

The American Society of Human Genetics
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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 Databases for Establishing the Clinical Relevance of Human Genetic Variants”

Docket #: FDA-2015-N-3015

Dear Sir or Madam:

The American Society of Human Genetics (ASHG) appreciates the opportunity to provide comments to the Food and Drug Administration (FDA) on the use of databases to inform the regulation of next-generation sequencing (NGS)-based tests. ASHG, founded in 1948, is the world’s largest genetics professional society, with some 8,000 members representing all areas of research and application in human genetics. The Society’s membership comprises diverse professionals in genetics, molecular biology, medicine, biochemistry, and other areas of experimental science, as well as computational science, statistics, and epidemiology. Members include those using NGS to deepen our knowledge of the human genome, of the relationship of genomic variation to health and disease, and of clinical applications of NGS such as diagnosis and assessment of disease risk.

General Comments

With the development of new technologies capable of reading genomic sequences quickly, cheaply, and accurately, it now is possible to use NGS as a clinical tool, for example, to detect the variant causing a patient’s rare disease or to identify the driver mutation in a tumor. The clinical interpretation of a patient’s genome sequence, however, is complex, and our limited knowledge of the human genome and its integrated function means that the significance of a particular variant observed in a patient’s genome often is unclear. To address this complexity, geneticists and genomicists are sharing information, establishing standards for integrating diverse sources of experimental and observational data, and collaborating to come to consensus on the clinical significance of individual variants. These collaborative efforts have produced summary databases such as ClinVar (<http://www.ncbi.nlm.nih.gov/clinvar/>) and the Clinical Genome Resource (ClinGen) program (<https://www.clinicalgenome.org/>).

It is appropriate for the FDA to explore whether such databases can be used for regulatory purposes as the agency seeks reliable sources of information regarding the clinical relevance of individual genomic variants. We agree with the FDA that a number of factors are important for determining the reliability of a database and the utility of the information provided, and we appreciate the need for FDA to consider those factors in determining the suitability of a database as a useful resource for regulatory purposes.

ASHG agrees that NGS-based tests that provide sequence data on a panel of genes, a whole exome, or a whole genome sequence represent a paradigm shift from tests that have hitherto routinely been used to detect variants in a single, well-characterized gene known to be associated with a specific disease. Given the relative complexity of results from genome-wide or multi-gene tests and the different possible uses of the information provided, the Society agrees that a different approach is warranted for regulation of tests based on such data. The Society applauds FDA for exploring alternative ways to regulate NGS-based tests. ASHG recognizes the novel approach the FDA took in its clearance of the MiSeqDx Cystic Fibrosis 139-Variant Assay, using the CFTR2 database to determine the clinical relevance of individual variants in a single gene, and believes that appropriate extensions of the principles captured in that approach may work more broadly for other NGS-based tests. Extension of such principles to genome-wide analysis, however, will present unique challenges that will require novel solutions.

If the FDA proceeds with certification of databases for regulatory purposes, the Society encourages the agency to take an approach that allows for continued development of database content and curation. Periodic certification of a list of variants with clinical relevance by the FDA will be problematic, as such a list will not continuously reflect the consensus of the scientific and medical communities as new discoveries occur. Instead, the agency should allow for this list to be updated continually without FDA's recertification, so long as the database curators adhere to baseline standards set by the FDA. This flexibility will allow regulation to evolve along with the science.

Value in different types of evidence relevant for interpreting variants (page 2)

Many types of evidence are useful in interpreting the clinical relevance of genetic variants. Although clinical data from randomized controlled trials represent the 'gold standard' in many biomedical contexts, such data rarely are available for determining the clinical relevance of a specific variant in the context of genomic medicine. The American College of Medical Genetics and Genomics (ACMG) recently published guidelines regarding consideration of different types of evidence in evaluating whether individual variants are pathogenic or benign (https://www.acmg.net/docs/Standards_Guidelines_for_the_Interpretation_of_Sequence_Variants.pdf), and ClinGen is encouraging adoption of these standards by diagnostic laboratories. The Society recommends that databases recognized by the FDA be required to apply such guidelines or similarly detailed and transparent methods that articulate how different types of evidence are used to determine pathogenicity of variants. It is important to recognize that all variants subject

to the described classification method and/or included in such databases need to have been derived from patients with a genetic disease or from individuals who are at high risk for such disease (e.g., a parent of an individual with cystic fibrosis).

Use of a common, single nomenclature (page 7, question 1)

The Society recommends that databases be required to use standard nomenclature to qualify for FDA recognition. That requirement will minimize ambiguity and facilitate comparisons between information housed in different databases. The genetics community recognizes the Human Genome Variation Society (HGVS), which could serve as an effective standard. HGVS standards can apply to somatic variants, where database entries should indicate the tissue of origin, the tumor proportion of the samples analyzed, and the mutation annotation format (MAF) from The Cancer Genome Atlas.

Updating of reference genomes (page 7, question 2)

This question appears to pertain more to analytic standards for NGS than to interpretation of sequence variation via curated databases.

Qualifications and training necessary for curation (page 7, question 3)

The curation process often must evaluate evidence generated by fields outside of genetics, and the complexity of the evidence would often require analysis by appropriately trained clinicians/scientists/analysts with specific backgrounds other than genetics. An appropriate model might be: 1) primary evidence collection by an MD- or PhD-degreed scientist; 2) score assignments by a director certified by the American Board of Medical Genetics and Genomics; and 3) optional, detailed interpretation language provided by genetic counselors. Data scientists play a special role in supporting this domain-specific work by establishing relevant tools for navigating content of the knowledge base as well as statistical and epidemiological information relevant to variant assessment.

