



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

Comments of the Association for Molecular Pathology

For the Food and Drug Administration Division of Dockets Management

Re: Docket # FDA-2014-N-2214

March 20, 2015

Comments submitted electronically at www.regulations.gov

Thank you for the opportunity to provide comments on the preliminary discussion paper titled, Optimizing FDA's Regulatory Oversight of Next Generation Sequencing Diagnostic Tests ("the white paper"). 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.

As the health professionals at the front lines of precision medicine, AMP was very pleased to hear President Obama's announcement of the Precision Medicine Initiative and looks forward to partnering with the Administration on this ambitious project. We are enthusiastic about this and other efforts that give molecular pathologists additional information and tools to develop and advance diagnostic testing which may lead to improved patient care. We share FDA's concerns that the medical device pathway is inapplicable to NGS testing services but caution that any regulatory pathway should not stifle innovation or the translation of information into vital medical services. While AMP is pleased that FDA recognizes the inappropriateness of applying the medical device regulatory pathways to NGS diagnostics, it hopes that the current dialog with stakeholders will clarify that similar challenges also exist with other molecular technologies. Specifically, all molecular tests would benefit from an alternative regulatory approach to the medical device pathway that includes enhancing the current oversight mechanisms provided by CLIA.

To prepare a response to the numerous questions on how to best assess analytical and clinical performance of NGS tests and the oversight mechanism described in the white paper, AMP formed a working group of

members who are leaders in the field of using NGS in clinical applications. After careful consideration of the white paper and the presentations and comments provided at the public workshop on February 20th, AMP has drafted these comments to provide guidance to the agency.¹

AMP believes that FDA can best contribute to patient care and public health by helping to ensure adequate performance of NGS test systems (and their components) that are sold and widely distributed to diagnostic laboratories. However, it is critical that FDA invest in novel, flexible, and speedy approaches to accommodate the rapidly changing landscape and ensure rapid translation of technical innovation to the bedside.

FDA defines an NGS test in the discussion paper as a “human DNA sequencing assay performed on a particular NGS instrument (e.g., MiSeqDx) with a workflow defined by standard operating procedures that specify all materials and procedures. This includes all steps from defining the patient sample type and method of DNA extraction to computational processing of sequencing data, and, if offered, any portion of interpretation of the clinical meaning of individual variants identified in that patient that is performed within the test system (including software) rather than by a *healthcare professional*.”²

AMP understands this definition and stresses that there are many elements of a testing service that clearly fall within the practice of medicine including the selection of the variants of interest, the interpretation of a test result, and off-label applications of a test system. Furthermore, any modifications made within a laboratory to adjust an NGS test to better suit the needs and requirements of the laboratory and the patient are within the

¹ In filing comments on this proposed guidance document, AMP does not waive any legal claim that the FDA lacks the statutory authority to regulate laboratory developed testing services. Furthermore, AMP strongly maintains that, to the extent that it is established that the FDA does have such authority, the overwhelming weight of legal authority dictates that the proposed new requirements for laboratories outlined in the draft guidance must be issued through notice and comment rulemaking. Nothing in these comments is intended to impact adversely in any way AMP’s right, alone or in combination with other stakeholders, to pursue separate comments, litigation, or other remedies with respect to the proposed regulatory framework or related issues.

² By the issues and questions it raises, FDA’s whitepaper appears to equate NGS with whole exome or whole genome sequencing, which indeed presents certain unique issues. In point of fact, the vast majority of medical NGS assays performed today are targeted, indication-based tests, such as moderately sized gene panels, which are very different in character than whole exome or genome sequencing. In such targeted assays the number of variants with possible, likely, or definitive clinical significance detected per patient is usually very small. Lastly, for targeted assays the NGS read depth, target coverage, and data quality can be substantially greater than is practical with genome or exome assays, and the possibility of incidental findings with targeted tests is extremely low.

The whitepaper also appears to equate NGS with population screening, stating that “the results of that test could be used to diagnose or predict an individual’s risk of developing many different conditions or diseases.” However, broad genetic testing is not widely performed for screening of healthy individuals in medical settings. Moreover, the average person is not at risk for “many different heritable conditions” as the document states, but rather is probably at risk for no more than a few such disorders.

purview of appropriately trained molecular professionals, and thus, should be regulated by the Centers for Medicare & Medicaid Services under the Clinical Laboratory Improvement Amendments (CLIA) program.

