4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 866

[Docket No. FDA-2025-N-2425]

Medical Devices; Immunology and Microbiology Devices; Classification of the Cancer Predisposition Risk Assessment System

AGENCY: Food and Drug Administration, HHS.

ACTION: Final amendment; final order.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is classifying the cancer predisposition risk assessment system into class II (special controls). The special controls that apply to the device type are identified in this order and will be part of the codified language for classification of the cancer predisposition risk assessment system. We are taking this action because we have determined that classifying the device into class II will provide a reasonable assurance of safety and effectiveness of the device. We believe this action will also enhance patients' access to beneficial innovative devices, in part by reducing regulatory burdens.

DATES: This order is effective [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The classification was applicable on March 6, 2018.

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SUPPLEMENTARY INFORMATION:

I. Background

Upon request, FDA has classified the cancer predisposition risk assessment system as class II (special controls), which we have determined will provide a reasonable assurance of safety and effectiveness. In addition, we believe this action will enhance patients' access to

beneficial innovation, in part by reducing regulatory burdens by placing the device into a lower device class than the automatic class III assignment.

The automatic assignment of class III occurs by operation of law and without any action by FDA, regardless of the level of risk posed by the new device. Any device that was not in commercial distribution before May 28, 1976, is automatically classified as, and remains within, class III and requires premarket approval unless and until FDA takes an action to classify or reclassify the device (see 21 U.S.C. 360c(f)(1)). We refer to these devices as "postamendments devices" because they were not in commercial distribution prior to the date of enactment of the Medical Device Amendments of 1976, which amended the Federal Food, Drug, and Cosmetic Act (FD&C Act).

FDA may take a variety of actions in appropriate circumstances to classify or reclassify a device into class I or II. We may issue an order finding a new device to be substantially equivalent under section 513(i) of the FD&C Act (21 U.S.C. 360c(i)) to a predicate device that does not require premarket approval. We determine whether a new device is substantially equivalent to a predicate device by means of the procedures for premarket notification under section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807).

FDA may also classify a device through "De Novo" classification, a common name for the process authorized under section 513(f)(2) of the FD&C Act (see also part 860, subpart D (21 CFR part 860, subpart D)). Section 207 of the Food and Drug Administration Modernization Act of 1997 (Pub. L. 105-115) established the first procedure for De Novo classification. Section 607 of the Food and Drug Administration Safety and Innovation Act (Pub. L. 112-144) modified the De Novo application process by adding a second procedure. A device sponsor may utilize either procedure for De Novo classification.

Under the first procedure, the person submits a 510(k) for a device that has not previously been classified. After receiving an order from FDA classifying the device into class III under

section 513(f)(1) of the FD&C Act, the person then requests a classification under section 513(f)(2).

Under the second procedure, rather than first submitting a 510(k) and then a request for classification, if the person determines that there is no legally marketed device upon which to base a determination of substantial equivalence, that person requests a classification under section 513(f)(2) of the FD&C Act.

Under either procedure for De Novo classification, FDA is required to classify the device by written order within 120 days. The classification will be according to the criteria under section 513(a)(1) of the FD&C Act. Although the device was automatically placed within class III, the De Novo classification is considered to be the initial classification of the device.

We believe this De Novo classification will enhance patients' access to beneficial innovation, in part by reducing regulatory burdens. When FDA classifies a device into class I or II via the De Novo process, the device can serve as a predicate for future devices of that type, including for 510(k)s (see section 513(f)(2)(B)(i) of the FD&C Act). As a result, other device sponsors do not have to submit a De Novo request or premarket approval application to market a substantially equivalent device (see section 513(i) of the FD&C Act, defining "substantial equivalence"). Instead, sponsors can use the less burdensome 510(k) process, when necessary, to market their device.

II. De Novo Classification

On September 5, 2017, FDA received 23andMe, Inc.'s request for De Novo classification of the 23andMe PGS Genetic Health Risk Report for BRCA1/BRCA2 (Selected Variants). 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.

We classify devices into class II if general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness, but there is sufficient information to establish special controls that, in combination with the general controls, provide reasonable

assurance of the safety and effectiveness of the device for its intended use (see section 513(a)(1)(B) of the FD&C Act). After review of the information submitted in the request, we determined that the device can be classified into class II with the establishment of special controls. FDA has determined that these special controls, in addition to the general controls, will provide reasonable assurance of the safety and effectiveness of the device.

