September 29, 2023

Invitae Corporation
Elaine Cull
Lead, US Regulatory Affairs
1400 16th Street
San Francisco, California 94103

Re: DEN210011
Trade/Device Name: Invitae Common Hereditary Cancers Panel
Regulation Number: 21 CFR 866.6095
Regulation Name: High throughput DNA sequencing for hereditary cancer predisposition assessment test system
Regulatory Class: Class II
Product Code: QVU
Dated: March 26, 2021
Received: March 29, 2021

Dear Elaine Cull:

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 Invitae Common Hereditary Cancers Panel, a prescription device with the following indications for use:

> The Invitae Common Hereditary Cancers Panel is a qualitative high-throughput sequencing based in vitro diagnostic test system intended for analysis of germline human genomic DNA extracted from whole blood for detection of substitutions, small insertion and deletion alterations and copy number variants (CNV) in a panel of targeted genes.
>
> This test system is intended to provide information for use by qualified health care professionals, in accordance with professional guidelines, for hereditary cancer predisposition assessment and to aid in identifying hereditary genetic variants potentially associated with a diagnosed cancer.
>
> The test is not intended for cancer screening or prenatal testing. Results are intended to be interpreted within the context of additional laboratory results, family history, and clinical findings.
>
> The test is a single-site assay performed at Invitae Corporation.

FDA concludes that this device should be classified into Class II. This order, therefore, classifies the Invitae Common Hereditary Cancers Panel, and substantially equivalent devices of this generic type, into Class II under the generic name high throughput DNA sequencing for hereditary cancer predisposition assessment test system.

FDA identifies this generic type of device as:

> **High throughput DNA sequencing for hereditary cancer predisposition assessment test system**. A high throughput DNA sequencing for hereditary cancer predisposition assessment test system is a qualitative in vitro diagnostic (IVD) system intended for analysis of human DNA extracted from human specimens to detect germline mutations in a panel of targeted cancer related genes. It is intended to aid in hereditary cancer predisposition assessment by qualified health care professionals in accordance with professional guidelines. The device is not intended for screening, prenatal testing or as a stand-alone diagnostic test. The device is for prescription use only.

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.

On March 29, 2021, FDA received your De Novo requesting classification of the Invitae Common Hereditary Cancers Panel. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the Invitae Common Hereditary Cancers Panel 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 Invitae Common Hereditary Cancers Panel 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:

| Risks to Health | Mitigation Measures |
|---|---|
| False positive, false negative, or failure to provide a result. | Certain design verification and validation including certain analytical and clinical studies, and mutation annotation and clinical interpretation rules identified in special control (1).<br><br>Certain labeling information including limitations, device descriptions, methodology and protocols, and performance information identified in special control (2). |
| Incorrect interpretation of variants/alterations by the lab. | Certain labeling information including limitations, device descriptions, methodology and protocols, and |

| Risks to Health | Mitigation Measures |
|---|---|
| | performance information identified in special control (2).<br><br>Certain design verification and validation including certain analytical and clinical studies, and mutation annotation and clinical interpretation rules identified in special control (1). |
| Incorrect interpretation of test results by the healthcare provider. | Certain labeling information including limitations, device descriptions, methodology and protocols, and performance information identified in special control (2).<br><br>Certain design verification and validation including certain analytical and clinical studies, and mutation annotation and clinical interpretation rules identified in special control (1). |

In combination with the general controls of the FD&C Act, the high throughput DNA sequencing for hereditary cancer predisposition assessment test system is subject to the following special controls:

