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Genomic newborn screening: a scoping review of the field's evolution and associated ethical, legal, and social implications

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The integration of genomic sequencing into newborn screening (genomic newborn screening; gNBS) has the potential to identify more presymptomatic babies who could benefit from early intervention compared to traditional universal newborn screening (NBS). Realizing these benefits requires careful navigation of ethical, legal, and social implications (ELSI) to minimize harms, promote equity, and maintain trust in NBS programs. The primary objective of this scoping review is to synthesize the ELSI discussed in the gNBS literature, to support implementation and identify knowledge gaps. A secondary objective is to characterize the landscape and contours of the gNBS field. This review, conducted in July 2025, includes academic literature addressing genomic sequencing as a first-line NBS screen. ELSI were identified within each publication, and these informed the development of a set of decision points with ELSI dimensions within gNBS. A total of 485 publications met inclusion criteria, with the first published in 1987. The volume of publications increased over time, with growing proportions of empirical studies and work associated with gNBS projects, alongside a decreasing proportion of publications from North America. In total, 3781 ELSI considerations were charted using AI-assisted methods, relevant to 59 decision points organized into nine areas. Current scholarship is concentrated on early implementation questions, while long-term operational needs—such as data stewardship, clinical follow-up, and sustainable governance—remain underexplored. These gaps, together with limited contributions from many regions due to a multitude of factors, highlight the need for more diverse, empirically grounded, and forward-looking research to support responsible decisions around gNBS.

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INTRODUCTION

Universal newborn screening (NBS) programs date from the 1960s and have since that time been identifying at-risk babies who may benefit from early treatment [1]. NBS programs have been a huge public health success story, enjoying very high uptake rates in the dozens of jurisdictions in which they are implemented [2]. The conditions screened for are mostly genetic, but assays based on DNA sequencing are not typically used as part of the initial screen, although sometimes they are used as a second-line screen or confirmatory test in babies identified as at-risk from a conventional test [1]. The prospect of using genetic or genomic assays or sequencing to screen healthy babies has long been discussed, and would potentially allow for many more conditions for which a reliable biochemical marker is not available or would be too costly to ascertain to be covered by NBS [3]. We use the acronym gNBS to refer to the integration of genomic sequencing into NBS. Beginning with the BabySeq project in 2012, there are now dozens of research projects assessing gNBS globally [4], and even one deployment of gNBS in Puglia, Italy [5].

Within the field of gNBS there are many ethical, legal, or social implications (ELSI) related to, for example, which conditions should be included, considerations around consent, and data management. Navigating ELSI appropriately is necessary in order to successfully deliver benefits to screened newborns and their families, whilst also mitigating possible harms, all while maintaining public trust in existing NBS and public health in general. And

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while there may be large evidence gaps to inform the rollout of gNBS [6], critical engagement with ELSI need not wait for this evidence to develop.

A synthesis of the ELSI raised by gNBS—whether this be in research projects, pilot studies, or full scale deployment—is essential for appropriate implementation. A synthesis of the literature can also help identify gaps that ELSI scholars could address. Although there are many publications directly focused on the ELSI of gNBS, e.g. [7–10], and a systematic review focused on principles of gNBS programs synthesizing empirical data on four questions relevant to gNBS implementation [11], there are no scoping reviews covering all the ELSI scholarship relevant to the gNBS field. There is a rapid review commissioned by Genomics England of the ethical issues associated with gNBS [12]. It organizes issues under: Overarching contextual factors (public health considerations, resource allocation and regulation); Direct contextual factors (public acceptability and equity); Consent and decision making; Interpreting, communicating and acting on findings (including what to return); and Governance and the involvement of commercial organizations.

The key question this scoping review is designed to answer is "What are the ethical, legal, and social implications when genomic sequencing is integrated into public health NBS programs?" And in particular, which issues have been identified, how have they been assessed (using conceptual or empirical methods), and what solutions have been proposed or actually implemented to address the identified issue? A secondary aim of this scoping review is to characterize the overall gNBS literature to clarify its contours, patterns of development, and areas of concentration, thereby providing essential context for interpreting the ELSI landscape identified in the primary aim. This scoping review was conducted as part of a Global Alliance for Genomics and Health (GA4GH)[1] effort to produce a policy tool designed to help gNBS researchers and implementers navigate ELSI [13].

METHODS

A scoping review allows for mapping the existing literature, including accommodating heterogeneous types of research (empirical, conceptual, etc.). This approach also lends itself to thematic organization of findings. We follow the PRISMA guidelines for reporting the results of scoping reviews [14].

Search strategy

Records representing reports discussing ELSI in the context of gNBS were identified by searching the electronic databases MEDLINE (Ovid), Embase (Elsevier), and Web of Science Core Collection (Clarivate). The searches required both mention of NBS (or synonyms) and sequencing (or synonyms). Key to our approach, the searches were not restricted to 'ELSI literature' or ELSI studies; we wanted to ensure that ELSI raised in papers that do not explicitly identify themselves as containing ELSI were still included. A medical librarian (PAB) designed the search based on the aims of the project and a set of thirteen publications pre-identified by the authors (see Supplementary Table 1). The final search captured 12 of the 13 pre-identified records. The missed record has no abstract and is in a journal that is not indexed for MEDLINE. The search was last run on July 2, 2025, with no publication date limit (Supplementary Table 2). Records were initially deduplicated in EndNote (EndNote, Clarivate, Philadelphia, PA) and then imported into Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org) for screening.