There is a role for FDA in evaluating performance characteristics of vendor supplied instruments, test kits, software, and reagents, and ensuring that the performance of FDA cleared or approved products is consistent with the a seller's claims in their labeling, promotional materials, and activities. However, an approach is needed that is sufficiently flexible and speedy to accommodate continual technological developments and exponentially increasing medical and scientific knowledge in a timely manner. Next generation sequencing is a rapidly advancing technology that requires complex lab processes and bioinformatics to bring usable results to treating physicians. In order to effectively regulate NGS instruments and test kits, FDA would need to develop a novel process to do so. Given the speed with which NGS technology and accompanying medical knowledge is progressing, the clearance or approval process in this complex area is likely to prove increasingly challenging and prevent patients' access to these important services if the regulatory pathway is not adjusted in a thoughtful way. Therefore, FDA should provide a mechanism by which manufacturers are permitted to have open platform instruments and a mechanism in the approval process whereby the test system could be easily and quickly updated by the manufacture or lab.

As an example, FDA recently cleared Illumina's MiSeqDx next generation sequencing platform for use with a universal reagent set which gives customer laboratories the ability to develop numerous types of assays. However, the test system, as approved and marketed, still has design and technical restrictions related to factors such as patient specimen quantity, target enrichment design, mandated read length and paired-end chemistry, data analysis software, implementation in high-volume settings, and limitations to a single instrument, all of which greatly limit the system's general clinical usefulness . Without the ability of a manufacturer to easily update its test system and the flexibility to allow laboratories to modify tests, a test instrument like the MiSeqDx is unusable in many situations.

Any regulatory approach for NGS tests should not interfere with the practice of medicine.

The section titled "Whether and How to Communicate Information About Less Well-Understood Variants" appears potentially inconsistent with the underlying premise that a test system is limited to interpretations made directly from the instrument rather than those rendered by a professional. Given the training and high level of skill of the professionals responsible for the implementation, operation, and interpretation of NGS tests, this current level of oversight will protect patients while allowing continued progress in this extremely important new area of medicine.³

³ Laboratory professionals made use of practice guidelines such as those produced by ACMG and AMP's own recent publication (Richards et al., Genet Med, see footnote 6), which factor in the many benign variants found in a single genome.

If FDA restricts communications between health professionals and patients, even for variants of uncertain significance, the agency is actively interfering with the practice of medicine. Whether and how to include such variants of uncertain significance requires professional judgment of highly trained healthcare professionals including ordering physicians, genetic counselors and diagnostic testing staff. These are typically highly individualized decisions depending on many factors including patient preferences as well as the ability to conduct follow up studies that can help clarify the significance of these variants. As such, any decisions about communication of less well-understood variants falls within the purview of the professional and instead of being subject to regulation by FDA should be supported by practice guidelines developed by the professional community. Therefore, AMP opposes any role for FDA in decisions about communication of variants from either the test system to the professional and most important, from the laboratory professional to the ordering provider.

The College of American Pathologists (CAP), the American College of Medical Genetics and Genomics (ACMG), the Clinical Laboratory Standards Institute (CLSI), and other organizations have already produced laboratory accreditation requirements and practice guidelines that are used to ensure high quality performance of NGS tests.

As an example of an existing performance standard, the CAP Molecular Pathology accreditation inspection checklist contains a section solely dedicated to NGS-based clinical applications, which is updated on a yearly basis by experts in response to changing technology and advancing medical and technical knowledge. In addition, CAP has begun providing method-based proficiency testing specifically intended for laboratories that perform NGS-based clinical testing. Therefore, AMP recommends that FDA work with existing entities in their efforts to ensure the accuracy and precision of genetic tests as outlined in the next section.

AMP recommends that FDA collaborate with private sector organizations and experts to develop an independent entity tasked with setting standards for FDA cleared or approved instruments, test kits, and software; and to assist in production of recommendations and practice guidelines for clinical laboratories implementing NGS testing.

