Genome Screening of Newborns: what can we find and what's next?

J. Balciuniene[1], R. Liu[1], J. Carmichael[2], M. Longoni[3], S Bhatt[3] M. Hegde[1]
[1]Revvity Omics, Revvity, Pittsburgh, Pennsylvania, USA, [2]ViaCord LLC, Revvity, Waltham, Massachusetts,
[3]Medical Affairs, Illumina, Inc., San Diego, CA, USA

1 Introduction

Early diagnosis of a genetic disease is critical to maximize clinical outcomes and reduce healthcare costs. Genome sequencing (GS) has shown great promise in rapidly providing diagnosis for critically ill newborns and has moved into the spotlight of national and international initiatives that explore the GS in the setting of newborn screening (GS for NBS). Studies exploring GS for NBS genomic findings and their net impact on clinical outcomes and psychosocial well-being of affected families are crucial to inform the successful design of GS for NBS program with maximized clinical utility

We previously published at-risk genomic findings from a large real-world cohort of ostensibly healthy newborns and children (N=1168) screened by GS (N=562) or an exome-based gene panel (ESGP, N=606) (Balciuniene et al 2023).

To further the clinical utility assessment of proactive genomic screen in pediatric population, we are conducting a single-arm follow-up study to gather additional data on the children and their families identified to carry unanticipated risks for pediatric genomic disorders.

2 Methods

The screening cohort consists of families who chose to voluntary enroll for an out-of-pocket proactive screening offered via commercial cord blood and tissue banking company.

Proactive screening of asymptomatic newborns or children (N=1168) was conducted using ESGP for actionable pediatric conditions (268 genes) or GS (~6000 genes).

Illumina short read sequencing followed by sequence and copy number analysis of target genes using clinically validated bioinformatics pipeline was performed. Only clinically significant variants consistent with the risk of developing pediatric-onset disease were reported.

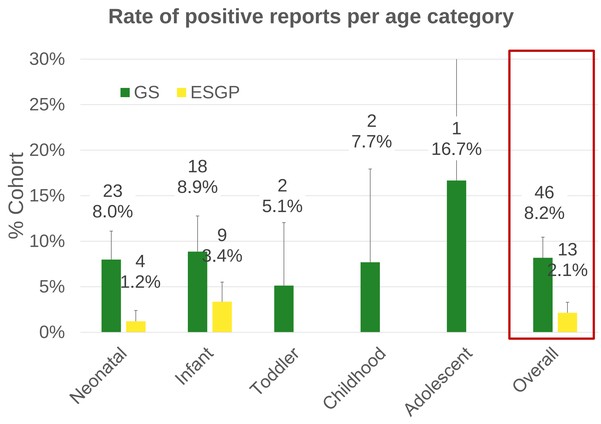
Stratification of the findings by low (<20%), moderate (20-80%) and high penetrance (>80%) was achieved by integrating information from literature sources and applying logical reasoning and extrapolations.

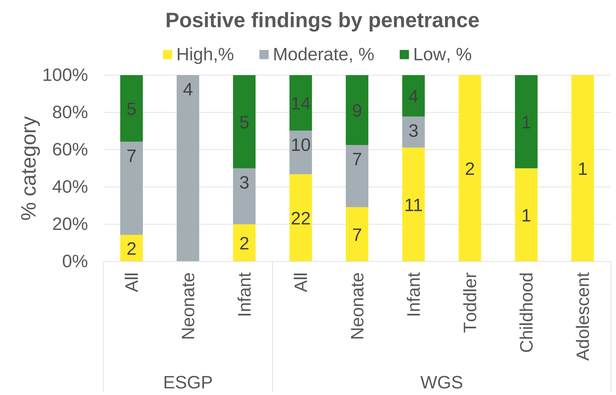
The follow-up study is focused on gathering further clinical and psychosocial impact data on families with children who received positive GS findings:

