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4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 866

[Docket No. FDA-2015-N-3472]

Medical Devices; Immunology and Microbiology Devices; Classification of Autosomal Recessive Carrier Screening Gene Mutation Detection System

AGENCY: Food and Drug Administration, HHS.

ACTION: Final order.

SUMMARY: The Food and Drug Administration (FDA) has classified an autosomal recessive carrier screening gene mutation detection system into class II (special controls). The special controls that apply to this device are identified in this order and will be part of the codified language for the autosomal recessive carrier screening gene mutation detection system classification. The Agency has classified the device into class II (special controls) in order to provide a reasonable assurance of safety and effectiveness of the device.

DATES: This order is effective [INSERT DATE OF PUBLICATION IN THE FEDERAL REGISTER]. The classification was applicable February 19, 2015.

FOR FURTHER INFORMATION CONTACT: Sunita Shukla, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, rm. 4647, Silver Spring, MD 20993-0002, 301-796-6406.

SUPPLEMENTARY INFORMATION:

I. Background

In accordance with section 513(f)(1) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 360c(f)(1)), devices that were not in commercial distribution before May 28, 1976 (the date of enactment of the Medical Device Amendments of 1976), generally referred to as postamendments devices, are classified automatically by statute into class III without any FDA rulemaking process. These devices remain in class III and require premarket approval, unless and until the device is classified or reclassified into class I or II, or FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval. The Agency determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807) of the regulations.

Section 513(f)(2) of the FD&C Act, as amended by section 607 of the Food and Drug Administration Safety and Innovation Act (Pub. L. 112-144), provides two procedures by which a person may request FDA to classify a device under the criteria set forth in section 513(a)(1). Under the first procedure, the person submits a premarket notification under section 510(k) of the FD&C Act for a device that has not previously been classified and, after receiving an order classifying the device into class III under section 513(f)(1) of the FD&C Act, the person requests a classification under section 513(f)(2). Under the second procedure, rather than first submitting a premarket notification under section 510(k) of the FD&C Act and then a request for classification under the first procedure, the person determines that there is no legally marketed device upon which to base a determination of substantial equivalence and requests a classification under section 513(f)(2) of the FD&C Act. If the person submits a request to

classify the device under this second procedure, FDA may decline to undertake the classification request if FDA identifies a legally marketed device that could provide a reasonable basis for review of substantial equivalence with the device or if FDA determines that the device submitted is not of "low-moderate risk" or that general controls would be inadequate to control the risks and special controls to mitigate the risks cannot be developed.

In response to a request to classify a device under either procedure provided by section 513(f)(2) of the FD&C Act, FDA will classify the device by written order within 120 days. This classification will be the initial classification of the device.

23andMe, Inc., submitted a direct de novo request for classification of the 23andMe PGS Carrier Screening Test for Bloom Syndrome under section 513(f)(2)(A)(ii) of the FD&C Act, based on a determination that there is no legally marketed device on which to base a determination of substantial equivalence.

In accordance with section 513(f)(2) of the FD&C Act, FDA reviewed the request in order to classify the device under the criteria for classification set forth in section 513(a)(1) of the FD&C Act. After review of the information submitted in the de novo request, FDA classified the device into class II because general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness, and there is sufficient information to establish special controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use.

Therefore, on February 19, 2015, FDA issued an order to the requestor classifying the device into class II. The classification of the device will be codified at 21 CFR 866.5940.

The device is assigned the generic name autosomal recessive carrier screening gene mutation detection system, and it is identified as a qualitative in vitro molecular diagnostic

system used for genotyping of clinically relevant variants in genomic DNA isolated from human specimens intended for prescription use or over-the-counter use. The device is intended for autosomal recessive disease carrier screening in adults of reproductive age. The device is not intended for copy number variation, cytogenetic, or biochemical testing.

A gene mutation detection system indicated for the determination of carrier status by detection of clinically relevant gene mutations associated with cystic fibrosis is separately classified under 21 CFR 866.5900--Cystic fibrosis transmembrane conductance regulator (CFTR) gene mutation detection system (class II, special controls), and is thus not included in the de novo classification.

FDA has identified the following risks to health associated with this type of device and the measures required to mitigate these risks in table 1.

