

Developing an ELSI readiness matrix for genomic newborn screening

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Abstract

Genomic sequencing is increasingly being explored as an extension of newborn screening, but its incorporation into population programmes creates longitudinal ethical, legal, social, organisational and governance obligations that cannot be assessed through analytical performance alone. We conducted a critical narrative review and iterative framework-development synthesis to identify recurrent programme-level ethical, legal and social implications (ELSI) and organise them into a non-scoring, stage-specific readiness matrix. Six interdependent domains were identified: (1) governance and decision-making architecture; (2) child-centred justification and proportionality; (3) consent, information and communication; (4) genomic data, residual samples and privacy governance; (5) structural equity; and (6) clinical, organisational and economic capacity. The synthesis indicates that genomic newborn screening reconfigures relationships between screening, clinical care, research, data infrastructures and families. The ELSI Readiness Matrix is intended to support multidisciplinary screening committees, health technology assessment bodies and public-health authorities in documenting evidence, identifying unresolved gaps, developing safeguards and defining responsibilities before initiating, scaling or substantially expanding a programme. It complements rather than replaces condition-specific screening criteria, health technology assessment and legal review. The matrix requires independent appraisal and prospective evaluation before it can inform routine implementation decisions. Its prospective value lies in supporting more transparent, accountable and equitable stage-specific deliberation on programme design and implementation of genomic newborn screening in public health settings.

Introduction

Newborn screening has long occupied a central place in preventive paediatrics and public health. Its authority as a population-based intervention has never rested solely on the capacity to detect disease early, but on the existence of a programme able to convert early detection into meaningful clinical benefit through reliable testing, timely confirmation, appropriate follow-up and effective intervention.[1, 2] Genomic medicine unsettles some of the assumptions on which this settlement was built. As sequencing technologies increase the capacity to identify genetic variants, susceptibilities and uncertain risks, they also challenge established understandings of what counts as a legitimate screening target and what forms of evidence are sufficient to justify testing asymptomatic newborns. In this context, population-based genomic screening requires renewed attention not only to analytical validity and clinical utility, but also to ethical justification, economic sustainability and the wider societal consequences of generating predictive or uncertain information at birth.[3]

Whole-genome and exome sequencing may generate carrier, familial and reproductive information beyond the immediate health needs of the infant. Direct clinical benefit to the screened child should remain the primary justification for newborn screening, while the deliberate generation or disclosure of additional family-level findings requires separate programme-level justification.[4]

Knoppers and colleagues argued that any redefinition of the goals of newborn screening should be debated prospectively, with explicit attention to the best interests of the child, clinical validity, medical actionability, consent, incidental findings, carrier status, data privacy and security, insurability, professional education and the capacity of health systems to manage genomic results over time.[4, 5] This warning remains highly relevant because genomic newborn screening (gNBS) expands not only what can be detected, but also the responsibilities, decisions and infrastructures required to manage genomic information over time.

The appeal of gNBS lies in its promise to support earlier diagnosis of rare genetic disorders, reduce diagnostic delay and create a more systematic route to timely intervention. For some conditions, this prospect is compelling, particularly where delayed recognition may lead to irreversible harm. Yet a genotype-first strategy in asymptomatic newborns also places screening within a more uncertain interpretative landscape. Genomic findings do not always translate into predictable clinical trajectories, and questions concerning penetrance, variable expressivity, variant interpretation, age of onset and actionability become central to decisions about which results should be generated, disclosed and acted upon. Current reviews and policy analyses suggest that the value of gNBS depends not on sequencing capacity alone, but on transparent condition selection, proportionate management of uncertainty, meaningful communication, responsible data governance, equitable downstream care and sufficient health-system capacity.[6–10]

The central issue is how analytical capability, evidence appraisal and programme design can be aligned so that expanded informational capacity yields timely, proportionate and equitable benefit for children while limiting avoidable uncertainty, medicalisation, parental distress, data misuse and unequal access to downstream care. Evidence from health technology assessment (HTA) reinforces this distinction, showing that decisions about candidate conditions remain constrained by gaps in knowledge concerning penetrance, expressivity, clinical effectiveness, cost-effectiveness and population-level harms.[11]

A growing body of studies has begun to define the ethical and policy boundaries within which gNBS might be considered acceptable as a public-health intervention. Targeted approaches have been defended on the grounds that publicly funded newborn screening should remain focused on serious, early-onset and treatable conditions.[12] Other frameworks refine the concept of actionability by linking disclosure to disease severity, penetrance, expected benefit, intervention burden and timing.[13] In this context, severity and utility require explicit and separate assessment. Recent frameworks further distinguish severity, actionability and clinical utility, emphasising that programme inclusion should consider untreated disease burden, the availability and burden of effective intervention, and incremental benefit over existing diagnostic pathways.[13, 14]

