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Perspectives on genomic newborn screening studies: design, implementation, and outcomes

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BACKGROUND: With decreasing sequencing costs and increasingly accurate and scalable methods to interpret genetic variation, genomic newborn screening (gNBS) is being assessed for feasibility, acceptability, and impact worldwide. The field is evolving to determine the genes and variants to report, how to communicate with parents and pediatricians, and confirm results, and how to medically manage children with confirmed diagnoses.
CONTENT: This review summarizes global gNBS studies, including recruitment methods, consent models, sample types, participant characteristics, sequencing methods, gene selection criteria, test performance, variant interpretation, automated reporting, turnaround time, methods to return results, confirmatory diagnostic testing, and comparisons with standard NBS (stdNBS) results.
SUMMARY: Early experience supports the feasibility and positive clinical impact of gNBS. Variability in study design, gene selection, and reporting limits direct comparability across studies but increasing and diverse experience will optimize parameters prior to broad implementation.

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IMPACT:

- Genomic newborn screening is feasible and expands the screening of treatable genetic conditions beyond standard newborn screening, and improves the diagnostic accuracy of standard newborn screening.
- Comparison of genomic newborn screening studies around the world, highlighting key differences in study design, technical approaches, clinical implementation, and current challenges.
- Key evidence supporting the implementation of genomic newborn screening is summarized to guide future policy and clinical practice.

BACKGROUND

Newborn screening (NBS), introduced in the 1960s, is a successful public health service that identifies infants at risk for treatable disorders.[1] NBS programs have been guided by 10 principles published by James Wilson and Gunnar Jungner in 1968.[2] The introduction of tandem mass spectrometry significantly increased the number of disorders screened to a total of 40–50 conditions across most states in the United States.[3] These NBS programs have had a substantial impact on public health worldwide, enabling early diagnosis and timely intervention, and thereby significantly reducing morbidity and mortality.

With advances in genomic sciences and decreasing DNA sequencing costs, genomic newborn screening (gNBS) has emerged as a promising approach to improve and expand NBS for treatable conditions.[4–7] Thirty-five international studies are currently investigating its use to broaden the range of genetic conditions detectable through NBS programs.[8]

There are many important challenges being addressed in gNBS pilot studies prior to broad implementation. These include: the optimal biological samples for testing, which genes, conditions, and variants to include, and how best to confirm diagnoses. In addition, important questions remain about effective strategies for communicating results to families and pediatricians and appropriate clinical management when ascertainment is via population-based screening rather than symptomatic diagnosis. In this review, we summarize results to date from gNBS studies worldwide.

OVERVIEW

Newborn sequencing was accelerated by the Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) program, a series of federally funded research initiatives launched by the National Human Genome Research Institute (NHGRI) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) in 2013. The program aimed to evaluate the feasibility, clinical utility, and ethical, legal, and social implications (ELSI) of integrating genome and exome sequencing into NBS and pediatric care. NSIGHT consisted of four research studies. These studies examined applications ranging from rapid genome sequencing in critically ill neonates in intensive care units to genetic screening of healthy newborns and infants to the use of population-based archived dried blood spots in individuals with

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suspected genetic disorders to post-hoc compare DNA sequencing as an alternative diagnostic method.[9]

A second major wave of genomic newborn screening (gNBS) studies has recently been initiated. We review gNBS studies defined by those that included asymptomatic newborn participants within the first 30 days of life and for which results describing this process have been published. Diagnostic sequencing of symptomatic children and genetic screening of children outside of the neonatal period (30 days of birth) are not included. In 2021, some gNBS pilots began to directly involve public health laboratories in prospective studies with the goal to study large cohorts, including over 100,000 newborns in both the GUARDIAN Study in the US and the Generation Study in the UK. There have been announced, ongoing or completed gNBS studies in North America (GUARDIAN, Early Check, and BeginNGS), 9 in Europe [BabyDetect (Belgium), Generation (United Kingdom), FirstSteps (Greece), Screen4Care (European Union), Genoma Puglia (Italy), Cradle (Netherlands), New Lives (Germany) and PERIGENOMED (France), NeoGen (Italy)], 4 in Australia (NewbornInSA, BabyScreen + , GenSCAN and TRAIL), 1 in the Middle East Emirati Genome (U.A.E.)[10,11], and 8 studies of targeted sequencing in Asia (China, Thailand).[8,12,13]

Table 1 compares the sample sizes, study designs, and results reported across studies, reflecting in part constraints of healthcare systems and research infrastructures. In this review, we focused on the key features of the study designs.

