1. APPENDIX: Literature Synopsis for each decision point

The cited articles are listed here. These articles were those identified by a scoping review of the genomic newborn screening (gNBS) field conducted in July 2025 (NOTE: scoping review will be published separately).

Note: these summaries were written by Claude (an AI), based on over 500 provided PDFs. Each summary has been checked, and, where appropriate, edited, by humans, including at least one expert in the field. Nonetheless, there may be errors, and these syntheses should be taken as an orientation to the existing literature on each decision point only.

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?

Two-Sentence Summary:
Implementation of genomic newborn screening programs requires meaningful engagement with a range of diverse families and stakeholders to ensure programs are culturally appropriate, equitable, and meet community needs. Current evidence indicates significant limitations in representation of diverse populations in research, program design, and implementation. This suggests a need for more inclusive approaches like community review boards and consultations that actively incorporate perspectives from varied racial, ethnic, socioeconomic, and cultural backgrounds, including both families with and without experiences of rare genetic conditions.

Extended Synthesis:

ELSI at Stake:
- Equity and representation in program design and implementation [194, 187, 463]
- Cultural sensitivity and respect for diverse values and beliefs [240, 143]
- Balance between medical expertise and community perspectives [294, 472]
- Trust building with historically marginalized communities [472, 440]
- Public acceptance and program sustainability [466, 289]

Arguments:
- Programs must be designed with rather than for communities to ensure acceptability and effectiveness [472, 440, 249]
- Diverse stakeholder engagement is essential for maintaining public trust and high participation rates [494, 478]
- Cultural and religious values significantly affect program implementation and must be considered [488, 240]

- Traditional expert-driven approaches may fail to account for important community perspectives [132, 517]
- Parent/family expertise is uniquely valuable for understanding impacts of screening [293, 447]

Empirical Evidence:
- Most research on genomic screening has predominantly included white, educated, higher socioeconomic status participants [346, 343, 163]
- Language barriers significantly affect participation rates, with non-English/Spanish speakers six times more likely to decline participation [218]
- Studies show different attitudes toward genetic testing across cultural groups [159, 358]
- Parents from diverse backgrounds strongly support expanded screening but have concerns about privacy and follow-up care [377]
- Low recruitment rates in studies suggest need for better engagement approaches [313, 449]

Proposed Solutions:
- Development of community advisory boards with diverse representation [440, 472]
- Cultural competency training for healthcare providers [347, 218]
- Multi-language educational materials and communication strategies [174, 240]
- Structured public dialogue processes [210, 249]
- Partnership with community organizations and leaders [331, 478]

Implemented Solutions:
- BabySeq2 project created community advisory board with diverse members from three enrollment cities [440]
- Generation Study (UK) conducted extensive consultations with public, patient groups and experts [517]
- Screen4Care project implemented two-cycle review process including patient advisory board [483]
- Early Check program working to assess values and priorities of diverse stakeholders in future research by utilizing the patients, parents, and public health professionals. [24]
- GUARDIAN study providing multilingual information materials and trained staff [174]

2: How should the voice of the child be incorporated in program design?

Two Sentence Summary:
The literature extensively discusses the ethical tension between parental proxy decision-making and preserving the child's future autonomy in genomic newborn screening (gNBS). A key challenge is balancing the potential benefits of early detection and intervention against the child's right to an open future and their ability to make informed decisions about their genetic information when they reach maturity.