Normative analyses have further expanded the debate by foregrounding the child's best interests, future autonomy, right not to know, informational self-determination, privacy and protection against unnecessary medicalisation.[15–18] At the same time, implementation experiences from national

programmes and pilot initiatives show that ethical advisory structures, public dialogue, co-design, consent workstreams, condition-selection procedures and evaluation mechanisms can be embedded before routine adoption rather than added retrospectively. Recent initiatives—including the UK Generation Study; GUARDIAN, BabySeq and BeginNGS in the United States; and Australian pilot programmes—illustrate how genomic newborn screening is increasingly being explored through evidence-generating models that integrate governance, stakeholder engagement and programme evaluation before large-scale implementation.[19–23]

Established screening criteria, health technology assessment (HTA) and implementation frameworks provide indispensable and often multidimensional foundations for decision-making. Whereas Brown et al. map the gNBS ELSI landscape through 59 decision points and Schnabel-Besson et al. define 18 criteria for target-condition selection and programme management, the present matrix organises longitudinal, interdependent obligations into a document-based, non-scoring assessment tailored to each implementation stage.[10, 14] Building on these and other contributions,[2, 24, 25] this article develops an ELSI Readiness Matrix to help determine the programme-level legitimacy of (proposed) genomic newborn screening programmes.

Programme-level legitimacy refers here to the defensibility of a proposed gNBS programme as a public-health intervention: its aims, scope, procedures and distribution of benefits and burdens should remain consistent with established ethical frameworks for newborn screening, including child-centred benefit, proportionality, equity, transparency, accountability and the capacity to provide appropriate follow-up. Legal permissibility is necessary but not sufficient. Alignment with these frameworks is therefore constitutive of legitimacy, while sustainability denotes the programme's capacity to maintain its clinical, organisational, economic and governance obligations over time. ELSI readiness is the ex-ante, jurisdiction-specific judgement that sufficiently credible evidence and institutional arrangements are in place to proceed to the next stage of implementation.

The review was undertaken to support framework development and was guided by the following research question: Which programme-level ELSI concerns recur across heterogeneous gNBS literature, and how can they be organised into a non-scoring framework to support documented, stage-specific and jurisdiction-sensitive assessments of readiness?

Results

The iterative synthesis identified six interdependent programme-level domains relevant to ELSI readiness assessment: (1) governance and decision-making architecture; (2) child-centred justification and proportionality; (3) consent, information and communication; (4) genomic data, residual samples and privacy governance; (5) structural equity; and (6) clinical, organisational and economic capacity. Although analytically distinct, these domains are mutually dependent: governance shapes how programme scope is justified and reviewed; scope determines consent, communication and data-governance requirements; and the equitable realisation of anticipated benefits depends on sufficient

clinical, organisational and economic capacity. Weakness in any one domain may therefore constrain readiness across the others, and no domain should be assessed in isolation.

1. Governance and decision-making architecture

Across policy recommendations, programme-development studies and recent evidence syntheses, governance emerged as a distinct programme-level domain concerning who is authorised to make decisions, through which procedures and with what accountability. The literature supports formally mandated and transparent arrangements for defining programme aims and scope; selecting and reviewing conditions and gene–condition pairs; specifying the composition and responsibilities of advisory, decision-making and oversight bodies; incorporating patient, parent and public perspectives; and managing conflicts of interest and commercial involvement.[6, 9, 14, 19, 20]

Governance also has a longitudinal and adaptive dimension. Condition lists, reporting policies and programme boundaries require periodic reassessment as evidence concerning severity, penetrance, actionability, utility, harms and health-system capacity changes, with explicit procedures for adding, restricting or removing conditions. Responsibility should also be assigned for ongoing evaluation, the governance of emerging issues, cross-jurisdictional coordination, reanalysis and recontact policies, and the transition or closure of research and pilot projects. Brown et al. mapped 59 ELSI decision points across nine areas and found that several downstream questions—including recontact, cross-jurisdictional consistency, project closeout and the governance of commercial involvement—had received uneven attention and, in several cases, few implemented solutions.[14] Governance readiness therefore concerns the durability, transparency and adaptability of decision-making arrangements across the programme life course, rather than authorisation at the point of launch alone.

2. Child-centred justification and proportionality

Across the literature, a second programme-level domain concerns whether the proposed scope of gNBS can be justified in child-centred and proportionate terms. Severity, actionability and utility are widely used in gene selection and panel design, but insufficiently defined.[26, 27] The concepts are related but should not be treated as interchangeable. Severity concerns the consequences of an untreated condition and should be assessed across the anticipated phenotypic spectrum, rather than inferred only from classically severe cases. Relevant considerations include age at onset, morbidity, mortality, quality of life, penetrance and variable expressivity.[28] In a genotype-first screening population, these distinctions are critical because some identified children may develop milder or later-onset disease or may never develop clinically significant manifestations. Because judgements about severity and acceptable effects on quality of life contain normative as well as empirical elements, their assessment should combine clinical and epidemiological evidence with input from people living with the condition and from patient and family representatives.[10, 11, 16]

