

## Sequencing Diagnostic Tests

*Presented by Roger Klein, MD, JD, Chair of Professional Relations Committee*

Thank you for the opportunity to provide the following comments and recommendations:

**1. FDA can best contribute to patient care and public health by helping to ensure the performance characteristics of next generation sequencing (NGS) products sold to customer laboratories.**

There is a role for FDA in evaluating the performance characteristics of NGS instruments, test kits, software, and reagents, and ensuring that the performance of these products is consistent with a seller's claims in its product labeling and promotional materials. However, any regulatory approach must be flexible enough to readily accommodate the rapid technological advances and exponentially increasing medical and scientific knowledge inherent to NGS testing.

Although FDA should be commended for its recent clearance of Illumina's MiSeq instrument for use with a universal reagent set, this accomplishment is only a first step. While this test system is useful for some applications, it is not useful for many others.

**2. AMP recommends that FDA partner with outside organizations and experts both to set standards for FDA-cleared or approved NGS products, and to assist in development of recommendations and practice guidelines for clinical laboratories engaging in NGS testing.**

Given our common goals of optimizing patient care and maximizing public health, we propose that FDA partner with professional organizations such as AMP to set performance standards and review parameters for instruments, test kits, and software. Moreover, FDA would be a welcome partner in helping us craft rigorous yet flexible guidelines and standards that laboratories, professional societies, and established oversight and laboratory accreditation programs could adopt to ensure high quality performance of NGS procedures. Indeed such efforts, independent of FDA, have already resulted in an important set of carefully considered standards that many clinical laboratories follow.

**3. The College of American Pathologists, the American College of Medical Genetics and Genomics, the Clinical Laboratory Standards Institute, 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 checklist contains a section solely dedicated to next generation sequencing, which is updated on a yearly basis. In addition, CAP has begun providing proficiency testing specifically intended for laboratories that perform next generation sequencing. Practice guidelines such as those produced by ACMG, when combined with current bioinformatics approaches, can for procedures as complex as whole exome sequencing effectively reduce the number of potentially causative variants to a manageable level.

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 laboratory oversight will protect patients while allowing continued progress in this extremely important new area of medicine.

**4. Although NGS represents a new technology, the operational, validation, and quality control processes of the majority of medical NGS procedures are extensions of those generally accepted for older technologies.**

By the issues and questions it raises, FDA's whitepaper appears to equate NGS with whole exome or whole genome sequencing. However, the vast majority of medical NGS procedures performed today are targeted, indication-based tests, such as moderately sized gene panels. These procedures are very different in character than whole exome or genome sequencing.

In such targeted tests the number of detected variants that require clinical interpretation is usually small, and the possibility of incidental findings is extremely low. Further, the analytic data quality is typically far greater than is practical with genome or exome procedures.

The concept of novel variant identification, including substantial use of public and private databases, is not unique to NGS. Laboratory professionals have been detecting, analyzing and reporting such variants to providers and patients for many years. Organizations such as the ACMG and AMP have established guidelines for the reporting of sequence variants.

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. The assay design, validation and interpretation of NGS procedures are essential medical services performed by highly qualified professionals. As these activities are central to the practice of medicine, they must remain outside the purview of FDA.