ENROLLMENT

Enrollment and recruitment strategies

gNBS studies employ several distinct recruitment and consent methods, including postnatal hospital-based in-person recruitment, population-wide invitations, and prenatal enrollment. Postnatal, hospital-based recruitment is one of the most commonly used methods and generally yields higher enrollment rates compared to other methods. The GUARDIAN study uses an in-person, hospital-based method in which research staff approach parents shortly after birth. This approach is supplemented by prenatal informational materials distributed in obstetrical offices, as well as phone calls and email invitations after hospital discharge for families not reached in person. With weekday staffing, 64.5% of eligible parents were approached, and 72% of those approached consented. Parents may provide electronic consent either in person or remotely after receiving study information, with enrollment allowed up to 30 days after birth.[14] Similarly, the Generation study obtains consent postnatally through hospital study staff[15] and BabyDetect uses a comparable in-maternity-unit recruitment strategy with enrollment rates of 90%. In BabyDetect, prenatal educational materials are provided, and trained personnel obtain electronic consent after birth prior to sample collection.[16]

In contrast, population-based recruitment strategies relying on mailed invitations tend to have lower participation rates. Early Check implemented a statewide mailing approach with electronic consent and had an overall enrollment rate of approximately 5%. However, its in-hospital recruitment component demonstrated 32% enrollment among postpartum mothers approached in person. This within-study contrast highlights the impact of recruitment modality on participation.[17]

Prenatal education and consent models represent another distinct approach, aiming to educate parents earlier. BabyScreen+ approaches prospective parents in public and private healthcare settings during the third trimester, using online educational tools such as videos and podcasts. Among 1288 prospective parents who initiated enrollment, 1003 newborns (88%) completed all enrollment steps. Recruitment was most effective when facilitated by healthcare professionals, accounting for 67% of completed enrollments.[18,19] Similarly, the BeginNGS study adopted a flexible, multi-stage recruitment model that includes prenatal, postnatal, and well-baby visits within the first 28 days of life, and enrollment opportunities across diverse clinical settings. This approach is supported by digital tools and an adaptive design to optimize recruitment strategies and improve population representation.[20]

Not participating in gNBS is reported to be due to a perceived sufficiency of existing NBS and a general lack of engagement or interest in research and highlights the need to clearly communicate the added clinical value of genomic screening.

Participant characteristics

The genetic ancestry of participants varied across studies. GUARDIAN has an ancestrally diverse population that represents all major global ancestry groups, including African (24.6%), Admixed American-Hispanic (30.7%), East Asian (9.1%), European (17.9%), Middle Eastern (14.0%), and South Asian (3.7%).[14] In Early Check, participant self-reported race and ethnicity data indicated an overrepresentation of White participants (58.8% vs 50.8% in the overall North Carolina birthing population). Representation was lower among participants with both parents identifying exclusively as Black or Hispanic. However, Early Check participants were more likely to report multiple race/ethnicity categories compared with state-level estimates (22.1% vs 2.9%).[17] BabyDetect participants broadly reflected the diversity of the Liège area in Belgium.[16] BabyScreen+ enrolled a multi-ethnic cohort, primarily European (56%) and Asian (33%), with smaller proportions of Middle Eastern (6%), Oceanian (3%), Aboriginal (1%), and African (2%) participants.[18] Recruitment setting is a major determinant of participant composition: studies embedded in specific practices and hospitals reflect the demographics of those patients served, while statewide all-inclusive programs theoretically can represent the state's diversity but do not exactly mirror that diversity. In general, individuals who agree to participate in genetic research often differ systematically from the general population, particularly in relation to socioeconomic status, based upon the burden of the study race/ethnicity and language spoken, due to differences in trust and understanding of research.[21,22] The gNBS studies with the highest enrollment and that most represent the population served are those that have engaged potential participants in person with individuals fluent in their native languages to enable the opportunity for conversation and understanding of the studies.