Record screening

Records were screened based on titles and abstracts independently by two screeners (ACFL and GB) in Covidence, with discrepancies discussed and resolved. Records were deemed to meet screening criteria if they were related to genomic sequencing of newborns as a first line approach. This did not need to be the primary focus on the publication, but the publication needed to at least discuss this topic. Research publications (including reviews), conference abstracts, and editorials were all included. News articles, even if published in academic journals, were not included. Full text records were then sought. We excluded records not in English, news articles, and those that did not discuss use of sequencing as first line screening.

Charting of characteristics of included publications

We used a mixture of initial AI charting using the Large Language Model (LLM) Claude (Claude Sonnet 3.5, run July 29th 2025) and manual review to collect the following information on each report, using methods as given in Supplementary Table 3: Year of publication; Which country (and state/territory if relevant) the corresponding author's institution is based in; What type of research the publication represented (empirical research, literature review, neither empirical nor review); What gNBS project, if any, the publication is associated with; Journal domain; Whether the authors reported a financial conflict of interest. For each gNBS research project captured by our search, we collected how many babies they enrolled for screening (or enrolled and were allocated to the sequencing arm in the case of BabySeq, which is a randomized control trial), the country in which they enrolled participants, and the underlying platform they used to capture sequencing data (genome, exome, panel).

ELSI charting from each source of evidence

A small set of test publications was chosen for testing of the charting process, including both empirical and conceptual publications. Several authors charted issues manually and then compared results. We found that while similar information was charted, what counted as "an issue" could be quite variable. To support consistency and given the large number of papers to screen, we chose to pursue AI charting. Use of AI for charting as part of literature reviews can achieve high accuracy and substantial efficiency gains when appropriately integrated and is increasingly recognized in scoping review methodology [15–18]. We designed an initial prompt reflecting the instructions we had given team members doing the manual charting. Several team members then tested this prompt, and suggested updates to it to improve the outcomes obtained. A consensus prompt was settled on, when no team members had suggestions to further improve it. This happened after well over 50 iterations on prompt design. The AI prompt we used is available in the Supplementary Information.

The prompt included, for each ELSI issue:

- Identification: category (Ethical/Legal/Social/combination); Characterization (e.g. specifying which values lie in tension, which legal domain, which social domain); Issue summary; Issue quotation
- Assessment of the issue (if applicable): assessment approach (e.g., empirical, non-empirical); Assessment stance: authors' position (critical, supportive, neutral, nuanced); Assessment summary; Assessment quotation
- Solution to the issue (if applicable): Solution type (Technical/Policy/Educational/Procedural/Conceptual/None); Solution status (i.e. proposed/hypothetical, implemented by the authors/reported decision taken by others); Solution scope (Individual/Institutional/Societal/Global); Solution summary; Solution quotation

The prompt was initially run on a different corpus of publications, which were focused on ELSI in NBS. The results of this charting were inputted again into Claude, where one author (ACFL) asked this AI for assistance identifying the gNBS decision points with ELSI dimensions. For the purposes of our study, we defined decision points to be the major operational and policy questions that those implementing gNBS—as part of a research project, pilot study, or deployment—must consider, such as how consent should be obtained, how genomic data should be stored, how results will be integrated into clinical care, and if periodic reanalysis should occur as variant interpretation evolves. The results of several different versions of this analysis were manually combined and organized, and further refined in consultation with another author (DV). In a series of conversations with gNBS researchers from several continents, input was sought for any refinement or additions to the list of decision points. A few decision points were added, some deleted, and some modified during this process.

[1]The Global Alliance for Genomics and Health (GA4GH) is a global not-for-profit organization that sets standards and develops policies to expand genomic data use informed by a human rights approach.

The prompt was then modified to not only chart ELSI from the included publications, but to also link them to none, one, or more of these decision points.

Data synthesis

Data for the region of the corresponding author, type of research, and whether the publication was associated with a gNBS research project were summarized by time period (up to 2010, 2011–15, 2016–20, 2021–5) to reveal the trends in the gNBS literature over time.

The charted ELSI were summarized manually by two reviewers (GB and LW). For each decision point we report counts of: the issues relevant to this decision point; the unique publications raising these issues; the publications that have an empirical assessment; the issues that have a non-empirical assessment; the solutions implemented (i.e., how a decision point has been addressed in a particular context). These numbers were further aggregated into the nine decision areas.

RESULTS

Included publications

Electronic database searching returned 3327 unique records. Records were excluded if they were written in a language other than English, if they did not discuss first line screening using sequencing, or if they were news articles. We sought 565 reports for full text screening, 485 of which met the inclusion criteria and were included in the analysis (Fig. 1). Several of the included publications focused on the use of sequencing for second line testing (post biochemical screen), but also discussed the possibility of using sequencing as a first line screen. The first publication categorized as gNBS was from 1987. Some of the very early publications discuss ELSI directly (e.g. #401, #525). Other early publications were predominantly centered around technical laboratory studies related to the feasibility of sequencing. The number of publications has increased steadily, see Fig. 2A, with a dramatic increase in recent years, especially 2021–2025 (270 publications).