Actionability, by contrast, concerns whether identification in the newborn period enables a specified, timely and available intervention or surveillance strategy that can improve the child's outcome.[26] It is

therefore not established merely by the existence of some form of treatment. Assessment should consider the intervention's effectiveness, timing, accessibility, risks and burdens, including those associated with repeated surveillance. Clinical utility concerns the net value of using gNBS within the relevant population and care pathway. Inclusion should therefore be supported by evidence of incremental benefit over established biochemical screening or symptom-led diagnostic routes, whether through earlier or more reliable identification or through better outcomes from pre-symptomatic intervention.[27] Analytical detection alone is insufficient; gene-condition validity, penetrance, expressivity, age of onset, diagnostic performance, treatment effectiveness, overdiagnosis, opportunity costs and the maturity of the evidence base must be considered together to determine the clinical utility of a newborn screening programme.[6, 10, 11, 13, 26]

The literature does not establish a single numerical threshold that is universally applicable to the dimensions of severity, actionability or utility. Readiness instead requires transparent thresholds, explicit treatment of uncertainty and procedures for periodic reassessment. The justificatory case is strongest where gNBS identifies a severe, childhood-onset, highly penetrant condition for which timely intervention produces a meaningful net benefit for the child. It becomes less straightforward where expansion includes uncertain variants, low-penetrance risks, non-actionable findings, adult-onset conditions, carrier status information or results that primarily benefit relatives rather than the newborn. Familial, reproductive, research or population-level benefits may be relevant, but should be reported separately from direct clinical benefit to the child.

Programme-level proportionality must therefore weigh anticipated benefits against uncertainty, psychosocial and clinical burdens, opportunity costs across the full pathway and the possible displacement of established screening and care. The literature consequently supports neither unrestricted expansion nor categorical rejection, but a targeted, staged and evidence-generating approach governed by explicit benefit thresholds and regular review.[4, 7, 9–13]

3. Consent, information and communication

Conventional newborn screening uses varied participation and consent arrangements, commonly justified by its focus on serious, early-onset and treatable conditions and the potential harm of delayed identification. Genomic screening changes this balance. It may generate information that is uncertain, familial, future-oriented or research-relevant, and may entail data retention and reanalysis over many years. Programme readiness therefore requires clear differentiation among parental authorisation for the initial screen, parental permission for research participation, permission or another specified legal basis for data retention and secondary use, and arrangements governing clinical reuse, including possible reanalysis and recontact. Acceptance of the initial screen should not be treated as blanket authorisation for downstream activities. Because programme improvement/QA-QI, research and clinical reuse serve different purposes and carry different benefits and risks, each may require a distinct information and authorisation regime.[14, 29–33]

The programme must also identify its model of parental participation, since mandatory, opt-out, informed compliance and informed choice models vary in parental authority to refuse and expected engagement. Mandatory screening permits no refusal, opt-out allows refusal without requiring an affirmative decision, informed compliance records a decision but may involve limited deliberation, and informed choice requires an opt-in decision and a genuine opportunity to consider and decline the offer. A signed form does not establish informed choice if participation remains routinised or refusal is not presented as a genuine option. The participation model adopted for gNBS should be justified by the nature and breadth of the information that the programme intends to generate and disclose. Where genomic testing is offered alongside conventional newborn screening, the programme should also specify whether parents may decline the genomic component while still accepting conventional screening.[33, 34]

Communication is challenging not simply because of the quantity of information, but because of the complexity, uncertainty and future implications of genomic findings within an emotionally and temporally constrained perinatal context. Parents may decide about their participation in newborn screening during pregnancy or shortly after birth, when vulnerability, time pressure and trust in health professionals shape the decision environment. Too little information makes the decision ethically thin; too much may make it practically unintelligible. Readiness therefore depends on antenatal information provision where feasible, and on accessible multimodal materials, trained professionals and proportionate access to counselling, culturally and linguistically appropriate communication, and processes for checking understanding. Plans should cover the entire pathway: how screen-negative results will be returned and their limitations explained; how positive, uncertain and carrier findings will be conveyed, and what support will be available when findings have implications for relatives or future reproductive decisions. A screen-negative result should not be presented as excluding all genetic disease, and familial or reproductive utility should not be conflated with direct clinical benefit to the child.[29–32, 35]

Where genomic data or findings are retained beyond infancy, parental authorisation should not remain the sole reference point indefinitely. Programmes should provide for age-appropriate disclosure to the child, increasing participation as their capacities develop and, where applicable, assent, recontact or transfer of decision-making authority over continued retention, secondary use, reanalysis and recontact preferences. Consent, information and communication thus form a longitudinal governance process rather than a one-off transaction at screening.[15–18, 36]

