THE AMERICAN SOCIETY OF HUMAN GENETICS

9650 Rockville Pike | Bethesda, MD 20814-3999 | 301.634.7300 | 1.866.HUMGENE | fax: 301.634.7079 | email: society@ashg.org | www.ashg.org

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Comments on "Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics"

Docket No. FDA–2016–D–1233

Dear Sir or Madam:

The American Society of Human Genetics (ASHG) welcomes the opportunity to provide comments to the Food and Drug Administration (FDA) on the use of genetic variant databases to support the clinical validity of next-generation sequencing (NGS)-based tests. Founded in 1948, ASHG is the world's largest genetics professional society, with some 8,000 members representing all areas of research and the clinical application of genetics. Members of the Society are using NGS to deepen our knowledge of the human genome and the relationship between genomic variation and health, and are at the forefront of developing new clinical applications of DNA sequencing technologies.

In previous comments submitted to the FDA (see letter submitted on 12/24/15 to docket: FDA-2015-N-3015 http://www.ashg.org/pdf/policy/ASHG_PS_December2015.pdf), the Society expressed support for the agency exploring innovative ways of establishing the oversight of NGS-based tests. With the issuance of this draft guidance and the companion draft guidance proposing a standards-based approach to assessing the analytical validity of NGS-based tests, ASHG would like to reaffirm the Society's support for the FDA's pursuit of a novel approach. As stated in the Society's comments on the latter draft guidance (docket #: FDA–2016–D–1270), the Society believes that NGS-based tests represent a paradigm shift from traditional genetic tests used to detect the presence or absence of variants in a single well-characterized gene associated with a specific disease. The complexity of results from multi-gene panel or genome-wide tests, and the variety of possible intended uses of such tests, warrants a different approach.

There is a growing but still very incomplete body of knowledge on how variation in the human genome contributes to health and disease, and this means that the clinical interpretation of an individual's genome sequence is complex. The significance of a single genomic variant for the health of an individual is often unknown. To address this, geneticists and genomicists are establishing collaborations to build a consensus on the clinical significance of individual variants, and are making their assessments available in databases accessible to the scientific community. Well-curated databases are becoming increasingly valuable resources for researchers and medical professionals for interpreting the results of DNA sequencing tests.

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General Comments

With the issuance of this draft guidance, FDA is taking advantage of the development of these databases by proposing a process by which they could be used for the regulation of NGS-based tests. The Society applauds the agency for recognizing that such genetic variant databases provide valuable scientific information on the pathogenicity of variants. The framework proposed by the agency for assessing the clinical validity of NGS-based tests allows test developers to rely on such databases for demonstrating the clinical validity of tests, thereby allowing tests to keep up-to-date with the rapid pace of discovery in the field of genomics. The Society supports this approach and further supports the use of such databases for evaluating the clinical validity of other genetic tests. In doing so, it is critical that the FDA recognition process allows the databases to continue to curate information about genomic variants, and does not require the data to be 'frozen' in order for the data to be used for regulatory purposes.

ASHG believes that the framework proposed could be used in the regulation of both tests analyzing germline variants and tests detecting somatic mutations. While these two categories of tests are very different, databases that reflect the consensus regarding the clinical significance of variants can provide an evidence base for the analytical and clinical validity of variants identified in both types of test. In the final guidance, or through the issuance of separate guidance, the Society encourages the FDA to address the recommended data elements for germline and somatic variant databases. ASHG proposes that databases providing information on somatic variants document when variants have been demonstrated to have been observed in tumor only (as observed in tumor-normal paired analyses) as opposed to analyses when only the tumor was analyzed and this is not known.

The Society believes strongly that databases recognized by the FDA should be public access, freely available to researchers, clinical laboratories, clinicians and patients. This will allow the independent verification of variant assessments and facilitate the interpretation of test results. It will further help identify discordance in variant assessments between databases. Such a mandate does not preclude test developers from using privately-held data to demonstrate the clinical validity of their tests.

In its 12/24/15 comments submitted to the FDA (docket: FDA-2015-N-3015 http://www.ashg.org/pdf/policy/ASHG_PS_December2015.pdf), the Society proposed details that databases should provide on each variant. Further to those comments, ASHG recommends that databases report artifacts commonly observed in tests detecting the absence or presence of a given variant. Also, it is important to ensure that the final guidance allows both for the recognition of databases providing information on single nucleotide polymorphisms and for databases with information on other types of genome variants, such as indels and exon duplications.

Changes in assessment of the clinical significance of genomic variants

Our knowledge of the clinical significance of genomic variants across the genome is evolving at a rapid rate, and it is inevitable that, in the light of new evidence, databases will change their assessments on the pathogenicity of some variants. It would be a major burden on the FDA if every database change to a variant classification triggered a regulatory action. Instead, the FDA should ensure that database personnel allow ongoing updates to information on variants, and that changes in interpretation are clear and time-stamped.

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It should be the responsibility of laboratories offering a test, where the laboratory uses database information to support the clinical validity of their test, to have a process that ensures that test interpretation keeps pace with scientific discovery. If, as proposed by FDA, the FDA determines a class of NGS-based *in vitro* diagnostics as class II-exempt, FDA could establish a special control requiring test developers to articulate how their interpretation of their test will accommodate scientific advances.

Discordant calls

The Society recognizes the value in consistency between databases and appreciates FDA's concerns about discordant calls. Discordant calls arise not only because different geneticists are observing different data, but commonly because they are interpreting the same data differently. For this reason, we encourage inclusion in the database of the arguments and/or data used to arrive at the pathogenicity call. It would be very challenging for the FDA to play a substantive role in identifying those variants where there is discordance, and resolving the conflicts. Similarly, it would be onerous for an administrator of a FDA-recognized database to seek out differences between their clinical validity interpretations and those of other databases.

It should be the responsibility of test developers to address differences in interpretation of variants that they report, such as using software that allows lab personnel to identify any discordance regarding the clinical validity of a given variant. If there is discordance in interpretation between FDA-recognized databases, the testing laboratory should provide a rationale for their interpretation and document the evidence they used to come to that determination.

Periodicity of review

Finally, in its questions on the draft published in the federal register, FDA solicited feedback on the appropriate periodicity of reviewing databases that have been recognized. The Society thinks that annual reviews are appropriate.

ASHG greatly appreciates the opportunity to comment on this draft guidance and to provide input to the FDA during its development.

Sincerely,

Harry C. Dietz, MD
President