# Furthering the Dialogue on Newborn Sequencing:
## Insights from Neonatal Rapid Whole Genome Sequencing

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## BACKGROUND

- **Traditional newborn screening (NBS)** has enabled early detection and management of many rare disorders[1].
- Early detection and treatment is associated with significantly improved health outcomes and reduced mortality.
- **Newborn sequencing** can detect a wider range of conditions beyond conventional NBS.
- There is preliminary evidence supporting the clinical utility of newborn sequencing[2].
- This study **examined rapid whole genome sequencing (rWGS) results from neonatal patients tested at a clinical laboratory**, exploring the potential benefits of this approach in neonatal care.

## METHODS

**Study Design:** Retrospective review of rWGS results

**Inclusion Criteria:**

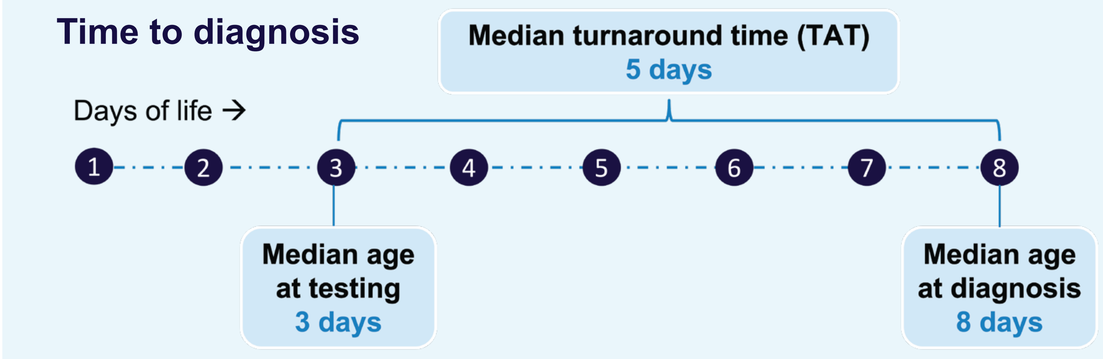
- Neonatal patients (≤28 days old)
- Inpatient referral for rWGS
- Positive test result (molecular diagnosis on rWGS)

**Analysis:**

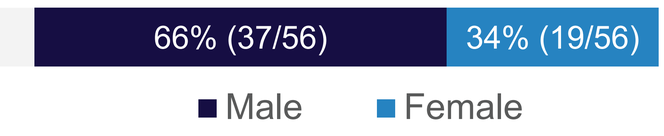
- Reviewed clinical indications and genetic results (specific gene, variant type, inheritance pattern) for 56 consecutive positive cases.
- Assessed medical intervention availability for each identified condition.
- Compared positive results with genes included in a commercially available panel of 250+ genes associated with conditions detected by NBS across all states within the U.S.

