American Association for Cancer Research
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October 6, 2016

Division of Dockets Management (HFA-305)
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

To Whom It May Concern:

On behalf of the American Association for Cancer Research (AACR), the oldest and largest scientific organization in the world dedicated to the prevention and cure of cancer through research, education, communication, and collaboration, we sincerely thank the U.S. Food and Drug Administration (FDA) for the opportunity to provide comments in response to the July 2016 draft guidance, "Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics."

NGS technologies, which allow for the rapid sequencing of whole genomes and exomes, have revolutionized the field of oncology from basic research to clinical treatment. The AACR is pleased to see the FDA's effort to "*create a flexible regulatory approach to the oversight of NGS-based tests as part of the White House's Precision Medicine Initiative (PMI)*." We commend the FDA's efforts to obtain community input to help shape this guidance, most notable in two public workshops on this issue: "Use of Databases for Establishing the Clinical Relevance of Human Genetic Variants" on November 13, 2015, and "Patient and Medical Professional Perspectives on the Return of Genetic Test Results" on March 2, 2016.

The explosion of NGS technologies and generation of high volume of genomic data has demonstrated a need for reliable, well-curated, high-quality, clinical-grade databases. This guidance describes the voluntary recognition process and the database policies and procedures that would be required to achieve and maintain FDA recognition, including recommendations for database procedures and operations; data quality; curation, variant interpretation and assertions; and professional training and conflicts of interest. The AACR is supportive of this draft guidance; however there are a few areas in which we believe additional guidance and clarification from the FDA would be beneficial.

In **Section II: Background** of the guidance, the FDA states that these recommendations are meant to apply to "*publicly accessible databases*"; however, "*public accessibility*" is not clearly defined. The AACR believes that further clarification is necessary to define whether "*publicly accessible*" means freely

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available or if there is a monetary cost associated to gain access to information within these databases. Additionally, it is not clear whether databases could begin the voluntary submission process for FDA recognition if all or portions of the database are closed. If so, would recognition be contingent upon public accessibility? We ask that the Agency further clarify this potential parallel review process.

In **Section IV.A: Database Procedures and Operations**, the FDA discusses recommendations to ensure that genetic variant databases are transparent and publicly accessible, have well-documented and versioned SOPs, maintain stable data linkages, and ensure the protection and privacy of patients and protected health information . To do this, the guidance states that "*genetic variant database administrators should employ commonly accepted data formats and identify which format is in use by the genetic database*." It would be helpful if the final guidance could include examples of what the FDA considers "commonly accepted data formats." For instance, is the format of the database just the text description of the mutation, or is it a higher order file, like a Virtual Contact File (VCF)? The current wording in the draft guidance is vague and further elaboration on specific format regulations, would help to eliminate confusion.

In **Section IV.B: Data Quality**, the draft guidance discusses how information entered into these databases must be of "*sufficient quality, and based on current scientific knowledge*" to ensure that "*assertions made linking specific genetic variants to diseases or conditions are accurate.*" The guidance also asks for "*consistent nomenclature that is widely accepted by the genomics community*." Additionally, the guidance states that "*variant data in the genetic variant database should be accompanied by metadata*" and "*clearly and transparently document evidence source(s) used to support variant interpretation*."

The AACR agrees that these FDA recognized databases must contain information of sufficient quality that is well-supported. First, there is the issue of the quality of the mutation itself and the accuracy of testing. Secondly, regarding nomenclature, the AACR agrees that databases should use widely accepted language for genomic variants, and there have been a number of reviews in the literature on existing nomenclature by the germline community (http://varnomen.hgvs.org/history/). The AACR supports the use of established, accepted nomenclature in reporting genetic variants in these FDA recognized databases, and an example would be the sequence variant nomenclature authorized by the Human Genome Variant Society (HGVS), the Human Variome Project (HVP), and the Human Genome Organization (HUGO). Lastly, the AACR believes that linking of mutations to diseases must be done in a high-quality way. Within **Section IV:B: Data Quality**, the FDA goes into further detail about metadata and data uniqueness, both of which will help to provide reasonable assurance regarding data quality. Regarding metadata, this will include "*the number of independent laboratories and/or studies reporting the variant classification, name of the laboroatory(ies) that reported the variant, the name of the test used to detect the variant, and, to the extent possible, details of the technical characteristics of the test that was*

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used…and variant characteristics." The AACR believes that this type of transparency and documentation of evidence sources will help to support high-quality linkage of mutations to diseases.

In **Section V.A: Recognition Process for Genetic Variant Databases**, the FDA outlines the steps necessary for participation in the FDA database recognition process, including submission for recognition, FDA's review of genetic variant database policies and procedures, and maintenance of FDA recognition. Although the FDA estimates that it should take an average of 80 hours to complete and submit an application for recognition, it is not clear as to the timeline for this submission process, more specifically, what period of time the recognition is valid (6-months, 1-year, etc.), how long the review process will be, and how frequently should the databases be reviewed, given that assertions for variants may change and new evidence generated. It would be helpful if the Agency could provide more concrete timelines concerning the submission process, recognition period, and review.

In conclusion, this draft guidance describes the process by which the FDA will determine whether a genetic variant database could be a source of valid scientific evidence that could support the clinical validity of an NGS-based test. Additionally this draft guidance outlines the voluntary process for FDA recognition of these databases. The AACR commends the FDA for its commitment to incorporating scientific advances into its regulatory framework and is pleased to extend its resources and broad expertise to the FDA as the Agency further refines its guidance for use of public human genetic variant databases to support clinical validity for NGS-based in vitro diagnostics.

If you have any further questions, please contact Anna Sadusky, PhD, Director, Regulatory Science and Policy, at 267-765-1028 or anna.sadusky@aacr.org.

Sincerely,

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