



ASSOCIATION FOR MOLECULAR PATHOLOGY

Education. Innovation & Improved Patient Care. Advocacy.

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October 6, 2016

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

Re: Docket No. FDA-2016-D-1233 for “Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics.”

Submitted electronically at www.regulations.gov

To Whom It May Concern:

On behalf of the Association for Molecular Pathology (AMP), thank you for the opportunity to submit written comments on the draft guidance entitled “Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics.” AMP is an international medical and professional association representing approximately 2,300 physicians, doctoral scientists, and medical technologists who perform or are involved with laboratory testing based on knowledge derived from molecular biology, genetics, and genomics. Membership includes professionals from the government, academic medicine, clinical testing laboratories, and the in vitro diagnostics (IVD) industry. Our members are among the early adopters and users of next generation sequencing (NGS) technology in a clinical setting, and have accumulated substantial knowledge and expertise as it relates to this novel and powerful technology.

AMP believes there is a need to modernize the Food and Drug Administration (FDA)’s approach to the regulation of IVD test kits that are manufactured and sold to laboratories. This includes development of more consistent and predictable regulatory pathways, with reasonable requirements that are appropriate to the context in which a test is generally used.¹

Variant Databases are Useful Tools in Interpreting NGS-Based IVD Tests:

AMP submitted written comments in response to two dockets in 2015 that focused on the oversight of NGS-based tests (Dockets FDA-2014-N-2214 and FDA-2015-N-3015) as well as provided verbal comments at the meetings held last November. As stated previously, AMP does support the approach of using databases for the collection of known clinical information associated with a given analyte/biomarker. Databases are already a widely used tool in the design and interpretation of laboratory testing and molecular professionals often consult at least one database as a source for information. However, to reiterate points made in our previous

¹ In filing comments on this proposed guidance document, AMP does not waive any legal claim that the FDA lacks the statutory authority to regulate laboratory developed testing services. Furthermore, AMP strongly maintains that, to the extent that it is established that the FDA does have such authority, the overwhelming weight of legal authority dictates that the proposed new requirements for laboratories outlined in the draft guidance must be issued through notice and comment rulemaking. Nothing in these comments is intended to impact adversely in any way AMP’s right, alone or in combination with other stakeholders, to pursue separate comments, litigation, or other remedies with respect to the proposed regulatory framework or related issues.

comments, databases are merely a source through which professionals can find gene/mutation specific information and pertinent articles and studies that aid the work of molecular professionals, and that information is always used in the context of other clinical information about a patient.

AMP is supportive of the use of databases to facilitate review and approval of boxed-and-shipped NGS-based IVDs. The use of databases for evidence of clinical validity would help to facilitate the review of these medical products and increases the number of tools health care professionals have at their disposal for patient care. If recognized, such databases shall only be used for the purpose of establishing review and approval of an in vitro diagnostic test kit and that such databases should not be intended for the ongoing utilization of such a kit.

AMP is concerned that there will be inherent challenges in updating and maintaining such databases over time. First, expecting a company with a commercial interest to invest in maintaining the database may be unrealistic particularly if the company/entity starts a database for the purpose of getting recognized by the FDA and second, establishing that a database should be created and maintained de facto suggests that other database resources would be considered less valid which is not the case as further discussed below.

In addition, we highly recommend that FDA work with the Centers for Medicare & Medicaid Services to facilitate streamlined coverage determinations and higher payment for tests offered by laboratories who submit their resultant data into publicly accessible databases. This would incentivize participation in these databases and the resultant data transparency would enhance information available to FDA and third parties for reviewing NGS-based tests. Moreover, it would provide laboratory professionals with additional and important information when making variant calls in the context of a patient's care.

