



Public Comment Submitted to the Food and Drug Administration (FDA) on Medical Devices; Exemptions from Premarket Notification: Class II Devices; Request for Comments

[Docket No. FDA-2017-N-1129]

Submitted by: The American Society of Human Genetics

January 8, 2018

Dear Dockets Management Staff (HFA – 305), Food and Drug Administration,

The American Society of Human Genetics (ASHG) appreciates the opportunity to provide comments to the Food and Drug Administration (FDA) regarding its intent to exempt a list of class II devices from premarket notification requirements, including tests assessing genetic health risks. First established in 1948, today ASHG is the world's largest genetics professional society with some 7,000 members of genetic leaders and innovators. The Society's membership represents all areas of research and application in human genetics, including medicine, genetic counselling, bioethics, genetics and genomics, molecular biology, biochemistry, and other areas of experimental science, as well as computational science, statistics, and epidemiology. Many of our members are at the forefront of genetic testing, investigating the relationship of genomic variation to health and disease, and applying that knowledge clinically such as for genetic assessment, diagnosis, and disease management. They have extensive knowledge and professional expertise regarding applications of genetics and genomics and the relationship of genomic variation to health and disease risk.

ASHG supports the FDA regulating genetics-based tests in innovative ways that help bring scientifically valid, evidence-based tests to market. The Society believes it is important to promote the timely translation of scientific discoveries regarding the genetic underpinnings of disease into clinical, evidence-based tests that enhance patient care. ASHG is supportive of the FDA seeking innovative approaches to achieve this. For instance, the Society has previously expressed support for the agency exploring new ways of establishing oversight of Next Generation Sequencing-based tests.

ASHG does not oppose direct-to-consumer genetic testing as a delivery model. Individuals should be able to access information about their genetics that is timely, analytically valid, clinically valid, and not misleading. This can help individuals make informed decisions related to their health. The Society supports the FDA ensuring access to valid direct-to-consumer (DTC) genetic health risk assessment tests where the tests are supported by current science and advertised truthfully, and when consumers have a clear understanding of what they are purchasing.



The DTC offering of genetic testing does present challenges, however. Genetic test results and their interpretation are often highly nuanced and technical, making it challenging for a consumer without expert knowledge to interpret. Genetic health risk tests specifically are designed to assess the *likelihood* that an individual will develop a disease, and not to yield absolute results on how harboring a variant or variants will affect a person's health. Consequently, it can be challenging for the average consumer to fully understand what the results of a genetic health risk test mean. This is in contrast to other tests already routinely offered DTC such as at home pregnancy tests, where the result is "binary" (i.e. the result will be one of two definitive outcomes, the condition being either present or absent), and where the consumer is familiar with the condition and can interpret the test easily.

In addition, what a test result means for an individual can depend on an assessment of the individual's medical background and family history, and the average consumer is not trained to make this assessment. Also, genetics researchers continue to make rapid scientific advances that further illuminate our understanding of how genetic variation interacts with other risk factors to affect disease risk, and this can change the correct interpretation of a test result over time. Therefore, where genetic health risk tests are offered DTC, it is especially important that companies use validated approaches for explaining the nuances of genetic health risk tests offered in a readily accessible and understandable format. It is also important that the information provided by companies is reflective of current scientific understanding underpinning the tests. In this way, individuals will be empowered to make informed decisions from their test results.

ASHG believes that an individual's understanding of his or her medically relevant test results can be greatly enhanced through consultation with a health care professional with expertise in the interpretation and application of genetic test results (e.g., genetic counselor or medical geneticist). The Society therefore wishes to underscore the importance of the requirement in the special controls accompanying the FDA's announcement that companies offering DTC genetic health risk assessment testing provide information about how consumers can obtain access to a genetic specialist. Indeed, such consultation is often best considered *before* testing is pursued by an individual, as specialists not only assist with interpreting test results but also play a vital role in determining the value to an individual of undergoing genetic testing and which genetic tests (if any) can provide them with reliable and useful information. We urge the agency to ensure compliance with this requirement.

In general, FDA oversight of DTC genetic health risk tests should ensure that companies are clear and transparent about what information tests can and cannot provide the consumer, and with whom the test results might be shared. The FDA should ensure that companies' claims about the tests that they offer are truthful and not misleading, and that they adequately convey tests' limitations. The FDA should further ensure that companies provide to consumers all relevant information in a readily accessible, easily understood, transparent manner. This information



should include, for each condition that is predicted (regardless of its severity), whether or not a test is recommended by geneticists or other healthcare professionals, and, if so, those contexts in which such a test may be useful.

