



Affymetrix, Inc.
Eric Fung, M.D., Ph.D.
Vice President, Research and Development Clinical Applications
3420 Central Expressway
Santa Clara, California 95051

June 06, 2025

Re: K130313 (DEN130018)
Trade/Device Name: Affymetrix® CytoScan® Dx Assay
Regulation Number: 21 CFR 866.5920
Regulation Name: Postnatal chromosomal copy number variation detection system
Regulatory Class: Class II
Product Code: PFX
Dated: December 19, 2013
Received: December 23, 2013

Dear Dr. Eric Fung:

This letter corrects the classification order, originally dated January 17, 2014, to align special controls with existing design controls requirements and clarify the qualified users of the device.

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your De Novo request for classification of the CytoScan® Dx Assay, a prescription device with the following indications for use:

CytoScan® Dx Assay is a qualitative assay intended for the postnatal detection of copy number variations (CNV) in genomic DNA obtained from peripheral whole blood in patients referred for chromosomal testing based on clinical presentation. CytoScan® Dx Assay is intended for the detection of CNVs associated with developmental delay, intellectual disability, congenital anomalies, or dysmorphic features. Assay results are intended to be used in conjunction with other clinical and diagnostic findings, consistent with professional standards of practice, including confirmation by alternative methods, parental evaluation, clinical genetic evaluation, and counseling, as appropriate. Interpretation of assay results is intended to be performed only by healthcare professionals, board certified in clinical cytogenetics or molecular genetics. The assay is intended to be used on the GeneChip® System 3000Dx and analyzed by Chromosome Analysis Suite Dx Software (ChAS Dx Software).

This device is not intended to be used for standalone diagnostic purposes, preimplantation or prenatal testing or screening, population screening, or for the detection of, or screening for, acquired or somatic genetic aberrations.

FDA concludes that this device should be classified into Class II. This order, therefore, classifies the CytoScan® Dx Assay, and substantially equivalent devices of this generic type, into Class II under the generic name postnatal chromosomal copy number variation detection system.

FDA identifies this generic type of device as:

Postnatal chromosomal copy number variation detection system. A postnatal chromosomal copy number variation detection system is a qualitative assay intended for the detection of copy number variations (CNVs) in genomic DNA obtained from whole blood in patients referred for chromosomal testing based on clinical presentation. It is intended for the detection of CNVs associated with developmental delay, intellectual disability, congenital anomalies, or dysmorphic features. Assay results are intended to be used in conjunction with other clinical and diagnostic findings, consistent with professional standards of practice, including confirmation by alternative methods, parental evaluation, clinical genetic evaluation, and counseling, as appropriate. Interpretation of assay results is intended to be performed by qualified healthcare professionals such as clinical cytogeneticists or molecular geneticists. This device is not intended to be used for standalone diagnostic purposes, pre-implantation or prenatal testing or screening, population screening, or for the detection of, or screening for, acquired or somatic genetic aberrations.

Section 513(f)(2) of the Food, Drug and Cosmetic Act (the FD&C Act) was amended by section 607 of the Food and Drug Administration Safety and Innovation Act (FDASIA) on July 9, 2012. This law provides two options for De Novo classification. First, any person who receives a "not substantially equivalent" (NSE) determination in response to a 510(k) for a device that has not been previously classified under the Act may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act. On December 13, 2016, the 21st Century Cures Act removed a requirement that a De Novo request be submitted within 30 days of receiving an NSE determination. Alternatively, any person who determines that there is no legally marketed device upon which to base a determination of substantial equivalence may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act without first submitting a 510(k). FDA shall, within 120 days of receiving such a request, classify the device. This classification shall be the initial classification of the device. Within 30 days after the issuance of an order classifying the device, FDA must publish a notice in the Federal Register announcing the classification.

In accordance with section 513(f)(1) of the FD&C Act, FDA issued an order on December 13, 2013 automatically classifying the CytoScan® Dx Assay in class III, because it was not within a type of device which was introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976, nor which was subsequently reclassified into class I or class II.

