COLLEGE of AMERICAN PATHOLOGISTS

Shorts on Standards

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Update on the frontier of NGS

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Next-generation sequencing has continued to deliver on its promises and potential in the diagnostic arena. However, as with any emerging and evolving technology, the medical and scientific community faces the challenge of assessing the implications and demonstrating definitive clinical uses of its expanding capabilities, especially in the context of medical efficacy, clinical utility, and cost efficiency.

At a 2015 workshop of the Association for Molecular Pathology, experts in the field shared their experiences around the utility of whole exome sequencing (WES) and targeted panels. The technical discussions focused on the limitations of the current WES approaches, such as completeness (how much of the exome) and depth of coverage (how many times each portion of the exome is sequenced), to ensure a complete assessment and identification of variants present in select genes, compared with targeted panels. While WES brings in higher sensitivity in rare genetic conditions, the higher costs and longer turnaround times associated with it may preclude its implementation.

Another common and continuing challenge of WES is the identification and significance of copy number variants (variation in number of copies of a specific genetic sequence) in specific and rare conditions, which the introduction of advanced algorithms may address. A related issue is interlaboratory variation in data storage practices and the lack of standardization of the reference databases the laboratories use for reporting.

The use of WES raises issues, too, around the appropriate reporting of the additional secondary data that sequencing reveals. The targeted panel's inherent lack of secondary data is one of its relative merits. Interestingly, recent surveys reveal that patients are increasingly receptive to the disclosure of this secondary information, and thus some may perceive the targeted approach as a missed opportunity to inform a patient of a potential future health issue.

Targeted panels have a more predictable financial model than WES, especially in the processing of generated data. While there are now CPT codes for a few targeted panels, billing practices and coverage

policies often are unclear or inconsistent. Payer concerns about the clinical utility and financial burden related to secondary findings were also brought forth.

Overall, this meeting was an update on the current state of affairs in the world of NGS as it is implemented in clinical practice. As significant progress has been made in the technical capabilities of NGS, pathology and non-pathology practitioners are steadily moving toward well-defined technical and operational parameters, the key ingredients to bringing this testing into clinical practice. The current questions center on the best diagnostic approach (targeted panel versus WES), which cases should qualify for a specific diagnostic approach, optimum depth and coverage, best practice to interpret the findings, and how to appropriately bill for the services. For now, while targeted panels are preferred for conditions that have a specific phenotype and a high clinical suspicion, WES has been found to be more sensitive in working up difficult cases with nonspecific findings.

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