Companies should inform consumers about genetic variation associated with disease risk that is not included in their test. For example, testing of common variants for Alzheimer's risk does not exclude risk from rarer highly penetrant pathogenic variants that are not measured. We therefore support that the special controls associated with this proposal include a requirement for a company to indicate whether a test detects all variants known to be related to a disease, and that the absence of one variant does not rule out the presence of another variant related to the disease. This information will help ensure that consumers are aware of the limits of test results.

The Society is also committed to the protection of individuals' genetic information and privacy. The FDA should ensure that companies accurately and obviously apprise the consumer of who will have access to their test results, what processes are in place to protect these results, and whether generated data may be sold or shared with third parties, even without identifying information.

ASHG is concerned that the proposed framework for the oversight of DTC genetic health risk assessment tests would provide inadequate oversight by the FDA of tests' analytical and clinical validity. It is not possible to assess the analytical and clinical validity of all genetic health risks a company might offer by conducting a one-time review of its 'assessment system', as proposed by the FDA. Such oversight will only allow the FDA to assess the analytical and clinical validity, and 'mitigate the risks of false negatives and positives', for tests initially proposed by the company during this one-time review. It does not appear that there will be assessment of the analytical or clinical validity of subsequent tests offered, nor any assessment of the risks to the consumer of an incorrect result. This framework will not prevent scientifically invalid tests from being marketed to the public and the ASHG opposes the proposed policy due to the lack of comprehensive assessment.

ASHG is further concerned that the proposed framework will mislead consumers regarding which tests the FDA has affirmed are scientifically valid. By suggesting that an FDA review of one test by a manufacturer is sufficient for establishing metrics of safety and effectiveness for subsequent tests offered, there is an implicit drawing of equivalency among tests whose scientific validity may vary dramatically, thus misleading and confusing consumers. After undergoing the one-time FDA review for genetic health risk assessment tests, companies will be able to market subsequent tests to the public as part of the same system and declare that the tests meet the FDA's standards. Such tests will not be held to any specific standards of analytical or clinical validity. The public will likely assume (and purveyors will likely advertise) that the FDA has reviewed and approved such tests as valid even though they have not been reviewed by the agency. Certainly, there will be no requirement for companies to communicate to consumers



which tests, or elements of tests, have been reviewed by the FDA. Thus, the oversight framework proposed threatens to mislead consumers about the level of agency oversight of these tests and will undermine the FDA's efforts to ensure test quality.

Given the vast heterogeneity of tests offered DTC, the FDA has an especially important role in ensuring that consumers are adequately informed about test quality. There is a vast range of quality (i.e., scientific merit) of DTC genetic health risk assessment tests on the market. The market's current mixing of entertainment tests, which make claims unsubstantiated by the scientific literature, with those tests which have a clinical utility, are clinically valid, and can be supported by current scientific literature, is particularly confusing for the average consumer. ASHG is concerned that the FDA's lack of oversight regarding subsequent tests may further mislead the consumer in an already ambiguous marketplace.

In conclusion, the Society thanks the FDA for the opportunity to comment on the agencies' intent to exempt genetic health risk tests (and other tests) from premarket notification requirements. We appreciate how, in general, the FDA is seeking more efficient ways to facilitate bringing genetic tests to market, and that the agency's intended approach for the oversight genetic health risk tests is in line with this.

However, the Society urges the agency to reconsider its plans announced through the federal register notice. It is insufficient for oversight of DTC genetic health risk tests to merely ensure a degree of transparency regarding the clinical validity of tests offered. Rather, the FDA clearance of these tests needs to indicate to the public that the claims associated with each test offered DTC are supported by a strong scientific evidence base. One approach would be for the FDA to review each test before it is marketed to ensure that it meets scientific standards. Alternatively, consistent with the agency's proposed approach for NGS-based tests, in many cases it could be possible for a company to demonstrate clinical validity of its tests by referencing scientific resources recognized by the FDA. We would welcome these or other similarly rigorous approaches.

We would welcome any opportunity to assist you as the agency advances its framework of the oversight of these tests.

Sincerely,

David L. Nelson, Ph.D.
President, ASHG Board of Directors