Shorts on Standards

The CAP has 30 official liaisons to various organizations who attend scientific meetings or designate others to do so. They report to the Standards Committee, which reports to the Council on Scientific Affairs. We publish periodically bits of what the CAP's outbound liaisons hear and see in their liaison roles.

Biomarkers Consortium and next-gen sequencing

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The Biomarkers Consortium is a public-private initiative that brings together government, academia, patient advocacy, and nonprofit private sector organizations that have the expertise and resources to identify, develop, and qualify potential biological markers to support drug development, preventive medicine, and medical diagnostics. The Foundation for the National Institutes of Health manages the consortium, which includes the Food and Drug Administration and Pharmaceutical Research and Manufacturers of America, Centers for Medicare and Medicaid Services, and Biotechnology Industry Organization. The consortium organized a workshop in Bethesda, Md., on May 3 and 4 to evaluate progress and issues in the use of next-generation sequencing methods as a tool for managing cancer patients.

The human genome is just over 3 billion base pairs long, and the recent advances in genomic medicine can be traced back to the sequencing of the reference human genome that was completed in 2003. This feat was accomplished using bacterial artificial chromosome (BAC) cloning that relied on complex and time-consuming techniques. Since then the sequencing technologies have moved away from bacterial cloning toward a streamlined and parallel direct sequencing model, often referred to as next-generation sequencing. Most platforms of NGS work by breaking the DNA into small strands and generating a fragment library by annealing platform-specific linkers to the fragments of DNA. Single strands of the fragment library are partitioned, amplified, and sequenced in parallel. Once sequencing is complete, specialized software is able to capture and analyze the sequence reads and localize them on the reference genome and assemble the entire target sequence. Being parallel and not dependent on any plasmids or bacterial cultures, this approach is quicker and cheaper and brings with it the possibility of a $1,000 genome with single-day turnaround time.

The emergence and the acceptance of this technology in routine clinical medicine would be a significant step because it would provide the pathologist and the clinician access to DNA information that could be useful in risk-stratification, diagnosis, and management of diseases and therapies that are influenced by the genome of an individual.

However, significant technological and other barriers must be overcome before NGS can go mainstream. At the May meeting, participants discussed the challenges of managing (and strategies to do so) the sheer amount of genomic data that would have to be converted to actionable information that can guide clinical care. The scale of information can be reduced by limiting NGS to specific targeted gene panels instead of attempting to sequence and analyze the entire exome or genome. In fact, this approach has become available at a few academic institutions and several others are evaluating it now. The CDC and other organizations are also developing guidelines for managing and archiving clinical NGS data.

The second biggest challenge is building a consensus on method validation and proficiency testing for NGS. The meeting was abuzz with discussions on analytical issues such as sensitivity, specificity, reproducibility, limit-of-detection, and depth of coverage with respect to a genetic analyte. For oncology-related testing, participants agreed that a gene of interest should have a minimum of 500× coverage. Since different laboratories may use NGS for a multitude of different gene targets, it was suggested that method validation and PT be method-specific rather than analyte-specific, the latter being the predominant approach in clinical practice today. Further, the CDC and FDA are creating reference standards that may be used for proficiency testing. The CAP will begin next year to develop a proficiency test for NGS.

The workshop participants emphasized the need for continued public support of the creation and curation of standardized online NGS-related databases that laboratories can access to analyze and report sequence variants. It was hoped that these databases will be expanded by ever increasing NGS case numbers and enriched by additional clinical information and annotation. This information would be invaluable in evaluating outcome data from clinical trials and linking efficacy of drugs with specific genetic variants.

Overall, this meeting was an extremely productive gathering of the

continued on page 36

Standards

continued from page 34

individuals and organizations that are facilitating the introduction of NGS technologies for clinical purposes. The participants agreed that NGS-enabled genomic medicine has the potential to completely change the practice of medical diagnostics and patient management. Information obtained by NGS would be critical in diagnosis, risk-stratification, therapeutic management, and monitoring of therapeutic response, and the pathologist would have a critical and central role in generating, managing, and interpreting genetic information for the rest of the health care team. □

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