Therefore, on March 6, 2018, FDA issued an order to the requester classifying the device into class II.[1] In this final order, FDA is codifying the classification of the device by adding 21 CFR 866.6090.[2] We have named the generic type of device "cancer predisposition risk assessment system," and it is identified as a qualitative in vitro molecular diagnostic system used for determining predisposition for cancer where the result of the test may lead to prophylactic screening, confirmatory procedures, or treatments that may incur morbidity or mortality to the patient. The test could help to inform conversations with a healthcare professional. This assessment system is for over-the-counter use. This device does not determine the person's overall risk of developing any types of cancer. This test is not a substitute for visits to a healthcare provider for recommended screenings or appropriate follow-up and should not be used to determine any treatments.

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

Table 1.--Cancer Predisposition Risk Assessment System Risks and Mitigation Measures

Identified Risks to Health	Mitigation Measures
Incorrect understanding of the device and test system	Special controls (1), (3), and (4)
Incorrect test results (false positives, false negatives)	Special controls (1), (2), (3), and (4)
Incorrect interpretation of test results	Special controls (1), (3), and (4)

[1] FDA issued a correction of this order to the requestor in a letter dated January 17, 2019.

[2] FDA notes that the "ACTION" caption for this final order is styled as "Final amendment; final order," rather than "Final order." Beginning in December 2019, this editorial change was made to indicate that the document "amends" the Code of Federal Regulations. The change was made in accordance with the Office of Federal Register's (OFR) interpretations of the Federal Register Act (44 U.S.C. chapter 15), its implementing regulations (1 CFR 5.9 and parts 21 and 22), and the Document Drafting Handbook.

FDA has determined that special controls, in combination with the general controls, address these risks to health and provide reasonable assurance of safety and effectiveness. For a device to fall within this classification, and thus avoid automatic classification in class III, it would have to comply with the special controls named in this final order. The necessary special controls appear in the regulation codified by this final order. This device is subject to premarket notification requirements under section 510(k) of the FD&C Act.

III. Analysis of 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.

IV. Paperwork Reduction Act of 1995

This final order establishes special controls that refer to previously approved collections of information found in other FDA regulations and guidance. 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. 3501-3521). The collections of information in part 860, subpart D, regarding De Novo classification have been approved under OMB control number 0910-0844; the collections of information in 21 CFR part 814, subparts A through E, regarding premarket approval have been approved under OMB control number 0910-0231; the collections of information in part 807, subpart E, regarding premarket notification submissions have been approved under OMB control number 0910-0120; the collections of information in 21 CFR part 820 regarding quality system regulation have been approved under OMB control number 0910-0073; 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 part 866 continues to read as follows:

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

2. Add § 866.6090 to subpart G to read as follows:

§ 866.6090 Cancer predisposition risk assessment system.

(a) *Identification.* A cancer predisposition risk assessment system is a qualitative in vitro molecular diagnostic system used for determining predisposition for cancer where the result of the test may lead to prophylactic screening, confirmatory procedures, or treatments that may incur morbidity or mortality to the patient. The test could help to inform conversations with a healthcare professional. This assessment system is for over-the-counter use. This device does not determine the person's overall risk of developing any types of cancer. This test is not a substitute for visits to a healthcare provider for recommended screenings or appropriate follow-up and should not be used to determine any treatments.

(b) *Classification*. Class II (special controls). The special controls for this device are:

(1) The labeling required under § 809.10 of this chapter and any pre-purchase page and test report generated, unless otherwise specified, must include:

(i) An intended use that specifies in the indications for use the genetic variants detected by the test. The specific variants must be appropriately validated as described in paragraphs (b)(4)(xii) and (b)(4)(xiii) of this section.

(ii) A section addressed to users with the following information:

(A) A warning statement accurately disclosing the genetic coverage of the test in lay terms, including information on variants not queried by the test, and the proportion of pathogenic variants in the genes that the assay detects in a specific population as identified in paragraph (b)(1)(i) of this section. The warning statement must indicate that the test [does not/may not, as

appropriate] 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 impact cancer risk. The warning statement must also include the relevant population for which the variants reported by the test are most relevant.

(B) A limiting statement explaining that some people may feel anxious about getting genetic test health results. This is normal. If the potential user feels very anxious, such user should speak to his or her doctor or other healthcare professional prior to collection of a sample for testing. This test is not a substitute for visits to a doctor or other healthcare professional. Users should consult with their doctor or other healthcare professional if they have any questions or concerns about the results of their test or their current state of health.

(C) A limiting statement that a user's ethnicity may affect whether the test is relevant for them and may also affect how their genetic health results are interpreted.

(D) A warning statement that the test is not a substitute for visits to a healthcare professional for recommended screenings, and should not be used to determine any treatments or medical interventions.

