DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

December 19, 2014

Ms. Jolette Franco
Regulatory Affairs Manager
Myriad Genetic Laboratories, Inc.
320 Wakara Way
Salt Lake City, UT 84108

Re: P140020
BRACAnalysis CDx™
Filed: September 24, 2014
Procode: PJG

Dear Ms. Franco:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the BRACAnalysis CDx™. This device is indicated as follows:

> BRACAnalysis CDx™ is an *in vitro* diagnostic device intended for the qualitative detection and classification of variants in the protein coding regions and intron/exon boundaries of the *BRCA1* and *BRCA2* genes using genomic DNA obtained from whole blood specimens collected in EDTA. Single nucleotide variants and small insertions and deletions (indels) are identified by polymerase chain reaction (PCR) and Sanger sequencing. Large deletions and duplications in *BRCA1* and *BRCA2* are detected using multiplex PCR. Results of the test are used as an aid in identifying ovarian cancer patients with deleterious or suspected deleterious germline *BRCA* variants eligible for treatment with Lynparza™ (olaparib). This assay is for professional use only and is to be performed only at Myriad Genetic Laboratories, a single laboratory site located at 320 Wakara Way, Salt Lake City, UT 84108.

We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). The device is further restricted under section 515(d)(1)(B)(ii) of the act insofar as the device is to be performed only at Myriad Genetic Laboratories, a single laboratory site located at 320 Wakara Way, Salt Lake City, UT 84108, using serial number-controlled instruments by professionals with the appropriate training and experience to use the device. FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the

requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Expiration dating for this device has been established and approved as follows: whole blood specimens may be stored at 4°C up to 30 days or at 30°C up to 5 days; PCR reagents and primers for the BRACAnalysis CDx™ Sanger sequencing test may be stored at 30°C for 24 hours and 7 days, respectively; Quantification Standards may be stored at 30°C for 48 hours or at 4°C for 30 days; Alternate Positive Control may be stored at 4 °C for less than 1 month and other DNA control samples may be stored at 4 °C for 2 months. This is to advise you that the protocols to establish expiration dating are considered approved protocols for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(7).

Continued approval of this PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. Two copies of this report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84. This is a reminder that as of September 24, 2014, class III devices are subject to certain provisions of the final UDI rule. These provisions include the requirement to provide a UDI on the device label and packages (21 CFR 801.20), format dates on the device label in accordance with 21 CFR 801.18, and submit data to the Global Unique Device Identification Database (GUDID) (21 CFR 830 Subpart E). Additionally, 21 CFR 814.84 (b)(4) requires PMA annual reports submitted after September 24, 2014, to identify each device identifier currently in use for the subject device, and the device identifiers for devices that have been discontinued since the previous periodic report. It is not necessary to identify any device identifier discontinued prior to December 23, 2013. For more information on these requirements, please see the UDI website, http://www.fda.gov/udi.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

You have agreed to provide the following data as part of future supplements:

1. As reflected in the labeling for BRACAnalysis CDx™, a limited range of variant types was included in some of the analytical validation studies. Additional testing of samples is required to establish the analytical performance characteristics of your device for all variant types that may be detected. Please ensure that samples adequately cover the range of small deletions, small insertions, and large rearrangements detected by your device, with consideration to variant lengths and genomic contexts. Please include the results from these studies in the labeling, and submit the results within 7 months from the date of this letter.

2. Since a limited range of variant types was included in the clinical validation study, results from ongoing clinical trials (Study D0816C00002 and Study D0816C00010) using the BRACAnalysis CDx™ are to be provided upon completion of the trials. If patients were enrolled based on results from a clinical trial assay (CTA), a bridging study between the CTA and BRACAnalysis CDx™ will be required. Also, please revise the labeling to include the results from these studies.

3. Defined criteria are used to classify variants detected by BRACAnalysis CDx™. Variant classifications may be subject to change over time based on newly available evidence that is evaluated in your classification process. To monitor the robustness of the variant classification process, continued evaluation of the process will be needed. When samples are received to be tested with BRACAnalysis CDx™, all variants that are detected should be treated as new variants and classified according to the current classification criteria. The current classification results should then be compared to the penultimate classifications (if variants were previously identified), with tabulation of agreement between the two classification results. Please provide a summary of the results annually. Please ensure that the following information is included: the variants detected, the agreement between the previous and current classifications per category, the numbers of variants that changed per classification category, description(s) of the classification changes, and the criteria used for each classification (e.g., the criteria used for the previous classification, the criteria used for the current classification, and the rationale for any differences or changes to the classification criteria). Please be advised that the results from these studies could lead to labeling changes.

The following data should be provided as part of the annual report:

1. There was limited representation of deleterious and suspected deleterious germline *BRCA1* and *BRCA2* variants in the registrational clinical study. As treatment outcome data (e.g., literature) becomes available with broader representation of variants, evaluation and reporting on whether or not the variant classification criteria are in line with the drug efficacy results are required.

2. Your device is intended to be used with EDTA blood collection tubes. Please track and report on the results from samples provided in K_2EDTA and K_3EDTA collection tubes. Please be advised that if the results from these studies lead to labeling changes, then a future PMA supplement would be required.

Be advised that the failure to conduct any such study in compliance with the good clinical laboratory practices in 21 CFR part 58 (if a non-clinical study subject to part 58) or the institutional review board regulations in 21 CFR part 56 and the informed consent regulations in 21 CFR part 50 (if a clinical study involving human subjects) may be grounds for FDA withdrawal of approval of the PMA.

Before making any change affecting the safety or effectiveness of the device, you must submit a

PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" (www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm).

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise become aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm.

CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm. Written requests for this information can also be made to the Food and Drug Administration, Dockets Management Branch, (HFA-305), 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. Final printed labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in 6 copies, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

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If you have any questions concerning this approval order, please contact Eunice Lee, Ph.D., at 301-796-4808.

Sincerely yours,

Alberto Gutierrez -S

Alberto Gutierrez, Ph.D.
Director
Office of *In Vitro* Diagnostics and
Radiological Health
Center for Devices and Radiological Health