Based on the country of the corresponding author, the proportion of publications from North America has been falling over time, with those from other regions growing, in particular from Europe, Asia and Oceania (see Fig. 2B). There have been publications from corresponding authors based in 41 countries, showing the international interest in gNBS, (see Supplementary Table 4).

Of the included publications, 192 were classified as empirical research, 74 as reviews, and 219 as neither of these types. Empirical studies have been increasing, however, (see Fig. 2C), from 18.9% (pre-2010) to 44.1% (2021–2025). The large volume of literature that neither presents new empirical data nor reviews the field may reflect the importance of both normative/ethical and legal ELSI [19]; these publications are largely relevant to the gNBS field because they discuss whether gNBS should proceed, and if so, how.

There is research from 27 gNBS research projects in the literature, (see Table 1). The first papers date from 2016 onwards; 22.2% of recent publications (2021–2025) are project-associated. These represent projects recruiting in 10 individual countries, and one project recruiting across the EU. The country with the most projects was China, with 12 projects. Most of the projects were not focused on a particular indication; seven were focused, including four for hearing loss. Eight of the projects did/are planning to do whole genome sequencing, three whole exome sequencing, and the remainder panels, ranging from single gene to several hundred genes. One project, the BabySeq Project, dominates in terms of the number of publications, with 21 publications.

There were publications in a range of journal types, see Supplementary Fig. 1. Biomedical research (219 publications) and clinical medicine (198 publications) journals dominate. Only 25 of the publications were published in public health journals.

145 publications (29.8%) listed a potential financial or non-financial conflict of interest for one or more authors, mostly in relation to employment at, funding from, and investment in pharmaceutical or genomic technology companies. Of the 27 gNBS projects, 17 of them had one or more articles with a declared COI.

gNBS decision points with ELSI

Our analysis revealed 59 decision points arising in gNBS with ELSI dimensions, which we grouped into nine areas, see Table 2.

Table 2 summarizes the 3781 ELSI charted from the included publications, organized by area (the full results of charting are available in the Supplementary Material). At least one issue was identified and charted from every included publication. Most issues raised per decision point were under the areas *Which Conditions to Include*, and *Testing and Laboratory Processes*, and the least under *Results Disclosure and Management* and *Data Revisiting for Clinical Purposes*.

The data broken down by decision point are given in Table 3. The decision points attracting the most attention in the literature related to which conditions should be included in gNBS and how those decisions are made. In particular, many publications examined the processes used to select and periodically update condition lists (decision point #14), as well as how "actionability" and clinical utility are defined in this context (#16). Other frequently discussed decision points focused on technical aspects of test design, including how to address challenges in variant interpretation across diverse populations (#26) and whether to adopt whole-genome or whole-exome sequencing, targeted panels, or genotyping approaches (#22).

In contrast, issues related to consent and ongoing communication received relatively limited attention, despite their centrality to the future of gNBS. Few publications engaged deeply with how consent for gNBS should be structured in relation to conventional NBS (#9 and #10), or with how negative results, i.e., findings indicating the absence of the screened-for conditions, should be handled and communicated (#31). Similarly, there was little discussion of whether and how programs should maintain the ability to recontact parents and, eventually, the child (#53).

Data management was the area with the fewest described implemented solutions. The literature rarely addressed how requests to delete data would be handled (#44), whether and how parents (and later the child) should be able to access their genomic data (#45), or how data "ownership" might transfer from parents to the child over time (#46). Other decision points that were discussed conceptually, but for which few concrete solutions were reported, included whether and how to involve commercial or industry partners in program design (#6), whether stored data should be available for later diagnostic use if a phenotype emerges (#52), how to achieve cross-jurisdictional policy consistency (#57), and how project closeout (i.e. the processes in place for concluding a research project or pilot study) should be managed (#59).

DISCUSSION

Summary of evidence

This scoping review identified 485 publications relevant to the integration of genomic sequencing into NBS, from which 3,781 ELSI considerations were charted using AI-assisted methods. These mapped to 59 decision points organized into nine areas, spanning from initial stakeholder engagement and consent through to data stewardship and program governance. The literature is growing rapidly, is increasingly empirical and project-associated, and is becoming more geographically diverse, though significant regional gaps remain. Attention in the literature is unevenly distributed: condition selection and laboratory processes dominate, while downstream operational questions—including clinical follow-up