Given our common goals of optimizing patient care and maximizing public health benefit, we propose that FDA join with organizations such as AMP, our expert members, and other professional societies as they together set forth parameters for FDA review of, and standards for instruments, test kits, and software. FDA would be a

When combined with current bioinformatics approaches, these guidelines can reduce the number of variants potentially responsible for a patient's phenotype to a manageable level for assays as complex as whole exome sequencing effectively.

welcome partner in helping us craft rigorous yet flexible guidelines and standards that laboratories, professional societies, and established oversight and accreditation programs for clinical laboratories could adopt to achieve high quality performance of NGS assays for the benefit of patients. Although NGS represents a new technology that offers the potential of extraordinary benefits to patients, it should be noted that the appropriate operational, validation, and quality control procedures of the majority of medical NGS based assays are extensions of those generally accepted for more established technologies that are already in widespread use. Indeed efforts to develop standards for these technologies, independent of FDA, have already resulted in an important set of carefully considered guidelines that many clinical laboratories follow.⁴

Although AMP believes curated databases can effectively serve as surrogates for demonstration of clinical validity, FDA must not restrict the databases that laboratory professionals may access to support clinical performance.

The use of public and private databases is not unique to NGS-based tests as laboratory professionals have been using databases to assist in detecting, analyzing, and reporting variants to providers and patients for many years. Even genome-wide testing, including the accompanying possibility of incidental findings, is not unique to NGS-based applications, as cytogenomic arrays have been used to identify novel genome-wide genetic changes for several years. Organizations such as the ACMG have published guidelines for the reporting of incidental findings.⁵ 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 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 remain outside the purview of FDA.

The white paper states, “FDA believes that it could use high quality curated genetic databases that provide information on genetic variants and their association with disease to better establish the clinical performance of NGS tests by providing evidence about such associations and the strength of that evidence.” We are pleased that FDA will be using its \$10 million allotment of the President’s requested funding for the Precision Medicine

⁴ Rehm et al. (2013) ACMG clinical laboratory standards for next-generation sequencing. [Genetics in Medicine](#) 15, 733–747; Gargis et al. (2012) Assuring the quality of next-generation sequencing in clinical laboratory practice. [Nature Biotechnology](#) 30, 1033–1036; Aziz et al. (2014) College of American Pathologists’ laboratory standards for Next-Generation Sequencing clinical tests. [Archives of Pathology & Laboratory Medicine](#); Schrijver et al. (2012) Opportunities and challenges associated with clinical diagnostic genome sequencing. [The Journal of Molecular Diagnostics](#) 14, 541-549.

⁵ Richards et al. (2015) Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. [Genetics in Medicine](#). doi:10.1038/gim.2015.30

Initiative to increase the development of high quality databases that support the regulatory structure necessary to continue the advancement of innovation in precision medicine while protecting public health. AMP recommends that FDA coordinate with the National Institute of Standards and Technology on this effort. AMP conceptually supports the use of such databases for this purpose and recognizes that expert-curated databases would be an immense asset to the clinical community (which is underscored by recent national consortia such as ClinGen that have been tasked with precisely this goal). However, it is critical to understand the nascent stage of development of such databases, and therefore, the negative effect any restriction (by FDA or others) would have on the advancement of genomics. 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 if and how to weight the available evidence.

We also strongly urge FDA to only support the use of databases that require submission of evidence used in variant interpretation so it is publicly available. In fact, 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 the use of databases and data transparency, and provide additional opportunities for third parties to review 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. In addition, laboratories should not be restricted to only one or two databases such as ClinVar because doing so could actually be used as tools to unduly monopolize the market.

Conclusion

Finally, the current process required obtaining FDA clearance or approval for instruments is very expensive, resulting in products being priced at an amount that is often prohibitively expensive for laboratories. Coupled with the limited coverage and reimbursement for most molecular diagnostics this further restricts a laboratory's ability to acquire multiple platforms and/or newer equipment. In developing or modifying any regulatory approach, AMP recommends that FDA consider the current inadequate reimbursement and fiscally constrained healthcare environment as an important factor that needs to be addressed in their development of a novel regulatory approach for this technology.

Thank you very much for the opportunity to submit these comments. AMP has always had a very productive relationship with FDA and we are pleased that the agency is considering the complexities and challenges with applying its current regulatory scheme to NGS tests. We encourage the agency to extend this to other molecular diagnostics. If you have any questions about these comments, please contact Mary Williams at mwilliams@amp.org.