Table 1.--Identified Risks and Required Mitigations

Identified Risks	Required Mitigations
Incorrect understanding of the device and test system	Special controls 1 and 4
Incorrect test results	Special controls 2, 3, 5, and 6
Incorrect interpretation of test results	Special controls 1, 3, 4, and 5

FDA believes that the following special controls, in addition to the general controls, address these risks to health and provide reasonable assurance of safety and effectiveness:

1. If the device is offered over-the-counter, the device manufacturer must provide information to a potential purchaser or actual test report recipient about how to obtain access to a board-certified clinical molecular geneticist or equivalent to assist in pre- and post-test counseling.

2. The device must use a collection device that is FDA cleared, approved, or classified as 510(k) exempt, with an indication for in vitro diagnostic use in DNA testing.
3. The device's labeling must include a prominent hyperlink to the manufacturer's public Web site where the manufacturer shall make the information identified in this subsection publicly available. The manufacturer's home page, as well as the primary part of the manufacturer's Web site that discusses the device, must provide a prominently placed hyperlink to the Web page containing this information and must allow unrestricted viewing access. If the device can be purchased from the Web site or testing using the device can be ordered from the Web site, the same information must be found on the Web page for ordering the device or provided in a prominently placed and publicly accessible hyperlink on the Web page for ordering the device. Any changes to the device that could significantly affect safety or effectiveness would require new data or information in support of such changes, which would also have to be posted on the manufacturer's Web site. The information must include:

a. A detailed device description including:
    i. Gene (or list of the genes if more than one) and variants the test detects (using standardized nomenclature, Human Genome Organization (HUGO) nomenclature, and coordinates);
    ii. Scientifically established clinical validity of each variant detected and reported by the test, which must be well-established in peer-reviewed journal articles, authoritative summaries of the literature such as Genetics Home Reference (http://ghr.nlm.nih.gov/), GeneReviews

(http://www.ncbi.nlm.nih.gov/books/NBK1116/), or similar summaries of valid scientific evidence, and/or professional society recommendations, including:

A. Genotype-phenotype information for the reported mutations.

B. Relevant American College of Medical Genetics (ACMG) or American Congress of Obstetricians and Gynecologists (ACOG) guideline recommending testing of the specific gene(s) and variants the test detects and recommended populations, if available. If not available, a statement stating that professional guidelines currently do not recommend testing for this specific gene(s) and variants.

C. Table of expected prevalence of carrier status in major ethnic and racial populations and the general population.

iii. The specimen type (e.g., saliva, whole blood), matrix, and volume;

iv. Assay steps and technology used;

v. Specification of required ancillary reagents, instrumentation, and equipment;

vi. Specification of the specimen collection, processing, storage, and preparation methods;

vii. Specification of risk mitigation elements and description of all additional procedures, methods, and practices incorporated into the directions for use that mitigate risks associated with testing;

viii. Information pertaining to the probability of test failure (e.g., failed quality control) based on data from clinical samples, description of scenarios in which a test can fail (i.e., low sample volume, low DNA concentration, etc.), how customers will be notified, and followup actions to be taken; and

ix. Specification of the criteria for test result interpretation and reporting.

b. Information that demonstrates the performance characteristics of the device, including:

i. Accuracy (method comparison) of study results for each claimed specimen type.

A. Accuracy of the device shall be evaluated with fresh clinical specimens collected and processed in a manner consistent with the device's instructions for use. If this is impractical, fresh clinical samples may be substituted or supplemented with archived clinical samples. Archived samples shall have been collected previously in accordance with the device's instructions for use, stored appropriately, and randomly selected. In some instances, use of contrived samples or human cell line samples may also be appropriate; the contrived or human cell line samples shall mimic clinical specimens as much as is feasible and provide an unbiased evaluation of the device's accuracy.

B. Accuracy must be evaluated as compared to bidirectional sequencing or other methods identified as appropriate by FDA. Performance criteria for both the comparator method and device must be predefined and appropriate to the test's intended use. Detailed appropriate study protocols must be provided.