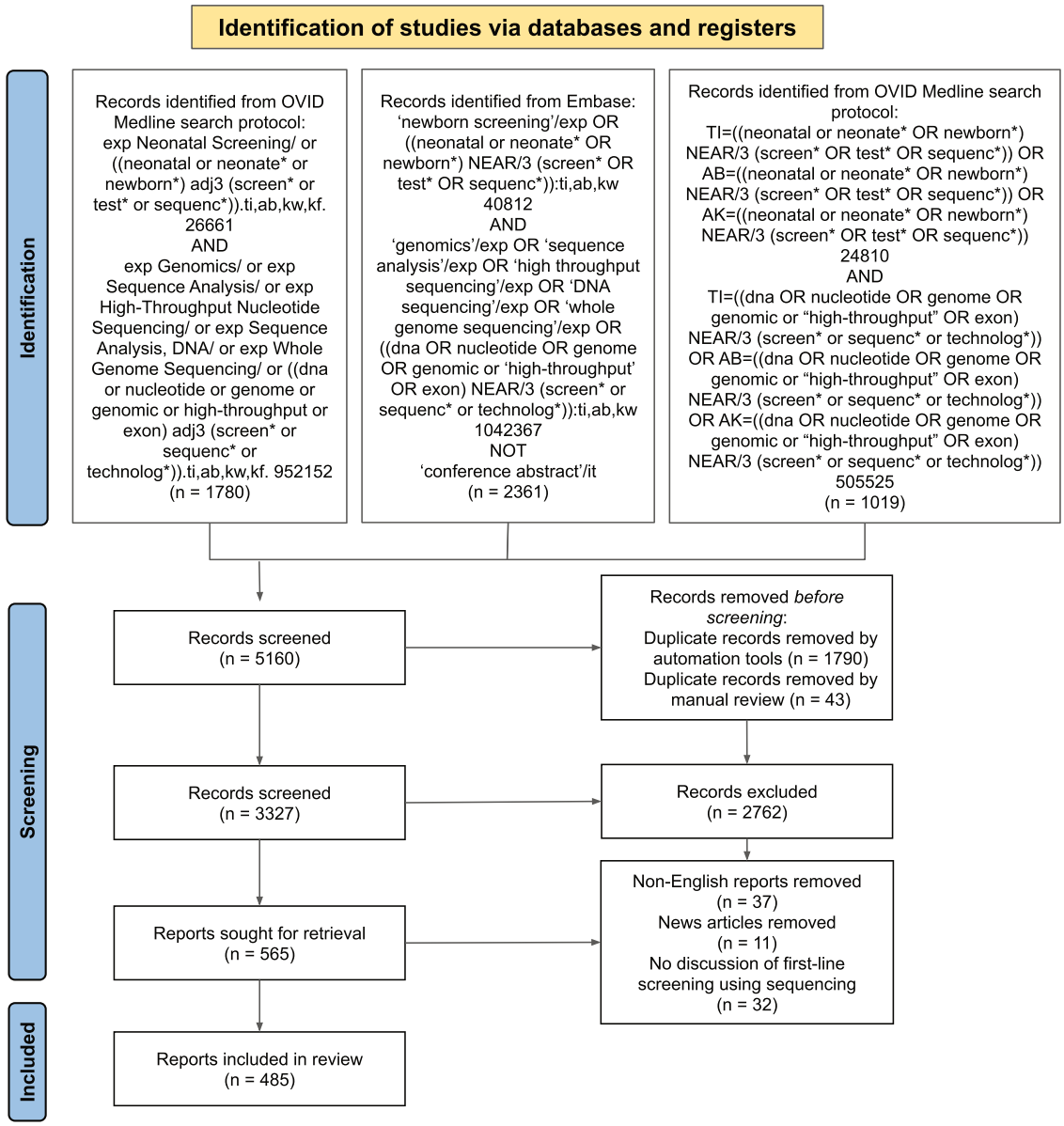

Fig. 1 Included publications. PRISMA flow diagram showing the identification, screening, and inclusion of sources of evidence for this scoping review, resulting in 485 included records.

of screen-positive results, data management, screening participant re-contact, and project closeout—have received comparatively little attention and have few implemented solutions described. This pattern suggests that the field's ELSI scholarship, like its evidence base more broadly, has thus far concentrated on the question of *whether and what* to screen, with less focus on *how to sustain and govern* screening over time.

How the shape of the field influences the ELSI landscape

Several structural features of the gNBS literature have direct implications for which ELSI have been identified and how they have been assessed. The gNBS field has grown steadily since the first publication in 1987, becoming increasingly empirical, project-associated, and geographically diverse. While the geographic spread has increased, there are still few publications from authors in Central America, South America, and Africa, likely largely due to their lack of infrastructure for traditional NBS and competing health priorities within these areas. Future research in these regions, and capacity building, will be needed to ensure a more globally representative perspective [20–22]. This is particularly relevant for ELSI, where legal frameworks governing consent and data protection, cultural norms around family decision-making, and health system capacity to deliver clinical follow-up may all shape how decision points are navigated in practice.

Beyond who is producing the research, where it is published reveals how the field conceives of gNBS. Despite gNBS being viewed as a public health concern [3, 23–25], the research is surprisingly limited in public health journals and instead is found in biomedical and clinical medicine journals. Only 25 publications included in the review were from a public health journal, and the decision points addressed by these reflected those addressed in the remainder of the literature; that is, they focused on the application of sequencing, rather than the population-level lens of public health. Khoury and Holt argued that translating genomic discoveries into population health impact requires implementation science, equity research, and sustained public health infrastructure—all areas that remain underdeveloped relative to discovery research [26]. Our finding that gNBS research

