Population-based 1st-tier Genomic Newborn Screening Results of BabyDetect Study

https://babydetect.com

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Background:

Newborn screening (NBS) has evolved significantly since its introduction into public health programs in the 1960s. Advances in technology have progressively enabled the inclusion of a broader range of metabolic, endocrine, and rare disorders, preventing severe disability and premature death in thousands of children. Within this framework, several genomic newborn screening (gNBS) initiatives have been launched worldwide, employing targeted next-generation sequencing (tNGS), whole-exome sequencing (WES), or whole-genome sequencing (WGS).

Objective:

In September 2022, the research project BabyDetect (ClinicalTrials.gov NCT05687474) was launched, aiming to explore the feasibility and the acceptability of first-tier gNBS in Liege, Belgium. The study focused on identifying actionable genetic variants and their impact on neonatal health. The study concluded on May 31st, 2025.

Method:

We have designed a tNGS panel consisting of 405 genes responsible for 165 severe, pediatric and treatable conditions (Figure 1). Only class 4 (likely pathogenic) and class 5 (pathogenic) variants documented in ClinVar or in our own managed variant list were reported.

Results:

Over 33 months, 7,515 parents were informed about the trial. 6,824 accepted to enroll their baby in the study (consent-rate 90,8 %). Of the 6,824 sequenced samples, 134 tested positive (Figure 2). All of these cases received appropriate follow-up and medical management. Among them, 118 were for conditions not covered by conventional NBS, including 94 cases of G6PD deficiency.

CPT2 deficiency was identified in one neonate and subsequently confirmed by orthogonal testing, whereas conventional NBS failed to detect the disorder.

Three results were identified as false-positives: two ‘allelic’ cases (one case of primary hyperoxaluria and one case of Wilson disease) and one ‘phenotypic’ case (SCAD deficiency).

Two false-negative cases (*TJP2*-related cholestasis and MTHFR deficiency) were identified retrospectively upon clinical presentation and WES analysis. The corresponding variants had not been reported through the BabyDetect trial, as they were absent from ClinVar, the published literature, and our own curated list.