On December 18, 2013, FDA received your De Novo requesting classification of the CytoScan® Dx Assay. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the CytoScan® Dx Assay into class I or II, it is necessary that the proposed class have sufficient regulatory controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use. After review of the information submitted in the De Novo request, FDA has determined that, for the previously stated indications for use, the CytoScan® Dx Assay can be classified in class II with the establishment of special controls for class II. FDA believes that class II (special) controls provide reasonable assurance of the safety and effectiveness of the device type. The identified risks and mitigation measures associated with the device type are summarized in the following table:

Table 1 – Identified Risks to Health and Required Mitigations

Identified Risks to Health	Mitigation Measures
Inaccurate test results that provide false positive and false negative results can lead to improper patient management.	Special controls (1) and (2)
Failure to correctly interpret test results can lead to false positive and false negative results and accordingly improper patient management.	Special controls (1)(iii) and (2)

In combination with the general controls of the FD&C Act, the postnatal chromosomal copy number variation detection system is subject to the following special controls:

- (1) Design verification and validation must include the following information:
 - (i) A detailed description of all components in the test system that includes:
 - (A) A description of the assay components, array composition and layout, all required reagents, instrumentation, and equipment, including illustrations or photographs of non-standard equipment or methods;
 - (B) A description of the design of the array in terms of chromosomal coverage and probe density for different regions;
 - (C) An identification of the number of probes and size of the copy number variations reported at the lower range of the assay;
 - (D) Detailed documentation of the device software, including standalone software applications and hardware-based devices that incorporate software;
 - (E) Methodology and protocols for detecting copy number and visualizing results;
 - (F) A description of the result outputs along with sample reports, and a description of any links to external databases provided by the device to the user or accessed by the device;
 - (G) Specifications for the methods to be used in specimen collection, extraction, including DNA criteria for DNA quality and quantity to perform the assay, and storage; and
 - (H) A description of appropriate internal and external controls that are recommended or provided. The description must identify those control elements that are incorporated into the testing procedure.
 - (ii) Information that demonstrates the performance characteristics of the system, including:
 - (A) Device reproducibility data generated, at a minimum, using three sites, with two operators at each site, for three non-consecutive days using at least three instruments. A well characterized panel of samples that provide a wide range of copy number variations (i.e., gains, losses, adequate size coverage across the range of sizes claimed by the device, adequate chromosomal coverage, challenging regions in the genome, copy number variations reported at the lower range of the assay, interstitial, subtelomeric, and pericentromeric rearrangements, aneuploidy, unbalanced translocations, mosaicism, and known syndromic regions) must be used. The results must be itemized for all copy number variations detected in each sample across all replicates and summarized in a tabular format stratified by size range and range of probe numbers for gains and losses separately and calculated for overall. The results must be analyzed using pairwise replicate agreement, and summarized as overall pairwise replicate agreement as well as pairwise replicate agreement conditional on