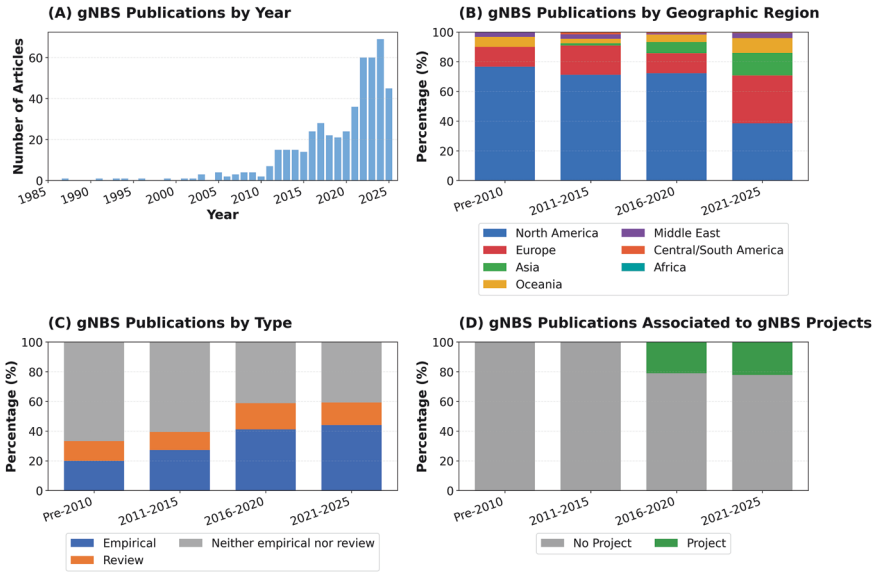

Fig. 2 Characteristics of included publications. Characteristic analysis of included publications by **A** year of publication, **B** geographic region of corresponding author, **C** type of research, and **D** whether or not the publication was associated with a gNBS project.

concentrates in biomedical rather than public health journals, and that even publications in public health journals focus on clinical application rather than population-level considerations, is consistent with this persistent translational gap. A public health framing would foreground questions of equity, population-level benefit-to-harm assessment, and sustainable program governance—precisely the areas where we found the literature to be thinnest.

The high fraction of publications with listed conflicts of interest (29.8%) reflects the many interests at stake (held by varied actors) [27], and the enthusiasm for gNBS from commercial entities [27–29]. Yet as noted in our results, how to involve commercial and industry partners in gNBS program design (decision point #6) is among the least addressed decision points, with only one described implemented solution (#345). This disconnect is particularly concerning given that commercial interests have been identified as one of the key forces driving the expansion of genomic sequencing in newborns, alongside technological imperatives and advocacy pressures [27]. The combination of widespread commercial engagement and minimal guidance for managing it represents a notable gap for the field, and one that cross-jurisdictional coordination could help address.

Gaps and imbalances

Overall, the literature has been focused on initial implementation decisions rather than long-term operational considerations. The imbalance between early implementation decisions and long-term operational needs is starkly illustrated by the vast amount of attention given to condition selection versus the paucity of attention to clinical management of screen-positive gNBS results, including providing diagnostic confirmation, follow-up monitoring and, if necessary, treatment for every child who screens positive—all necessary steps for gNBS to provide any benefit as a public health intervention. Moreover, all are areas in which data will be crucial to assess the overall balance of benefits to harms for extended screening. This imbalance echoes a broader pattern: recent comparative analyses have documented extensive international investment in gene and condition selection for gNBS [30, 31], while a series of systematic reviews evaluating the evidence needed for policy decisions found no studies addressing penetrance in screening populations, test accuracy, or benefit of earlier treatment for most conditions under consideration.6.

There is also relatively little attention to what should happen to the data after initial result return is complete, despite enthusiasm to retain genomic data for research or clinical re-use. There are very few implemented solutions described for data management, including how requests to delete data will be managed, whether parents should be able to access the data, and whether there should be a process of transferring data ownership from the parents to the child. This last point, combined with the paucity of discussion of maintaining contact with the parents and then the child, reflects low attention to date for integrating the children and family, who are the patients and caretakers who will live with the outcomes of gNBS. This reflects the reality of short-term funding for research projects; funding for long-term followup and evaluation of these cohorts is necessary. The near-absence of discussion around project closeout and onward data governance is striking when viewed against the cautionary history of residual NBS blood spots [32]. Moreover, there is a growing literature on the specific ethical complexities of genomic data collected from minors, including the principle that children should have the opportunity to make their own decisions about ongoing data storage and sharing upon reaching maturity [9, 27]. Only two publications were identified as discussing research project closeout, despite these projects holding or planning to hold sensitive data on tens or even hundreds of thousands of participants. A proper management plan for closure of gNBS research projects, including plans for onward data governance, is important.

Consent represents a distinct kind of gap in the literature: not an area that has been overlooked, but one where the current research context constrains what can be learned. A key question for the gNBS field is whether explicit consent will be sought, and if so, how [23]. Because all current gNBS programs operate as research studies, they necessarily seek informed consent for research. This means there is currently no evidence on how uptake and public perception of gNBS would differ under the consent models—such as mandatory, opt-out, or streamlined approaches—that a public health program might adopt. Surprisingly few publications were identified as directly related to the fundamental question of the nature of consent appropriate when gNBS is actually implemented as a public health program. This gap is significant because the consent traditions of population-based screening and genomic medicine pull in opposite directions: traditional NBS has operated in many (but not all) countries under mandatory or implied consent frameworks justified by clear child benefit [32, 33], while genomic sequencing typically demands

Table 1. Overview of gNBS projects with publications in the literature.