C. Information provided shall include the number and type of specimens, broken down by clinically relevant variants, that were compared to bidirectional sequencing or other methods identified as appropriate by FDA. The accuracy, defined as positive percent agreement (PPA) and

negative percent agreement (NPA), must be measured; accuracy point estimates must be greater than 99 percent (both per reported variant and overall) and uncertainty of the point estimate must be presented using the 95 percent confidence interval. Clinical specimens must include both homozygous wild type and heterozygous genotypes. The number of clinical specimens for each variant reported that must be included in the accuracy study must be based on the variant prevalence. Common variants (greater than 0.1 percent allele frequency in ethnically relevant population) must have at least 20 unique heterozygous clinical specimens tested. Rare variants (less than or equal to 0.1 percent allele frequency in ethnically relevant population) shall have at least three unique mutant heterozygous specimens tested. Any no calls (i.e., absence of a result) or invalid calls (e.g., failed quality control) in the study must be included in accuracy study results and reported separately. Variants that have a point estimate for PPA or NPA of less than 99 percent (incorrect test results as compared to bidirectional sequencing or other methods identified as appropriate by FDA) must not be incorporated into test claims and reports. Accuracy measures generated from clinical specimens versus contrived samples or cell lines must be presented separately. Results must be summarized and presented in tabular format, by sample, and by genotype. Point estimate of PPA should be calculated as the number of positive results divided by the number of specimens known to harbor variants (mutations) without “no calls” or invalid calls. The point estimate of NPA

should be calculated as the number of negative results divided by the number of wild type specimens tested without "no calls" or invalid calls, for each variant that is being reported. Point estimates should be calculated along with 95 percent two-sided confidence intervals.

D. Information shall be reported on the clinical positive predictive value (PPV) and negative predictive value (NPV) for carrier status (and where possible, for each variant) in each population. Specifically, to calculate PPV and NPV, estimate test coverage (TC) and the percent of persons with variant(s) included in the device among all carriers: PPV = (PPA*TC * π) / (PPA*TC*π + (1- NPA) * (1-π)) and NPV = (NPA*(1-π)) / (NPA*(1-π) + (1- PPA*TC) * π) where PPA and NPA described either in paragraph (3)(b)(i)(D)(1) or in (3)(b)(i)(D)(2) that follow and π is prevalence of carriers in the population (pre-test risk to be a carrier for the disease).

1. For the point estimates of PPA and NPA less than 100 percent, use the calculated estimates in the PPV and NPV calculations.

2. Point estimates of 100 percent may have high uncertainty. If these variants are measured using highly multiplexed technology, calculate the random error rate for the overall device and incorporate that rate in the estimation of the PPA and NPA as calculated previously. Then use these calculated estimates in the PPV and NPV calculations. This type of accuracy study is helpful in determining that there is no systematic error in such devices.

ii. Precision (reproducibility): Precision data must be generated using multiple instruments and multiple operators, on multiple non-consecutive days, and using multiple reagent lots. The sample panel must include specimens with claimed sample type (e.g. saliva samples) representing different genotypes (i.e., wild type, heterozygous). Performance criteria must be predefined. A detailed study protocol must be created in advance of the study and then followed. The "failed quality control" rate must be indicated. It must be clearly documented whether results were generated from clinical specimens, contrived samples, or cell lines. The study results shall state, in a tabular format, the variants tested in the study and the number of replicates for each variant, and what testing conditions were studied (i.e., number of runs, days, instruments, reagent lots, operators, specimens/type, etc). The study must include all nucleic acid extraction steps from the claimed specimen type or matrix, unless a separate extraction study for the claimed sample type is performed. If the device is to be used at more than one laboratory, different laboratories must be included in the precision study (and reproducibility must be evaluated). The percentage of "no calls" or invalid calls, if any, in the study must be provided as a part of the precision (reproducibility) study results.

iii. Analytical specificity data: Data must be generated evaluating the effect on test performance of potential endogenous and exogenous interfering substances relevant to the specimen type, evaluation of cross-reactivity of known cross-reactive alleles and pseudogenes, and assessment of cross-contamination.

iv. Analytical sensitivity data: Data must be generated demonstrating the minimum amount of DNA that will enable the test to perform accurately in 95 percent of runs.

v. Device stability data: The manufacturer must establish upper and lower limits of input nucleic acid and sample stability that will achieve the claimed accuracy and reproducibility. Data supporting such claims must be described.

vi. Specimen type and matrix comparison data: 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.

c. If the device is offered over-the-counter, including cases in which the test results are provided direct-to-consumer, the manufacturer must conduct a study that assesses user comprehension of the device's labeling and test process and provide a concise summary of the results of the study. The following items must be included in the user study:

i. The test manufacturer must perform pre- and post-test user comprehension studies to assess user ability to understand the possible results of a carrier test and their clinical meaning. The comprehension test questions must directly evaluate the material being presented to the user in the test reports.