4. Genomic data, residual samples and privacy governance

A fourth area of convergence concerns how gNBS extends the informational and temporal scope of newborn screening beyond the relatively bounded framework traditionally associated with dried blood spot programmes. Although conventional programmes may retain residual specimens and associated records, genomic sequencing can generate a wider range of durable materials and data products. Governance should distinguish the residual biological specimen from raw sequence data, processed sequence files, variant calls and clinically reported results; within data holdings, it should also distinguish

aggregated outputs from individual-level data held in identifiable, pseudonymised or anonymised form. These categories differ in their storage burden, privacy risks, capacity for linkage and potential for future analysis. The relevant question is therefore not simply whether material or data should be retained or destroyed, but what should be retained, for which purpose, for how long and under whose stewardship. [4, 33, 37, 38]

Lewis, Goldenberg and Knoppers provide a purpose-based basis for this distinction by identifying three principal reasons for retaining genomic data: programme improvement, including quality assurance and quality improvement (QA/QI); research; and clinical reuse.[33] These purposes have different ethical justifications and may require distinct legal bases, retention periods and authorisation arrangements within the applicable legal and institutional framework. Research retention and reuse should be governed separately and, where required, be subject to informed authorisation.[33, 37–39]

Where clinical reuse is contemplated—including reinterpretation as genomic knowledge changes, reporting findings that become actionable later in childhood or accessing the data when a relevant phenotype emerges—programmes should establish a jurisdiction-specific policy, proportionate retention periods, appropriate parental education and an operational pathway for clinical action. Programmes should also explicitly delineate the boundaries among QA/QI activities, research and clinical reuse, as these activities may be subject to different governance and authorisation requirements.[33] For each retained object and permitted use, programmes should document these arrangements and specify the responsible data or sample steward; the authority to approve access and linkage; the applicable security safeguards; and the scope and limits of withdrawal, deletion or sample destruction.

Responsibilities for reanalysis, clinical validation, recontact and follow-up must be allocated prospectively, particularly where retention may create expectations of surveillance that the programme cannot fulfil. Privacy protection cannot rest on formal classifications alone, as re-identification risks may evolve as genomic and clinical datasets accumulate. Long-term retention may facilitate function creep, commercial exploitation or discriminatory use. As the child develops decision-making capacity, governance should specify whether and how they will be informed and involved in decisions about continued research or clinical reuse. These arrangements cannot be left to post hoc compliance, as they determine whether gNBS remains a bounded screening intervention or assumes longitudinal research and clinical obligations.[17, 18, 26, 37–39]

5. Structural equity

Equity in genomic newborn screening cannot be assumed merely because the same test is offered universally across a population. Even under formally universal programmes, outcomes may remain deeply unequal when families differ in their capacity to understand genomic information, access confirmatory testing, reach specialist services, obtain effective treatment, trust healthcare institutions or benefit from genomic interpretation generated from datasets that inadequately represent population diversity.

This concern is compounded by the persistent under-representation of non-European populations in many genomic reference databases, which may reduce diagnostic accuracy, increase uncertainty in variant interpretation and limit the equitable distribution of potential benefits across populations. For this reason, equity-oriented analyses increasingly move beyond the question of nominal access and instead examine the unequal capacities through which genomic information can be transformed into meaningful clinical and social benefit. Within this perspective, the critical issue is not simply who receives genomic results, but who is realistically positioned to benefit from them and who may instead experience additional forms of burden, uncertainty or exclusion.[40, 41] Equity is conceptually constitutive of programme-level legitimacy but is retained as a separate analytical domain because a universal offer may conceal unequal capacities to understand results, obtain confirmation, access treatment and benefit from genomic interpretation.

This point is particularly important for decentralised or federated health systems. Stakeholder studies from Australia identify national coordination, workforce capacity, laboratory and data infrastructure, downstream services, legally agreed data uses and equitable access for Indigenous and under-represented populations as prerequisites for responsible implementation.[42] Spanish ELSI analyses similarly emphasise the need for greater coordination between national and regional authorities, alongside common service portfolios, legal safeguards, public communication and equity across autonomous communities.[25, 43] More recently, the Spanish Uniform Newborn Screening Panel (SUSP) provides an operational example of this challenge, using nationwide professional consensus, standardized nomenclature and harmonized diagnostic pathways to promote equitable screening within a decentralised healthcare system.[44] Although developed for conventional DBS-based newborn screening rather than gNBS, the SUSP illustrates how national scientific standardisation can coexist with regional implementation and may therefore provide a relevant organisational precedent for future genomic screening.[44]

6. Clinical, organisational and economic capacity

The final convergence concerns the system's ability to act. Genomic newborn screening cannot be considered ready for routine implementation if it identifies infants for whom confirmatory diagnosis, counselling, surveillance, treatment or psychosocial support are unavailable. Sequencing capacity may increase health-system burden rather than health benefit if laboratories, paediatric services, genetics teams, metabolic clinics, primary care, data systems and health technology assessment processes are not aligned.[7, 11, 42] Sustainability refers here to the capacity to maintain over time the workforce, confirmatory pathways, treatment access, data stewardship, quality assurance, monitoring and financing required to fulfil the programme's obligations without displacing higher-value care.

