COLLEGE of AMERICAN PATHOLOGISTS

December 24, 2015

Stephen Ostroff, M.D
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Docket No. FDA-2015-N-3015 for “Use of Databases for Establishing the Clinical Relevance of Human Genetic Variants";

Dear Dr. Ostroff:

The College of American Pathologists (CAP) appreciates this opportunity to comment on the Food and Drug Administration (FDA) discussion paper entitled, *Use of Databases for Establishing the Clinical Relevance of Human Genetic Variants.* The CAP is a medical society serving more than 18,000 physician members and the global laboratory community. It is the world's largest association composed exclusively of board-certified pathologists and is the worldwide leader in laboratory quality assurance. The College advocates accountable, high-quality, and cost-effective patient care. The CAP Laboratory Accreditation Program (LAP) is responsible for accrediting more than 7,000 clinical laboratories worldwide. Our members have extensive expertise in providing and directing laboratory services and also serve as inspectors in the Centers for Medicare & Medicaid Services (CMS)-deemed CAP accreditation program. The CAP welcomes the opportunity to work with the FDA to address uses of clinical variant databases.

The CAP Accreditation Program improves patient safety by advancing the quality of pathology and laboratory services through education and standard setting, and ensuring laboratories meet or exceed regulatory requirements. The CAP also provides laboratories with a wide variety of proficiency testing (PT) programs and has the responsibility to evaluate the accuracy of test performance and interpretation in more than 23,000 laboratories worldwide. Particularly relevant to this discussion, the CAP Personalized Healthcare Committee recently published an article outlining pathologists’ perspective on clinical variant databases entitled *Standards for Clinical Grade Genomic Databases*[1].

In response to the specific questions posed in the discussion paper, the CAP offers the following:

[1] Arch Pathol Lab Med. 2015;139:1400–1412.

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1. *Since differences in nomenclature can cause difficulty in comparing evidence, reviews, and interpretations of gene variants, should there be a single standard nomenclature adopted by all certified databases?*

   Where possible databases should uses a standard nomenclature; however older databases the uses different nomenclatures may still provide relevant information.

   If so, is there a preferred nomenclature that should be used and what are the benefits of using it over others? HUGO is the preferred nomenclature.

2. *As reference genomes are updated, what processes should be employed by database holders to assess whether and when to update the reference genome used for sequence alignment?*

   The CAP believes that database information and processes should be transparent so that users can independently determine whether the database is of high enough quality.

3. *What criteria should curators use to evaluate evidence from clinical studies*?

   The CAP recommends that each database establish its evidence criteria and use established methodologies. Each database should make its evidence criteria readily available. The database must contain sequences and/or variants that are produced from human samples in a laboratory that meets clinical quality standards for the analysis that generates the sequence and/or the variant (the so-called high-quality human sequence/variant [HQHSV]). In the United States, a laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and accredited by CLIA or a CLIA-deemed organization for high-complexity testing meets high clinical quality standards.

   From basic research? From literature sources? From other databases? How can data quality be assured long-term?

   Data from sources other than a CLIA laboratory such as animal models, sequence conserved across species, and/or cell-line data may provide helpful information however, those data cannot be considered clinical grade. The CAP believes this type of data will require both a notation in the database as to the limitation of the sources used for classification. Transparency and consistent use of evidence criteria by well-trained curators are the best ways to assure long term quality data.

4. *How often should previous variant classifications be reviewed?*

   Databases stewards should review variant classifications when new evidence becomes available. Strict timelines may be inappropriate at this time given the fast past of research in genomics.

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How should variant interpretation changes be handled? Should discrepancies between databases be looked for and resolved?

Variant interpretation in clinical care is the practice of medicine and should remain under the auspices of physicians. The CAP considered the differences between variant interpretations in different databases and notes that in many cases those differences may be due to the populations covered by the databases and so may not need resolution. The CAP agrees that is important to understand these differences.

5. *What information should databases include on each variant?*

   The CAP recommends that FDA refer to the recent paper *Standards for Clinical Grade Genomic Databases*[2] for detailed description of information associated with each level of clinical variant database.

6. *How can databases ensure sustainability?*

   The CAP recognizes the importance of continued curation of clinical variant databases and would support public funding for these efforts.

   Should the test developer state the version that was used?

   Variant databases need to be updated as new information becomes available, therefore it will be important when using a database for clinical interpretations or in support of FDA submissions to identify the version and/or date accessed.

The CAP welcomes the opportunity to work with the FDA to address oversight of Next Generation Sequencing technologies by developing appropriate regulations and policies to allow innovative test development and patient access while assuring public health and safety. Please contact Helena Duncan, CAP Assistant Director, Economic and Regulatory Affairs at hduncan@cap.org or Fay Shamanski, PhD, CAP Assistant Director, Economic and Regulatory Affairs at fshaman@cap.org if you have any questions on these comments.

Sincerely,

The College of American Pathologists

Sent via www.regulations.gov

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