ii. The test manufacturer must provide a carrier testing education module to potential and actual test report recipients. The module must define terms that are used in the test reports and explain the significance of carrier status.

iii. The user study must meet the following criteria:

A. The study participants must be comprised of a statistically justified and demographically diverse population (determined using methods such as quota-based sampling) that is representative of the intended user population. Furthermore, the users must be comprised of a diverse range of age and educational levels that have no prior experience with the test or its manufacturer. These factors shall be well-defined in the inclusion and exclusion criteria.

B. All sources of bias (e.g., non-responders) must be predefined and accounted for in the study results with regard to both responders and non-responders.

C. The testing must follow a format where users have limited time to complete the studies (such as an onsite survey format and a one-time visit with a cap on the maximum amount of time that a participant has to complete the tests).

D. Users must be randomly assigned to study arms. Test reports given to users must: (1) Define the condition being tested and related symptoms, (2) explain the intended use and limitations of the test, (3) explain the relevant ethnicities regarding the variant tested, (4) explain carrier status and relevance to the user's ethnicity, (5) provide links to additional information pertaining to situations where the user is concerned about their test results or would like followup information as indicated in test labeling). The study shall assess participants' ability to understand the

following comprehension concepts: The test's limitations, purpose, and results.

E. Study participants must be untrained, naive to the test subject of the study, and be provided only the materials that will be available to them when the test is marketed.

F. The user comprehension study must meet the predefined primary endpoint criteria, including a minimum of a 90 percent or greater overall comprehension rate (i.e. selection of the correct answer) for each comprehension concept to demonstrate that the education module and test reports are adequate for over-the-counter use.

iv. A summary of the user comprehension study must be provided and include the following:

A. Results regarding reports that are provided for each gene/variant/ethnicity tested.

B. Statistical methods used to analyze all data sets.

C. Completion rate, non-responder rate, and reasons for non-response/data exclusion, as well as a summary table of comprehension rates regarding comprehension concepts (purpose of test, test results, test limitations, ethnicity relevance for the test results, etc.) for each study report.

4. Your 21 CFR 809.10 compliant labeling and any test report generated must include the following warning and limitation statements, as applicable:

a. A warning that reads "The test is intended only for autosomal recessive carrier screening in adults of reproductive age."

b. A statement accurately disclosing the genetic coverage of the test in lay terms, including, as applicable, information on variants not queried by the test, and the proportion of incident disease that is not related to the gene(s) tested. For example, where applicable, the statement would have to include a warning that the test does not or may not detect all genetic variants related to the genetic disease, and that the absence of a variant tested does not rule out the presence of other genetic variants that may be disease-related. Or, where applicable, the statement would have to include a warning that the basis for the disease for which the genetic carrier status is being tested is unknown or believed to be non-heritable in a substantial number of people who have the disease, and that a negative test result cannot rule out the possibility that any offspring may be affected with the disease. The statement would have to include any other warnings needed to accurately convey to consumers the degree to which the test is informative for carrier status.

c. For prescription use tests, the following warnings that read:

    i. "The results of this test are intended to be interpreted by a board-certified clinical molecular geneticist or equivalent and should be used in conjunction with other available laboratory and clinical information."

    ii. "This device is not intended for disease diagnosis, prenatal testing of fetuses, risk assessment, prognosis or pre-symptomatic testing, susceptibility testing, or newborn screening."

d. For over-the-counter tests, a statement that reads "This test is not intended to diagnose a disease, or tell you anything about your risk for developing a disease in the future. On its own, this test is also not intended to tell you anything about the health

of your fetus, or your newborn child's risk of developing a particular disease later on in life."

e. For over-the-counter tests, the following warnings that read:

i. "This test is not a substitute for visits to a healthcare provider. It is recommended that you consult with a healthcare provider if you have any questions or concerns about your results."

ii. "The test does not diagnose any health conditions. Results should be used along with other clinical information for any medical purposes."

iii. "The laboratory may not be able to process your sample. The probability that the laboratory cannot process your saliva sample can be up to [actual probability percentage]."

iv. "Your ethnicity may affect how your genetic health results are interpreted."

f. For a positive result in an over-the-counter test when the positive predictive value for a specific population is less than 50 percent and more than 5 percent, a warning that reads "The positive result you obtained may falsely identify you as a carrier. Consider genetic counseling and followup testing."

g. For a positive result in an over-the-counter test when the positive predictive value for a specific population is less than 5 percent, a warning that reads "The positive result you obtained is very likely to be incorrect due to the rarity of this variant. Consider genetic counseling and followup testing."