Year of first publication	Number of publications	Project	Reported enrolled	Restricted to particular phenotype(s)?	Platform	Location of recruitment
2016	21	BabySeq	127		Genome	United States
2016	10	NC NEXUS	61		Exome	United States
2017	1	First 1,000 Days of Life and Beyond Longitudinal Cohort Study	1,349		Genome	United States
2019	1	[SLC19A3 sequencing in Saudi newborns]	3000	Biotin-thiamine-responsive basal ganglia disease	Single gene	Saudi Arabia
2020	1	[A pilot study of expanded newborn screening, a cohort from Shanghai]	1127		Panel (573 genes)	China
2021	1	[Multi-Center in-Depth Screening of Neonatal Deafness Genes: Zhejiang, China]	5120	Hearing	Panel (22 genes)	China
2022	2	[A pilot study of whole genome sequencing in newborn screening from Qingdao]	321		Genome	China
2022	1	[Concurrent newborn hearing and genetic screening of common hearing loss genes in Jiangxi province]	24,349	Hearing	Panel (4 genes)	China
2022	5	BeginNGS	0		Genome	United States
2022	2	Early Check	0		Genome	United States
2022	6	Generation Study	0		Genome	United Kingdom
2022	2	Newborn Screening with Targeted Sequencing (NESTS)	15,407		Panel (465 genes)	China
2022	5	Screen4Care	0		Panel (245 genes)	Europe
2023	1	[Combined genetic screening and traditional newborn screening of congenital hypothyroidism, cohort from Chongqing]	3158	Congenital hyperthyroidism	Panel (13 genes)	China
2023	3	[Genomic Sequencing as a First-Tier Screening Test and Outcomes of Newborn Screening]	29,601		Panel (142 genes)	China
2023	4	Baby Detect	4005		Panel (405 genes)	Belgium
2024	1	[Cohort in Huzhou, Zhejiang province]	1263		Panel (542 genes)	China
2024	1	[Deafness susceptibility gene of neonates in northern Guangdong, China]	1907		Panel (4 genes)	China
2024	1	[Genomic newborn screening, first clinical experience in Spain]	800		Exome	Spain
2024	1	[WES-based screening of 7,000 newborns: A pilot study in Russia]	7000		Exome	Russia
2024	4	BabyScreen+	0		Genome	Australia
2024	5	Guardian	4000		Genome	United States
2024	1	[Targeted exome sequencing strategy (NeoEXOME) for Chinese newborns]	3423		Panel (601 genes)	China
2024	1	Perigenomed	0		Panel (~800 genes)	France
2025	1	[Newborn genomic screening for lysosomal storage disorders, Nanjing cohort study]	22,687	Lysosomal disorders	Panel (164 genes, of which 18 for LSDs)	China

Table 1. continued

Year of first publication	Number of publications	Project	Reported enrolled	Restricted to particular phenotype(s)?	Platform	Location of recruitment
2025	1	[Screening for hearing impairment in newborns using targeted genomic sequencing]	8261	Hearing	Panel (46 genes)	Taiwan
2025	1	Newborn Screening with Targeted Sequencing (NESTS) - hearing cohort	7501	Hearing	Panel (90 genes)	China

This includes number of publications, year of first publication, enrolled participants, any phenotype restrictions, platform, and recruitment location.

Table 2. Overview of ELSI raised in the included publications ranked by issues per decision point, organized by nine areas.

Area	Number of decision points	Issues per decision point	Empirical assessments per decision point	Non-empirical assessments per decision point	Implemented solutions per decision point
Which conditions to include	8	221.2	75.5	142.2	24.9
Testing and laboratory processes	6	220	99.5	115.8	35.5
Post-test clinical management	6	137	49	84.3	9.5
Consent models	7	106.1	37.9	65.3	9.9
Evaluation framework, governance systems, and implementation continuity	6	101.3	23.7	75	6.8
Stakeholder engagement during planning	6	96.8	34.7	60.7	5.3
Data management	9	82.7	15.3	62.7	3.2
Results disclosure and management	6	69.8	31	37.8	6.3
Data revisiting for clinical Purposes	5	51.6	9.4	40	4.6

The full list of 59 decision points organized under these nine areas is given in Table 3. For each area counts are shown for: number of decision points; issues identified; relevant empirical assessments (e.g., surveys, interviews, and laboratory studies); relevant non-empirical assessments (e.g., conceptual analysis); implemented solutions, i.e., description of how a decision point has been addressed in a particular context.

Table 3. ELSI issues organized by 59 decision points within gNBS.

Area	Decision Point	Count of Issues	Count of Unique Publications	Count of Empirical Assessment	Count of Non-empirical Assessment	Count of Actual Solution
Stakeholder Engagement During Planning	1. How should the perspectives and preferences of families, both with and without children with rare genetic conditions, and from varied backgrounds, be included in program design?	193	136	100	90	17
	2. How should the voice of the child be incorporated in program design?	62	47	25	37	1
	3. How should the perspectives of the general public, who will fund any implemented program with their taxes, be included in program design?	92	78	31	60	4
	4. How should healthcare providers be included in design to ensure implementation feasibility?	68	57	31	36	4
	5. How should policy-makers be included in design to help assess feasibility and optimize implementation?	135	96	19	113	5
	6. Should commercial/industry partners be involved in program design, and if so, how should conflicts be managed?	31	30	2	28	1
Consent Models	7. Will there be a separate research and clinical consent?	167	143	38	123	13
	8. When will consent be obtained?	133	111	50	79	18
	9. If conventional NBS uses a model of explicit consent, what are the considerations for making gNBS a separate versus combined consent?	75	70	22	50	1
	10. If conventional NBS is not explicitly consented, what are the considerations on making gNBS explicitly consented versus not?	114	104	31	79	2
	11. What constitutes appropriate engagement materials for gNBS?	204	139	112	89	32
	12. Will consent be obtained for secondary uses of the data, and if so, how should this be obtained?	47	42	11	35	2
	13. How will withdrawals from the study be handled, particularly for screen positive findings where there might be a duty of clinical care?	3	3	1	2	1
Which Conditions to Include	14. What process (including who) is used to decide and update the condition list?	438	294	141	289	61
	15. How should advocacy influence be balanced with evidence-based decision making when it comes to condition selection?	110	96	27	80	13
	16. How are "actionability" and clinical utility defined for condition selection (including considerations of availability and accessibility)?	401	283	139	255	54
	17. Should conditions with variable onset, penetrance, expressivity, or pleiotropy be included?	255	199	90	159	18

