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

Comments re: Docket No. FDA-2015-N-3015 submitted electronically at www.regulations.gov

To Whom It May Concern:

Thank you for the opportunity to provide comments on the discussion paper titled, Use of Databases for Establishing the Clinical Relevance of Human Genetic Variants. The Association for Molecular Pathology (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 supports the idea of using databases for the collection of known clinical information associated with a given analyte/biomarker. In fact, databases are already a widely used tool in the design and interpretation of laboratory testing. Molecular professionals often consult at least one database as a source for information. However, the database is merely that - a source through which professionals can find pertinent articles and studies that further inform the work of molecular professionals, and that information is always used in the context of other clinical information about a patient. With regards to an individual's patient test result, analysis and interpretation of any database information is part of a molecular professional's scope of practice. The clinical databases currently available to molecular professionals do vary in quality, coverage, accessibility, etc. We hope it was apparent from the discussion during the public workshop on November 13, 2015 that even the best databases are far from being a standalone one stop tool for data on clinical validity.

Given the nascent stage of development of such databases, we encourage the FDA to consider the negative effect any restriction (by FDA or others) would have on the advancement of NGS. If FDA were to restrict our access to specific databases, it would severely limit our ability to best serve our patients. 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 on how to weigh the available evidence. Each database is useful for different reasons and AMP urges FDA to not exclusively consider or limit one database as a resource

for clinical validity data. 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.

In particular, AMP is concerned with perceptions that would emerge if FDA were to deem itself the appropriate arbiter of certain databases as clinical-grade, especially with regards to its use for interpretation. 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. Contributions to these databases by researchers and clinicians provide health care professionals with evidence about clinical validity. However, interpretation of a laboratory test result remains within the practice of medicine and AMP believes that while databases aid in the interpretation of a test result, no database can or should replace the professional interpretation provided by molecular professionals. 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.

In the discussion paper, FDA explores potential principles and factors for assuring database quality for the purpose of assessing the clinical validity of a NGS-based test. AMP believes that this is also best established through the professional associations' development of guidelines. 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 for assays as complex as whole exome sequencing effectively reduce the number of variants potentially responsible for a patient's phenotype to a manageable level. 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. The concept is also not exclusively tied to NGS-based technology. Sequencing and other genotyping tests represent an established standard of care in medical practice, and have improved the treatment and benefitted the lives of thousands of patients. This is true whether they have definitively identified pathogenic variants, have failed to reveal the cause of a disorder, or

yielded variants that are as yet uncertain as to their significance. The design, development, and use of the information derived from such tests is at the heart of what we and ordering providers do. As these activities are central to the practice of medicine, they must also remain outside the purview of FDA.

We are supportive of the use of databases for boxed-and-shipped NGS-based testing. 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 had at their disposal for patient care. 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.

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

Sincerely,

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AMP President