Recognizing the Promise and Potential Pitfalls of Genomic Medicine Through Routine Rapid Whole Genome Sequencing

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BACKGROUND

Genome sequencing has many advantages over capture-based next-generation sequencing (NGS) methods particularly for critically ill patients in need of a rapid turn-around-time. Clinical utility of such rapid testing has been demonstrated by several large studies; however, these studies must be translated to routine testing for their full potential to be realized. Minimal processing of the isolated DNA for a non-capture based assay, such as genome sequencing (GS), reduces the time from sample receipt to the start of sequencing. GS produces relatively non-biased even sequence coverage across the genome allowing detection of deep-intronic variants, even if not previously reported. The evenness of the depth of coverage provides high specificity for copy number variant (CNV) calling from the cytogenomic to the intra-genic level. In addition to deletions and duplications, this large dataset also allows confident calling of absence of heterozygosity, aneuploidy, mosaic deletions and duplications and uniparental disomy.

RESULTS

Diagnostic Yield of 45% Across a Mixed Cohort
285 Pediatric Cases (74%) 101 Adult cases (26%)

Proband vs Trio Yield from WGS
Based on 285 Pediatric Cases

Types of Variants Identified through WGS

Cytogenomic yield from WGS + CNGenome
Based on 485 Cases

WGS and Beyond from the Dried Blood Spot

WGS Sequence Quality
- Coverage of intronic sequences
- Better CNV calling than capture-based assays
- Deep mitochondrial sequencing
- SNV/copy number calling

WGS has even more potential
- cCMV from DBS
- Metagenomics – microbiome / virome

DBS Sample
- Amino acids / Organic acids / Acylcarnitine
- Recommended Universal Newborn Screening + Other targets to exceed state panels

CONCLUSION

- WGS from DBS greatly reduces the challenges associated with sample collection from an ill newborn.
- Minimal processing steps in WGS result in rapid turn around time
- WGS results in deep coverage of mtDNA sequence
- Increased diagnostic yield due to detection of deep intronic and cytogenomic variants
- Use of DBS also allows for comprehensive biochemical testing (70+ disorders) by the same methods used for newborn screening