(1) Design verification and validation must include:
  (i) A description of genomic coverage that includes:
    (A) A list of all genes, variant types, and target regions within each gene that the device detects;
    (B) Summary information regarding the clinical significance of each gene, including references;
    (C) A description of the genes with high clinical significance that are detected by the device, defined as genes for which the test result(s) may lead to prophylactic screening, confirmatory procedures, or treatment that may incur morbidity or mortality; and
    (D) A description of any within-gene targeted regions that cannot be reported.
  (ii) Specifications for specimen requirements, including any specimen collection devices, handling, and storage.
  (iii) Specifications of the DNA extraction method and criteria for DNA quality and quantity that are prerequisite to performing the assay.
  (iv) Detailed documentation of the methodology and protocols for each step of the test, including reagents, instrumentation, and software required. The documentation must include the analysis algorithms used for mutation detection and annotation, and specify the quality metrics, variant calling thresholds, and filters at each step of the test, including the criteria for run-failures, batch-failures, specimen-failures, invalid calls (e.g., failed quality control), and “no calls” (i.e., absence of a result), as applicable.
  (v) Description of required instrumentation and equipment, and any ancillary reagents, instrumentation, or equipment.

(vi) Detailed documentation of device software, including software applications and hardware-based devices that incorporate software. The documentation must include verification, validation, and hazard analysis and risk assessment activities.

(vii) Documentation of internal and external controls that are recommended or provided and control procedures. The documentation must identify those control elements that are incorporated into the testing procedure.

(viii) Detailed documentation pertaining to the probability of test failure based on data from clinical samples, description of scenarios in which a test can fail, and any risk mitigations, including follow up actions to be taken.

(ix) Detailed documentation of the rules, procedures, tools, and criteria used for establishing mutation-hereditary disease relationships and mutation annotation, evaluation, and classification (e.g., pathogenic, likely pathogenic, variant of unknown significance, benign, and likely benign).

(x) Detailed documentation of any internal or external database(s) or decision rules used for mutation annotation, including:

(A) The protocol(s) used for variant interpretation, including training of personnel, monitoring accuracy of decision, resolution of discordant interpretations, and updating interpretations;

(B) Detailed documentation of the basis for interpretation, including the use of alternate databases, literature and guidelines, and the basis for risk reporting;

(C) Methods for data preservation and security; and

(D) Data formats and nomenclature.

(xi) Information that demonstrates the performance characteristics of the device, evaluated either specifically for each gene/mutation or, when determined to be acceptable and appropriate by FDA, using a representative approach based on other mutations of the same type, including:

(A) Data that adequately support the intended specimen type(s) (e.g., whole blood), specimen handling protocol, and DNA extraction method.

(B) A summary of the evidence that demonstrates how the analytical quality metrics and thresholds used to determine the acceptability of reporting support the minimum accuracy requirements.

(C) Data to adequately support device accuracy using clinical specimens representing all indicated specimen types, mutation types, and size ranges intended to be detected and reported by the device. Accuracy data must fulfill the following:

*(1)* Accuracy of the device must be evaluated with clinical specimens collected in accordance with the device labeling and selected without bias, or well characterized human cell line samples, when determined to be acceptable and appropriate by FDA.

*(2)* Accuracy must be evaluated by comparison to bidirectional Sanger sequencing or other orthogonal methods identified as appropriate by FDA. Performance criteria for both the comparator method(s) and the device must be pre-defined and appropriate to the device's intended use. Detailed study protocols must be documented.

*(3)* A sufficient number of specimens must be tested. For *BRCA1* and *BRCA2* genes, a minimum of 120 variant positive specimens must be tested. For other genes with high-clinical significance, at least 40 variant positive specimens must be tested per gene, including representative specimens for each indicated variant type based on a justification determined to be appropriate and acceptable by FDA. For remaining genes detected by the device, testing must include variant positive specimens representing each variant type, unless the variant type has a prevalence of less than 0.01%. Specimen selection must be prioritized based on clinical significance. The

selected specimens must be representative of zygosity and challenging genomic context (e.g., G-C content, near tandem repeats and homopolymer stretches, pseudogene, etc.), and must cover the range of sizes (for insertions, deletions, copy number variant (CNV) amplifications and CNV deletions) intended to be detected and reported by the device.