TECHNICAL ASPECTS OF GNBS STUDIES

Sample type and sequencing target

The most common sample type in gNBS studies is dried blood spots (DBS), and the most common sequencing method is short-read genome sequencing (GS). Key examples of this approach include GUARDIAN Study, BeginNGS Study, BabyScreen+ Study, and Early Check Study.[14,17,18,20] In contrast, NeoGen uses DBS as the sample source with exome sequencing.[23] The Generation Study primarily uses umbilical cord blood collected immediately after delivery, with heel-prick or venous blood as an alternative when cord blood is unavailable. GS is used in the Generation Study.[24] In China, Chen et al. used DBS samples to sequence a 142-gene panel, reflecting a more focused screening strategy.[12]

Gene inclusion criteria and current gene lists

gNBS programs demonstrate substantial heterogeneity in genes included, reflecting differences in genetic ancestry, actionability definitions, clinical priorities, and healthcare system constraints.

In GUARDIAN, all enrolled participants currently receive screening results for 314 genes (Group 1 conditions), which include disorders with >90% penetrance or need for intervention before age 5 years. In addition, parents may opt in to receive results for an additional 93 genes (Group 2 conditions) for seizure-related disorders associated with neurodevelopmental issues which may

Table 1. Comparison of the gNBS studies regarding all steps and their results.

		GUARDIAN	BeginNGS	Generation	BabyDetect	BabyScreen +	Early Check	NewbornsInSA	Chen et al.	NeoGen
1	Location	New York, USA	California, USA	Nationwide, UK	Liege, Belgium	Victoria, Australia	North Carolina	South Australia	China	Turin, Italy
2	Started	September 2022	July 2024	Spring 2024	September 2022	July 2023	September 2023	June 2024	Feb 2021-December 2021	October 2023- July 2024
3	Cohort size (number of participants)	4,000	120	NA	3,847	1,000	816	46	29,601	4,067
4	Enrollment and Recruitment Strategies	Postnatal, hospital-based in-person recruitment	Hybrid / multi-stage recruitment models	Postnatal, hospital-based in-person recruitment	Postnatal, hospital-based in-person recruitment	Prenatal education and consent models	Population-based (remote invitation) recruitment	Prenatal education and consent models	NA	Postnatal, hospital-based in-person recruitment
5	Participant characteristics	AME 30.7% AFR 24.6% MDE 14.0% EU 17.9% EAS 9.1% SAS 3.7%	NA	NA	Patients of this hospital reflect the general population of the Liege area	EU 56% Asia 33% MDE 6% Oceania 3% AFR 2% Aboriginal- 1%	Over-enrollment of white participants (58.8% versus 50.8%)	NA	NA	AFR 7.2% ASN 2.2% EU 86.8% SAM 1.4% MULT 2.4%
6	Consent timeline and consent type	Consented in person or electronically Birth to day 30	Consented in person or electronically Shortly after birth	Written informed consent Shortly after birth	Electronic consent Shortly after birth	Electronic consent During pregnancy	Electronic consent Shortly after birth	Written informed consent During pregnancy	Written consent Shortly after birth	Written consent Shortly after birth
7	Sample type	DBS	DBS	Preferred sample: Umbilical cord blood, alternative is DBS	DBS	DBS	DBS	Retrospective DBS	DBS	DBS
8	Method	GS	GS	GS	Targeted panel	GS	GS	GS	Targeted panel	ES
9	Gene inclusion criteria and current gene lists	149 genes and opt in 99 genes for NDD and seizure syndromes	342 genes	463 genes	405 genes	605 genes	169 genes and opt in 29 genes for condition with promising treatment options	613 genes	142 genes	521 genes
10	Successful screening (%)	99.6	NA	NA	97.80	91.8	93	None	98.7	99.7
11	TAT and auto reporting	42–49 days	NA	NA	64 days for the first 300 samples to 51 days for the last 300 samples	13 days	35 days for negative results 38 days for positive results	42–56 days	NA	Average TAT for gNBS was 32 days

