October 6, 2016

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852
Submitted electronically via http://www.regulations.gov

RE: 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

The American Medical Informatics Association (AMIA) appreciates the opportunity to provide input on the Draft Guidance for Industry on Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics. The Notice announcing this document was published by the Food & Drug Administration (FDA) in the July 8, 2016 issue of the *Federal Register*.

AMIA is the professional home for more than 5,000 health informatics professionals, representing clinical researchers, translational scientists, educators and front-line clinicians who bring meaning to data, manage information and generate new knowledge across the healthcare and clinical research enterprise. As the voice of the nation's biomedical and health informatics professionals, AMIA plays a leading role in advancing health and wellness by moving basic research findings from bench to bedside, and evaluating interventions, innovations and public policy across settings and patient populations.

AMIA also hosts a 200+ member Genomics and Translational Bioinformatics Working Group (Gen-TBI WG). The mission of the Gen-TBI WG is to facilitate communication, collaboration, training, and networking for researchers working at the interfaces between bio-molecular and clinical data in order to advance the clinical use of genomics data through TBI, thereby furthering the practice of precision medicine.

AMIA enthusiastically supports FDA's efforts to develop modern, flexible and adaptive regulatory approaches to the oversight of NGS-based tests as part of the Precision Medicine Initiative (PMI). We see the work ongoing at the FDA as foundational to a host of discoveries and treatments that will transform healthcare as we know it. While we support this document, and agree with many of its precepts, we also note a lack of standards – for ontologies, metadata and other technical aspects of using human genetic variant databases for NGS-based diagnostics. We understand, and largely agree with FDA's modus operandi to omit specific standards in such guidance documents; however, we underscore the opportunity FDA has in helping industry find consensus on a host of standards that will be necessary to achieve our shared goals.

Below we provide input from our community of health informatics experts regarding select portions of the Draft Guidance.

Recommendations to Support Recognition of Publically Accessible Genetic Variant Databases of Human Genetic Variants as Sources of Valid Scientific Evidence Supporting Clinical Validity of NGS Tests

AMIA convened a group of clinical research and translational biomedical informatics experts to review the draft recommendations and provide feedback to the agency. Based on that feedback, AMIA maintains that, since a publicly accessible database is going to consist of data not generated by the primary applicant for pharmacogenetic approval, it will be very important in the first decade of this type of research that the publicly accessible database has been very carefully curated.

Database Procedures and Operations

In response to FDA's question about the application of the guidance, we maintain that the recommendations should apply equally to somatic and germline variants.

SOP Version Control

AMIA agrees with the SOP Version Control recommendations as outlined in the draft guidance, and offers some additional suggestions to make this section more robust based on feedback from our experts. First, AMIA maintains that the investigating organization, when it uses a publicly accessible database, should be responsible for making sure that the version of the data that was used is kept in a separate repository. Since new versions of the database could result in invalidation of previously valid data, AMIA maintains that new versions should be compared against old versions with repeat analyses when newly curated data is released. We encourage FDA to incorporate these additional protocols into the SOP Version Control recommendations.

Data Preservation

AMIA agrees with FDA's data preservation recommendations and encourages FDA to incorporate them as written in the final guidance.

Security and Privacy

AMIA agrees with the security and privacy guidance articulated by this draft guidance.

Data Formats

We agree that genetic variant database administrators should employ commonly accepted data formats and identify which format is in use by the genetic database. While we do not believe FDA needs to reference specific standards, we note this is an area where consensus on standards does not exist.

Data Quality

Nomenclature

While AMIA experts generally agree with FDA's recommendation on nomenclature, FDA must clarify in the final guidance that use of a standardized nomenclature is required, such as those maintained by the National Library of Medicine (NLM). AMIA wants to ensure that the genetic nomenclature is standardized and accepted by more than just the host of the genetic database

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developer. Again, this is another area where FDA could help lead a conversation towards uniformity.

Metadata
AMIA experts agree that coding variant data as metadata will help with automated or code-based analysis. We encourage FDA to, again, focus on helping industry identify appropriate metadata standards for this purpose.