*(4)* Tested specimens must be selected based on results obtained from the orthogonal method. Positive percent agreement (PPA) and negative percent agreement (NPA) must be calculated and demonstrated for each variant type detected and reported by the device, as well as for clinically relevant variants. PPA is calculated as the number of variants that are tested positive by both the device and the orthogonal method (true "positives" (TP)) divided by the number of variants tested positive as determined by the orthogonal method (TP plus false negatives (FN) by the device). NPA is calculated as the number of variants that are tested negative (wild type) by both the device and the orthogonal method (true "negatives" (TN)) divided by the number of variants tested negative (wild type) by the orthogonal method (TN plus false positives (FP) by the device). Point estimates for PPA and NPA must be calculated along with 95% two-sided confidence intervals (CI). Uncertainty of the point estimate must be within an acceptable range, as identified by FDA, and must be demonstrated using the 95% CI.

*(5)* When instead determined by FDA to be appropriate and acceptable to select samples based on the results obtained with the device, accuracy must be presented as technical positive predictive value (TPPV) and technical negative predictive value (TNPV). TPPV relates to the likelihood that a variant call is a true positive and reflects the number of false positives per test. TPPV is calculated as the number of variants that are tested positive by both the device and the orthogonal method (TP) divided by the number of variants tested positive by the device (TP plus FP). TNPV relates to the likelihood that a variant call is a true negative and reflects the number of false negatives per test. TNPV is calculated as the number of variants that are tested negative by both the device and the orthogonal method (TN) divided by the number of variants tested negative by the device (TN plus FN).

*(6)* Any "no calls" or invalid calls in the study must be reported separately. The percent of final "no calls" or invalid calls must be clinically justifiable.

*(7)* Accuracy as a function of each performance metric (e.g., coverage depth, base quality scores) must be documented to provide evidence of the accuracy of the overall run.

*(8)* Detailed documentation for accuracy of the device must include information and results for the overall study, each mutation type, and each gene. The accuracy must further be described based upon stratification within each mutation type by zygosity, genomic context and size (for indels and CNVs). Overall accuracy for reporting of substitutions must be ≥99.0%, insertion and deletions ≥99.0%, CNVs ≥99.0% for positive agreement (PPA, TPPV) and ≥99.9% for negative agreement (NPA, TNPV).

(D) Documentation of the data to adequately support device precision using clinical specimens representing all specimen types, mutation types, and sizes intended to be detected and reported by the device. The precision study must fulfill the following:

*(1)* The study must be performed using multiple instruments and multiple operators, on multiple non-consecutive days, and using multiple reagent lots. If the device is to be

performed at more than one site, different sites must be included and reproducibility across sites must be evaluated.

*(2)* Representative clinical specimens of each mutation type must be tested (both positive and negative), considering clinical significance, prevalence, zygosity, genomic context, and size (for indels and CNVs). The precision for CNV detection must be demonstrated on the gene level for genes with high clinical significance. Alternatively, a justification for why such data are not needed must be found acceptable and appropriate by FDA.

*(3)* The study must assess the performance of all steps, including DNA extraction, unless a separate extraction study is performed.

*(4)* The study must use predefined performance criteria. Agreement estimates such as PPA/NPA and average positive agreement (APA)/average negative agreement (ANA) must be provided, including point estimates and 95% confidence intervals. Documentation from the precision study must be demonstrated for the overall precision study, in addition to each mutation type, each gene and each sample. Precision must further be demonstrated upon stratification within each mutation type by zygosity, genomic context, and size (for indels and CNVs). The overall precision point estimates for each variant type must be >99.0%.

*(5)* Any "no calls" or invalid calls in the study must be included in precision study results and reported separately. The percent of "no calls" or invalid calls and key quality control metrics parameters (e.g., coverage, sequencing score, etc.) must be summarized and based on stratification in the same way as the precision estimates.

(E) Documentation of the nucleic acid assay input range and the evidence to adequately support the range.