Economic appraisal should therefore extend beyond the price of sequencing to encompass the entire pathway, including confirmatory testing, variant interpretation, genetic counselling, specialist assessment, surveillance, treatment, data stewardship and long-term follow-up, and should make opportunity costs explicit. Implementation also requires recurrent, long-term funding matched to

anticipated caseloads and explicit workforce planning for clinical genetics and genetic counselling, rather than reliance on capacity assembled temporarily for pilot studies.[3, 7, 11, 42, 45, 46] Before any condition is added, programmes should establish that timely confirmation, counselling, treatment and surveillance can be provided on equitable terms across geographical areas and population groups; otherwise, a universal offer may produce unequal capacity to benefit.[40–42]

Sustainability also depends on adaptive programme governance. Post-implementation surveillance should distinguish false-positive results (screen-positive findings not confirmed by diagnostic assessment) from overdiagnosis (findings that are valid but would not have caused clinically significant disease during the child's lifetime), and should monitor confirmatory burden, unnecessary investigations and interventions, psychosocial effects, treatment or surveillance uptake, clinical outcomes and resource use.[2, 11, 21, 47] These outcomes should be reviewed against predefined, condition-specific thresholds through accountable procedures that allow programmes to modify reporting rules or follow-up pathways, pause individual components, or withdraw conditions when the evidence no longer supports clinical utility, proportionality, equitable benefit or cost-effectiveness. Any such change should preserve continuity of care for children already identified.[2, 10, 48]

Implementation protocols are beginning to specify programme-relevant outcomes, including clinical utility, acceptability, turnaround time, diagnostic confirmation, follow-up and cost-effectiveness.[21] These initiatives frame gNBS as an evidence-generating programme rather than as an inevitable consequence of cheaper sequencing. We therefore propose that programme evaluation should consider not only what the test can detect but also whether the health system can provide timely confirmation, treatment and follow-up responsibly and equitably to the children and families identified.[25]

Operational application of the ELSI Readiness Matrix

The matrix is intended for multidisciplinary screening committees, HTA bodies and public-health authorities, with structured participation from parents, affected communities and relevant professionals. It should be applied once the proposed programme's scope, reporting policy, consent pathway, data flows and downstream care arrangements have been specified, and before a decision to initiate, scale or substantially expand gNBS. For each coded item, users should document the supporting evidence, unresolved gaps, required mitigations or conditions, responsible bodies and deadline or review trigger. After considering the four items within a domain, users should record a reasoned, stage-specific domain judgement. A single overall conclusion (proceed, proceed conditionally or defer) is then justified across domains without numerical aggregation. The matrix does not replace condition-specific screening criteria, HTA, local legal review or continuing programme governance.

To support consistent application and source-level traceability, the 24 items specifying the evidence and arrangements to be documented were assigned stable identifiers (D1.1–D6.4): the first numeral identifies one of the six domains, whereas the second identifies one of the four items within that domain. Supplementary Table S1 presents the critical extraction of the included sources, Supplementary Table S2

maps supporting sources to each coded item and domain, and Supplementary Table S3 reproduces all 24 identifiers as separate application rows, with a reasoned judgement after each four-item domain block and one non-additive overall conclusion.

Discussion

The literature supports neither unqualified adoption nor categorical rejection of genomic newborn screening (gNBS). Sequencing does more than expand laboratory capacity; it links screening more closely with diagnosis, research and longitudinal care, creating responsibilities for laboratories, clinicians, public-health authorities and health systems.[4, 7, 8, 49, 50] Earlier diagnosis of severe childhood-onset conditions may improve access to treatment and reduce diagnostic uncertainty, but uncertain or low-penetrance findings may also increase overdiagnosis, surveillance and parental anxiety, while generating obligations that an underprepared system cannot fulfil.[8, 11, 42, 50, 51] Meaningful public-health benefit therefore cannot be inferred from analytical performance alone. It depends on programme design, responsible governance, child-centred decisions about scope, proportionate communication, durable stewardship of genomic information, equitable access and timely downstream care. ELSI considerations are consequently constitutive of programme readiness rather than safeguards to be added after implementation.[4–10, 16–20, 42, 49–52]

The ELSI Readiness Matrix addresses this programme-level problem by organising recurrent responsibilities into six connected domains. It is a non-scoring framework for structured and documented deliberation, not a mechanism for producing a universal score or deciding automatically whether implementation should proceed. At each proposed transition, screening committees, HTA bodies and public-health authorities could use it to record evidence, uncertainties, safeguards, responsibilities and critical unmet obligations. Its domains are analytically distinct but operationally interdependent: governance determines who defines programme scope; scope shapes information, consent and data-governance requirements; and equitable benefit depends on clinical, organisational and economic capacity. Readiness, sustainability and legitimacy therefore remain related but distinct. A programme may be ready for research or a pilot without being ready for wider provision; sustainability concerns whether obligations can be maintained, whereas legitimacy is the broader judgement that a programme is publicly defensible. The matrix can inform, but cannot settle, that judgement.