5. The testing done to comply with paragraph 3 must show the device meets or exceeds each of the following performance specifications:

a. The accuracy must be shown to be equal to or greater than 99 percent for both PPA and NPA. Variants that have a point estimate for PPA or NPA of less than 99 percent (incorrect test results as compared to bidirectional sequencing or other methods identified as appropriate by FDA) must not be incorporated into test claims and reports.

b. Precision (reproducibility) performance must meet or exceed 99 percent for both positive and negative results.

c. The user comprehension study must obtain values of 90 percent or greater user comprehension for each comprehension concept.

6. The distribution of this device, excluding the collection device described in paragraph 2, shall be limited to the manufacturer, the manufacturer's subsidiaries, and laboratories regulated under the Clinical Laboratory Improvement Amendments.

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. For this type of device, FDA believes premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device type and, therefore, is planning to exempt the device from the premarket notification requirements of the FD&C Act. Elsewhere in this issue of the Federal Register, FDA is publishing a notice of intent to exempt an autosomal recessive carrier screening gene mutation detection system under section 510(m) of the FD&C Act. If there are questions about 510(k) submission prior to finalization of the 510(k) exemption, you should contact FDA at the number provided in this Final order. Once finalized, persons who intend to market this device type need

not submit a 510(k) premarket notification containing information on the autosomal recessive carrier screening gene mutation detection system prior to marketing the device.

II. Environmental Impact

The Agency has determined under 21 CFR 25.34(b) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

III. Paperwork Reduction Act of 1995

This final administrative order establishes special controls that refer to previously approved collections of information found in other FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in part 807, subpart E, regarding premarket notification submissions have been approved under OMB control number 0910-0120, and the collections of information in 21 CFR parts 801 and 809 regarding labeling have been approved under OMB control number 0910-0485.

List of Subjects in 21 CFR Part 866

Biologics, Laboratories, Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 866 is amended as follows:

PART 866--IMMUNOLOGY AND MICROBIOLOGY DEVICES

1. The authority citation for 21 CFR part 866 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

2. Add § 866.5940 to subpart F to read as follows:

§ 866.5940 Autosomal recessive carrier screening gene mutation detection system.

(a) Identification. Autosomal recessive carrier screening gene mutation detection system is a qualitative in vitro molecular diagnostic system used for genotyping of clinically relevant variants in genomic DNA isolated from human specimens intended for prescription use or over-the-counter use. The device is intended for autosomal recessive disease carrier screening in adults of reproductive age. The device is not intended for copy number variation, cytogenetic, or biochemical testing.

(b) Classification. Class II (special controls). Autosomal recessive carrier screening gene mutation detection system must comply with the following special controls:

(1) If the device is offered over-the-counter, the device manufacturer must provide information to a potential purchaser or actual test report recipient about how to obtain access to a board-certified clinical molecular geneticist or equivalent to assist in pre- and post-test counseling.

(2) The device must use a collection device that is FDA cleared, approved, or classified as 510(k) exempt, with an indication for in vitro diagnostic use in DNA testing.

(3) The device's labeling must include a prominent hyperlink to the manufacturer's public Web site where the manufacturer shall make the information identified in this section publicly available. The manufacturer's home page, as well as the primary part of the manufacturer's Web site that discusses the device, must provide a prominently placed hyperlink to the Web page containing this information and must allow unrestricted viewing access. If the device can be purchased from the Web site or testing using the device can be ordered from the Web site, the same information must be found on the Web page for ordering the device or provided in a prominently placed and publicly accessible hyperlink on the Web page for ordering the device. Any changes to the device that could significantly affect safety or effectiveness

would require new data or information in support of such changes, which would also have to be posted on the manufacturer's Web site. The information must include:

(i) A detailed device description including:

(A) Gene (or list of the genes if more than one) and variants the test detects (using standardized nomenclature, Human Genome Organization (HUGO) nomenclature, and coordinates).

