



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-2881 for “Standards-Based Approach to Analytical Performance Evaluation of Next-Generation Sequencing In Vitro Diagnostic Tests”

Dear Dr. Ostroff:

The College of American Pathologists (CAP) appreciates this opportunity to comment on the Food and Drug Administration (FDA) discussion paper entitled, *Standards-Based Approach to Analytical Performance Evaluation of Next-Generation Sequencing In Vitro Diagnostic Tests*. 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 standards for Next-Generation Sequencing In Vitro Diagnostic Tests.

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. The program allows laboratories to evaluate their performance regularly and improve the accuracy of the patient results they provide. Through these programs, the CAP provides individual laboratories with unknown specimens for testing. Pertinent to this workshop, the College launched in 2015 PT for next generation sequencing where laboratories have the ability to test up to 200 variants in a method-based challenge using either gene panels, exome, and/or genome sequencing. The CAP plans to follow the initial NGS PT program for germline variants with NGS PT for the detection of somatic variants and other NGS clinical testing applications. The participants analyze the specimens and return the results to the CAP



for evaluation. In turn, each participating laboratory receives a report of its performance as well as a report summarizing the results of all participating laboratories.

The CAP's accreditation and proficiency testing programs address assessment of analytical performance, and CAP has developed a specific checklist to address Next Generation Sequencing technologies. FDA should not require a parallel approval process, and we encourage FDA to consider the existing quality control mechanisms in place.

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

1. *Would either a performance standard based approach or a design process based approach as described here be sufficient to ensure the development of high quality NGS tests? Would a hybrid approach or a completely different approach be more appropriate?*

CAP supports a standard-based approach be applied to all NGS-based tests, however the hybrid approach described in the FDA discussion paper is essentially what laboratories who provide NGS tests already do today and demonstrate through CAP accreditation and NYS DOH requirements. The CAP agrees that it is reasonable to demonstrate analytical test performance “for a representative subset of types of variants in various sequence contexts.” The CAP has termed this “methods-based” analysis, and endorses using this approach for NGS test validation and PT¹.

2. *What elements are essential for a design concept standard for NGS-based tests?*

Considering the broad applications of NGS and different standards that would likely need to be developed to support all of these applications, the CAP reiterates its suggestion for piloting standards with defined applications (e.g., use of exome/genome sequencing for the evaluation of patients with unexplained heritable disease, use of NGS for the detection of somatic SNVs and indels to assist in the selection of therapy, etc.). These pilots would be invaluable to test the general approach. The CAP's ongoing NGS efforts will provide considerable data on the analytical performance of a significant number of laboratories performing NGS testing.

3. *What elements are essential for a performance standard for NGS-based tests? Are there elements that should not be a part of such standard?*

¹ Methods-based proficiency testing in molecular genetic pathology. Schrijver I, et al. J Mol Diagn. 2014 May;16(3):283-7. PMID: 24650895



The CAP has previously provided FDA with in depth descriptions of the standards CAP recommends through its Accreditation Program, and specifically through its NGS checklist.

4. *Would separate performance standards be needed for tests with different intended uses?*

As CAP previously commented, different performance characteristics would change given the intended use. FDA should treat the broad application categories (listed below) separately, as each have unique technical characteristics. Screening vs. diagnostic, vs. prognostic vs. monitoring tests would not fall into the same 'performance' characteristics. Categories to consider include:

- Detection of somatic variants associated with cancer
- Detection of germline variants associated with Mendelian disease
- Screening for aneuploidy in the prenatal population
- Identification of infectious agents
- Evaluation of B- or T-cell gene rearrangements for evaluation of clonality
- Evaluation of promoter methylation status
- HLA typing for transplantation
- Expression profiling

A single set of universal performance characteristics would be too lax for some tests and for others too stringent.

5. *What types of samples can be used in lieu of clinical specimens to develop NGS assay and determine performance characteristics? What should the expectation be for whether clinical samples need to be used or whether reference materials, reference sample panels, and other well characterized samples can be used?*

There are two 'sample' types that should be used in developing NGS assays and determining performance characteristics - wet and dry. The wet samples would assess the sequencing components of the assay, the dry would assess the informatics component (ie. in silico proficiency testing which CAP already has in place). Carefully designed spiked samples could assess a wide range of variants in a single sample.

6. *FDA has traditionally used well-established methods such as bidirectional sequencing as an acceptable comparator to establish performance of a new genetic test, which may not be feasible for all NGS tests. What comparators may be best suitable to evaluate NGS test accuracy?*

CAP does not believe it makes sense in all cases to use bidirectional sequencing as a comparator and discretion be applied for such a requirement. Creating bidirectional Sanger confirmation is incredibly tedious, and in some cases would require using a non- approved test to confirm an approved test.

7. *For developers specializing in providing bioinformatics data analysis, what information should be provided that is not covered here?*



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As a component of any good standard operating procedures (SOP), database stewards should maintain strict version history of the bioinformatics in the SOP and should retain metadata for each run so the data can be queried and identified at a future date.

8. *What might be the most suitable and efficient models for developing new standards and are there groups already working to develop some of the needed standards?*

The CAP already has a Committee in place that is continuously working to improve and update the CAP NGS checklist to reflect advances in NGS technology and the ever growing diversity of clinical applications to which NGS is being applied.

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