Restricting Access to Databases Interferes with the Practice of Medicine:

AMP is pleased that the FDA did not identify specific databases in the draft guidance, but we are concerned about the lack of clarity in the criteria for recognition by the agency. AMP believes that the interpretation of a laboratory test result remains within the practice of medicine and while databases aid in the interpretation of a test result, no database can or should replace the professional interpretation provided by molecular professionals. AMP commented previously that if FDA were to restrict access to specific databases, it would severely limit our ability to best serve our patients. It remains unclear if a professional consulted a non-recognized database, if that would incur higher liabilities, be considered as off-label use, etc. It is imperative that molecular professionals maintain the ability to access and use any and all information available for a given sequence variant and use their professional judgment along with consensus guidelines from professional societies on how to weigh the available evidence. The draft guidance states the agency's intention to implement a recognition process for publicly accessible genetic variant database and their assertions, but provides little specifics about how the databases will be evaluated including how the agency will verify variant assertions. Furthermore, by 'certification' of some databases as having FDA recognition may imply, likely without merit, that data from alternate database sources is less reliable, limiting the ability of a practitioner to utilize all available information in good faith, thereby impinging on the practice of laboratory medicine.

Professional Societies Should Establish Criteria for Evaluating Quality of Databases:

Given the training and high level of skill of the professionals responsible for the implementation, operation, and interpretation of NGS tests, allowing them to establish the criteria for evaluating the quality of clinical databases will protect patients while allowing continued progress in this extremely important new area of medicine. AMP recognizes that standards will improve the quality and reliability of a database but believes that these are best established by professional societies. Databases are important tools for medical professionals to use in their professional interpretation activities. Professional societies have long held the responsibility for, and have been very successful in, providing guidelines for medical practice. Instead of deeming some

databases as adequate and others not, AMP encourages FDA to engage with professional societies and contribute to their efforts to develop practice guidelines that can then be readily implemented. For instance, the *CFTR* database, which was accepted by FDA as support for the Illumina submission, represents multiple professional contributions to the common good that occurred over the course of time in the absence of FDA oversight. The interpretation of every *CFTR* test is a professional activity. However, the *CFTR* database is an excellent example of what is needed in this space: FDA support for and collaboration with the professional community rather than unilateral oversight.

Indeed such efforts, independent of FDA, have already resulted in an important set of carefully considered standards that many clinical laboratories follow. The College of American Pathologists, the American College of Medical Genetics and Genomics, the Clinical Laboratory Standards Institute, and other organizations have already produced laboratory accreditation requirements and practice guidelines that are used to ensure high quality performance of NGS tests. Practice guidelines such as those produced by ACMG, when combined with current bioinformatics approaches, can effectively reduce the number of variants potentially responsible for a patient's phenotype to a manageable level, even for assays as complex as whole exome sequencing. AMP is currently developing standards for both the interpretation of sequence variants in somatic conditions in collaboration with ACMG, CAP, and ASCO and validation standards for the NGS bioinformatics pipeline addressing single nucleotide variants, small insertion and deletions, and multi-nucleotide variants. It is anticipated that addressing the quality and availability of appropriate databases will additionally be addressed by both of these working groups.

We would also like to take the opportunity to emphasize that databases will not address situations in which a novel variant is identified as being tied to the underlying etiology of a disease or condition. This situation is still widespread and especially relevant to those afflicted with a potentially rare disease. The concept of novel variant identification is not new, as laboratory professionals have been detecting, analyzing and reporting such variants to providers and patients for many years.

FDA Recognition Program May Restrict Access to Commercial Databases:

Some of the best curated and useful databases for use in professional interpretation of NGS-based tests are available only through licensing or subscriptions. Often times, molecular professionals cross-reference this information with publicly available databases and the literature as they make an assessment about the pathogenicity of a variant. While AMP is concerned that proprietary databases can be a way, post-AMP *v Myriad*, for entities to control access to gene sequence information as effectively as can a patent, the requirement that all databases participating in the recognition program be publicly accessible may deter some owners of proprietary databases from participating in the program, as an unintended negative consequence. Hence, this policy may inadvertently restrict IVD manufacturers from utilizing high quality proprietary databases to establish clinical validity through this regulatory approach.

Thank you for the opportunity to submit these comments. If AMP may be of further assistance, please contact Tara Burke at tburke@amp.org.

Sincerely,

Federico Monzon, MD
AMP President-Elect