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Expanded Newborn Screening Using Genome Sequencing for Early Actionable Conditions

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IMPORTANCE The feasibility of implementing genome sequencing as an adjunct to traditional newborn screening (NBS) in newborns of different racial and ethnic groups is not well understood.

OBJECTIVE To report interim results of acceptability, feasibility, and outcomes of an ongoing genomic NBS study in a diverse population in New York City within the context of the New York State Department of Health Newborn Screening Program.

DESIGN, SETTING, AND PARTICIPANTS The Genomic Uniform-screening Against Rare Disease in All Newborns (GUARDIAN) study was a multisite, single-group, prospective, observational investigation of supplemental newborn genome screening with a planned enrollment of 100 000 participants. Parent-reported race and ethnicity were recorded at the time of recruitment. Results of the first 4000 newborns enrolled in 6 New York City hospitals between September 2022 and July 2023 are reported here as part of a prespecified interim analysis.

EXPOSURE Sequencing of 156 early-onset genetic conditions with established interventions selected by the investigators were screened in all participants and 99 neurodevelopmental disorders associated with seizures were optional.

MAIN OUTCOMES AND MEASURES The primary outcome was screen-positive rate. Additional outcomes included enrollment rate and successful completion of sequencing.

RESULTS Over 11 months, 5555 families were approached and 4000 (72.0%) consented to participate. Enrolled participants reflected a diverse group by parent-reported race (American Indian or Alaska Native, 0.5%; Asian, 16.5%; Black, 25.1%; Native Hawaiian or Other Pacific Islander, 0.1%; White, 44.7%; 2 or more races, 13.0%) and ethnicity (Hispanic, 44.0%; not Hispanic, 56.0%). The majority of families consented to screening of both groups of conditions (both groups, 90.6%; disorders with established interventions only, 9.4%). Testing was successfully completed for 99.6% of cases. The screen-positive rate was 3.7%, including treatable conditions that are not currently included in NBS.

CONCLUSIONS AND RELEVANCE These interim findings demonstrate the feasibility of targeted interpretation of a predefined set of genes from genome sequencing in a population of different racial and ethnic groups. DNA sequencing offers an additional method to improve screening for conditions already included in NBS and to add those that cannot be readily screened because there is no biomarker currently detectable in dried blood spots. Additional studies are required to understand if these findings are generalizable to populations of different racial and ethnic groups and whether introduction of sequencing leads to changes in management and improved health outcomes.

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Editorial

Supplemental content

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Newborn screening (NBS) enables the diagnosis of conditions within days of birth, thereby providing the opportunity for early treatment prior to the onset of symptoms and irreversible effects. NBS was first implemented for phenylketonuria in 1963.[1] In the US, NBS has been gradually expanded to include inborn errors of metabolism, cystic fibrosis, hearing impairment, critical congenital heart disease, endocrine disorders, hemoglobinopathies, severe combined immunodeficiency (SCID), and other genetic conditions.[2] There is growing support from rare genetic disease advocates, parents, and public health professionals to expand NBS to enable timely access to new, and often precision, rare disease therapies.[3,4] For example, a pilot NBS study in New York State for spinal muscular atrophy[5] demonstrated high opt-in rates (93%) and supported the addition of spinal muscular atrophy to the recommended uniform screening panel[6] following US Food and Drug Administration approval of nusinersen.

The current use of DNA sequencing in NBS is largely restricted to second-tier testing, including assessment of *CFTR* (Online Mendelian Inheritance in Man [OMIM] 602421) for cystic fibrosis.[5] The declining cost of DNA sequencing, improved ability to interpret genomic data, and advancements in treatments have raised the questions of whether and how to implement first-tier targeted sequencing, exome sequencing, or genome sequencing to expand NBS for conditions lacking biomarkers.[7,8]

The use of genome sequencing for NBS has raised concerns, including acceptability, equity, and scalability, with expected challenges such as potentially adverse psychosocial impact, assay costs, workforce limitations, patient privacy concerns, and difficulty in variant interpretation across diverse ancestral groups.[3] Ten studies[7,9-17] differing in the conditions assessed and target populations (eTable 1 in Supplement 1) have evaluated the use of sequencing for NBS in cohorts of more than 100 children. Although these studies supported the potential use of genome sequencing as a supplement to traditional NBS, many were limited in sample size, characteristics of conditions included, and/or ancestral diversity. Implementation of genome sequencing within the NBS framework has continued to be debated with respect to cost, turnaround time, and feasibility in the public health setting and in ensuring high sensitivity and specificity compared with biochemical screening. Universal genome sequencing for NBS could raise issues in public perception. NBS programs need to incorporate specific policies to protect the public's trust by ensuring confidentiality of data gleaned from genome sequencing.