(B) Scientifically established clinical validity of each variant detected and reported by the test, which must be well-established in peer-reviewed journal articles, authoritative summaries of the literature such as Genetics Home Reference (http://ghr.nlm.nih.gov/), GeneReviews (http://www.ncbi.nlm.nih.gov/books/NBK1116/), or similar summaries of valid scientific evidence, and/or professional society recommendations, including:

(1) Genotype-phenotype information for the reported mutations.

(2) Relevant American College of Medical Genetics (ACMG) or American Congress of Obstetricians and Gynecologists (ACOG) guideline recommending testing of the specific gene(s) and variants the test detects and recommended populations, if available. If not available, a statement stating that professional guidelines currently do not recommend testing for this specific gene(s) and variants.

(3) Table of expected prevalence of carrier status in major ethnic and racial populations and the general population.

(C) The specimen type (e.g., saliva, whole blood), matrix, and volume.

(D) Assay steps and technology used.

(E) Specification of required ancillary reagents, instrumentation, and equipment.

(F) Specification of the specimen collection, processing, storage, and preparation methods.

(G) Specification of risk mitigation elements and description of all additional procedures, methods, and practices incorporated into the directions for use that mitigate risks associated with testing.

(H) Information pertaining to the probability of test failure (e.g., failed quality control) based on data from clinical samples, description of scenarios in which a test can fail (i.e., low sample volume, low DNA concentration, etc.), how customers will be notified, and followup actions to be taken.

(I) Specification of the criteria for test result interpretation and reporting.

(ii) Information that demonstrates the performance characteristics of the device, including:

(A) Accuracy (method comparison) of study results for each claimed specimen type.

(1) Accuracy of the device shall be evaluated with fresh clinical specimens collected and processed in a manner consistent with the device's instructions for use. If this is impractical, fresh clinical samples may be substituted or supplemented with archived clinical samples. Archived samples shall have been collected previously in accordance with the device's instructions for use, stored appropriately, and randomly selected. In some instances, use of contrived samples or human cell line samples may also be appropriate; the contrived or human cell line samples shall mimic clinical specimens as much as is feasible and provide an unbiased evaluation of the device's accuracy.

(2) Accuracy must be evaluated as compared to bidirectional sequencing or other methods identified as appropriate by FDA. Performance criteria for both the comparator method

and device must be predefined and appropriate to the test's intended use. Detailed appropriate study protocols must be provided.

(3) Information provided shall include the number and type of specimens, broken down by clinically relevant variants, that were compared to bidirectional sequencing or other methods identified as appropriate by FDA. The accuracy, defined as positive percent agreement (PPA) and negative percent agreement (NPA), must be measured; accuracy point estimates must be greater than 99 percent (both per reported variant and overall) and uncertainty of the point estimate must be presented using the 95 percent confidence interval. Clinical specimens must include both homozygous wild type and heterozygous genotypes. The number of clinical specimens for each variant reported that must be included in the accuracy study must be based on the variant prevalence. Common variants (greater than 0.1 percent allele frequency in ethnically relevant population) must have at least 20 unique heterozygous clinical specimens tested. Rare variants (less than or equal to 0.1 percent allele frequency in ethnically relevant population) shall have at least three unique mutant heterozygous specimens tested. Any no calls (i.e., absence of a result) or invalid calls (e.g., failed quality control) in the study must be included in accuracy study results and reported separately. Variants that have a point estimate for PPA or NPA of less than 99 percent (incorrect test results as compared to bidirectional sequencing or other methods identified as appropriate by FDA) must not be incorporated into test claims and reports. Accuracy measures generated from clinical specimens versus contrived samples or cell lines must be presented separately. Results must be summarized and presented in tabular format, by sample and by genotype. Point estimate of PPA should be calculated as the number of positive results divided by the number of specimens known to harbor variants (mutations) without "no calls" or invalid calls. The point estimate of NPA should be calculated as the number of negative

results divided by the number of wild type specimens tested without “no calls” or invalid calls, for each variant that is being reported. Point estimates should be calculated along with 95 percent two-sided confidence intervals.

