Unparalleled power of genome sequencing in screening ostensibly healthy newborns and children: findings from the first real-world dataset

J. Balciuniene, R. Liu, C. Collins, L. Bean, F. Guo, B.R.R. Nallamilli, N. Guruju, X. Chen-Deutsch, R. Yousaf, Fura, E. Chin, C. da Silva, A. Mathur, Z. Ma, M. Hegde

Introduction

Early diagnosis of a genetic disease is critical to maximize clinical outcomes and reduce healthcare costs. Genome sequencing (GS) is emerging as a method of choice to diagnose genetic conditions, with its clinical utility best documented for critically ill children. With rapidly decreasing sequencing cost, GS is becoming a feasible option for healthy population screening, particularly newborn screening. To gauge the clinical value of GS in newborn screening, large scale studies are needed to explore the rate and scope of potential genetic diagnoses in ostensibly healthy children.

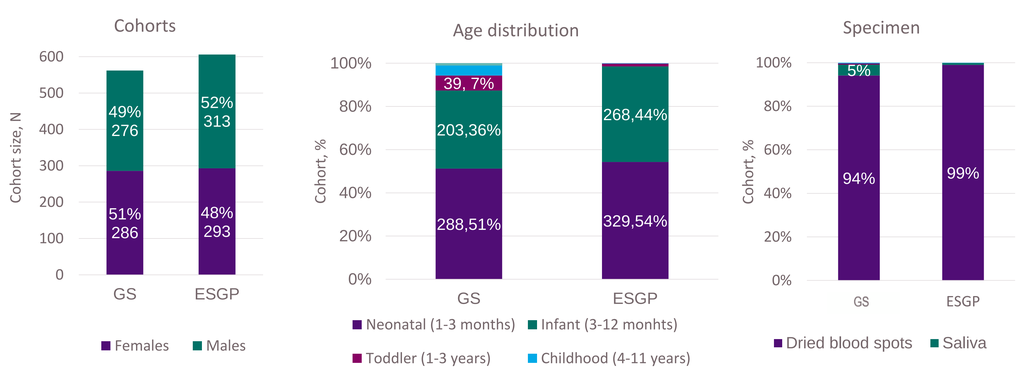
Here we present the findings from a large real-world dataset on using clinical grade GS to screen a large unsolicited cohort of ostensibly healthy newborns and children. We compare the rate and scope of the genetic risks identified by GS to those uncovered by a targeted screen of genes associated with medically actionable conditions.

Study design

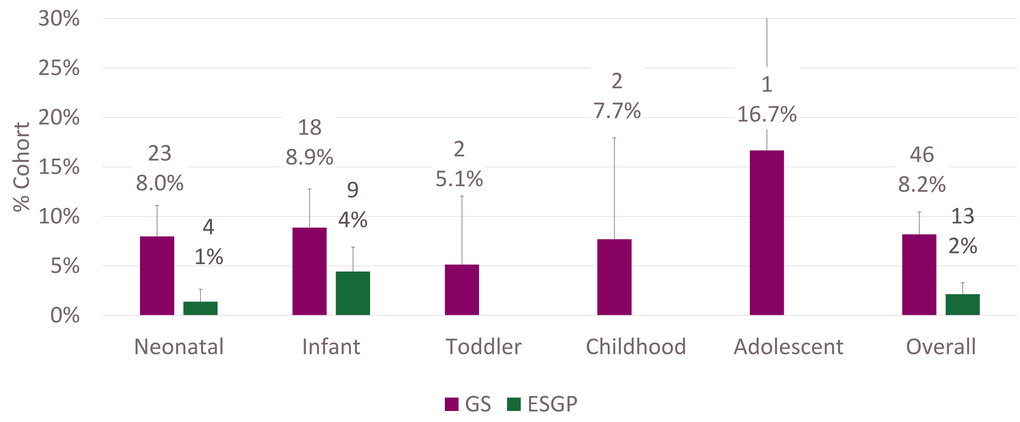
Proactive screening of ostensibly healthy newborns or children was initiated by parents/guardians and coordinated by virtual medical practice physicians. Two genetic screening options were offered.