Table 1. continued

		GUARDIAN	BeginNGS	Generation	BabyDetect	BabyScreen +	Early Check	NewbornsInSA	Chen et al.	NeoGen
12	Variant interpretation	P/LP variants are reported; VUS leaning LP may be included with a P/LP variant in recessive, treatable conditions	Report only P/LP variants with different variant prioritization strategies	Report only P/LP variants with different variant prioritization strategies	Report only P/LP variants with different variant prioritization strategies	Report only P/LP variants	Report only P/LP variants	Report only P/LP variants with different variant prioritization strategies	Report only P/LP variants	Report only P/LP variants
13	Screen-positive results (%)	3.7	4.2	NA	1.8	1.6	2.5	NA	2.7	13.4
14	Returning results to the participants	Tiered model (low-touch negatives, high-touch positives) Negative results: automated or low-intensity (email, letter, portal) Positive results: phone/ telemedicine, genetic counseling and specialist referral	NA	Tiered model (low-touch negatives, high-touch positives) Negative results: automated or low-intensity (email, letter, portal) Positive results: phone/ telemedicine, genetic counseling and specialist referral	Selective reporting model (only abnormal results returned)	Tiered model (low-touch negatives, high-touch positives) Negative results: automated or low-intensity (email, letter, portal) Positive results: phone/ telemedicine, genetic counseling and specialist referral	Tiered model (low-touch negatives, high-touch positives) Negative results: automated or low-intensity (email, letter, portal) Positive results: phone/ telemedicine, genetic counseling and specialist referral	NA	NA	Selective reporting model (only abnormal results returned)
15	Comparison with stdNBS	-No false negative -An additional 110 cases were identified	-Increased the true positive rate of standard NBS from 3.6% to 4.2%.	NA	-One false negative - An additional 30 cases were identified	-No false negative -An additional 15 cases were identified	-Two false negatives - An additional 5 cases were identified	-One false negative -No additional case was detected	-No false negative -An additional 59 cases were identified	-No false negative -An additional 93 cases were identified

AFR Africa, *AME* Admixed America, *ASN* Asian, *DBS* Dried blood spot, *EAS* East Asian, *ES* Exome sequencing, *EU* Europe, *GS* Genome sequencing, *MDE* Middle East, *MULT* Multiple nationalities, *NBS* Newborn screening, *P/LP* Pathogenic or likely pathogenic, *SAM* South America, *SAS* South Asian, *TAT* Turnaround time, *VUS* Variant of uncertain significance.

benefit from early diagnosis and timely intervention.[14] Following updates in the literature and evolving clinical evidence, these gene lists were expanded in March 2024 to 314 genes for Group 1 and 131 genes for Group 2.[25] The Age-based Semi-Quantitative Metric (ASQM) served as the foundation for developing the Early Check Panel 1 framework. It evaluates five aspects of clinical actionability—disease severity, likelihood of manifestation, intervention efficacy and acceptability, and strength of evidence for the gene–condition relationship—each scored from 0 to 3 (maximum total: 15). Higher scores indicate greater actionability. Gene–condition pairs scoring ≥13 were prioritized for Panel 1, while those scoring ≥9 were also considered, and group 1 comprised 169 genes.[17,26] Panel 2 consisted of gene–condition pairs chosen for two main categories: (i) conditions with existing approved therapies that still required further evidence in newborns before being considered for Panel 1, and (ii) conditions without approved treatments but with active interventional clinical trials. While ASQM scores were calculated, no cutoff was required for inclusion in Panel 2. Eligible trials had to be conducted in the U.S. and include children within the first 2 years of life. Panel 2 included 29 gene-condition pairs.[17] Additionally, Early Check screens for the risk of type 1 diabetes separately as a group 3 condition. All enrolled participants are screened for group 1 conditions however group 2, and screening for type 1 diabetes risk is optional.[15,27] The Generation study includes 209 severe, early-onset conditions associated with 463 genes, for which early intervention may improve outcomes, and delayed diagnosis is expected to substantially impair quality of life.[28] The BeginNGS study includes 388 pediatric-onset genetic conditions for which established medical interventions are currently available. They updated their list to include 342 genes with 412 conditions.[20] The gene inclusion criteria are for conditions that start before age 5, cause severe disability or reduced life expectancy if untreated, and have effective treatment available. The BabyDetect study initially screened 359 genes, and after an update, the number increased to 405, with 61 genes added and 15 removed.[16] BabyScreen+ includes 605-genes targeting early-onset, severe, and treatable conditions.[18] NewbornInSA has been using the same panel as BabyScreen +, developed by the Genomic Screening Consortium for Australian Newborns (GenSCAN), with an additional 8 genes.[29] The Screen4Care study screens 245 genes called the TREAT-panel. They used four criteria including (i) clinical validity of the gene [0; no established genotype/phenotype correlation 1; partial correlation 2; clear correlation], (ii) age of onset [0; adolescence-onset 1; pediatric onset 2; presenting in early childhood], (iii) disease severity [0; not causing health problems 1; spectrum of severity and variable 2; cause significant health problem] and (iv) penetrance [0; low penetrance (< 20%)1; intermediate penetrance (20–80%) and 2; penetrance > 80%)], and each category contributes 0–2 points. Genetic conditions with a score of 7 points or greater have been included in the panel.[30] Chen et al. selected 128 conditions linked to 142 genes using criteria aligned with national screening programs and regional disease prevalence, particularly focusing on treatable genetic disorders.[12] NeoGen included 521 genes using criteria similar to other NBS studies and also reported adulthood-onset conditions, in addition to including early-onset diseases.[23]