The matrix complements rather than replaces established screening criteria, condition-specific evidence reviews, HTA or jurisdiction-specific decision-making. Revised screening principles already connect disease and test assessment with programme objectives, service integration, informed choice, confidentiality, equity, quality assurance, evaluation and the overall balance of benefits and harms.[2] Contemporary HTA likewise encompasses clinical and economic evidence alongside ethical, social, cultural, legal and organisational consequences. [24] More specifically, Schnabel-Besson et al. proposed 18 criteria for target-condition selection and programme development,[9] while Brown et al. mapped 59 ELSI decision points and identified less-developed downstream responsibilities, including data stewardship, disclosure, follow-up, recontact, project close-out and sustainable governance. [14] The

matrix's contribution is to integrate these interconnected responsibilities into six programme-level domains suitable for transparent, stage-specific assessment.

Future research should assess the matrix across diverse health-system contexts. The initiatives discussed here are illustrative and were selected using common criteria across jurisdictions: public documentation, prospective gNBS activity, multidomain relevance and sufficient protocol or early implementation detail for comparison. In Spain, the SUSP provides a recent organisational precedent for nationwide consensus-based harmonisation within a decentralised newborn-screening system,[44] while CRINGENES [53] and GENEBOEN represent emerging Spanish initiatives relevant to the prospective evaluation of genomic approaches to newborn screening. Internationally, the Generation Study illustrates engagement, co-design and consent,[54] whereas BabyScreen + and GUARDIAN provide protocol or early implementation evidence on recruitment, reporting, diagnostic confirmation and follow-up.[55–58] Their inclusion illustrates variation in programme design and does not imply ranking, endorsement or readiness for routine implementation.

Any prospective application would require prior institutional agreement, a prospectively specified protocol, appropriate ethical, legal and data-governance approvals, and transparent management of relevant interests. Formal content appraisal should first involve evaluators external to the matrix-development team who have no operational, governance, advisory or financial role in the programmes considered, alongside intended users and representatives of affected communities. Subsequent applications should use a predefined documentary corpus, an explicit analytical protocol and an independent evaluation component. Application alone would not constitute empirical validation. Evaluation should examine the clarity and relevance of the domains, feasibility and practical value, how disagreements are recorded, and whether the matrix improves the transparency, accountability and equity of decision-making without reducing complex judgements to a score.

These conclusions must be interpreted considering the review's limitations. The critical narrative approach was selected for conceptual integration and framework development, not exhaustive retrieval, theme-frequency estimation or the reproducibility expected of a systematic review or meta-analysis. The evidence base is evolving rapidly and remains uneven across health systems.[25, 59, 60] Protocols and preprints were used cautiously to identify emerging implementation questions. Convergence denotes recurrence across evidence types or jurisdictions, not agreement about how each concern should be resolved. The domains and their proposed relationships therefore remain an interpretive synthesis, and the matrix has not yet undergone independent content appraisal or prospective empirical evaluation as an assessment instrument.

Overall, the matrix offers a common structure for judging whether evidence, safeguards and service capacity are adequate for a specified stage of gNBS. A critical unmet obligation in one domain may constrain several others and justify deferral even when technical performance is strong. Progression should therefore require documented evidence that sequencing capability is matched by governance

arrangements, ethical safeguards and sustainable health-system capacity capable of converting genomic detection into equitable and clinically meaningful care.

Methods

Design and methodological record

We conducted a critical narrative review with iterative framework synthesis to identify recurrent programme-level ethical, legal and social implications (ELSI) of genomic newborn screening (gNBS) and organise them into a non-scoring readiness matrix. The review sought conceptual integration rather than effect estimation or exhaustive systematic coverage. A manual methodological record specified the question, scope, principal sources, date and language limits, eligible source types and intention to develop a programme-level matrix. Coding, domain refinement, source classification and item wording were developed iteratively and recorded in a decision log.

Search, eligibility and selection

Searches covered publications from 1 January 2010. Initial searches on 10, 22 and 26 April 2026 captured records available to 31 March 2026. Updates were run on 23 May, 22 June, 22 and 25 July 2026. PubMed (Medical Subject Headings and title/abstract), Scopus (TITLE-ABS-KEY) and Web of Science (Topic) combined newborn screening and genomic sequencing with ELSI, governance, equity, consent, data or sample governance, implementation, capacity and evaluation. Searches were limited to English and Spanish. Human filters were applied in PubMed where appropriate and Scopus was restricted to medicine and the social sciences. Dialnet and Google Scholar supported regional and grey-literature retrieval. The first 100 Google Scholar results ranked by relevance were inspected.

Citation searching, reference checking, hand-searching and programme, governmental and legal sources supplemented the databases. Official and grey literature provided context but did not alone establish a domain. Only published or otherwise publicly accessible information was used. No unpublished programme information, internal documents or private communications from CRINGENES, GENEBOORN or any other initiative informed the corpus, framework development or description of candidate settings. Peer-reviewed versions replaced corresponding preprints. Online-first and accepted or in-press articles were retained with their status recorded, and reports from the same programme only when analytically distinct. Eligible sources addressed programme-level ELSI, governance, implementation or health-system implications of gNBS. Purely technical, narrowly disease-specific, non-substantive or redundant reports were excluded unless they had transferable programme implications. Table 2 reports the documented selection. Later updates and targeted enrichment produced a final corpus of 60 analytically distinct sources.

