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**High-throughput sequencing of Mendelian disorders: From raw data to diagnosis with lifetime value**

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**Abstract:**
Introduction: High-throughput sequencing (HTS) is widely used for clinical applications such as the molecular diagnosis of Mendelian disorders. As the applied technology/workflow substantially affects the diagnostic yield, knowledge about the pitfalls and advantages of HTS technologies and analysis pipelines is crucial for the successful application of hitherto unprecedented large-scale genetic testing.
Materials and Methods: We address the chances and challenges of HTS in the molecular diagnosis of Mendelian disorders as well as assess the sensitivity/recall, precision, computation time, and disk footprint of four corresponding HTS analysis pipelines.
Results: We exemplify the limitations of targeted (gene panel) and whole-exome sequencing (WES) as well as emphasize the potential of whole-genome sequencing (WGS) in the detection of single nucleotide variants (SNVs) and copy number variations (CNVs). In addition, we elucidate limitations of short-read HTS on exemplary cases including the influence of homologous/repetitive regions (mappability <1) on variant calling and the impact of sequence composition on read depth, as well as show differences in the performance of WGS analysis pipelines.
Conclusions: We recommend to select the HTS method with care and to combine more than one independent bioinformatics pipeline for the most comprehensive data analysis. The use of PCR-free WGS (>60×) instead of WES or panels and the inclusion of CNV analysis can contribute to increased diagnostic yield in molecular diagnosis with lifetime value. As long-read HTS may overcome limitations of short-read HTS, it is envisioned as the future of (clinical) sequencing.
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Author Disclosure Information:

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