Extended Synthesis:

ELSI at stake:
- Child's right to an open future vs. parental authority in medical decision-making [30, 82, 83, 192, 222, 228, 466]
- Child's right to autonomy and self-determination vs. potential medical benefits [82, 505]
- Child's right not to know genetic information vs. parental desire for comprehensive testing 188, 252, 282]
- Tension between viewing children as autonomous persons vs. belonging to parents [279, 505]

Arguments:
Protecting Child's Autonomy:
- Children should have the right to decide whether and when to learn genetic information about themselves [83,192]
- Testing for late-onset conditions violates the child's future right not to know [466, 505]
- Parents cannot legitimately consent to procedures that might reveal information affecting their child's adult life [228, 282]

Supporting Earlier Testing:
- Early detection and intervention can provide significant medical benefits [30, 505]
- Parents are responsible for child welfare and should have authority to make medical decisions [126, 195]
- Knowledge can enable better preparation and planning for conditions [505]

Empirical Evidence:
Studies with Young Adults/Children:
- Young adults generally prefer limiting results to treatable childhood-onset conditions [505]
- Children tend to favor broader disclosure of results and trust healthcare professionals more [505]
- Some young adults express concern about parents making decisions that impact their adult lives [505]

Parent/Family Perspectives:
- Parents report minimal psychological impact when genetic risk information is disclosed to children at age 12 [354]

- Parents struggle with balancing their desire for information against preserving child autonomy [349, 350]

Proposed Solutions:
1. Age-based genomic screening (ABGS) approach:
- Gradually introduce genetic information as children develop [192]
- Allow children to participate in decision-making as they mature [195]

2. Policy/Guidelines:
- Limit testing to conditions with childhood onset and available treatments [466]
- Develop clear guidelines for balancing child and parental interests [30]

3. Educational/Communication:
- Design age-appropriate information disclosure [505]
- Provide support for families in communicating genetic information [354]

4. Procedural:
- Include mechanisms for transferring data ownership to children when they mature [222, 505]
- Create processes for children to provide assent when appropriate [192]

Implemented Solutions:
The extracted literature does not describe any implemented solutions specifically addressing how the voice of the child has been incorporated into existing gNBS programs.

3: How should the perspectives of the general public be included in program design?

Two-Sentence Summary:
Public engagement in gNBS program design is crucial for maintaining trust, ensuring acceptability, and achieving high participation rates. Evidence suggests that public perspectives can evolve through deliberative processes and vary by context. Implementers should refer to existing evidence and recommendations, and consider using multiple engagement approaches (like public dialogues, citizens' juries, focus groups, and surveys) while ensuring representation from diverse stakeholder groups, including parents, minority communities, and healthcare providers.

Extended Synthesis:

ELSI at Stake:
- Tension between public health benefits and individual/community perspectives [4, 16, 17]
- Need to balance expert decision-making with broader stakeholder input [24, 63]
- Public trust vs. technological advancement [311]
- Cultural sensitivity vs. universal standards [331]
- Privacy concerns vs. program implementation [293]

Arguments:
Supportive:
- Public engagement is foundational to program success and acceptance [213, 240, 313, 524]
- Diverse stakeholder input helps ensure equitable implementation [249]
- Public dialogue enhances transparency and trust [279]

Critical:
- Political polarization and social media could threaten public trust [311]
- Risk of undermining existing screening programs if public concerns aren't addressed [249]
- Challenge of balancing multiple stakeholder perspectives [294]

Empirical Evidence:
- Studies show variable public willingness to participate in genomic screening vs. traditional screening [30, 404]
- Deliberative engagement leads to more nuanced public attitudes [63]
- Public attitudes differ between supporting availability and personal use intention [63]
- Political orientation does not significantly influence attitudes toward gNBS [343]
- Cost is a major factor in public acceptance [403]

Proposed Solutions:
- Multi-modal engagement approaches (surveys, focus groups, citizen juries) [249]
- Deliberative engagement processes that provide information and allow discussion [63]
- Public education programs about genetics and genomics [12, 240]
- Ongoing dialogue between stakeholders [450]

Implemented Solutions:
- UK Newborn Genomes Programme conducted national public dialogue regarding the ethicality of genome sequencing to non-curable or non-treatable conditions based on public perception and harm [210, 476]
- BabyScreen+ in Australia using focus groups, surveys and discreet choice experiments [391, 403]
- Generation study in UK conducted extensive public dialogue, stakeholder consultations, community advisory boards, and questionnaires [157]

Note: The implementation examples are relatively limited in the extracted literature, suggesting a need for more reporting of real-world engagement strategies.