(F) Detailed documentation of additional analytical validation studies, including endogenous and exogenous interfering substances, specimen and reagent stability, cross-reactivity, carryover and cross contamination, guard-banding, and index misassignment, as applicable. If specimens are pooled, index cross-contamination must be evaluated and demonstrate that pooling does not negatively impact test performance.

(G) Specimen type and matrix comparison data must be generated if more than one specimen type or anticoagulant can be tested with the device, including failure rates for the different specimen types.

(xii) Information that adequately supports the variant annotation and clinical interpretation of the test must include:

(A) A summary documenting the clinical significance for each gene on the test panel, including the associated conditions/cancers, the most prevalent and representative mutations, and summary of clinical evidence with references, including expected frequency in the general population and different ethnicities, and risks of developing the disease in relevant ethnic populations and the general population.

(B) Detailed documentation of the data to adequately support the performance of the variant annotation algorithms (e.g., concordance studies between the device generated variant classifications and externally established variant classifications, manual classifications by medical professionals, or classifications generated from clinical test reports).

(C) Documentation of any procedures or protocols for incorporation of any updates of valid scientific evidence into variant classification algorithms.

(2) The labeling required under 21 CFR 809.10 must include the following, as applicable:

(i) The intended use must include a description of the intended specimen type(s) and matrix (e.g., whole blood), the validated germline mutation types (e.g., single nucleotide variant, insertion, deletion, CNV, etc.), and a statement that the test is for hereditary cancer predisposition assessment and to aid in identifying hereditary genetic variants potentially associated with a diagnosed cancer.

(ii) The name of the testing facility or facilities (e.g., for single-site assays).

(iii) A summary of device description in accordance with paragraphs (b)(1)(i), (b)(1)(ii), (b)(1)(iii), (b)(1)(iv), (b)(1)(v), (b)(1)(vi), (b)(1)(vii), and (b)(1)(viii).

(iv) A section that provides summary information on how the test works, how to interpret the results of the test, and an explanation on the database(s) used for mutation annotation.

(v) A summary of the information that demonstrates the performance characteristics of the device as required under paragraph (b)(1)(xi).

(vi) The following limiting statements:

(A) A statement that the test is not intended for use as a stand-alone diagnostic to diagnose cancer or other health conditions. The test is not intended for use for prenatal testing nor as a cancer screening test.

(B) A statement that the test is specifically designed for heritable germline mutations and is not appropriate for the detection of somatic mutations.

(C) A description of the intended test population.

(D) A statement that the risk of cancer or disease for an individual cannot be predicted.

(E) A statement that test results should be interpreted in the context of clinical findings, family history, lifestyle, environment, and other factors. Molecular testing may not detect all possible mutations leading to cancer disposition. A negative result does not rule out the possibility that the individual has an unidentified variant leading to cancer. For more information, physicians ordering the test may wish to consult with a clinical medical geneticist or genetic counselor.

(F) A statement that other factors, such as ethnicity, may affect whether the test results are relevant for a particular patient and may also affect how their genetic health results are interpreted.

(G) A statement describing the situations that a patient should not receive the test (e.g., a patient with bone marrow transplant).

(H) A statement describing the challenging genomic contexts that may have reduced performance, where results should be interpreted with care.

(I) A statement disclosing the genetic coverage of the test, including any gaps in coverage.

(J) Statements describing testing conditions that were identified to cause test failures (e.g., low specimen volume, poor DNA quality).

(vii) For variants detected and reported by the device under the category of "variants of uncertain significance" or equivalent designation, a limiting statement that the clinical significance has not been demonstrated with adequate clinical evidence in accordance with established guidelines (e.g., professional guidelines).

(viii) For variants detected and reported by the device under the category of "variants with evidence of clinical significance" or equivalent designation, reference(s) for physicians to access internal or external information concerning decision rules or conclusions about the level of evidence for clinical significance.

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 high throughput DNA sequencing for hereditary cancer predisposition assessment test 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).

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 Jingya Wang at 301-837-7257.

Sincerely,

Donna M. Roscoe -S

Donna Roscoe, Ph.D.
Acting Director
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