To assess the feasibility of scaling genomic NBS, the Genomic Uniform-screening Against Rare Disease in All Newborns (GUARDIAN) study was initiated with the aim of screening a diverse population by parent-reported race and ethnicity of newborns in New York City within the context of the New York State Department of Health Newborn Screening Program. This study reports on the first 4000 patients assessed through GUARDIAN to highlight both the feasibility and potential impact of genomic NBS and to support the ongoing dialogue regarding potential challenges to state or nationwide implementation.

Key Points

Question What is the parental acceptance, feasibility, and screen-positive rate of targeted genome screening in newborns of different racial and ethnic groups?

Findings In this study of 4000 newborns, 72.0% of approached families consented to participate. Genome sequencing was successfully completed for 99.6% of participants. The screen-positive rate in a predefined gene panel was 3.7%.

Meaning Targeted analysis of a predefined set of genes from genome sequencing for screening in a diverse newborn population is feasible and could expand the scope of newborn screening.

Methods

Study Design, Setting, and Population

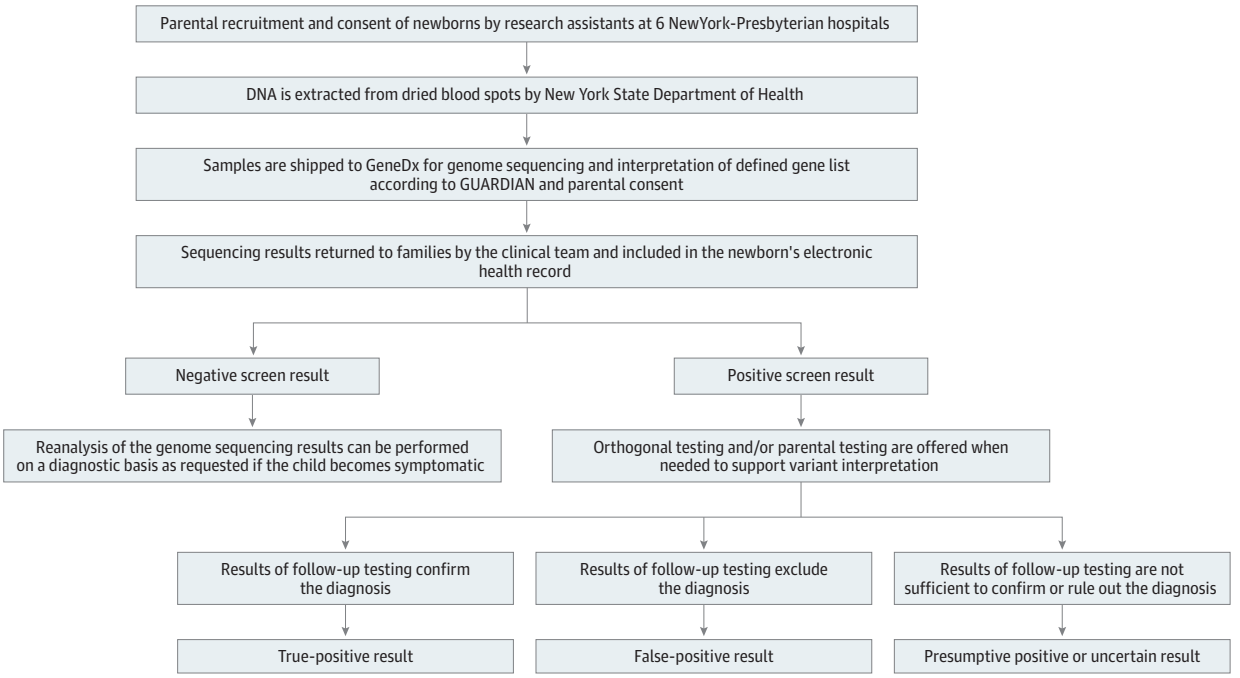
This multisite, single-group, prospective, observational study was designed over a period of 4 years with extensive community, clinical, and technical input and was approved by the WCG IRB (20215102). The design of the study is outlined in **Figure 1**. Parents were approached in person or by phone and provided electronic consent linked to a REDCap database.[18] Privacy was protected by a certificate of confidentiality issued by the National Institutes of Health. There was no cost to participate. The results reported are preliminary, as the study is planned to enroll 100 000 newborns. The interim analysis was performed at the end of the first year of recruitment and aimed to assess the diversity of the recruited population, acceptance of genomic screening, the rate of successful genomic sequencing from dried blood spots, and screen-positive rate.

