November 05, 2020

Agendia Inc.
Janice Hogan
Partner
Hogan Lovells US LLP
1735 Market Street Suite 2320
Philadelphia, PA 19103

Re: K201902
Trade/Device Name: MammaPrint® FFPE
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: July 8, 2020
Received: July 8, 2020

Dear Janice Hogan:

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. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. 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. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to 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 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Soma Ghosh, Ph.D.
Chief
Molecular Pathology and Cytology Branch
Division of Molecular Genetics and Pathology
OHT7: Office of In Vitro Diagnostics
and Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 6/30/2023
See PRA Statement on last page

510(k) Number *(if known)*

K201902

Device Name

MammaPrint® FFPE

Indications for Use *(Describe)*

MammaPrint® FFPE is a qualitative in vitro diagnostic test, performed in a central laboratory, using the gene expression profile obtained from formalin-fixed paraffin embedded (FFPE) breast cancer tissue samples to assess a patient's risk for distant metastasis within 5 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 FFPE result is indicated for use by physicians as a prognostic marker only, along with other clinicopathological factors.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510 (k) Summary

1.Submitter

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Date prepared: November 3, 2020

2. Device

MammaPrint FFPE

3.Predicate Device

MammaPrint FFPE K141142

4. Device Description

The MammaPrint service is a microarray-based gene expression analysis of a tumor. The analysis is based on several processes: isolation of RNA from formalin-fixed paraffin embedded (FFPE) tumor tissue sections, DNase treatment of isolated RNA, amplification and purification DNase treated RNA resulting in cDNA, labeling and purification of amplified cDNA, hybridization of the cDNA to the diagnostic 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 FFPE tissue sample. The result is an expression profile, or fingerprint, of the sample.

The molecular profile of the sample is determined (Low Risk, High Risk) by calculating the MammaPrint index (MPI) by determining the correlation of the sample expression profile to the mean expression profiles of risk templates of tumors with a known good and poor outcome.

5. Indications for Use

MammaPrint® FFPE is a qualitative in vitro diagnostic test, performed in a central laboratory, using the gene expression profile obtained from formalin-fixed paraffin embedded (FFPE) breast cancer tissue samples to assess a patient's risk for distant metastasis within 5 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 FFPE result is indicated for use by physicians as a prognostic marker only, along with other clinicopathological factors.

6. Comparison to Predicate Device

The predicate is Agendia Inc's MammaPrint (K141142). The predicate device, with product code NYI, is regulated under 21CFR866.6040. The modified MammaPrint device subject of this 510(k) is substantially equivalent to Agendia's MammaPrint device covered under K141142. It has the identical indications for use and very similar technological features. The only difference is that the modified MammaPrint device allows the use of Agilent SureScan Dx microarray scanners, part #G5761AA. The minor change in the specific scanner that is used does not raise any new types of safety or effectiveness questions. Performance testing confirms that the change in scanner does not adversely impact functioning of the system compared to the predicate.

7. Performance Data

Analytical Performance Compared to Predicate

Analytical performance of MammaPrint was investigated by assessing concordance between results from Agilent scanners part #G2505 (C-scanner) and Agilent SureScan Dx microarray scanners, part #G5761AA (D-scanner). Additionally, precision was also assessed for the Agilent SureScan Dx microarray scanners, part #G5761AA.

1- **Technical equivalence of MammaPrint between scanner part #G2505 and SureScan Dx microarray scanner, part #G5761AA**

Concordance experiments were performed based on designs as previously included in K080252 as well as K101454.

For this validation, a set of 92 8-pack arrays were analyzed as part of regular diagnostics on the FDA cleared scanners (US45103019 and US811R3213). Subsequently, these were scanned a second time on the SureScan Dx scanners, SG18309119 and SG18449122. The text files generated as output were used to generate MammaPrint indices according to standard procedures.

The samples included in this dataset covered the entire MammaPrint readout range, including the borderline region. Additionally, there were four diagnostic control samples included that cover the MammaPrint categorical results; PLEP3 (Low Risk), PHHE2 (High Risk), PHTR2 (High Risk), PBCL2 (Low Risk -close to classification threshold).