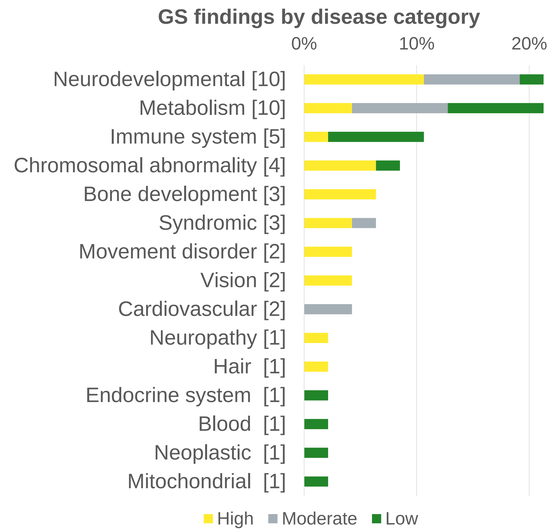
- comprehensive review of medical records provided to the clinicians at the time of screening consent and return of results
- conducting a follow-up phone interview to gather data pertinent to the child's findings and their impacts to the family.

3 Results

8.2% of ostensibly healthy babies were found to be at-risk for pediatric onset mendelian condition by GS;
4% were found to be at risk for high-penetrance disease.







4 At risk genomic findings from GS by presumed penetrance

Disease category	High penetrance	Moderate penetrance	Low penetrance
Neurodevelopment	*ASH1L*, *PPM1D, CHD8*, 7q11.23 dup, 20q13.33 del	*NRXN1*, 1q21.1 del 16p11.2 dup	22q11.2 dup, 16p13.11 del
Metabolism	*HNF1A, CYP21A2,*	*LDLR, G6PD*	*BTD*
Immune	*MEFV*		*IFNGR1*, *TNFRSF13B*
Chromosomal	Wolf-Hirschhorn, Pallister-Killian Mosaic Trisomy 8		16UPD
Bone	*COL10A1, FGFR3, SHOX*		
Syndromic	*COL11A1, MITF*	COL4A3	
Movement	*SGCE*		
Vision	*SLC39A5, ABCA4*		
Cardiovascular		*MYBPC3*, *PLN*	
Neuropathy	*PMP22*		
Hair	*RPL21*		
Endocrine			*PROKR2*
Blood			*SPTA1*
Neoplastic			*SDHA*
mtDNA			mt-TS1 (7%)

5 Follow-up interview questions

I. DEMOGRAPHIC INFORMATION ABOUT THE RESPONDENT

II. REASONS FOR CHOOSING THE TESTING

- Why did they choose to do genetic screening for their child?
  - Family history, medical concerns during pregnancy or after birth, being proactive, other
- Actionable Gene Panel versus Genome Sequencing: which and why?
  - Actionability/comprehensiveness/budget
- Did the child's siblings receive genetic screening as newborns, too?

III. FAMILY HISTORY

- Is there a family history of the disease identified by genome screening and was it known before testing?

IV. PROBAND PHENOTYPE

- Does the child currently show any symptoms related to the genetic screening results?
- What are the child's symptoms or main health concerns? At what age they first begin?
  - <1 years of age/ 2-5 y or >5 y of age
- What is the child's diagnosis? Was the diagnosis picked up at the standard newborn screening?
- Was the child referred to a specialist because of their genetic screening results? Which specialist?
- Has the child ever been on a specific medication, therapy, or regimen (diet) because of this genetic diagnosis?
- Which specific medication, therapy, or regimen is/was the child on because of their genetic diagnosis?

V. FAMILY AND CASCADE TESTING

- Were the child's genetic screening results and implications discussed with family relatives at risk?
- What challenges, if any, were encountered when discussing the child's genetic screening results and their implications with relatives?
  - Anxiety at reaching out to family members, lack of knowledge, no family contact
- Was additional genetic testing performed on relatives who might also be at risk?
- Which of the child's relatives decided to undergo genetic testing and who received positive report?

VI. PSYCHOSOCIAL IMPACT

- What was their initial reactions to receiving the results of the child's genetic screen?
- How do they feel about their child's results now?
  - Feeling of empowerment to act without delay
  - Helplessness, stress, anxiety
  - Worry of possible health stigma, insurance/professional discrimination
  - Regret for agreeing to the testing

Reference:
Balciuniene J, Liu R, et al. At-Risk Genomic Findings for Pediatric-Onset Disorders From Genome Sequencing vs Medically Actionable Gene Panel in Proactive Screening of Newborns and Children. JAMA Netw Open. 2023 Jul 3;6(7) PMID: 37523181; PMCID: PMC10391308.