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Clinical Utility of Genome Sequencing Data Reanalysis

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Before the advent of exome and genome sequencing, genetic testing typically followed a sequential strategy, analyzing one or a few genes at a time. A negative result often led to retesting with a different gene panel or another single-gene assay. However, with the introduction of exome and genome sequencing, a paradigm shift occurred. By sequencing approximately 20,000 genes simultaneously, the need for repeated testing diminished. Instead, attention shifted toward reanalysis of existing data as new knowledge emerged. Reanalysis has become a powerful tool to leverage prior data without requiring additional sampling or sequencing, enabling diagnoses that were previously unattainable. Reanalysis is typically performed on cases with negative initial exome or genome results. Despite the comprehensive coverage of all genes, a substantial proportion of patients still remain undiagnosed after exome/genome sequencing. Reanalysis addresses this gap by incorporating discoveries of novel disease-associated genes, updated variant classifications, and refined clinical phenotyping to uncover previously undetected diagnoses. Several studies have demonstrated that systematic reanalysis, typically conducted around two years after the initial analysis, can improve diagnostic yield by approximately 10%. Most new diagnoses are driven by advancements in gene-disease knowledge. In this presentation, we will review real-world case examples that highlight the clinical value of reanalysis and propose strategies for integrating reanalysis efficiently into the bioinformatics pipeline to accelerate diagnoses and improve patient outcomes. Additionally, we will discuss challenges, including the need for standardized workflows, consistent data access, and substantial resource investments. Importantly, not all negative cases yield a diagnosis even after reanalysis, underscoring the necessity of managing patient and provider expectations. As genomic databases and analytic tools continue to evolve, systematic reanalysis stands as an essential component of precision medicine and long-term patient care.

Keywords: Exome/Genome, Rare disease, Genetics, Diagnosis, Reanalysis