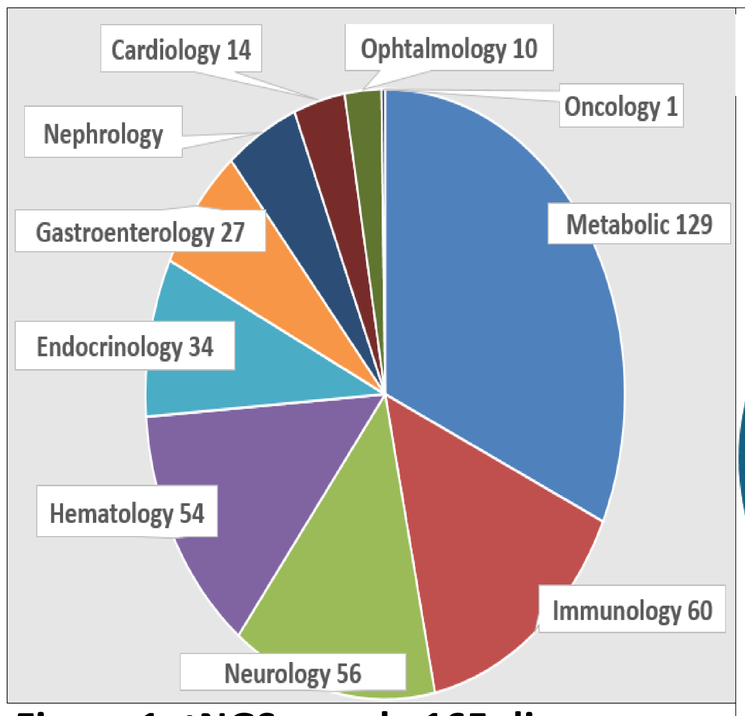

Figure 1: tNGS panel : 165 diseases

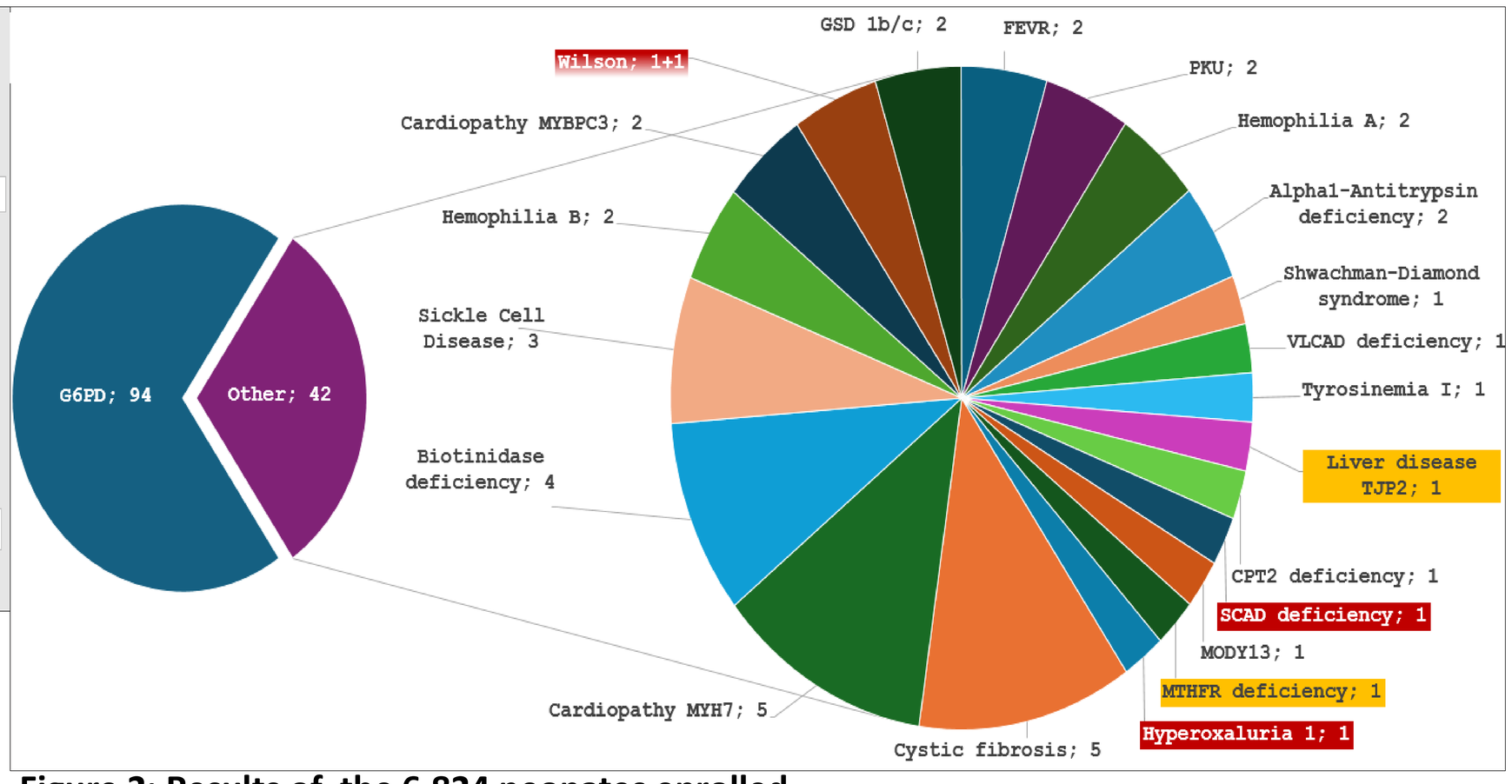

Figure 2: Results of the 6,824 neonates enrolled

Orange frame: false-negative cases. Red frame: false-positive cases

Conclusion:

The data demonstrate the high acceptability of gNBS in a properly informed population.

Our results indicate the feasibility of mid-scale gNBS, highlighting also the importance of combining biochemical and genomic approaches in NBS.