(4) Information shall be reported on the clinical positive predictive value (PPV) and negative predictive value (NPV) for carrier status (and where possible, for each variant) in each population. Specifically, to calculate PPV and NPV, estimate test coverage (TC) and the percent of persons with variant(s) included in the device among all carriers: $PPV = (PPA*TC * \pi) / (PPA*TC*\pi + (1- NPA) * (1-\pi))$ and $NPV = (NPA*(1- \pi)) / (NPA*(1-\pi) + (1- PPA*TC) * \pi)$ where PPA and NPA described either in paragraph (b)(3)(ii)(A)(4)(i) or in paragraph (b)(3)(ii)(A)(4)(ii) of this section and π is prevalence of carriers in the population (pre-test risk to be a carrier for the disease).

(i) For the point estimates of PPA and NPA less than 100 percent, use the calculated estimates in the PPV and NPV calculations.

(ii) Point estimates of 100 percent may have high uncertainty. If these variants are measured using highly multiplexed technology, calculate the random error rate for the overall device and incorporate that rate in the estimation of the PPA and NPA as calculated previously. Then use these calculated estimates in the PPV and NPV calculations. This type of accuracy study is helpful in determining that there is no systematic error in such devices.

(B) Precision (reproducibility): Precision data must be generated using multiple instruments and multiple operators, on multiple non-consecutive days, and using multiple reagent lots. The sample panel must include specimens with claimed sample type (e.g. saliva samples) representing different genotypes (i.e., wild type, heterozygous). Performance criteria must be predefined. A detailed study protocol must be created in advance of the study and then

followed. The "failed quality control" rate must be indicated. It must be clearly documented whether results were generated from clinical specimens, contrived samples, or cell lines. The study results shall state, in a tabular format, the variants tested in the study and the number of replicates for each variant, and what testing conditions were studied (i.e., number of runs, days, instruments, reagent lots, operators, specimens/type, etc). The study must include all nucleic acid extraction steps from the claimed specimen type or matrix, unless a separate extraction study for the claimed sample type is performed. If the device is to be used at more than one laboratory, different laboratories must be included in the precision study (and reproducibility must be evaluated). The percentage of "no calls" or invalid calls, if any, in the study must be provided as a part of the precision (reproducibility) study results.

(C) Analytical specificity data: Data must be generated evaluating the effect on test performance of potential endogenous and exogenous interfering substances relevant to the specimen type, evaluation of cross-reactivity of known cross-reactive alleles and pseudogenes, and assessment of cross-contamination.

(D) Analytical sensitivity data: Data must be generated demonstrating the minimum amount of DNA that will enable the test to perform accurately in 95 percent of runs.

(E) Device stability data: The manufacturer must establish upper and lower limits of input nucleic acid and sample stability that will achieve the claimed accuracy and reproducibility. Data supporting such claims must be described.

(F) Specimen type and matrix comparison data: 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.

(iii) If the device is offered over-the-counter, including cases in which the test results are provided direct-to-consumer, the manufacturer must conduct a study that assesses user comprehension of the device's labeling and test process and provide a concise summary of the results of the study. The following items must be included in the user study:

(A) The test manufacturer must perform pre- and post-test user comprehension studies to assess user ability to understand the possible results of a carrier test and their clinical meaning. The comprehension test questions must directly evaluate the material being presented to the user in the test reports.

(B) The test manufacturer must provide a carrier testing education module to potential and actual test report recipients. The module must define terms that are used in the test reports and explain the significance of carrier status.

(C) The user study must meet the following criteria:

(1) The study participants must be comprised of a statistically justified and demographically diverse population (determined using methods such as quota-based sampling) that is representative of the intended user population. Furthermore, the users must be comprised of a diverse range of age and educational levels that have no prior experience with the test or its manufacturer. These factors shall be well-defined in the inclusion and exclusion criteria.

(2) All sources of bias (e.g., non-responders) must be predefined and accounted for in the study results with regard to both responders and non-responders.

(3) The testing must follow a format where users have limited time to complete the studies (such as an onsite survey format and a one-time visit with a cap on the maximum amount of time that a participant has to complete the tests).

(4) Users must be randomly assigned to study arms. Test reports given to users must: Define the condition being tested and related symptoms; explain the intended use and limitations of the test; explain the relevant ethnicities regarding the variant tested; explain carrier status and relevance to the user's ethnicity; and provide links to additional information pertaining to situations where the user is concerned about their test results or would like followup information as indicated in test labeling. The study shall assess participants' ability to understand the following comprehension concepts: The test's limitations, purpose, and results.

