Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing Based In Vitro Diagnostics (Draft Guidance)

Provides guidelines to aggregate, curate and interpret publicly accessible genetic variant databases and outlines conditions for their FDA recognition.

Updated last August 8, 2016 for the 07/08/2016 draft guidance.

WHAT IT DOES

“In support of the President’s Precision Medicine Initiative, the U.S. Food and Drug Administration [FDA]” ... issued a draft guidance that “will provide a flexible and streamlined approach to the oversight” of next generation sequencing (NGS), which can detect genomic variations in DNA. These variations may determine if a person has or is at risk of disease. While current regulatory approaches are appropriate for conventional diagnostics that measure a limited number of substances associated with a disease or condition”... “new sequencing technologies can examine millions of DNA variants at a time, and thus require a flexible approach to oversight that is adapted to the novel nature of these tests” (FDA Press Release).

The draft guidance (noticed via 81 Federal Register 44611) describes an approach wherein test developers may rely on FDA-recognized public genome databases to support clinical claims for their tests and provide assurance of accurate clinical interpretation of genomic test results, possibly negating the requirement to submit additional valid scientific evidence. The draft proposal specifies procedures, data quality, variant interpretation and essential professional training required for database operation. The recommendations include:

- With regards to database procedures and operations, genetic variant database administrators should:
  - Make publicly available sufficient information regarding data sources and standard operating procedures (SOPs) for better interpretation of evidence and informed medical decisions;
  - Employ commonly accepted data formats to enable better comparisons of variant assertions between different databases;
  - Define how variant information is aggregated, curated and interpreted in documented SOPs together with any modifications to the standard (at a minimum, review annually);
  - Have processes for assessment of database stability and architecture to ensure proper preservation of database content; and
  - Ensure that database operations are in compliance with all applicable federal laws and regulations regarding protected health information, patient privacy and data security including privacy rules in Health Insurance Portability and Accountability Act (HIPAA).

- To ensure data quality to avoid ambiguity and enable accurate diagnosis, genetic variant databases should:
  - Use consistent nomenclature that is widely accepted by the genomics community and include detailed descriptions of terminology used; and
  - Accompany variant data with metadata, including information about other laboratories reporting the variant data as well as the test conducted.

- Ensure that all genetic variant database curation and interpretation rules and future modifications should be explained and made available to the public:
  - Include any assertions together with the types of evidence that personnel may use for an interpretation of variants;

- The team interpreting genetic databases should consist of qualified professionals with appropriate level of training and oversight in place:
  - Include multiple levels of review.
  - Include proficiency testing to ensure that such personnel meet and maintain high standards over time.

To better implement these recommendations, the FDA also specifies a recognition process for publicly accessible genetic variant
databases and their assertions to streamline premarket review of NGS tests. The FDA’s suggested recognition process involves three steps: (1) Voluntary submission for recognition following recommended guidelines as state above, (2) FDA review of genetic variant database policies and procedures, and (3) maintenance of FDA recognition, which involves regular reviews on a set schedule. The FDA also considers use of a third party to assist with genetic variant database recognition in the future. Ultimately, the FDA expects that NGS-based test developers will be able to use FDA-recognized genetic variant databases to establish the clinical validity of their test.

**RELEVANT SCIENCE**

DNA is the template for all biological information and is made up of different bases. Much like letters create words, individual DNA bases create long strands of DNA that are the genetic code for life. We can determine the precise order of DNA molecules by a process called sequencing. The first generation of sequencing techniques such as Chan-termination methods (Sanger sequencing) relied on the difference between fluorescence of bases. The critical difference between Sanger Sequencing and NGS technologies is that instead of sequencing a single DNA fragment, NGS extends this process across millions of fragments in a massively parallel fashion. Multiple fragmented sequence reads are then assembled together on the basis of their overlapping areas. The use of NGS-based tests in both research and clinical practice allows identification of more genetic variants, including rare variants of unknown significance. NGS-based tests also reduce the time needed for sequencing the genome of a large population. By comparing the genome aggregates, researchers can reveal rare disease-related genetic variants.

To ensure the validity of NGS-based test, researchers often use evidence presented in genetic variant databases to support the assertions. Currently, most of the data from NGS testing are inaccessible from the public. Largely, genetic variant databases use a multitude of resources and formats. In order to achieve ease of public use, the FDA suggests that standard guidelines need to be established. The FDA hopes to reduce regulatory burden on test developers and stimulate advancements in the interpretation and implementation of precision medicine with well established, publicly recognize standards.