Comparing studies, there are few genes included across all studies. Downie et al. identified 55 genes included by five of five gNBS studies (BabyScreen +, GUARDIAN, BeginNGS, NC NEXUS, Generation). Notably, only 7 of the 25 genes that more than 85% of rare disease experts considered appropriate for gNBS (OTC, *G6PC, SLC37A4, SLC2A1, SLC25A15, CPS1*, and *NAGS*) were included in this consensus gene set, underscoring the need for continued refinement and consensus-building.[31]

Variant interpretation. All studies use the standard American College of Medical Genetics and Genomics (ACMG) variant interpretation criteria. The interpretation of GS variants in asymptomatic newborns presents different challenges compared with diagnosing symptomatic patients. There are variations in variant reporting criteria across studies, largely regarding variants of uncertain significance. BabyScreen +, Early Check, and NeoGen report only pathogenic/likely pathogenic (P/LP) variants consistent with the expected inheritance pattern, and intentionally exclude variants of uncertain significance (VUS).[17,18,23] GUARDIAN reports P/LP variants that match the condition and one VUS leaning LP when it occurs with a P/LP variant in recessive genes for disorders with effective treatments and independent methods of confirmation.[14]

Some studies employed automated methods of variant filtering. The BabyDetect study reports variants as P/LP when they are classified as such in either an internally curated list or in ClinVar, and classifies samples as negative when consensus is not achieved across databases or prediction tools (e.g., ClinVar, VarSome, Franklin).[16] BeginNGS uses ClinVar with Genomenon and does not include VUS unless at least one curated source supports it as P/LP.[20] Variants in the Generation Study are prioritized if they fall within the curated gene–disease list and are either previously classified as P/LP in sources such as ClinVar, QIAGEN Clinical Insights (QCI) reported variants, NHS Genomic Medicine Service records, the 100,000 Genomes Project, or Genomics England's Clinical Variant Ark, or if they are predicted to result in protein loss-of-function when loss of function is the disease mechanism. All prioritized variants undergo manual review by clinical experts according to ACMG criteria, and only those considered clinically significant are reported.[28] In NewbornInSA, a semi-automated approach has been used. Variants were reported if they were reported in ClinVar as P/LP, predicted to have high-impact or loss-of-function effects, or were missense variants with moderate/high impact supported by splice or in silico predictions.[29] Overall, while all studies apply ACMG criteria, they differ substantially in which and how variant databases are integrated to interpretation and how VUS are handled, ranging from highly restrictive reporting of only P/LP variants to more inclusive, multi-database prioritization frameworks that require expert review before clinical reporting.

Technical limitations and failures

Technical failures and the need for repeat samples and/or sequencing have been low across studies. The GUARDIAN Study reported a sequencing success rate of 99.6% among the first 4000 screened. Eighteen participants failed because there was insufficient DNA in the DBS samples, resulting in no sequence data. 2.6% ($n = 105$) of participants were successfully sequenced using a repeat sample.[14] In the BabyDetect Study, 2.2% of samples required retesting due to technical issues, including cross-contamination, sequencing workstation failures, and poor library quality.[16] In the Early Check Study, 7% (146/2125) failed screening due to unmatched consent with the NBS cards, insufficient DBS, or inadequate DNA yield from the DBS.[17] Higher failure rates have been reported in the BabyScreen+ Study with 8.2% of samples requiring reprocessing, due to both sample-related (insufficient DBS sample, insufficient DNA yield or library preparation failure) (3.2%) and DNA extraction batch failure (5.0%).[18] Thus, across studies, 2.6–8.2% of participants did not yield sequencing results on the first attempt, but methods are improving with experience.