- replicates having a positive copy number state call (gains or losses), call rate, copy number variation size variation, and endpoint agreement;
- (B) Device accuracy data using cell lines and clinical samples representing a variety of copy number variations and syndromes. In this analytical study, accuracy must be determined for every copy number variation detected in a particular sample. The accuracy data provided must include the copy number state determination and endpoint accuracy. The accuracy samples must cover different genomic variations across the genome (i.e., gains, losses, adequate copy number variation size coverage across the range of sizes claimed by the device, adequate chromosomal coverage, challenging regions in the genome, copy number variations reported at the lower range of the assay, interstitial, subtelomeric, and pericentromeric rearrangements, aneuploidy, unbalanced translocations, mosaicism, and known syndromic regions). Copy number variations identified by the device must be compared to comparator method(s). Agreement between the copy number variations detected by the array and the comparator must be summarized in a tabular format that includes the positive percent agreement and false positive rate stratified by size range and range of probe numbers for gains and losses separately and calculated for overall;
 - (C) Assay performance data for copy number variations reported at the lower range of the assay for both gains and losses;
 - (D) Device analytical sensitivity data, including DNA input and limit of detection for mosaicism, if applicable;
 - (E) Device analytical specificity data, including interference, carryover, and cross-contamination data;
 - (F) Device stability data, including real-time stability under various storage times, temperatures, and freeze-thaw conditions;
 - (G) Specimen matrix comparison data if more than one specimen type or anticoagulant can be tested with the device;
 - (H) Data that demonstrates the clinical validity, including diagnostic yield, of the device using a minimum of 800 retrospective clinical samples that were collected prospectively and obtained from three or more clinical laboratories, with results interpretation equally divided between two or more qualified healthcare professionals (e.g., cytogeneticists). Patients must be representative of the intended use population and not limited to common syndromes. Diagnostic yield data must be summarized in tabular format and stratified by the comparison methodologies. Data must be summarized in tabular format comparing interpretation of results, with description of reasons for variability in calls between the device and the standard of care methods. Data to support the accuracy of calls for known syndromes must be included; and
 - (I) Data that demonstrates device results when a minimum of 100 apparently healthy, phenotypically normal individuals are tested and interpreted by one or more cytogeneticists blinded to the patient status.
- (iii) Identification of risk mitigation elements used by the device, including a description of all additional procedures, methods, and practices incorporated into the directions for use that mitigate risks associated with testing.
- (2) The labeling required under § 809.10 of this chapter must include:

- (i) A warning statement that the device is not intended to be used for standalone diagnostic purposes, pre-implantation or prenatal testing or screening, population screening, or for the detection of, or screening for, acquired or somatic genetic aberrations;
- (ii) Limitations regarding the assay's performance with respect to validated copy number variations reported at the lower range of the assay, stratified by size range and range of probe numbers for gains and losses separately. Limitations regarding problematic (hypervariable) regions; loss of heterozygosity; mosaicism; and inability to detect balanced translocations, as appropriate;
- (iii) A warning statement that interpretation of assay results is intended to be performed by qualified healthcare professionals such as clinical cytogeneticists or molecular geneticists; and
- (iv) A description of the performance studies performed in accordance with paragraph (b)(1)(ii) of this section and a summary of the results.

Although this letter refers to your product as a device, please be aware that some granted products may instead be combination products. If you have questions on whether your product is a combination product, contact CDRHProductJurisdiction@fda.hhs.gov.

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act, if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device type. FDA has determined premarket notification is necessary to provide reasonable assurance of the safety and effectiveness of the device type and, therefore, the device is not exempt from the premarket notification requirements of the FD&C Act. Thus, persons who intend to market this device type must submit a premarket notification containing information on the postnatal chromosomal copy number variation detection system they intend to market prior to marketing the device.

Please be advised that FDA's decision to grant this De Novo request does not mean that FDA has made a determination that your device complies with other requirements of the FD&C Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the FD&C Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 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 FD&C Act; 21 CFR 1000-1050).

All medical devices, including Class I and unclassified devices and combination product device constituent parts are required to be in compliance with the final Unique Device Identification System Rule ("UDI Rule"). The UDI Rule requires, among other things, that a device bear a unique device identifier (UDI) on its label and package (21 CFR 801.20(a)) unless an exception or alternative applies (21 CFR 801.20(b)) and that the dates on the device label be formatted in accordance with 21 CFR 801.18. The UDI Rule (21 CFR 830.300(a) and 830.320(b)) also requires that certain information be submitted to the Global Unique Device Identification Database (GUDID) (21 CFR Part 830 Subpart E). For additional information on these

requirements, please see the UDI System webpage at <https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/unique-device-identification-system-udi-system>.

A notice announcing this classification order will be published in the Federal Register. A copy of this order and supporting documentation are on file in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852 and are available for inspection between 9 a.m. and 4 p.m., Monday through Friday.

As a result of this order, you may immediately market your device as described in the De Novo request, subject to the general control provisions of the FD&C Act and the special controls identified in this order.

For comprehensive regulatory information about medical devices and radiation-emitting products, 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).

If you have any questions concerning the contents of the letter, please contact Zivana Tezak at 301-796-6206.

Sincerely,

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