Between September 2022 and July 2023, parents were approached by research staff in person at 1 of 6 NewYork-Presbyterian hospitals after delivery. Research staff covered the hospitals on certain days during regular business hours. Some parents were contacted by phone. Parents had the opportunity to consent until 30 days after birth. Parents who declined enrollment were asked to provide the reason for their decision.

Parent-reported race and ethnicity were used when characterizing the participants recruited (**Table**). In addition, to address acculturation as a factor that may influence participant preferences, the uptake of disorders with established interventions only vs both groups was assessed in the context of the primary household language.

This study interpreted data for 237 genes that are associated with 255 discrete conditions, most with reported penetrance of 90% or higher affecting young children (age ≤5 years) (eTables 2 and 3 in Supplement 2). Each condition was classified by a team of pediatricians, geneticists, and genetic counselors as belonging to either disorders with established interventions (156 conditions), composed of treatable conditions using ClinGen Actionability criteria,[19] or neurodevelopmental disorders associated with seizures (99 conditions), primarily composed of neurodevelopmental disorders that may benefit from early interventions or treatment of associated epilepsy.[20]

Figure 1. Study Flow of Interim Analysis of the First 4000 Enrolled Newborns



GUARDIAN indicates Genomic Uniform-screening Against Rare Disease in All Newborns.

Disorders with established intervention conditions were screened in all participants, while neurodevelopmental disorders associated with seizures were optional. Orthogonal assays were available for confirmatory testing (eg, assessment of metabolites for an inborn error of metabolism; eTables 2 and 3 in Supplement 2) of all disorders with established interventions and 33.3% (33) of neurodevelopmental disorders associated with seizures.

DNA Sequencing and Variant Interpretation

To reduce burden on participating newborns, the dried blood spot used for routine NBS was also used for genome sequencing. After completion of standard NBS, genomic DNA was extracted from dried blood spot punches.

Genome sequencing was performed at 30 times or more mean coverage. Repeat extractions, when needed, were performed using the same method and on the same Guthrie card. Using genomic DNA, polymerase chain reaction (PCR)-free whole-genome sequencing libraries were prepared using an Illumina DNA PCR-Free Prep kit following the manufacturer's protocol (Illumina Inc). Genomic sequencing was performed on NovaSeq 6000 at 2 × 150 bp. Alignment and variant calling was performed using Dragen version 3.5.7. Additional details of the sequencing protocol have been previously reported.[21] The analyzed variants were restricted to this study's gene list and were analyzed using a proprietary variant annotation, filtering, and viewing interface (Xome Analyzer), which included population data from public databases, such as gnomAD v2 and GeneDx's database of more than 600 000 clinical sequencing samples, in silico tools, and individual variant resources, including published literature and ClinVar.[21] For GUARDIAN samples, classifications of variants previously reported at GeneDx were available within the analysis interface to facilitate review and prioritization (Supplement 1).

Computed Genetic Ancestries

To address missing data for self-reported ancestry and reports of 2 or more races, we used computed genetic ancestry to assess the impact on interpretation workload. Principal component analysis was performed using single-nucleotide variation calls from genome sequencing samples for ancestry prediction as described previously[22] (see Supplement 1 for additional details).

Selection of Variants for Screening

Variants were classified according to the American College of Medical Genetics and Genomics (ACMG) criteria.[23] Pathogenic and likely pathogenic variants were reported in genes with autosomal recessive, autosomal dominant, and X-linked inheritance. Variants of uncertain significance likely to be benign were excluded. Other variants of uncertain significance were only reported for autosomal recessive conditions if they co-occurred with a pathogenic or likely pathogenic variant (eTable 4 in Supplement 1). Results from the preliminary analyses were used to adjust the selection of variants to be reported (eg, after the first 1000 enrolled, variants in *CFTR* with varying clinical phenotypes, including the recurrent p.D1270N and p.R74W variants, were not reported). All positive results were confirmed by an independent molecular