**RELEVANT EXPERTS**

Elizabeth Cirulli, PhD is Assistant Professor in Medicine and Molecular Genetics and Microbiology. She is interested in the genetics underlying normal variation in healthy humans, with a focus on traits relevant to disease and involving neuronal function. She also does research on the application of genome sequencing for disease gene discovery and in studying people with extreme traits.

Simon Gregory, PhD is a Professor in the Departments of Medicine and Molecular Genetics and Microbiology and the Director of Genomics and Epigenetics at the Duke Molecular Physiology Institute. He is interested in the identification of the genetic and genomic factors that underlie the development of chronic complex disease.

“Remarkable advances in the generation of sequence data, and a commensurate decrease in cost below that of Moore’s law, has contributed to an explosion in the availability of whole genome and exome sequence. Akin to the MIAME (Minimum Information About a Microarray Experiment) principals that eventually governed the fidelity of gene expression data, this policy aims to establish the conditions under which genetic data from the public domain can be used as a reference by test developers. While not dictating the same protocol needs to be used for data generation, variant calling and storage, it at least sets forth recommendations for uniform, minimum constraints for data generation and formatting, variant aggregation with supporting statistical evidence for the association of genetic risk and disease, and database security. Critical in the success of this policy is, however, the interpretation of the underlying genetic association and its implementation as an FDA approved genetic test; that is, the clarity in the sale of genetic tests around the strength of the underlying penetrance of genetic risk, the clinical and biological variables associated with the genetic association of the aggregated data, and the understanding that the genetic association represents a ‘current state’ of disease risk, ahead of the identification of additional variants by e.g. epistatic interaction, that may influence/alter genetic risk and require retesting or further genetic counseling.”
ENDORSEMENTS & OPPOSITION

Endorsements:

- According to a news article by Industry insiders GenomeWeb, many laboratories believe that the draft can “push the genetic testing industry in a positive direction as the increasing use of NGS testing is revealing a large number of exceedingly rare variants and a growing group across academia and industry believes the best way to advance knowledge is to share and aggregate data in public repositories.”

Opposition:

- GenomeWeb, despite recognizing the importance of a public accessible database, expressed concern towards this draft in a news article that “there aren’t too many databases available right now that would meet the criteria FDA has proposed and that there is a lack of incentives for submitting to and maintaining such resources.” Furthermore, “maintaining public variant databases will require funding and will depend on researchers and diagnostics developers submitting and continually updating variant data as the evidence evolves” and “it’s very difficult for the FDA to provide detailed guidance in the absence of an actual application. Details are only going to become clear once the FDA has an application before it.” Executive director of Emory Genetics Laboratory, Madhuri Hegde stated that “many labs in the US, including startups, don’t maintain variant databases of the type FDA has described. While EGL and larger labs in the country do have databases with the level of transparency, version control, and documentation that FDA is asking for, many organizations are still using rudimentary methods to track variants, such as excel spreadsheets.”

STATUS

The draft proposal was issued on July 8, 2016 by the Center of Device and Radiological Health (CDRH). Public comments will be received until Oct 06, 2016. Based on the comments, FDA might decide to end the rulemaking process, to issue a new proposed rule, or to issue a final rule. If a final rule is issued, FDA will publish the final rule in the Federal Register. Once the final rule is completed, before it is published in the Federal Register, it may be reviewed by other parts of the federal government. If proposed rules are deemed “significant” pursuant to Executive Order 12866, the Office of Management and Budget’s (OMB) Office of Information and Regulatory Affairs (OIRA) must review them and coordinate review with other federal agencies that have an interest in the issues.

RELATED POLICIES

On January 20, 2015, President Obama announced the Precision Medicine Initiative (PMI). PMI aims to encourage research in precision medicine to enable health care providers to tailor treatment and prevention strategies to people’s unique characteristics, including their genome sequence, microbiome composition, health history and diet. NGS’s huge potential in detecting genetic variability among individuals makes it one of the key players in the project.

“Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Used for Diagnosing Germline Diseases” introduces FDA guidance for designing, developing, and validating NGS-based tests for germline diseases. The draft provides specific standards for conducting NGS-based tests as well as interpreting result to assure safety and validity of the test. The draft also outlines consideration for possibly classifying NGS-based tests for germline diseases as class II devices and potentially exempting them from premarket notification requirement. The draft was issued by the Center for Devices and Radiological Health (CDRH) on July 8, 2016; the public comment period closes October 6, 2016.

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