Turnaround time (TAT) and auto-reporting

The GUARDIAN TAT from consent to report delivery was 42–49 days initially. The mean TAT was 49.5 days for the first 1,000 cases, and for the 3000–4000 cases improved to 32.5 days with workflow optimization.[14] A similar reduction in TAT was seen in the BabyDetect Study, from 64 days for the first 300 samples to 51 days for the last 300 samples.[16] In the BabyScreen+ Study, the average TAT was 24 days for stdNBS followed by gNBS. The mean TAT for gNBS alone was 13 days (range: 6–56 days), with 73% of

Table 2. Summary of the classification criteria used in gNBS studies.

Category	Classification Criteria
True Positive	Results were classified as true positives when the diagnosis was supported by clinical evidence or confirmatory testing. For recessive disorders, this required confirmation that the identified variants were located in trans.
False Positive	Results were considered false positives when follow-up evaluation did not support the diagnosis. This included cases in which variants were found in cis for autosomal recessive disorders (allelic false positives), when expected age-related symptoms were absent, or when confirmatory testing failed to validate the suspected condition (phenotypic false positives).
Presumptive Positive	Presumptive positives referred to results suggestive of a potential disorder that required longitudinal follow-up, as clinical manifestations could develop later. These cases lacked sufficient evidence for definitive classification because confirmatory testing was unavailable, and no symptoms were present at the time of assessment.
False Negative	False negatives were clinically confirmed cases identified through alternative screening approaches or routine clinical evaluation but not detected by gNBS.

reports issued within the 14-day target.[18] With improvements in sequencing workflows, 81% of reports were issued within the target timeline. The Early Check Study reported a median TAT of 35 days for negative results and 38 days for positive results. The median times were 11 days from consent to laboratory delivery of DBS, 13 days from DBS delivery to reporting, and 5 days from report transfer to portal availability.[17] The target TAT for the NewbornsInSA Study was 42–56 days, and this was achieved in 41% of the first 100 cases. The underlying reason for prolonged TAT was postnatal consent procedures, sample batching, and multidisciplinary review of complex variants.[29]

POST-REPORTING CLINICAL ASPECTS OF GNBS STUDIES

Screen-positive performance

Across gNBS studies, screen-positive rates vary widely depending on the number of genes, reporting criteria, and whether findings include carrier status. In GUARDIAN, the screen-positive rate was 3.7%, with G6PD deficiency representing the most frequent finding (2.3%). When excluding *G6PD*, the positive rate for the remaining 237 genes was ~0.6%, compared to 0.3% in stdNBS, indicating a modest increase in detection.[14] The BeginNGS study reported a true positive rate of 4.2% in a cohort of 120 newborns.[20] BabyDetect identified a 1.8% positive rate in 3,847 participants. Seventeen of 71 TP were not included in stdNBS, and *G6PD* deficiency was the most frequently detected condition overall (44 newborns).[16] In BabyScreen +, 16 infants (1.6%) had positive results, and only one case was identified by stdNBS methods.[18] Early Check reported that 50 newborns (2.5%) had positive screening results, with *G6PD* accounting for nearly half of all positives (1.2%); after excluding *G6PD* and off-target *MITF* findings, the adjusted positive rate decreased to 0.8%.[16] Chen et al. reported 813 screen-positive results among 29,601 newborns (2.7%), and follow-up studies confirmed the diagnosis in 402 of those infants (1.4%). Panel sequencing identified 20 positive results that were also expected to be detected by stdNBS, with an additional 39 positive results identified exclusively through gNBS.[12] Carli et al. reported a 13.4% screen-positive rate in 4,054 infants.[23] The number of genes included, reporting criteria, and study populations are the key factors explaining the differences across studies.

Returning results to participants

gNBS programs demonstrate a wide range of strategies for returning results to participants. GUARDIAN employs a structured, clinician-led return model in which negative results were communicated initially via phone and then subsequently evolved to encrypted email, while positive findings are delivered by telemedicine with a medical geneticist and genetic counselor, followed by in-person consultation with a specialist to support diagnostic confirmation and care coordination.[14] All results are available to pediatricians and specialists through the electronic health record and the state newborn screening portal. In the Generation study, negative results are communicated to families by letter or email within a few months after birth, with a copy sent to the general practitioner. Positive results are communicated by telephone within a similar timeframe, and are subsequently referred to a specialist National Healthcare System (NHS) team for further clinical evaluation and follow-up.[32] BabyDetect utilizes a model in which only relevant or abnormal findings are returned; negative results are not routinely reported. Positive findings are conveyed to pediatricians and specialist teams who then initiate family contact and coordinate further clinical evaluation, with routine NBS findings managed separately under standard care pathways.[16] In BabyScreen +, low-chance results are considered presumed negative findings and are delivered digitally via secure messaging systems, while high-chance results are considered presumed positive findings and are communicated by genetic counselors and followed by confirmatory testing, segregation analysis, and specialist referral.[18] Early Check reports screen-positive results through telephone communication, typically involving a structured counseling call, whereas screen-negative results are provided electronically to participants.[17] Overall, returning results in gNBS programs is characterized by tiers, including automated, low-intensity communication for negative findings to high-touch genetic counselor and specialist disclosure for screen-positive results, underscoring the need for scalable yet robust result communication systems.