Table. Cohort Characteristics of the GUARDIAN Study

Characteristic	No. (%)
Sex	
Male	2055 (51.4)
Female	1945 (48.6)
Enrollment	
In person	3800 (95.0)
Reported ethnicity of the newborn[a]	
Hispanic	1503 (44.0)
Not Hispanic	1916 (56.0)
Reported race of the newborn[a]	
American Indian or Alaska Native	15 (0.5)
Asian	462 (16.5)
Black	701 (25.1)
Native Hawaiian or Other Pacific Islander	3 (0.1)
White	1249 (44.7)
2 or more races	362 (13.0)
Primary language spoken by the parents[b]	
English	3185 (79.6)
Spanish	651 (16.3)
Mandarin	34 (0.1)
Other	130 (3.3)
Parent consenting	
Mother	3062 (76.5)
Father	936 (23.4)
Legal guardian	2 (0.1)

Abbreviation: GUARDIAN, Genomic Uniform-screening Against Rare Disease in All Newborns.

[a] For race and ethnicity, newborns for whom information was not available were not included in the calculation of the percentage.

[b] Participants speaking 1 language referenced as other were able to speak English, Spanish, or Mandarin fluently.

genetic test on a new DNA aliquot prior to issuing the study screen report. Turnaround time was defined as the time between parental consent and time when the genomic screen report was available.

Return of Results and Outcome Measures

Negative results were returned to parents by phone and encrypted email. Positive results were returned by phone by a medical geneticist and genetic counselor, followed by an in-person clinical visit with a genetic counselor, medical geneticist, social worker, and other clinicians relevant to the potential diagnosis. During this appointment, additional orthogonal clinical testing was ordered as appropriate to confirm the diagnosis, including parental genetic testing for the variant(s) identified in the newborn and/or biochemical testing. True positives were defined as individuals with variants confirmed by orthogonal clinical testing and/or supported by published functional data supporting pathogenicity of the genetic variant prior to the initial reporting. Presumptive positives were defined as screen-positive individuals for whom it was not possible to confirm the diagnosis with orthogonal clinical testing due to the age of the infant. False positives were defined as individuals for whom orthogonal clinical testing and/or phasing of the variant excluded the disease.

Statistical Analyses

Enrollment in disorders with established interventions only vs both groups by language spoken and frequency of positive reports for European computed ancestry vs other computed ancestries were compared with a χ^2 test.

Results

Study Enrollment

A total of 8617 newborns were eligible for the study from September 2022 to July 2023. A total of 5555 parents (64.5%) were approached. Of those parents approached, 4000 (72.0%) consented to the study (**Figure 2**). Parent-reported race and ethnicity are detailed in the Table. Most parents (90.6%; n = 3624) consented for both groups of conditions. Spanish speakers were more likely to choose disorders with established interventions only compared with English speakers (16.3% vs 8.1%; $P < .001$; eFigure 1 in Supplement 1).

Of the 1555 individuals who declined enrollment, 927 (59.5%) provided reasons for declining (eTable 5 in Supplement 1). Lack of interest in the study, the perception that standard NBS was sufficient, or feeling overwhelmed were reported by 286 (30.9%), 196 (21.2%), and 131 (14.1%) individuals, respectively. Concerns about engaging in genetic research or the privacy of genetic information were rare and expressed by 3.8% and 2.3% of respondents, respectively.