Genetic counselors are specifically trained to contribute to the task of interpreting and integrating complex genetic information in the context of health and disease and in communicating such information in a manner that is accessible to care providers and patients. Degree-granting programs in genetic counseling include training on this process, and many genetic counselors already perform this function. It should be permissible therefore for databases certified by the FDA to include master's-level genetic counselors in the curation process.

There currently is no obvious training or accreditation that FDA could require for all curators. Rather, FDA should require that curators interpreting variant pathogenicity have a suitable terminal degree, and that the curators employ rigorous, scientifically based, and transparent methods to infer pathogenicity. The FDA could award contracts for proficiency testing, e.g., independent analysis of a subset of variants in a database to verify the quality of the analysis.

The information about each variant (page 7, question 6)

Qualifying databases should adhere to standards of practice established by the scientific community. They should present a clear assessment of the pathogenicity of the variant and the reasoning behind the determination, and should note the evidence used in the determination. Sufficient information should be available to enable a visitor to the database to review the evidence and perform an independent assessment. Databases should include fields for zygosity, phasing, and cis/trans relationships; completion of all fields should be encouraged but not mandatory. Similarly, clinical and phenotypic characteristics including suspected mode of inheritance should be included where known, and a strong emphasis should be placed on the development of resources where phenotype is as meticulously collected and as rigorously validated as is genotype. In addition, when possible, databases should provide data on observed frequencies of specific variants in population groups and on the sources of those frequencies. Evidence used for curation should be characterized additionally by its nature, such as clinical data, population frequency, and functional assessment of variants. Databases should have the structure to sort all types of evidence. Clinical indications derive from clinical data, which is desirable, but may not be completely available for a significant number of variants. As we noted above, high-quality phenotypic information is as important as genotype.

Periodicity of FDA re-reviewing certified databases (page 7, question 8)

ASHG recommends that those responsible for databases submit annual reports to the FDA with respect to the current number of variants, new variants classified during the last year, and any changes in the classification process. ASHG recognizes that FDA must recertify databases regularly, but remains agnostic on the frequency of recertification at the moment.

Other factors for assessing database quality (page 5)

The Society agrees that all factors listed under ‘database operations’ are important. The purpose of the database should be clear (A), as should the identity of the organization hosting the database and its sources of financial support. The FDA should ensure broad public access to certified databases to maximize the independent assessment of determinations of variant clinical significance. Sustainability of the database through steady funding would be highly valuable (B); NIH can play a leadership role in ensuring that funding continues to support ClinVar and the ClinGen project. It also is critical that each database has a system in place to revisit the methods for determinations of clinical validity on a regular basis (D). We also note, however, that even if a database is not updated, it can still be a valued asset for clinical interpretation. For example, update of the CFTR2 database would likely have no relevance for the list of 139 mutations deemed as pathogenic that is used by the approved Illumina protocol.

Two additional points are important. First, the approach to use of curated databases in the clinic and considerations for FDA approval are intimately tied to intended use. ASHG believes that everything described herein as well as in the FDA document upon which we comment, including the ACMG guidelines referenced above, applies only in the setting of testing individuals with presumed Mendelian genetic disease or at high risk for such disease (e.g., parent or sibling of an affected individual) – in other words, that the test is used for diagnostic and not predictive purposes. The reason is that while a variant may be characterized as “pathogenic,” the fact that a variant exists in such a database says nothing about the risk of disease in an individual who possesses it. Pathogenic simply means that the variant can cause disease, not that it always does. That information is critical in a predictive setting and requires a different level of evaluation and standardization. For example, such data require statistical analysis and could derive from a prospective study of carriers or from a well-designed case-control study. The number of times a variant appears in a curated database also may not be sufficient to draw conclusions about penetrance, because the denominator generally is unknown and control frequencies for comparison generally are unavailable.

Second, we also recognize that such databases will only be of partial utility in clinical application of NGS. Although they will be helpful for variants detected in the patient in terms of aiding in the diagnosis, very often variants are detected that do not exist in any database. Hence, the procedures described herein for evaluating the pathogenicity of a variant will need to be employed by the clinical group using the technology. It would be overly burdensome to allow only return of genetic variants that appear in curated databases and not those that have never appeared in any database but can be subject to the same principles as have been applied to the inclusion of variants in these databases.

Public support for and trust in databases for regulatory purposes will depend on privacy measures that ensure that individuals’ genetic and health information is not revealed (E). ASHG has long advocated for strong measures to protect the privacy of research participants and patients. Databases should require that submissions of data follow strict privacy guidelines where genomic, clinical, and phenotypic information is de-identified.

Summary

ASHG commends the FDA for exploring innovative approaches to regulation of NGS-based tests. The Society offers its assistance and encourages the agency to make use of the expertise within the Society’s membership.

Yours sincerely,

A handwritten signature in black ink, appearing to read "J.D. McInerney". The signature is fluid and cursive, with a large, sweeping flourish at the end.

Joseph D. McInerney
Executive Vice President
On behalf of the Board of Directors
American Society of Human Genetics