(E) A warning statement that the test does not diagnose cancer or any other health conditions and should not be used to make medical decisions. The warning statement must indicate that the results should be confirmed in a clinical setting before taking any medical action.

(F) A limiting statement explaining that other companies offering a genetic risk test may be detecting different genetic variants for the same disease, so the user may get different results using a test from a different company.

(G) If applicable, a limiting statement that states the test does not test for variants in other genes linked to hereditary cancer.

(H) A limiting statement explaining that this test does not account for non-genetic factors and that other factors such as environmental and lifestyle risk factors may affect the risk of developing a given disease.

(I) 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.

(J) A limiting statement explaining that this test is not intended to tell you anything about your current state of health, or be used to make medical decisions, including whether or not you should take a medication or how much of a medication you should take.

(K) A limiting statement explaining that the laboratory may not be able to process a sample, and a description of the next steps to be taken by the manufacturer and/or the customer, as applicable.

(iii) A section in the labeling required under § 809.10 of this chapter and any test report generated that is for healthcare professionals who may receive the test results from their patients with the following information:

(A) A limiting statement explaining that this test is not intended to diagnose a disease, determine medical treatment or other medical intervention, or tell the user anything about their current state of health.

(B) A limiting statement explaining that this test is intended to provide users with their genetic information to inform health-related lifestyle decisions and conversations with their doctor or other healthcare professional.

(C) A limiting statement explaining that any diagnostic or treatment decisions should be based on confirmatory prescription testing and/or other information that is determined to be appropriate for the patient (e.g., additional clinical testing and other risk factors that may affect individual risk and health care).

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

(3) The device's labeling must include a hyperlink to the manufacturer's public website where the manufacturer must make the information identified in paragraph (b)(3) of this section publicly available. The manufacturer's home page, as well as the primary part of the manufacturer's website that discusses the device, must provide a hyperlink to the web page containing this information and must allow unrestricted viewing access. If the device can be purchased from the website or testing using the device can be ordered from the website, the same information must be found on the web page for ordering the device or provided in a 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 must also be posted on the manufacturer's website. The information must include:

(i) An index of the material being provided to meet the requirements in paragraph (b)(3) of this section and its location.

(ii) Technical information about the device, as specified in paragraph (b)(4) of this section.

(iii) A section that highlights summary information that allows the user to understand how the test works and how to interpret the results of the test. This section must, at a minimum, be written in plain language understandable to a lay user and include:

(A) Consistent explanations of the risk of disease associated with all variants included in the test, variants not included in the test, and specific considerations by ethnicity. If there are different categories of risk, the manufacturer must provide literature references and/or data that support the different risk categories. If there will be multiple test reports and multiple variants,

the risk categories must be defined similarly among them. For example, “increased risk” must be defined similarly between different test reports and different variant combinations.

(B) Clear context for the user to understand the context in which the cited clinical performance data support the risk reported. This includes any risks that are influenced by ethnicity, age, gender, environment, and lifestyle choices.

(C) Materials that explain the main concepts and terminology used in the test that include:

(1) Definitions: scientific terms that are used in the test reports.

(2) Pre-purchase page: this page must contain information that informs the user about what information the test will provide. This includes variant information, the condition(s) or disease(s) associated with the variant(s), professional guideline recommendations for general genetic risk testing, the limitations associated with the test (e.g., test does not detect all variants related to the disease), relevance of race/ethnicity, and any precautionary information about the test the user should be aware of before purchase. When the test reports the risk of a life-threatening or irreversibly debilitating disease or condition for which there are few or no options to prevent, treat, or cure the disease, a user opt-in page must be provided. This opt-in page must be provided for each disease type that falls into this category and must provide specific information relevant to each test result. The opt-in page must include:

(i) An option to accept or decline to receive this specific test result;

(ii) Specification of the risk involved if the user is found to have the specific genetic test result;

(iii) Summary of professional guidelines that recommend when genetic testing for the associated target condition is or is not recommended;

(iv) A recommendation to speak with a healthcare professional, genetic counselor, or equivalent professional before getting the results of the test;

(v) The implications of receiving a no variants detected result; and

(vi) The statement that the test does not diagnose cancer or any other health conditions and should not be used to make medical decisions. Results should be confirmed in a clinical setting before taking any medical action. Users should consult with a healthcare professional before taking any medical action.

(3) Frequently asked questions (FAQ) page: This page must provide information that is specific for each variant/disease pair that is reported. Information provided in this section must be scientifically valid and supported by corresponding peer-reviewed publications. The FAQ page must explain the health condition/disease being tested, the purpose of the test, the information the test will and will not provide, the relevance of race and ethnicity to the test results, information about the population to which the variants in the test is most applicable, the meaning of the result(s), other risk factors that contribute to disease, appropriate follow-up procedures, how the results of the test may affect the user's family, including children, and links to resources that provide additional information.