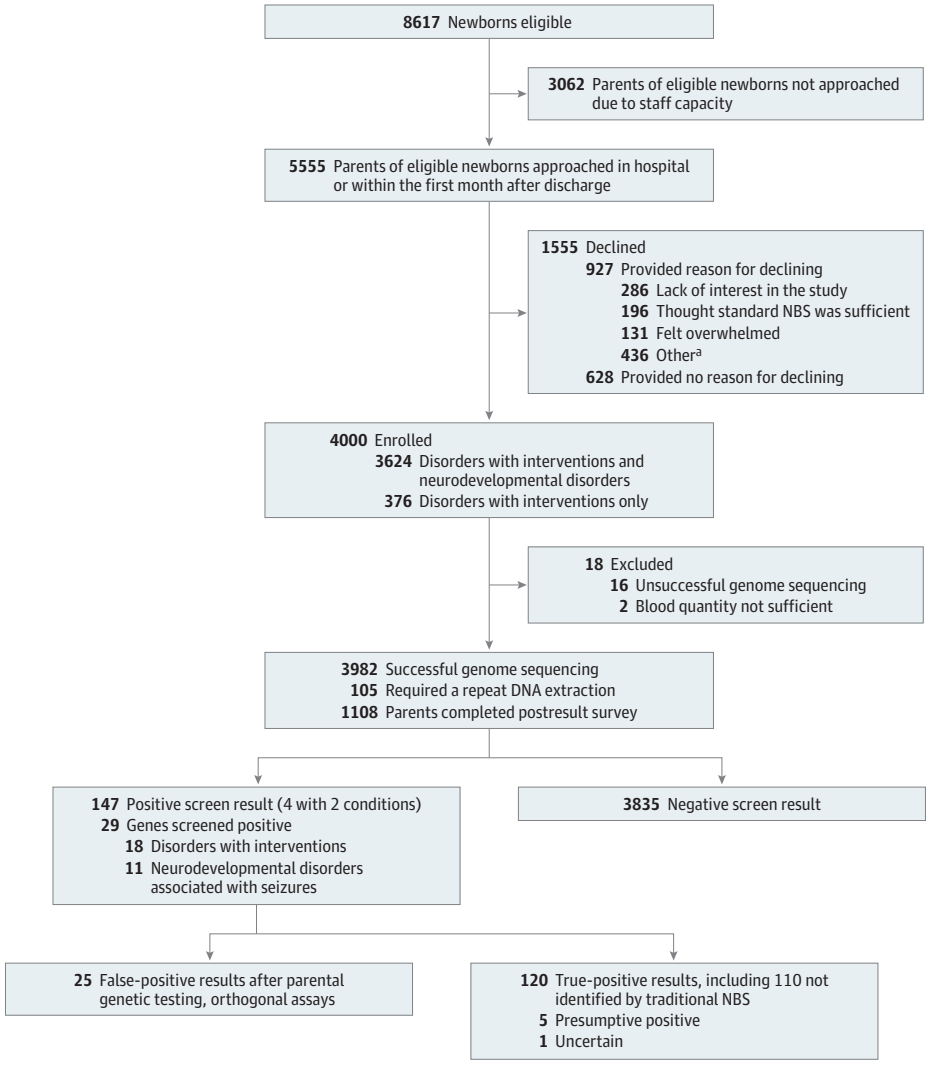
Data Generation and Reporting

Sequencing was successful for 3982 participants (99.6%) (Figure 2). For 2 participants, insufficient blood remained on the dried blood spot card after standard NBS, and genome sequencing was not performed. Genome sequencing failed for 16 individuals for whom a repeat specimen was not tested. A total of 105 participants (2.6%) were successfully sequenced from a repeat. Our target turnaround time from consent to report delivery was 42 to 49 days. For the first 1000 cases for which sequencing was successful, the mean (SD) turnaround time was 49.5 (19.8) days (range, 19-195 days). The mean (SD) turnaround time for the last 1000 cases decreased to 32.5 (6.9) days (range, 19-88 days) as a result of improvements in both laboratory and return of result processes (eFigure 2 in Supplement 1).

Screen-Positive Results

Among the 3982 individuals for whom sequencing was successful, 147 (3.7%) screened positive, including 4 newborns with findings associated with 2 conditions (Figure 2). The most frequent positive screen result was *G6PD* deficiency (OMIM 305900) in 92 infants. Overall, 120 of the 151 positive screens were true positives. A further 6 findings were classified as presumptive positives. A total of 25 positive GUARDIAN screens were false positives (eTables 6 and 7 in Supplement 1), 11 of which were due to a single recurring

Figure 2. Genomic Uniform-Screening Against Rare Disease in All Newborns (GUARDIAN) Flow of Participants



A total of 8617 newborns were eligible for inclusion from study launch in September 2022 to July 2023. At least 1 parent was approached in person or by phone for 5555 of these newborns (approach rate, 64.5%). Parents were approached in person only on weekdays. Of those approached, 4000 consented to the study (consent rate, 72.0%), with 3624 (90.6%) consenting for the disorders with established interventions group and neurodevelopmental disorders associated with seizures group. Sequencing was successful for 3982 participants (99.6%). A total of 147 newborns (3.7%) received a positive screen result, including 4 newborns with positive screen results for G6PD deficiency and for a second condition (cystic fibrosis, sickle cell disease, mucopolysaccharidosis type VII, and TRIO-related neurodevelopmental disorder). Among the 151 positive results reported, 120 (79.5%) were confirmed as true positives, including 110 not previously identified by traditional NBS.