Confirmatory testing and follow-up on the screen-positive results

gNBS programs require systematic follow-up testing to confirm initial screening findings with orthogonal tests, parental testing and clinical assessment to establish a final diagnosis. According to these further assessments, results are categorized as true positive (TP), presumptive positive (PP), or false positive (FP). Results were classified as TP when clinical findings or confirmatory testing supported the diagnosis, and for recessive conditions, when variants were in trans. Results were classified as FP if variants were in cis for autosomal recessive conditions (allelic FP), or if the newborn had no symptoms when symptoms were expected at that age, or confirmatory testing did not support the diagnosis (phenotypic FP). A presumptive positive indicates a result suggesting a possible disease that requires a follow-up period to manifest clinical findings. False negatives are detected by another screening method or clinical care and confirmed clinically but not identified by gNBS. PP results are cases for which no definitive result could be established due to a lack of confirmatory testing and lack of symptoms at assessment, when symptoms may emerge over time (Table 2). All gNBS studies perform additional confirmatory tests and medical follow-up.[14,16–18,20,32]

In GUARDIAN, 120 of 151 (79%) positive screening results were confirmed as TP, and an additional 6 were considered presumptive positives, which will be clarified with subsequent clinical

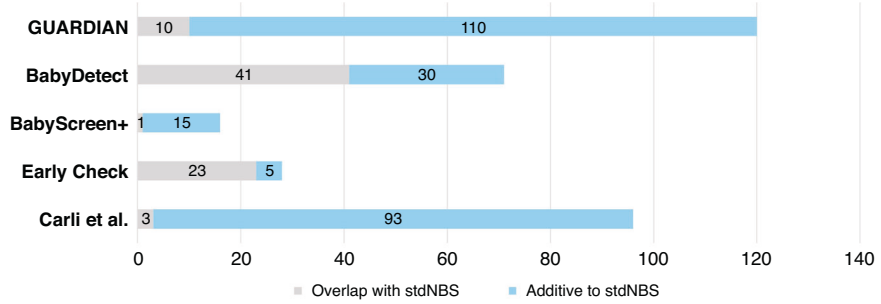

Fig. 1 Identified cases in gNBS studies reporting early childhood conditions, showing overlap with standard screening, and additional cases identified only by gNBS.

follow-up. In total, 25 GUARDIAN positive screens (17%) were FP, 11 of which were attributed to a recurrent combination of *CFTR* variants (p.D1270N and p.R74W) in cis identified in newborns who had normal immunoreactive trypsinogen results on stdNBS.[14]

Of 72 positive cases in BabyDetect, one showed two variants inherited from one parent and was classified as a FP.[16] In Early Check, 55% ($n = 28$) were classified as TP or probable TP, while 8% remained uncertain and required further follow-up. About 24% ($n = 12$) were phenotypic FP, where variants were detected in genes unrelated to the targeted actionable conditions, such as the *MITF* variant associated with melanoma risk in adults. Additionally, parental testing clarified cis variants in one case as allelic FP, and our additional allelic FPs were attributed to heterozygous variants consistent with carrier status in genes with both autosomal dominant and autosomal recessive inheritance patterns.[17] In contrast to other studies, no FPs have been reported in Babyscreen + .[18] Chen et al. reported phenotypic FPs, including 361 *G6PD* cases (44.4%), 21 congenital hypothyroidism (2.5%), and 7 cases (0.08%) from other metabolic disorders among 813 positive screens. Notably, 359 of the FP *G6PD* cases (99%) were female. In the same cohort, 328 newborns had *G6PD* deficiency (40%), 18 had congenital hypothyroidism (22%), and 17 had metabolic disorders (22%); these cases were classified as phenotypic TPs.[12]