(4) The device labeling must include a technical information section containing the following information:

(i) Gene(s) and variant(s) the test detects using standardized nomenclature, Human Genome Organization (HUGO) nomenclature and coordinates, as well as Single Nucleotide Polymorphism Database (dbSNP) reference SNP numbers (rs#).

(ii) A statement indicating that more than 1,000 variants in the BRCA1 and BRCA2 genes are known to increase cancer risk, as applicable.

(iii) Scientifically established disease-risk association of each variant detected and reported by the test. This risk association information must include:

(A) Genotype-phenotype information for the reported variants.

(B) When available, a table of expected frequency in the general population and different ethnicities, and risks of developing the disease in relevant ethnic populations and the general population.

(C) Information such as peer-reviewed published literature and/or professional guidelines used to determine what types and levels of evidence will distinguish whether the selected variants are reported as "are associated with increased risk" versus "may be associated with increased risk" of developing other cancers. All selected variants must be appropriately validated as required under paragraph (b)(1)(i) of this section. For selected variants reported as "are associated with increased risk," the clinical evidence must be demonstrated with sufficient information (e.g., professional guidelines and consistent associations in peer-reviewed published literature). For the selected variants reported as "may be associated with increased risk," the clinical evidence must be reported in professional guidelines, but peer-reviewed published literature may not be consistent.

(D) A statement about the current professional guidelines for testing these specific gene(s) and variant(s) for the specified disease(s).

(1) If professional guidelines are available, provide the recommendations in the professional guideline(s) for the gene, variant, and disease for when genetic testing should or should not be performed, and cautionary information that should be communicated when a particular gene and variant is detected.

(2) If professional guidelines are not available, provide a statement that the professional guidelines are not available for these specific gene(s) and variant(s).

(iv) The specimen type (e.g., saliva, whole blood).

(v) Assay steps and technology used.

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

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

(viii) 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.

(ix) Information pertaining to the probability of test failure (e.g., percentage of tests that failed quality control) based on data from clinical samples, a description of scenarios in which a test can fail (e.g., low sample volume, low DNA concentration), how users will be notified of a test failure, and the nature of follow-up actions on a failed test to be taken by the user and the manufacturer.

(x) When available, information specifying the probability of a false negative and false positive analytical result and any additional considerations by ethnicity.

(xi) Specification of the criteria for test result interpretation and reporting, including any distinctions between risk categories (i.e., increased risk and greatly increased risk; are associated and may be associated).

(xii) Information that demonstrates the performance characteristics of the test including:

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

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

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

(3) Information provided must include the number and type of specimens, broken down by clinically relevant variants for each indicated report that were compared to bidirectional

sequencing or other methods identified as appropriate by FDA. The accuracy as positive percent agreement (PPA) and negative percent agreement (NPA) must be measured, and accuracy point estimates must be >99 percent (both per reported variant and overall). Uncertainty of the point estimate must be within an acceptable range, as identified by FDA, and must be presented using the 95 percent confidence interval.

(4) Sufficient specimens must be tested per genotype and must include all genotypes that will be included in the tests and reports. The number of samples tested in the accuracy study for each variant reported must be based on the variant frequency.

(5) 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. The percent of final 'no calls' or 'invalid calls' must be clinically acceptable. Variants that have a point estimate for PPA or NPA of <99 percent (incorrect test results 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.

(6) Point estimate of PPA for each genotype must be calculated as the number of correct calls for that genotype divided by the number of samples known to contain that genotype. The point estimate of NPA for each genotype must be calculated as the number of correct calls that do not contain that genotype divided by the number of samples known to not contain that genotype. 'No calls' must not be included in these calculations. Point estimates must be calculated along with 95 percent two-sided confidence intervals.

(B) Precision and reproducibility data must be provided using multiple instruments and multiple operators, on multiple non-consecutive days, and using multiple reagent lots. The sample panel must include specimens from the claimed sample type (e.g., saliva) representing all genotypes for each variant (e.g., wild type, heterozygous, and homozygous). 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 (i.e., the total number of sample replicates for which a sequence variant cannot be called (no calls) or that fail sequencing quality control criteria divided by the total number of replicates tested). It must be clearly documented whether results were generated from clinical specimens, contrived samples, or cell lines. The study results must state, in a tabular format, the variants tested in the study and the number of replicates for each variant, and what conditions were tested (e.g., number of runs, days, instruments, reagent lots, operators, specimens/type). The study must include all 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 across sites must be evaluated). Any no calls or invalid calls in the study must be listed as a part of the precision and reproducibility study results.