NBS indicates newborn screening.

[a]See eTable 5 in Supplement 1.

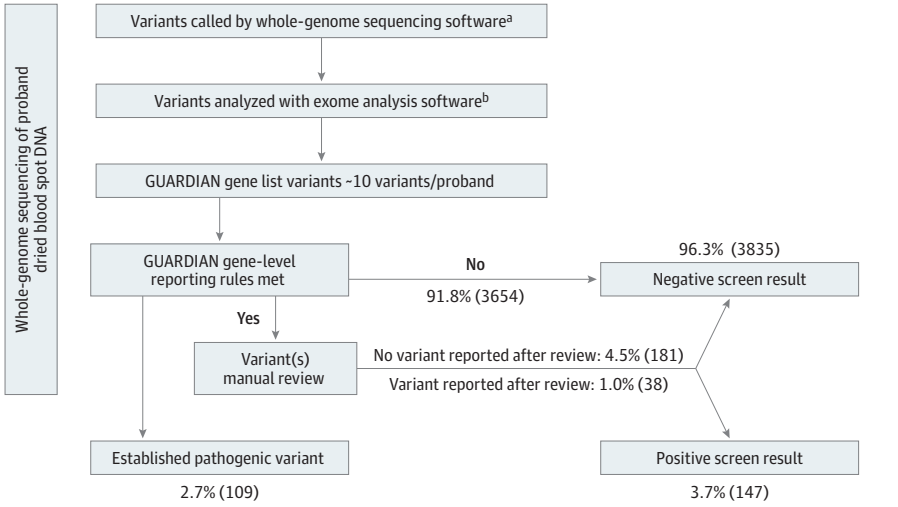
combination of p.D1270N and p.R74W variants in *CFTR* in newborns who had negative immunoreactive trypsinogen screens by traditional NBS. These variants were determined to mostly occur in *cis*[24] and were excluded from reporting after the first 1000 newborns.

Traditional NBS and GUARDIAN Screening Concordance

A total of 26 infants screened positive by traditional NBS assays. There were no false negatives with genome sequencing for confirmed monogenic diseases detected by traditional NBS for conditions within the scope of this study (eTable 8 in Supplement 1). Eight infants were screen positive by both traditional NBS and this study, all of whom were orthogonally clinically confirmed: 5 infants with sickle cell disease, 1 with congenital hypothyroidism, and 2 with short-chain acyl-CoA dehydrogenase deficiency.

In 1 case, genome sequencing yielded a screen-positive result that was missed by traditional NBS: 1 male screened negative with T-cell receptor excision circles (TRECs)-based NBS for SCID, but was found to carry a hemizygous likely pathogenic hypomorphic variant in *IL2RG* (OMIM 308380) (c.664C>A p.R222S). This variant had been reported twice in the literature,[25,26] including in a patient who also had a false-negative TREC[26] screen result and another requiring salvage gene therapy who died.[25] Follow-up testing at age 2 months confirmed "leaky" X-linked SCID. Absolute CD3 counts were low (1319 cells/μL; normal range [NR], 2500-5500 cells/μL), but exceeded cutoffs for typical SCID. T cells were polyclonal, with 63% naive CD4+ T cells (healthy age-specific median = 90), and there was no evidence of transplacental maternal engraftment. Proliferation of T cells to phytohemagglutinin was within normal at 67% (NR, >58.5%), but interleukin 2-induced phosphorylated STAT5 (pSTAT5) activation was markedly reduced in total T cells as well as in CD4 T cells. Interleukin 7-induced pSTAT5 activation, which is fully dependent on *IL2RG*, was found to be abolished in total lymphocytes and memory T cells. The *IL2RG* variant was found to be de novo. Infection precautions were implemented,

Figure 3. Schematic of Variant Interpretation Workflow



A total of 3654 probands (91.8%) did not meet the study gene reporting requirements (ie, single rare variant identified in a recessive disease gene) and were automatically reported as having negative screen results.

GUARDIAN indicates Genomic Uniform-screening Against Rare Disease in All Newborns.

[a]Dragen whole-genome sequencing.

[b]Variant analysis in the Xome Analyzer[21] platform with the study gene list filtering results in a mean of 11 variants displayed for each proband.

and a haploidentical bone marrow transplant was successfully performed at age 4 months.