MammaPrint indices were compared between both C and D-scanners using Passing and Bablok regression. The MammaPrint categorical results (High/Low Risk) were compared using a 2x2 contingency table after which concordance, Negative Percent Agreement (NPA) and Positive Percent Agreement (PPA) were determined. The Passing and Bablok regression comparing the MammaPrint indices between the C-scanners and SureScan Dx scanner SG18309119 is y=0.00 +1.00 x (95%CI – slope: 1.000 – 1.002, 95%CI intercept: -0.0002 to 0.000). The Passing and Bablok regression comparing the MammaPrint indices between the C-scanners and SureScan Dx scanner SG18449122 is y=0.0010 +1.00 x (95%CI – slope: 1.000 – 1.0021, 95%CI intercept: 0.0014 to 0.001). The overall concordance in MammaPrint categorical result between the C-scanners and the SureScan Dx scanners, SG18309119 and SG18449122 is 99.7% and 100%, respectively. For this comparison C-scanners versus SG18309119 and SG18449122 the NPA is 100 % (95%CI: 98.1-100) and 100% (95%CI: 97.1 – 100), the PPA is 99.3% (95%CI: 96.0 – 99.9) and 100% (95%CI: 97.5 - 100), respectively.

The results of the Passing and Bablok regression of both D-scanners compared to the C-scanner are within the pre-defined acceptance criteria. Furthermore, the concordance, NPA and PPA determined for each D-scanner versus the FDA cleared C-scanners were all within the predefined acceptance criteria.

2- **Test performance - precision assessment of the SureScan Dx scanners - SG18309119 and SG18449122**

Precision assessment was performed using the four diagnostic control samples (PLEP3 [Low Risk], PHHE2 [High Risk], PHTR2 [High Risk], PBCL2 [Low Risk -close to classification threshold]) that were measured as

part of the validation. These control samples have a known MammaPrint result and cover all MammaPrint categorical results.

In order to assess the precision of both D-scanners versus the FDA cleared scanners, the variability of repeated measurements of these controls were compared between both scanners using the F-test. The F-test p-values for all four control samples were all well below the significance level of 0.05, indicating there is no significant difference in precision between C and D-scanners.

Correlation between MammaPrint Index and Clinical Outcome

Two analyses were conducted to show the correlation between the MammaPrint index and clinical outcome of the RASTER study (previously submitted in K141142):

1- Result distribution

In order to show a correlation between the MammaPrint index and clinical outcome, clinical results were placed into bins consisting of 4 MammaPrint Index levels.

Table 1: Distribution of observed 5 year Distant Recurrence (DR) Risk in RASTER study over 4 Bins of MammaPrint Index Levels

Bin	MPI Range	Number of Patients	Percentage of Patients	Observed 5-yr DR risk
1	0.36 < MPI ≤+1	37	10.7%	0%
2	0.00 <MPI≤0.36	142	41.2%	1.4%
3	-0.57<MPI≤ 0.00	100	29.0%	9.0%
4	-1 ≤MPI≤-0.57	66	19.1%	13.6%
Total		**345**	**100.0%**	

2- Cox regression analysis

Cox regression analysis of the 5 year DR risk with MPI as an independent covariate shows a correlation between MammaPrint index and risk of recurrence. A higher MammaPrint index shows a lower risk for a recurrence. With each increase in MammaPrint index unit, there is a 0.224 (i.e., 4.5 folds) decrease in recurrence risk at 5 years (p=0.001; 95% CI: 0.092-0.543).

The categorical analysis and Cox regression analysis thus demonstrate a correlation between the unit change in the MammaPrint index and the clinical outcome.

8. Conclusion

MammaPrint is a clinically and analytically accurate prognostic method for providing a risk assessment of distant metastasis of breast cancer when performed either using the Agilent scanner #partG2505 or the SureScan Dx scanner, part #G5761AA, supporting a finding of substantial equivalence.