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

Lora H. Bean PhD, FACMG, Christin D. Collins, PhD, FACMG, Fen Guo, PhD, FACMG, FCCMG, Jorune Balciuniene, PhD, FACMG, ErCLG, Xiangwen Chen-Deutsch, PhD, Babi Ramesh Reddy Nallamilli, PhD, FACMG Naga M. Guruju, PhD, FACMG, Rizwan Yousaf, PhD, Kristina Fura, BS, Amber Woodman, BS, Ruby Liu, PhD, CGC, Jenny Zhang, MS, Kate Liebmann, MS, Julia C. Gerow, MS, Ephrem Chin, MBA, MB(ASCP) CM, Madhuri Hegde, PhD, FACMG

PerkinElmer Genomics, Pittsburgh, PA

## 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.

## DRIED BLOOD SPOT vs WHOLE BLOOD

**DNA QUANTITY BY SAMPLE TYPE**

| Sample Type | Average Concentration | Total Yield | Count of Sample |
|---|---|---|---|
| DBS | 4.08 ng/ul | 244.6 ng | 20 |
| WP | 37.97 ng/ul | 3251.6 ng | 20 |

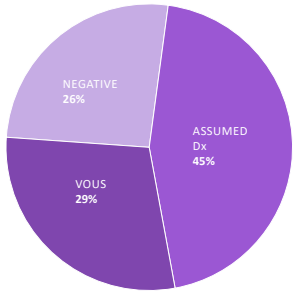
**SEQUENCING METRICS BY SAMPLE TYPE**

| Sample Type | Average of Yield (Mb) | Average of % >=Q30 bases | Average of Coverage | Average of % Mapped Reads | Average of % Duplicate Reads | Average of % Regions >10x | Count of Sample |
|---|---|---|---|---|---|---|---|
| DBS | 146260.13 | 93.11 | 40.80 | 0.99 | 0.06 | 90.58 | 13 |
| WP | 146255.73 | 93.68 | 40.06 | 0.99 | 0.07 | 90.67 | 11 |

## RESULTS

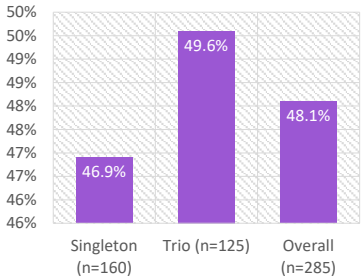
### Diagnostic Yield of 45% Across a Mixed Cohort

285 Pediatric Cases (74%) 101 Adult cases (26%)




### Proband vs Trio Yield from WGS

Based on 285 Pediatric Cases




### 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
- *SMN1* copy number calling

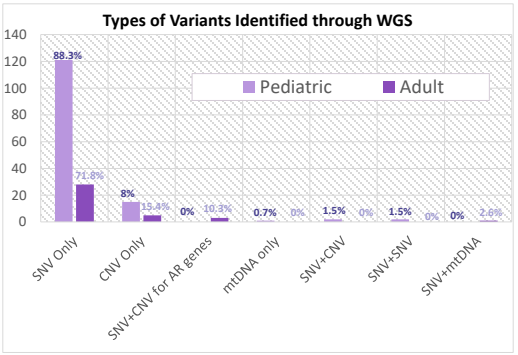
**WGS has even more potential**

- cCMV from DBS
- Metagenomics – microbiome / virome

**DBS Sample**

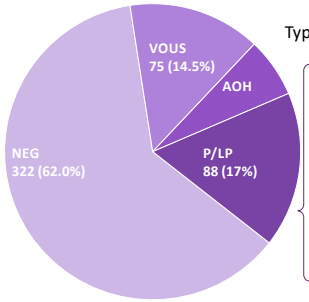
- Amnio acids / Organic acids / Acylcarnitine
- Recommended Universal Newborn Screening + Other targets to exceed state panels

### Types of Variants Identified through WGS




### Cytogenomic yield from WGS + CNGenome

Based on 485 Cases

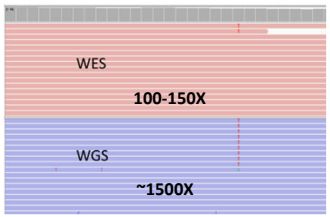



Types of Diagnostic Findings (n=88)

**PATHOGENIC & LIKELY PATHOGENIC FINDINGS**

| | Diagnostic | Carrier |
|---|---|---|
| **Aneuploidy** | 9 (10.2%) | 0 |
| **Microdel/dup** | 48 (9.2% | 3 (0.6%) |
| **Intragenic** | 13 (2.5%) | 12 (2.3%) |
| **UPD** | 1 (0.2%) | 0 |
| **Suspected unbalanced translocation** | 2 (0.4%) | 0 |
| **Total** | **73 (14.1%)** | **15 (2.9%)** |

### mtDNA Coverage




WGS detected a pathogenic m.14658C>T mtDNA variant that was missed by WES due to lower coverage

## 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