or questions on the promotion and advertising of your device, please contact the Office of In Vitro Diagnostic Device Evaluation and Safety at (240) 276-0450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (240) 276-3150 or at its Internet address <http://www.fda.gov/cdrh/industry/support/index.html>.

Sincerely yours,

A handwritten signature in black ink that reads "Robert L. Becker, Jr." in a cursive script.

Robert L. Becker, Jr., M.D., Ph.D.

Director

Division of Immunology and Hematology Devices  
Office of In Vitro Diagnostic Device Evaluation and Safety  
Center for Devices and Radiological Health

Enclosure

## Indications for Use

510(k) Number (if known): k070675

Device Name: MammaPrint®

Indications For Use:

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.

The test is performed for breast cancer patients who are less than 61 years old, with Stage I or Stage II disease, with tumor size  $\leq 5.0$  cm and lymph node negative. The MammaPrint® result is indicated for use by physicians as a prognostic marker only, along with other clinicopathological factors.

Prescription Use X  
(Part 21 CFR 801 Subpart D)

AND/OR

Over-The-Counter Use \_\_\_\_\_  
(21 CFR 807 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

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Concurrence of CDRH, Office of In Vitro Diagnostic Devices (OIVD)

Maria M Chan  
Division Sign-Off

Office of In Vitro Diagnostic  
Device Evaluation and Safety

510(k) k070675