Table 1
ELSI Readiness Matrix for genomic newborn screening

Domain	Core readiness question	Evidence and arrangements to be documented
1. Governance and decision-making architecture	Who decides, under what authority, with whose participation, for which programme stage and through what review procedures?	D1.1. Programme mandate, legal authority and responsible decision-making bodies. D1.2. Transparent condition-selection criteria, procedures and public rationales. D1.3. Stakeholder and public participation, representation, expertise and conflicts of interest. D1.4. Accountability, review, appeal and programme change-control procedures.
2. Child-centred justification and proportionality	Does the proposed scope offer a proportionate, evidence-based net benefit, primarily to the child, relative to existing screening and diagnostic pathways?	D2.1. Untreated phenotypic spectrum, severity, penetrance, expressivity and age at onset in screened populations. D2.2. Clinical validity, actionability, intervention effectiveness and burden. D2.3. Incremental child-centred benefit over existing screening and diagnostic pathways. D2.4. Proportionality assessment of uncertainty, false positives, overdiagnosis, psychosocial harms and opportunity costs, with non-child utilities reported separately.
3. Consent, information and communication	Can parents make a voluntary and meaningful decision about gNBS and its distinct downstream uses, with increasing involvement of the child over time?	D3.1. Antenatal, accessible and evaluated information. D3.2. Publicly justified participation and consent model, including genuine refusal. D3.3. Distinct authorisation or legal bases, where applicable, for screening, research, retention and clinical reuse.

Note. Each domain comprises four coded readiness items (D1.1–D6.4), whose identifiers and descriptors are reproduced consistently across the Supplementary Tables. The matrix is non-scoring; a critical unmet obligation may justify deferring the decision under assessment, irrespective of readiness in other domains. gNBS, genomic newborn screening; QA/QI, quality assurance and quality improvement.

Domain	Core readiness question	Evidence and arrangements to be documented
		D3.4. Communication and counselling for negative, positive, uncertain, carrier and familial findings, including age-appropriate disclosure and later assent or reconsent.
4. Genomic data, residual samples and privacy governance	What is retained, for which purpose, for how long, by whom and on what legal or authorisation basis, with which access and lifecycle rules?	D4.1. Retained specimens, data products, data flows and permitted purposes. D4.2. Legal bases, responsible stewardship, access, linkage and security. D4.3. Retention periods, secondary or commercial use, parent or child access, withdrawal, deletion or destruction. D4.4. Validation, reanalysis, clinical reuse, recontact, follow-up and the child's developing authority.
5. Structural equity	Can all groups understand, access, complete and benefit from gNBS and downstream care without predictable or unmitigated disparities?	D5.1. Equitable access to information, the screening offer and informed participation. D5.2. Population and ancestry representation and equitable genomic interpretation. D5.3. Territorial, socioeconomic and cultural access to confirmation, treatment, surveillance and follow-up. D5.4. Subgroup outcomes, equity impact assessment, public trust, mitigation and monitoring.
6. Clinical, organisational and economic capacity	Can the system confirm, communicate, treat, follow up, monitor and finance findings at scale without displacing higher-value care?	D6.1. Laboratory, bioinformatics and quality systems, including turnaround and QA/QI. D6.2. Workforce and referral, confirmation, counselling, treatment and surveillance pathways. D6.3. Recurrent financing, economic evaluation, opportunity costs and long-term sustainability.
Note. Each domain comprises four coded readiness items (D1.1–D6.4), whose identifiers and descriptors are reproduced consistently across the Supplementary Tables. The matrix is non-scoring; a critical unmet obligation may justify deferring the decision under assessment, irrespective of readiness in other domains. gNBS, genomic newborn screening; QA/QI, quality assurance and quality improvement.		

Domain	Core readiness question	Evidence and arrangements to be documented
		D6.4. Registries, outcome and harm monitoring, evaluation and predefined procedures to modify, pause or withdraw components.
Note. Each domain comprises four coded readiness items (D1.1–D6.4), whose identifiers and descriptors are reproduced consistently across the Supplementary Tables. The matrix is non-scoring; a critical unmet obligation may justify deferring the decision under assessment, irrespective of readiness in other domains. gNBS, genomic newborn screening; QA/QI, quality assurance and quality improvement.		