	Exome Sequencing Gene Panel (ESGP) N=606	Genome sequencing N=562
Sequencing	• Exome at 100x • 22,000 genes • Coding regions, and flanking exon/intron boundaries	• Whole genome at 40x • ~22,000 genes • Coding and non-coding regions • Intergenic sequences • mtDNA (1000x)
Analysis	• ~270 genes associated with medically actionable pediatric onset conditions • ±Exonic SNV • CNVs affecting panel genes only	• ~6000 genes associated with disease: • Exonic and intronic SNVs • Whole genome CNVs and other copy number/allelic imbalances • mtDNA SNVs • *SMN1* deletion screening
Reporting	• Genotypes at-risk for disease in the panel genes	• Genotypes at-risk for pediatric onset mendelian disease • Pharmacogenomic findings of CPIC level A and PharmGKB 1A

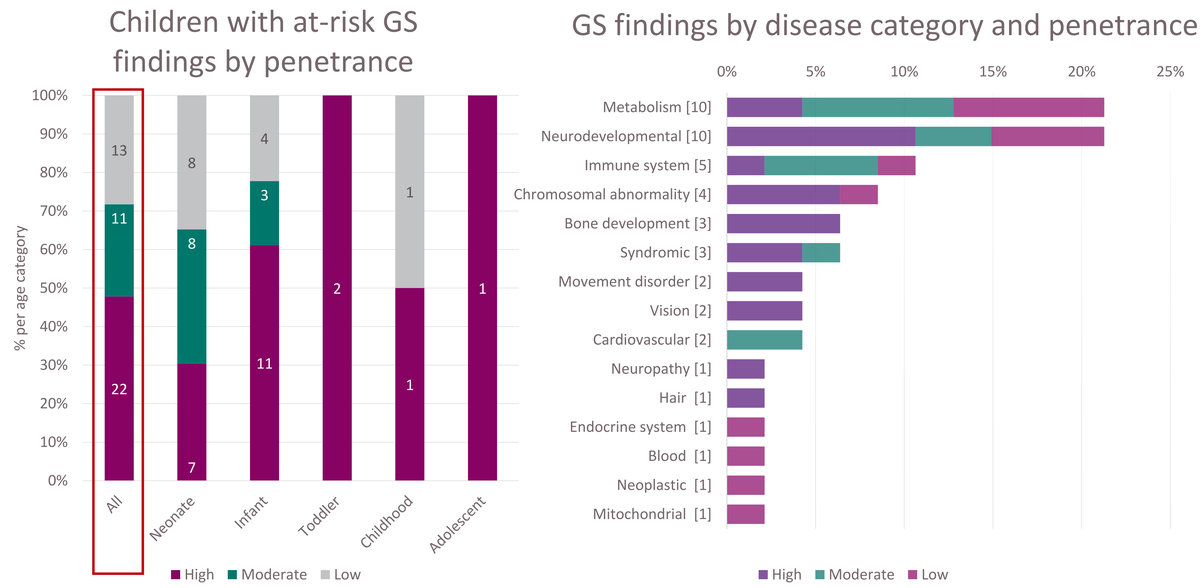
Cohort and specimen characteristics



Children at risk for genomic disease



GS findings by penetrance and disease



Conclusions

- 8.2% of ostensibly healthy babies are at-risk for pediatric onset mendelian condition
- 4% were found to be at risk for high-penetrance disease
- Molecular findings uncovered by GS are highly heterogeneous and cannot be easily captured by a limited number gene panels
- Majority of the findings are likely to influence healthcare management of babies at risk, and provide valuable information for other family members
- A nationwide study is needed to gauge the impact of newborn GS on clinical outcomes and economic costs
- Early GS is the “encyclopedia for life” that holds medically relevant information throughout the continuum of care from birth to adulthood