Table 3. continued

Area	Decision Point	Count of Issues	Count of Unique Publications	Count of Empirical Assessment	Count of Non-empirical Assessment	Count of Actual Solution
	18. Should there be an age-of-actionability cut-off, and, if so, what should this be?	236	176	71	164	17
	19. Should carrier status for recessive conditions be reported?	109	89	41	68	12
	20. Should there be any parental choice in categories of results returned?	178	133	74	102	19
	21. Should major pharmacogenetics variants be included?	43	29	21	21	5
Testing and Laboratory Processes	22. Should whole genome, whole exome, targeted panel sequencing or genotyping be adopted?	355	260	174	168	75
	23. What sample collection methodology should be used?	114	92	77	33	35
	24. How and when should test limitations be communicated?	79	74	40	37	7
	25. Should variants of uncertain significance ever be reported?	276	221	99	174	31
	26. How should the challenges of variant interpretation across diverse populations be addressed?	356	253	149	202	48
	27. How should the process for disclosure of provisional results be managed?	140	112	58	81	17
Results Disclosure and Management	28. For positive results, who should deliver results (pediatrician, genetics professional, specialist)?	40	39	22	17	8
	29. For positive results, how should return be done (including what information should be provided, whether virtual or in person)?	58	53	27	29	10
	30. For positive results, how can the psychological impacts on families be assessed, addressed and minimized, and with what role for advocacy and patient community input?	163	127	86	76	9
	31. For negative results, will results be returned, and if so, using what model?	13	12	8	5	5
	32. How to build sufficient genomics expertise in the healthcare provider workforce, particularly pregnancy providers and pediatricians?	142	131	43	97	5
	33. What should be done if a newborn dies before or soon after result return (including what should happen to their data)?	3	3	0	3	1
Post-test Clinical Management	34. What standards should be established for clinical follow-up after screening (including resources provided for healthcare providers, and the role of advocacy groups)?	223	179	103	115	24
		128	113	43	82	7

Table 3. continued

Area	Decision Point	Count of Issues	Count of Unique Publications	Count of Empirical Assessment	Count of Non-empirical Assessment	Count of Actual Solution
	35. How should referral networks and other follow-up care infrastructure be developed to support families after positive genomic findings?					
	36. Should the program plan for surveillance and follow up of positive findings, including those with later-onset conditions?	48	45	20	26	6
	37. To what extent should the program coordinate cascade testing, and if so what degree relatives?	80	66	31	48	4
	38. How should healthcare system disparities that affect follow-up care be addressed?	288	224	81	198	11
	39. What aggregate outcomes data should the program plan to collect?	55	52	16	37	5
Data Management	40. What data should be stored on each baby (e.g., fastq files, bam files, vcf files, only data related to genes currently included in the gNBS program, only gNBS results reported back to patient's physician or family)?	121	96	18	96	7
	41. For how long should sequence data be maintained (legal minimum or longer)?	104	103	20	75	5
	42. Who will store the data and where will it be stored?	84	81	17	61	5
	43. What security and privacy measures should be implemented to protect genomic data?	167	141	36	123	5
	44. How will requests to delete data be managed?	28	28	3	23	0
	45. Should parents or the child be able to access their data (this may be legally required), and, if so, what information should be provided?	40	37	5	32	0
	46. Will there be a process of transferring data ownership from the parents to the child?	52	47	8	43	0
	47. Who will the data be shared with, for which purposes, (e.g. data federation for purposes of directly improving the public health program), and which data will be shared?	58	53	9	46	3
	48. Will there be any allowed secondary use of the data (beyond purpose of screening, quality assurance, program development), and if so, what governance structures would oversee it?	90	82	22	65	4
Data Revisiting for Clinical Purposes	49. Should genomic data be periodically reanalyzed as knowledge that impacts variant interpretation advances (and if so, with what time limit)?	84	81	18	61	10
	50. Should genomic data be periodically reanalyzed as the gene list changes (and if so, with what time limit)?	42	42	5	34	8

Table 3. continued

Area	Decision Point	Count of Issues	Count of Unique Publications	Count of Empirical Assessment	Count of Non-empirical Assessment	Count of Actual Solution
	51. Should there be any planned disclosures of information that is relevant later in life?	79	72	14	64	3
	52. Should the data be available for diagnostic purposes, if the child develops a phenotype?	36	35	7	27	1
	53. Should the ability to recontact parents, and eventually the child, be maintained, and if so, how?	17	17	3	14	1
Evaluation Framework, Governance Systems, and Implementation Continuity	54. How should project success be defined and measured?	233	187	54	172	19
	55. What governance system should be put in place for managing emerging issues?	49	44	6	41	2
	56. How can transparency be assured in decision-making processes?	45	44	8	36	6
	57. What are the priorities for cross-jurisdiction policy consistency, both across regions and internationally?	52	51	10	42	0
	58. How should sustainability of any ongoing implementation be planned for, including expansion of downstream capacity?	227	189	64	157	14
	59. How should closing the project be managed?	2	2	0	2	0