Conditions Not Included in Traditional NBS

Of the 3982 newborns screened by genome sequencing, there were 110 true positives not identified by traditional NBS (eTables 6 and 7 in Supplement 1). These included the identification of variants that led to the initiation of targeted interventions.

Two infants with pathogenic variants in genes associated with long QT syndrome (*KCNQ1* [OMIM 607542] [c.1031C>T p.A344V] and *KCNH2* [OMIM 152427] [c.3172dup p.A1058Gfs*61]) were identified by genome sequencing. A prolonged QT was confirmed in both the child with the *KCNQ1* variant by electrocardiogram (corrected QT interval [QTc] of 470 milliseconds; NR, <440 milliseconds) and in the child with the *KCNH2* variant (QTc of 509 milliseconds; NR, <440 milliseconds). Following recommendations from the American College of Cardiology, β-blocker treatment was recommended for both children. The variant in *KCNQ1* occurred de novo. The variant in *KCNH2* was inherited from a mother who was found to have a borderline QTc only after her child's NBS result.

Interpretation According to Predicted Genetic Ancestry

The majority of positive screen results (74% [109/147]) involved established pathogenic variants (eg, recurrent pathogenic variant in *G6PD*) and 94% of the newborns tested did not require expert variant vetting by clinical genomic scientists (**Figure 3**). Across all ancestries, a mean of 11.0 variants (range, 0-30) of potential interest in the genome sequencing gene panel were identified (eTable 9 in Supplement 1). For individuals with computed African ancestry, the positive report frequency was 6.9%, compared with 1% of individuals with European ancestry and 3.2% for admixed American individuals. The frequency of reports requiring a manual review was higher for individuals with an ancestry other than European (4.1% European ancestry compared with 6.5% non-European ancestry; $P = .02$; eTable 9 in Supplement 1).

Discussion

This study demonstrated the feasibility of targeted interpretation of a predefined set of genes for early-onset treatable conditions from genome sequencing using DNA from dried blood spots in a population of different racial and ethnic groups. The enrollment rate of this study (72.0%) was only slightly lower than an NBS pilot for Duchenne muscular dystrophy[27] (84%), suggesting that the breadth of the screen was not a considerable concern for participants. The majority (90.6%) of consented participants also requested inclusion of screening for optional neurodevelopmental disorders (associated with seizures), highlighting parental preferences to screen for diseases beyond the traditional NBS definition of actionability.[20] Spanish speakers were statistically slightly more likely to choose screening limited to disorders with established interventions than English or Mandarin speakers, and future studies will investigate the rationale for these preferences. The impact of the diversity of the populations screened on the interpretation workflow and outcomes should be evaluated in future studies and over time.

The most frequent positive screen result was G6PD deficiency, with 92 positive results. This frequency (2.3%) is consistent with the estimated prevalence of G6PD deficiency of 35 to 48 per 1000 live births in the US.[28] In 2022, New York State public health law was amended to include quantitative diagnostic G6PD deficiency testing for infants with hemolytic anemia, hemolytic jaundice, early-onset increasing neonatal jaundice persisting beyond the first week of life (bilirubin >40th percentile for age in hours), admitted to hospital for jaundice following discharge, or familial or population risk for G6PD deficiency. G6PD testing is performed as a hospital diagnostic test, not by dried blood spot testing.

When excluding *G6PD*, the frequency of positive screening for this first set of 237 genes is approximately twice that of traditional NBS in New York State (0.6% vs 0.3%) and this frequency is expected to increase with the expansion of

the gene list. Genome sequencing identified 4 treatable conditions not identified by routine NBS: SCID, long QT syndrome, achondroplasia and hypochondroplasia, and Wilson disease. Management of SCID is hematopoietic stem cell transplant or gene therapy. Early detection of SCID followed by hematopoietic stem cell transplant before the onset of infection has been shown to substantially improve outcomes.[29] Cumulative mortality of untreated long QT syndrome before age 40 years is estimated between 6% and 8%[30] and avoidance of QT prolongating drugs is recommended in all individuals carrying a pathogenic variant in *KCNQ1* or *KCNH2*.[31] Liver transplant was shown to be required in 21.4% of pediatric cases of Wilson disease[32] and early zinc supplementation combined with low-copper diet was shown to be highly effective when started in presymptomatic children.[33]

The data presented provide proof-of-principle evidence that genome sequencing can identify newborns with conditions that may otherwise be clinically undetected until symptom onset and that a subset of these patients will receive changes in management as young children as a result of this information. To achieve widespread implementation at scale, several factors must be addressed (eTable 10 in Supplement 1).