Table 2
Source-identification and selection account

Stage	Documented count	Outcome or qualification
Initial identification (April 2026)	417 records: 354 from PubMed, Scopus and Web of Science in aggregate; 63 from complementary methods	The surviving record does not preserve separate database yields.
Initial selection	201 duplicates removed; 216 titles/abstracts screened; 81 full texts assessed; 31 excluded	Fifty reports entered the initial synthesis. Exclusions reflected insufficient programme-level ELSI relevance, a purely technical or narrow focus, ineligible type, or redundancy.
Updates and final corpus	Updates: 23 May, 22 June, 22 and 25 July 2026; final corpus: 60 sources	The sources considered during the update and the general basis for exclusion were noted.
Note. A PRISMA-style flow diagram was not used because the study was designed as a critical narrative review with iterative framework-development synthesis rather than as a systematic review. The documented counts are reported to support transparency about source identification and selection.		

Extraction, appraisal and framework synthesis

For each source, design, jurisdiction, programme stage, contribution, concern, proposed safeguard, unresolved tension, limitation and provisional domain were manually recorded. The source was the unit of inclusion; the coding unit was a discrete empirical finding, normative claim, legal obligation, implementation problem or governance decision relevant to programme design or delivery. Supplementary Table S1 presents the extraction.

A separate manual appraisal record assessed methodological quality or source credibility using design-appropriate criteria, including clarity and suitability of methods, evidential limitations, authority, transparency of reasoning, currency and fitness for the claim. Protocols, preprints and early programme reports were treated as preliminary. The ‘Critical limitation’ column in Supplementary Table S1 summarises source-specific constraints and is not a formal quality score. Given the heterogeneous

empirical and normative corpus, appraisal informed interpretation but was not converted into a single cross-design rating.

Framework development comprised six documented rounds: four rounds of coding, consolidation, clustering and boundary revision, followed by two rounds translating domains into coded items and verifying the mapping. The first author performed the primary coding of the corpus; co-authors reviewed successive framework versions, mappings and item wording, and disagreements were resolved by consensus. Convergence required a similar concern in at least two independent sources spanning more than one evidence type or jurisdiction. Discordant positions were retained as tensions, and single concerns were retained when they identified a binding obligation, serious potential harm or material programme failure. Domains had to represent distinct, documentable programme decisions or responsibilities; overlapping clusters were merged and redundant, purely clinical or non-transferable clusters were removed or absorbed.

The resulting domains were governance and decision-making architecture (D1); child-centred justification and proportionality (D2); consent, information and communication (D3); genomic data, residual samples and privacy governance (D4); structural equity (D5); and clinical, organisational and economic capacity (D6). Cross-cutting concerns retained supporting mappings across domains.

Classification, verification and matrix construction

Mappings were primary (P) when a source directly defined, justified or operationalised an item, and supporting (S) when it corroborated or contextualised it. Sources designated as core constituted a selective subset of high-priority sources making a direct and distinctive contribution to a domain; the designation did not imply superior methodological quality and was not intended to provide an exhaustive list of relevant sources. Priority was High for direct and material contributions, Moderate for narrower, indirect, preliminary or less transferable contributions, and Contextual for background or jurisdiction-specific value. Supplementary Table S2 provides the complete source-to-domain and source-to-item mapping and identifies the domain or domains for which each source was designated as core.

All co-authors checked the final corpus, coding and framework of this manuscript.

Each domain was expressed as one readiness question and four documentary items (D1.1–D6.4). Supplementary Table S3 reproduces the 24 identifiers as separate application rows. Each four-item domain block ends with a reasoned stage-specific judgement, followed by a single non-additive overall conclusion. No aggregate score was developed because the matrix supports structured deliberation and has not yet undergone independent content appraisal or empirical validation.

Ethics approval

was not required because this article is based on published and publicly available sources and does not involve human participants, animals or identifiable personal data.

Declarations

Data availability

All sources analysed in this review are identified and cited in the article. The accompanying Supplementary Information contains the source-level records and methodological materials generated during the study: Supplementary Table S1 reports the critical extraction for each included source, Supplementary Table S2 maps primary and supporting sources to the coded matrix items and corresponding domains, and Supplementary Table S3 provides a non-scoring application template. No primary empirical or participant-level data were generated.

Author contributions

M.A.E. conceived and led the study, designed and conducted all stages of the critical narrative review, led the development of the ELSI Readiness Matrix, and drafted the manuscript and supplementary tables.

P.B., D.G.-L. and **E.M.B.** contributed to the conceptual development of the ELSI Readiness Matrix, interpretation of the literature, and critical revision of the manuscript.

M.L.C. and **J.G.-V.** contributed to the clinical and public-health interpretation of genomic newborn screening and to the analysis of governance, stakeholder engagement and implementation considerations related to the ELSI Readiness Matrix, informed by their experience in the CRINGENES project.

All authors reviewed and approved the final manuscript.

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Statement of Competing Interests

M.L.C. and J.G.-V. are investigators in the CRINGENES project, with M.L.C. serving as principal investigator. CRINGENES is discussed solely as a potential setting for prospective application of the matrix. No unpublished data, internal project information or private communications from CRINGENES were used in the development or validation of the framework. M.A.E., D.G.-L., E.M.B. and P.B. declare no competing interests.

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