(C) Analytical specificity data: data must be provided evaluating the test performance (e.g., specimen extraction and variant detection) effect of potential endogenous and exogenous interferents relevant to the specimen type, and assessment of cross-contamination. Alternatively, for each suspected interfering mutation for which data is not provided demonstrating the effect of the interfering variant, the manufacturer must clearly identify the suspected interfering variants in the labeling to user test reports, and indicate that the impact the interfering variants may have on the test's performance has not been studied by providing a statement that reads, "It is possible that the presence of [insert identifying information for the suspected interfering variant] in a sample may interfere with the performance of this test. However, its effect on the performance of this test has not been studied."

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

(E) Device stability data: the manufacturer must establish upper and lower limits of input nucleic acid, sample, and reagent stability that will achieve the test's claimed accuracy and reproducibility. The manufacturer must evaluate stability using wild-type, heterozygous, and homozygous samples. Data supporting such claims must be provided.

(F) Specimen type and matrix comparison data: specimen type and matrix comparison data must be generated if more than one specimen type can be tested with this device, including failure rates for the different specimens.

(xiii) Clinical Performance Summary.

(A) Information to support the clinical performance of each variant in the specific condition which is labeled as "are associated with increased risk" and reported by the test must be provided, as identified in paragraph (b)(4)(iii)(C) of this section.

(B) Manufacturers must organize information by the specific variant combination as appropriate (e.g., wild type, heterozygous, homozygous, compound heterozygous, hemizygous genotypes). For each variant combination, information must be provided in the clinical performance section to support clinical performance for the risk category (e.g., not at risk, increased risk). For each variant combination, a summary of key results must be provided in tabular format or using another method identified as appropriate by FDA to include the appropriate information regarding variant type, data source, definition of the target condition (e.g., disease), clinical criteria for determining whether the target disease is present or absent, description of subjects with the target disease present and target disease absent (exclusion or inclusion criteria), and technical method for genotyping. When available, information on the effect of the variant on risk must be provided as the risk of a disease (lifetime risk or lifetime incidences) for an individual compared with the general population risk.

(xiv) User comprehension study: information on a study that assesses comprehension of the test process and results by potential users of the test must be provided, including the following, as appropriate:

(A) The test manufacturer must provide a genetic health risk education module to naïve user comprehension study participants prior to their participation in the user comprehension study. The module must define terms that are used in the test reports and explain the significance of genetic risk reports.

(B) The test manufacturer must perform pre- and post-test user comprehension studies. The comprehension test questions must directly evaluate the material being presented to the user as described in paragraph (b)(3)(ii) of this section.

(C) The manufacturer must provide a justification from a physician and/or genetic counselor that identifies the appropriate general and variant-specific concepts contained within the material being tested in the user comprehension study to ensure that all relevant concepts are incorporated in the study.

(D) The user comprehension study must meet the following criteria:

(1) The study participants must comprise a statistically sufficient sample size and demographically diverse population (determined using methods such as quota-based sampling) that is representative of the intended user population. Furthermore, the study participants must comprise a diverse range of age and educational levels and have no prior experience with the test or its manufacturer. These factors must 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 on-site 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 in the user comprehension study given to users must define the target condition being tested and related symptoms, explain the intended use and limitations (including warnings) for the test, explain the relevant ethnicities in regard to the variant tested, explain genetic health risks and relevance to

the user's ethnicity, and assess participants' ability to understand the following comprehension concepts: the test's limitations, purpose, appropriate action, test results, and other factors that may have an impact on the test results.

(5) Study participants must be untrained, be naïve to the test subject of the study, and be provided the labeling prior to the start of the user comprehension study.

(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. Other acceptance criteria may be acceptable depending on the concept being tested. Meeting or exceeding this overall comprehension rate demonstrates that the materials presented to the user are adequate for over-the-counter use.

(7) The analysis of the user comprehension results must include:

(i) Results regarding reports that are provided for each gene/variant/ethnicity tested;

(ii) Statistical methods used to analyze all data sets; and

(iii) Completion rate, non-responder rate, and reasons for nonresponse/data exclusion. A summary table of comprehension rates regarding comprehension concepts (e.g., purpose of test, test results, test limitations, ethnicity relevance for the test results, appropriate actions following receipt of results) for each study report must be included.

Grace R. Graham

Deputy Commissioner for Policy, Legislation, and International Affairs.

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