



ASSOCIATION FOR MOLECULAR PATHOLOGY
Education. Innovation & Improved Patient Care. Advocacy.
9650 Rockville Pike. Bethesda, Maryland 20814

Tel: 301-634-7939 | Fax: 301-634-7995 | amp@amp.org | www.amp.org

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

Re: Docket No. FDA-2015-N-4990 - Next Generation Sequencing-Based Oncology Panels
Comments submitted electronically to the docket at www.regulations.gov

To Whom It May Concern:

Thank you for the opportunity to provide these written comments on behalf of the Association for Molecular Pathology (AMP) to the request for comments in Docket No. FDA-2015-N-4990, "Next Generation Sequencing-Based Oncology Panels." 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.

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. Thus, the following comments should solely be viewed in reference to FDA oversight of instrumentation and reagents manufactured for distribution.

FDA seeks to understand issues surrounding validation of next generation sequencing (NGS) assays for oncology applications. However, FDA should recognize that such conservations have been taking place in the professional community for several years, and that accreditation agencies such as the College of American Pathologists and state regulators, for example New York State, have made substantial progress to oversight of next generation sequencing assays. Although the efforts of these oversight entities at ensuring the quality of NGS testing address the total test process, that is pre-analytical considerations, analytical performance, and post-analytical return of results rather than instrument and reagent manufacture, they should prove informative to the Agency. We encourage FDA to explore the consensus that professional organizations have already reached.

In particular, it should be noted that the entire field of gene sequencing using Sanger methods arose with essentially no FDA oversight, including capillary sequencers and reagent components, allowing countless patients to derive the benefits of genetic and other molecular pathology testing. AMP is pleased that FDA is considering ways that a test manufacturer could demonstrate robustness for a particular NGS-based oncology panel. NGS test systems interrogate extraordinarily large regions of DNA, typically with limited prospective

knowledge of most of the mutations that will be encountered. Variant assessment requires knowledge of the performance characteristics of the assay used. But it is also dependent on key intrinsic specimen parameters such as the allele proportion of a variant, which itself is dependent on: the proportion of tumor cells in a sample; the zygosity of a mutation; and features such as copy number, aneuploidy, and chromosome loss. Conversely, NGS systems have no understanding of the clinical purpose for which a test is ordered, with the assay's performance dependent on the range and types of variants that will be encountered, not their medical use. These features of NGS testing differ from FDA's historical work, which lent itself to a review of tests in narrow, well-defined contexts. Thus, validation of the performance characteristics of NGS instruments and reagents, and assays themselves, must inherently rely on a method-based approach that is reflective of the nature and types of variants likely to be seen in clinical practice. Such an effort would require that FDA exercise enormous flexibility, in order to support the accuracy and reliability of tests, without harmfully interfering with the introduction of new NSG assays.

Specifically, when considering next generation sequencing, AMP urges FDA to abandon the companion diagnostics paradigm on which it has relied for tests for biomarkers that are linked to therapeutic selection. This approach is inherently unsuitable for, and inconsistent with the use of, next generation sequencing technologies. Thus, the single test, single drug paradigm as described by the term "companion diagnostic," is obsolete as NGS technologies allow for the testing of multiple analytes simultaneously with greatly reduced per-analyte costs.

Importantly, because NGS test systems are akin to general purpose instruments and reagents, FDA should not limit a manufacturer of a new test to the specific context in which the original test was developed. Such an approach would restrict the incorporation of new and better medical knowledge or approaches (i.e. using specimen types collected from minimally invasive procedures). Further, FDA has asked for information about, and distinguishes putative requirements for, establishing analytical validity for variants used as "companion diagnostics," and other variants used to guide treatment in patients who have exhausted therapeutic options. However, from the standpoint of the analytical performance of sequencing instruments and reagents, these two applications should not differ. An ideal tool to help ensure accuracy and reliability as tests and technologies advance is standardized reference materials. AMP strongly recommends that standardized reference materials be created for targeted therapies, whether produced in a public-private partnership such as Pharma-NIST or through Pharma-funded private mechanisms. Furthermore, to facilitate the development of future and more advanced testing, AMP believes that drug labels should not specify the brand name of diagnostic tests.

Moreover, we urge the Agency to be careful to keep analytical approaches distinct from the fields' understanding of a biomarker's clinical usefulness. FDA should focus on safety and performance characteristics of IVD tests. Intended Use statements should not dictate the professional interpretation or the clinical use of test results. Interpretation of NGS results is a complex process, involving significant literature review in the context of knowledge of patients' cancer types, other phenotypic and molecular tumor features, and other clinical and pathologic characteristics. Thus, NGS result interpretation requires considerable medical judgment, placing it outside the Agency's jurisdiction. These clinical activities are the work of pathologists and other medical laboratory professionals who perform NGS tumor testing. Most important, they are well beyond the scope of FDA's expertise and the Agency's ability to positively contribute to patient outcomes.

FDA must recognize that the clinical interpretation of accurately called bases is an integral part of professional and medical practice, and does not lie within the Agency's purview. Instead, FDA should focus its limited

resources on establishing means to ensure accurate and reproducible interrogation of the genes or gene regions sequenced. Rather than inserting itself into medical practice, any FDA efforts in this area should be directed toward ensuring that instruments and reagents perform accurately and reliably. This validation should be method-based, should primarily entail proving the reliability and reproducibility of the range of mutations likely to be representative of those faced in clinical settings, and should include a representative sample of specimen matrices with which the test will likely be utilized.

Further, we believe that FDA can play an important role in encouraging companies to develop products in a more transparent way. This will improve the pathology community's ability to assist FDA in detecting flaws or limitations in testing after a product has been cleared or approved. Additionally, this would allow better comparisons between tests to be made. More importantly, as the professionals who purchase and use IVD test kits, it would contribute to our ability to re-validate the test in our laboratories, handle special patient-specific considerations during sample preparation, and interpret test findings. As indicated during the workshop, we stand to miss out on giving patients the best possible outcome if we are not able to see that raw data. In order to ensure that molecular pathologists can give the best patient care, AMP would like to see greater transparency in the validation steps, informatics pipelines, cell lines, and samples used by manufacturers.

Lastly, we are concerned that FDA will apply their thinking about IVD NGS-based oncology panels to laboratory developed testing procedures (LDPs). Because of the unique risk mitigating measures that exist as a result of developing, validating, and performing an LDP within a single laboratory, the same criteria for regulating widely distributed IVD kits is not scientifically warranted and cannot be reasonably applied without severely and unnecessarily hindering patient care. Moreover, AMP maintains that it is inappropriate to apply medical device regulations to LDPs which are offered to patients as medical services and therefore not within FDA's authority. These professional activities are within the scope of our medical practices and are comparable to ways that other health care professionals used FDA-regulated instruments. As an example, radiologists do not define what they are going to look for before a CT scan. These medical professionals look at the whole image and determine what information is necessary and useful for patients. With regards to NGS-based LDPs, AMP believes that FDA can help contribute to patient care by ensuring the instruments and test components work properly and safely.

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,

Charles E. Hill, MD, PhD
AMP President