## RESULTS

### Time to diagnosis

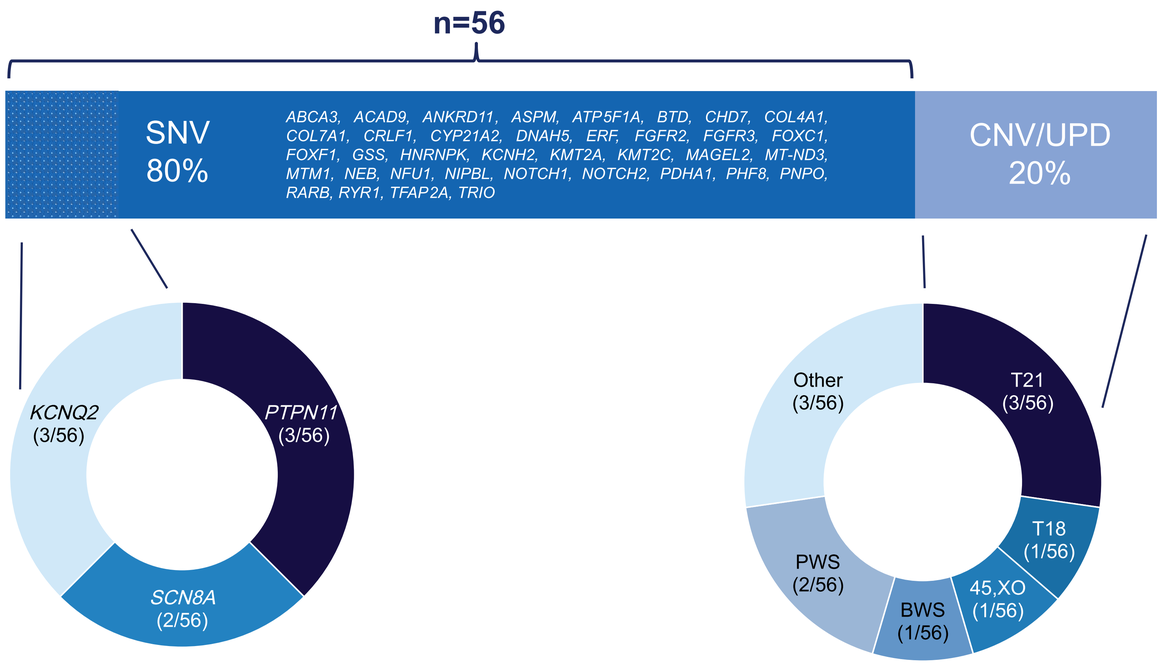



**Reported Sex:** 2/3 male




**Referral Indications:** 89% (50/56) multisystemic findings

- **Pulmonary** 54% (30/56)
- **Cardiac** 52% (29/56)
- **Neurology** 46% (26/56)




Genes with single nucleotide variants (SNVs) present in more than one patient

Copy number variants (CNVs) and uniparental disomies (UPDs), including Down syndrome (T21), Prader-Willi syndrome (PWS), Edwards syndrome (T18), Turner syndrome (45,XO), and Beckwith-Wiedemann syndrome (BWS).

**Medical Intervention:** All patients had conditions that could potentially benefit from medications, surgery, and/or dietary modifications

- **Medication** 62.5% (35/56)
- **Surgery** 59% (33/56)
- **Dietary** 9% (5/56)
- **Supportive therapy** 61% (34/56)

**Comparison of single gene findings against NBS panel**

| 73% (33/45) not identifiable by NBS panel | 27% (12/45) identifiable by NBS panel |
|---|---|
| *ABCA3, ACAD9, ANKRD11, ASPM, ATP5F1A, CHD7, COL4A1, COL7A1, CYP21A2, DNAH5, ERF, FGFR2, FGFR3, FOXC1, FOXF1, HNRNPK, KCNH2, KMT2A, KMT2C, MAGEL2, MT-ND3, MTM1, NEB, NFU1, NIPBL, NOTCH1, NOTCH2, PDHA1, PHF8, RARB, RYR1, TFAP2A, TRIO* | *BTD, CRLF1, GSS, KCNQ2, PNPO, PTPN11, SCN8A, SCN1A* |

**Conclusions:** Rapid WGS for neonatal patients identified a broad range of genetic conditions and various inheritance patterns, many of which are not detectable by routine newborn screening. Results had medical management implications for patients and their family members. Newborn sequencing can complement newborn screening to support public health goals.

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**References:**

(1) Centers for Disease Control and Prevention (CDC). CDC Grand Rounds: Newborn screening and improved outcomes. MMWR Morb Mortal Wkly Rep. 2012;61(21):390-393.

(2) Bodian DL, Klein E, Iyer RK, et al. Utility of whole-genome sequencing for detection of newborn screening disorders in a population cohort of 1,696 neonates. Genet Med. 2016;18(3):221-230. doi:10.1038/gim.2015.111