The decision points are grouped into nine areas and show counts of: issues identified related to that decision point; unique publications raising issues; relevant empirical assessments (e.g., surveys, interviews, and laboratory studies); relevant non-empirical assessments (e.g., conceptual analysis); implemented solutions, i.e., description of how a decision point has been addressed in a particular context.

detailed, individualized informed consent to address the complexity and evolving nature of its results [34, 35]. As a consequence, gNBS pilot programs have developed a range of hybrid consent models, from prenatal digital platforms to in-person genetic counseling sessions, that remain largely untested outside the research context in which they were designed [36–39].

Several additional gaps warrant note. There is little attention in the literature to how negative results—which will constitute the vast majority of gNBS outcomes—should be communicated and managed, despite the implications for parental understanding and public trust. There were also few implemented solutions offered for discussion or setting of cross-jurisdiction policy consistency, whether across regions or internationally, despite the increasingly global nature of the field. In 2022 an organization was formed, the International Consortium of Newborn Sequencing (ICoNS), precisely to enable gNBS projects to learn from each other and to collaboratively work on topics, such as policy development across jurisdictions.

Study limitations

Our search strategy did not find one of the 13 publications we had pre-identified as relevant, so it is likely that this scoping review misses other literature. As an independent check, we confirmed that all papers associated with the BabySeq Project, the gNBS project with the most associated publications, were included. Further, we limited publications to those in English. It was not straightforward to identify papers associated with particular projects, particularly given the lack of names for several of the projects, and this analysis may have missed some associations of publications to projects.

This study used the LLM Claude, from Anthropic, at various points in the workflow. We did not rely on the AI for any of the publication level data, but we did rely on it for charting ELSI from the literature. The process of the AI charting from the direct text of publications is more reliable than asking an AI just to summarize aspects of the literature without access to full-texts of the included papers. We did not identify issues with hallucination when asking Claude to chart information from PDFs. However, broader limitations of LLM use for reviews have been identified, including lack of reproducibility and the potential for incomplete information. Outputs may differ significantly from minor changes in prompting and require refined prompting, which is why we implemented iterative prompt refinement and manual (human) review of charted data [40]. Our manual process of charting ELSI from papers revealed that there are many defensible ways to do this. We found that Claude's process made sense and was adequate to serve our purposes of identifying the breadth of issues in the literature, but we certainly do not claim that this was a uniquely valuable way to manage that charting. For this reason, we do not view the actual count of issues as meaningful. We did not manually review all 3781 issues identified, so it is possible that some are not relevant to gNBS.

CONCLUSION

This scoping review identified 59 decision points with ELSI dimensions across nine areas of gNBS, drawing on 3781 considerations charted from 485 publications. The ELSI scholarship remains heavily concentrated on early implementation questions, particularly condition selection and laboratory processes, with far less attention to the ethical, legal, and social dimensions of long-term operational needs, such as data stewardship, results disclosure, clinical follow-up, project closeout, and sustainable governance. These gaps point to several priorities for ELSI research. Scholars should direct attention to the downstream decision points where few implemented solutions have been described, particularly data governance and re-contact, areas where the ethical stakes are high but the literature offers little guidance. The governance of commercial involvement also warrants dedicated ELSI analysis, given the combination of widespread commercial engagement and minimal normative or policy scholarship addressing it. The structural difficulty of studying consent outside a research context means that ELSI scholarship should anticipate the transition to public health implementation, developing normative frameworks for consent that go beyond the research models currently in use. Finally, the geographic concentration of the literature means that ELSI considerations from many legal, cultural, and health system contexts remain unrepresented. The literature nonetheless provides a sizable corpus of considerations for gNBS decision-makers, and this scoping review hence provides a starting place for navigating ELSI. It also enabled us to provide syntheses of the literature for each of these decision points as part of a policy tool for those in the gNBS field [41].

DATA AVAILABILITY

The underlying data, both publication metadata and ELSI, are available as a separate spreadsheet (data here).

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AUTHOR CONTRIBUTIONS

ACFL and YB conceived of the study, with input from the remaining co-authors. PB designed the search strategy. GB and ACFL screened records. GB, LW, and ACFL identified full texts and publications not meeting inclusion criteria. LW constructed the PRISMA diagram. GB, LW and ACFL charted meta data from the publications. GB, LW, AW, AN, DV, JMF, AG, MAA, ZD, AB, SJ, and ACFL co-designed the ELSI charting prompt based on manual review of publications and comparisons to LLM outputs, which ACFL executed. LW and GB did the data synthesis. ACFL drafted the initial draft, all authors revised the draft and approved of the final version.

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RCG receives compensation for advising the following companies: Allelica, Atria, Fabric, and Genomic Life; and is co-founder of Genome Medical and Nurture Genomics. YB is co-Founder of Genetics Adviser. The remaining authors declare no competing interests.

ETHICAL APPROVAL

Not relevant as no human subjects.

ADDITIONAL INFORMATION

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