Data Uniqueness
AMIA agrees with FDA's recommendations on data uniqueness and urges the agency to incorporate this into the final guidance.

Curation, Variant Interpretation and Assertions
AMIA agrees that the processes that genetic variant database personnel use for curation and variant interpretation should be based on well-defined SOPs and carried out by qualified professionals. We encourage FDA to incorporate this recommendation into the final guidance.

Assertions
In the accompanying Federal Register notice, FDA asks "*If an assertion regarding a variant changes over time, how should FDA assess what regulatory actions may be appropriate with respect to in IVDs supported by such assertions? How often should FDA conduct ongoing review of an FDA-recognized database?"* Our experts noted that linking a variant to a disease is a good general term, but forgoes the details, which led them to question whether the word "disease" should be used. It was suggested that phenotype combinations could be a more appropriate terminology to use here. For example, when referring to asthma, can that be broken into different phenotypes such as mild/mod/severe symptoms, lung function (FEV1), eosinophilic/neutrophilic, immune globulin levels of various types, etc. Clinical phenotyping vs biomarker phenotyping can provide a more specific gene variant link which would be more appropriate.

In addition, AMIAs expert panel raised questions as to whether an epidemiologic link should be included in the metadata. That is, the expected variant frequency in the general US population vs other racial, ethnic, geographic, or disease-specific populations.

We urge FDA to consider these issues as it finalizes the guidance.

Finally, in response to FDA's important questions related to "discordant calls" with other databases, AMIA suggests that FDA work in collaboration with the NLM to develop an arbitration system to allow for discordant calls to be adjudicated with a final name being assigned.

Professional Training and Conflicts of Interest

Professional Training
Increasingly, informatics training has become a necessary qualification for professionals working in health research and care delivery. Having a basic literacy in how to collect, analyze and apply data should be a core competency of every health professional. Additionally, we believe that advanced

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informatics training is necessary for tasks such this. We agree that team concepts are important and would encourage FDA to look for ways to ensure that properly trained informatics experts are well represented in the operations of human genetic variant databases and activities to support clinical validity for NGS-based diagnostics.

Conflicts of Interest

The guidance explains that, to be considered for recognition by FDA, efforts should be made to minimize, and make transparent, any potential conflicts of interest pertaining to a genetic variant database or its personnel. FDA also seeks feedback on conflicts of interest for curators and personnel of databases seeking FDA recognition. We appreciate these concerns, however, it must be recognized that this is a very new and growing field, with a very small community of experts. AMIA experts note that the community is too small to ban those with a conflict of interest with test developers. To that end, AMIA recommends that the metadata include the curator/interpreter with their organization, as well as the test/developer and their organization. This would enable the search to can see who developed the test and who is using it as a tool. Requirements for disclosing relationships with holding companies, as well as other indirect conflict management, must also be established.

FDA's Genetic Variant Database Recognition Process

Submission for Recognition

While AMIA experts are in agreement with FDA's proposed submission process, it believes FDA must also establish an appeals process for database administrators whose databases are not recognized. Similarly, if the public disagrees with FDA's decision to recognize a database, there must also be an appeals process to have that decision reversed.

FDA Review of Genetic Variant Database Policies and Procedures

AMIA recommends that the list of recognized databases be maintained by the FDA to ensure that only recognized databases are listed. AMIA maintains this is an appropriate precaution in these early stages of this enterprise.

Maintenance of FDA Recognition

AMIA agrees with FDA's recommendations for Maintenance of FDA Recognition and urges FDA to finalize it.

Use of Third Parties

The skill sets associated with professionals engaged with NGS database recognition and those engaged with validation are distinct. Thus, the COI policies will have to be separate to ensure individuals are not inappropriately or unfairly barred from serving as third parties.

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Thank you for considering our comments. Should you have questions about these comments or require additional information, please contact Jeffery Smith, Vice President of Public Policy at jsmith@amia.org or (301) 657-1291. We look forward to continued partnership and dialogue.

Sincerely,

Douglas B. Fridsma, MD, PhD, FACP, FACMI
President and CEO
AMIA