Comparison with the standard NBS

gNBS programs consistently demonstrate both overlap with and improved screening beyond stdNBS, while also highlighting differences in sensitivity, specificity, and disease spectrum. In GUARDIAN, comparison with stdNBS identified 26 infants who screened positive by biochemical assays, with no false negatives for conditions within the study scope. Importantly, GUARDIAN identified 100 TP cases that were not detected by stdNBS, including 92 cases of G6PD deficiency, 5 cases of GJB2-related hearing loss, and 1 infant with a pathogenic *IL2RG* variant associated with severe combined immunodeficiency, which was missed by TREC-based screening.[14] In BabyDetect, 13 cases were not identified by stdNBS, of which 10 were G6PD deficiency (77%). There was one FN case in BabyDetect with a homozygous variant in *TJP2*. This variant was identified in the BabyDetect sequencing dataset; however, the variant did not meet reporting criteria because it was not in the study-curated variant list and was absent from ClinVar. A patient with *CPT2* variants was detected only by gNBS, not by stdNBS, which is known to have poor sensitivity for *CPT2* screening.[16] Early Check identified two cases with SLC26A4-related Pendred syndrome and COL2A1-related Stickler syndrome, both with normal newborn hearing screening. Also, a stdNBS negative case with a *DUOX2* variant required follow-up due to possible incomplete age-dependent penetrance. Early Check identified two cases not detected by gNBS but confirmed by stdNBS, including sickle cell disease (later retrospectively confirmed in the genomic data) and late-onset Pompe disease with a pathogenic variant and a VUS (did not meet reporting criteria).[17]

The BeginNGS study shows that compared with California stdNBS, the TP rate increased from 2.7% to 4.2%.[20] In BabyScreen + , 6 *G6PD* cases and 1 *GJB2* case were not identified by the stdNBS.[18] In NewbornsInSA, 30 of the 31 cases with known positive screening results were correctly reported as positive. This one missed case involved a homozygous VUS in *ETHE1* in a patient with an ethylmalonic encephalopathy. VUS were not reported.[29] Chen et al. reported that gNBS identified 402 affected newborns, including 59 cases missed by biochemical NBS. Twelve of those can be identified by stdNBS, including G6PD deficiency, amino acid, organic acid, or fatty acid oxidation disorders.[12] Overall, these findings indicate that gNBS can substantially enhance the diagnostic yield of conditions targeted by stdNBS (Fig. 1).

Detection of conditions not included in stdNBS using gNBS

stdNBS only covers a limited set of conditions, mainly those detectable by tandem mass spectrometry or hearing screening. Because of this, stdNBS does not include most genetic diseases. gNBS can assess a much wider range of conditions, making it more comprehensive. GUARDIAN identified 11of 151 (7%) screen-positive cases that could not be identified by stdNBS; 5 cases in group 1 conditions, and 4 of 5 were *FGFR3*-related skeletal dysplasia or long QT syndrome, and 6 cases were identified in group 2 that cause epilepsy/neurodevelopmental disorders.[14] In BabyDetect, 17 of 71 (24%) screen-positive cases could not be identified by stdNBS, including cardiomyopathy and hemophilia A/B.[16] Of the 16 identified cases in Babyscreen + , only half of them were covered by stdNBS.[18] Chen et al. identified that 39 cases were only identifiable by gNBS (Fig. 1).[12]

FUTURE DIRECTIONS

The International Consortium on Newborn Sequencing (ICoNS) is an organization founded in 2022 that aims to aggregate experience across gNBS studies to develop a consensus. The ICoNS gene list subcommittee was created with the aim of defining principles of gene and variant selection for public health gNBS. The aim of the study was to define principles to guide gene selection for gNBS in a population health screening context. The ten consensus recommendations for gene inclusion can guide future research and public health programs performing gNBS. This process also identified key areas for which there was no consensus, highlighting important topics for future research.[11]

CONCLUSIONS

Evidence from international gNBS initiatives demonstrates both feasibility and the potential clinical utility. However, variability in study design, gene and variant selection, sample types, interpretation frameworks, and reporting practices continue to limit comparability across programs. In addition, critical issues remain regarding long-term follow-up. Further data generation and real-world experience demonstrating successful implementation and

effective patient management pathways will provide valuable insights.

DATA AVAILABILITY

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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AUTHOR CONTRIBUTIONS

Mehmet Bugrahan Duz (Writing—original draft-Lead), and Wendy K. Chung (Conceptualization-Lead, Writing—review & editing-Lead).

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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