(5) Study participants must be untrained, naive to the test subject of the study, and be provided only the materials that will be available to them when the test is marketed.

(6) The user comprehension study must meet the predefined primary endpoint criteria, including a minimum of a 90 percent or greater overall comprehension rate (i.e. selection of the correct answer) for each comprehension concept to demonstrate that the education module and test reports are adequate for over-the-counter use.

(D) A summary of the user comprehension study must be provided and include the following:

(1) Results regarding reports that are provided for each gene/variant/ethnicity tested.

(2) Statistical methods used to analyze all data sets.

(3) Completion rate, non-responder rate, and reasons for non-response/data exclusion, as well as a summary table of comprehension rates regarding comprehension concepts (purpose of test, test results, test limitations, ethnicity relevance for the test results, etc.) for each study report.

(4) Your 21 CFR 809.10 compliant labeling and any test report generated must include the following warning and limitation statements, as applicable:

(i) A warning that reads "The test is intended only for autosomal recessive carrier screening in adults of reproductive age."

(ii) A statement accurately disclosing the genetic coverage of the test in lay terms, including, as applicable, information on variants not queried by the test, and the proportion of incident disease that is not related to the gene(s) tested. For example, where applicable, the statement would have to include a warning that the test does not or may not detect all genetic variants related to the genetic disease, and that the absence of a variant tested does not rule out the presence of other genetic variants that may be disease-related. Or, where applicable, the statement would have to include a warning that the basis for the disease for which the genetic carrier status is being tested is unknown or believed to be non-heritable in a substantial number of people who have the disease, and that a negative test result cannot rule out the possibility that any offspring may be affected with the disease. The statement would have to include any other warnings needed to accurately convey to consumers the degree to which the test is informative for carrier status.

(iii) For prescription use tests, the following warnings that read:

(A) "The results of this test are intended to be interpreted by a board-certified clinical molecular geneticist or equivalent and should be used in conjunction with other available laboratory and clinical information."

(B) "This device is not intended for disease diagnosis, prenatal testing of fetuses, risk assessment, prognosis or pre-symptomatic testing, susceptibility testing, or newborn screening."

(iv) For over-the-counter tests, a statement that reads "This test is not intended to diagnose a disease, or tell you anything about your risk for developing a disease in the future. On

its own, this test is also not intended to tell you anything about the health of your fetus, or your newborn child's risk of developing a particular disease later on in life."

(v) For over-the-counter tests, the following warnings that read:

(A) "This test is not a substitute for visits to a healthcare provider. It is recommended that you consult with a healthcare provider if you have any questions or concerns about your results."

(B) "The test does not diagnose any health conditions. Results should be used along with other clinical information for any medical purposes."

(C) "The laboratory may not be able to process your sample. The probability that the laboratory cannot process your saliva sample can be up to [actual probability percentage]."

(D) "Your ethnicity may affect how your genetic health results are interpreted."

(vi) For a positive result in an over-the-counter test when the positive predictive value for a specific population is less than 50 percent and more than 5 percent, a warning that reads "The positive result you obtained may falsely identify you as a carrier. Consider genetic counseling and followup testing."

(vii) For a positive result in an over-the-counter test when the positive predictive value for a specific population is less than 5 percent, a warning that reads "The positive result you obtained is very likely to be incorrect due to the rarity of this variant. Consider genetic counseling and followup testing."

(5) The testing done to comply with paragraph (b)(3) of this section must show the device meets or exceeds each of the following performance specifications:

(i) The accuracy must be shown to be equal to or greater than 99 percent for both PPA and NPA. Variants that have a point estimate for PPA or NPA of less than 99 percent (incorrect

test results as compared to bidirectional sequencing or other methods identified as appropriate by FDA) must not be incorporated into test claims and reports.

(ii) Precision (reproducibility) performance must meet or exceed 99 percent for both positive and negative results.

(iii) The user comprehension study must obtain values of 90 percent or greater user comprehension for each comprehension concept.

(6) The distribution of this device, excluding the collection device described in paragraph (b)(2) of this section, shall be limited to the manufacturer, the manufacturer's subsidiaries, and laboratories regulated under the Clinical Laboratory Improvement Amendments.

Dated: October 20, 2015.

Leslie Kux,

Associate Commissioner for Policy.

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