Diseases for Inclusion

Multiple newborn sequencing studies are planned or will soon be underway. At present, there are notable differences in disease selection, leading to a wide range in the genes screened (eTable 1 in Supplement 1). Establishing a clear framework for the inclusion of conditions will decrease the discrepancies in the numbers and types of conditions screened between studies.

Threshold for Variant Reporting

Variant interpretation for diagnostic genome sequencing using ACMG guidelines incorporates patient phenotypes and family history. Targeted analysis of genome sequencing in newborns, like traditional NBS, must be optimized to compensate for the absence of clinical information by carefully considering reportable variants and making adjustments to optimize sensitivity while minimizing false-positive results. Prospective studies, such as this study, will generate data to further define screen reporting criteria.

Results Reporting

Returning initial screening results to families can be challenging because additional testing (parental segregation and/or orthogonal clinical testing) is needed to further assess positive screening results. Particular attention should be paid to providing families and health care professionals with sufficient information to enable them to understand the differences between screening and diagnostic tests. The findings presented here support the hypothesis that the implementation of genome sequencing–based NBS may improve equitable access to screening, but additional data are needed to assess the ability to interpret genomic findings in diverse populations.[34] Moreover, screening is only the first step in achieving health equity and ensuring equitable access to appropriate care is also required. This study provided explicit support to newborns and their families with a navigator as they accessed care and began treatment with subspecialists. In previous experience of disclosing GUARDIAN results, a close partnership with the pediatrician/family physician is critical for providing information and supporting the family through this process. Training was conducted of these health care professionals prior to study launch, which should be included in future genome-based NBS programs.

Scalability

This study's large-scale and population-based ascertainment provide insights into the scalability of targeted analysis of genome sequencing in NBS, which is dependent on the number of infants screened, genes included, criteria for variant reporting, and ability to automate analytic pipelines (Figure 3). In the highly automated genetic analysis, manual review by a geneticist was still required for approximately 6% of all individuals. The proportion of reports requiring manual review was influenced by ancestry, suggesting that publicly available reference datasets remain underpopulated with individuals of non-European ancestry. This suggests that the generation of additional publicly available genome data from diverse populations may improve the interpretation and scaling of genomic NBS. Additional studies specifically examining the effect of genetic ancestry on variant interpretation in the context of genomic NBS are warranted. The proportion of positive screens, which is higher than traditional NBS, also requires significant resources for follow-up confirmatory testing and clinical care once diagnosed. Further improvements in automation will be necessary to scale to 210 000 annual births in New York State. Scalable, cost-efficient solutions are needed for DNA extraction, library preparation and sequencing, accurate variant interpretation, and follow-up of screen-positive newborns. Regionalization of testing and analysis could alleviate issues with implementing first-tier genetic analysis into NBS programs, which requires infrastructure, experienced staff, and funding. Decreasing reporting times will also be critical.

Limitations

This study has limitations. First, the number of participants currently included in this preliminary study was insufficient to draw conclusions about the sensitivity and specificity of genome sequencing for most of the conditions screened. Sample sizes of at least 100 000 with follow-up will be needed to assess the treatable rare genetic diseases affecting young children included in the screening panel. Second, the study is still at an early stage and cannot yet provide long-term data about the negative impact of unnecessary assessments and interventions. Follow-up studies of newborns with a positive genome sequencing screen result are underway to assess long-term outcomes of the newborns and their parents. Third, because most individuals included in the study were too young to have been diagnosed through standard of care, the study is currently unable to identify false-negative results and the negative predictive value cannot yet be reliably estimated. Fourth, the turnaround time for this study exceeds that of traditional NBS and needs to be improved before determining how the 2 methods operate synergistically.

Conclusions

These preliminary findings demonstrate the feasibility of targeted interpretation of a predefined set of genes from genome sequencing for screening in a newborn population of different racial and ethnic groups. DNA sequencing offers an additional method to improve screening for conditions already included in NBS (eg, SCID) and to add treatable conditions that cannot be readily screened for because there is no biomarker currently detectable in dried blood spots. Additional studies are required to understand if these findings generalize to other populations and whether introduction of sequencing leads to improved health outcomes across diverse population groups.

ARTICLE INFORMATION

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