4: How should healthcare providers be included in design to ensure implementation feasibility?

Two Sentence Summary:
Healthcare provider involvement in gNBS design is crucial for successful implementation, with evidence indicating that providers have more cautious attitudes than the public and face significant challenges around workforce capacity, knowledge gaps, and workflow integration. Implementers must carefully consider both technical aspects (like system integration and workflow automation) and social aspects (like provider education and engagement strategies), while ensuring representation from diverse provider types including primary care, managing specialists, and genetics professionals.

Extended Synthesis:

ELSI at Stake:
- The core ethical and social issues involve balancing provider autonomy and expertise with implementation feasibility [246,388], ensuring adequate workforce capacity while maintaining quality care [167,246,480], and managing the tension between technological advancement and clinical practicality [7,32,482].
- There are also concerns about healthcare access inequality and implementation barriers across diverse populations [32,370].

Arguments:
- Proponents argue that healthcare provider engagement is essential for successful implementation [169,187,249], with emphasis on the need for interdisciplinary collaboration [242,480] and provider input in program design [63,246].
- Critics highlight concerns about workforce capacity constraints [167,246] and the need to maintain professional autonomy alongside technological advancement [388].- Some argue for the importance of primary care provider involvement [385], while others emphasize the need for specialist expertise [422]. There is general agreement that implementation requires careful consideration of provider perspectives and workflow integration [246,482].

Empirical Evidence:
Studies show that healthcare providers generally have more cautious attitudes toward gNBS than the public [207,363]. Survey data indicates significant generational differences, with younger providers more likely to support genomic screening [363].

Research has identified several implementation challenges:
- Workforce capacity and training gaps [167,246]
- System integration and workflow impacts [246,388]
- Variable provider confidence in delivering results [385]
- Different perspectives between provider types [523]

Proposed Solutions:
Technical/Procedural:
- Workflow automation and system integration [371,388]

- Standardized training and result delivery protocols [246]
- Development of care coordination procedures between pediatricians and specialists to provide ongoing integrated care [363]

Educational:
- Provider education programs [32,252]
- Decision support tools [214]
- Cross-professional education initiatives [523]

Policy/Institutional:
- Multi-stakeholder working groups [65,187]
- Phased implementation approaches [482]
- Professional guideline development [289]

Implemented Solutions:
Several programs have implemented specific approaches:
- BabyScreen+ uses theory-informed interviews of a variety of healthcare professionals to identify implementation barriers [391]
- Ontario Newborn Screening adopted a multi-step policy development process and providers identified barriers to educating parents. [266]
- The China Neonatal Genomes Project established a network of participating hospitals [392]

5. How should policy-makers be included in design to help assess feasibility and optimize implementation?

Two Sentence Summary

Policy-maker involvement in genomic newborn screening (gNBS) design is essential for addressing systemic barriers, ensuring adequate infrastructure, and aligning programs with health system priorities and regulatory frameworks. Implementers must engage policy-makers early in design to address governance gaps, resource constraints, cross-jurisdictional coordination challenges, and health equity concerns, while balancing standardization with local adaptation and innovation with evidence requirements.

Extended Synthesis

ELSI at Stake

- The core governance challenges involve fragmented state-based programs lacking coordinated leadership [26,29,187,194,195], unclear decision-making authority [33,195,287,289], and the complex intersection of technology with politics, ethics, and resource constraints [190].
- Feasibility issues include inadequate assessment of health system capacity [187,192,194,323], laboratory and workforce constraints [323,394], and insufficient follow-up care infrastructure, particularly in low-resource settings [4,5,268,269].
- Health equity concerns include geographic disparities in access [187,194,268,269], and the risk that screening without adequate follow-up infrastructure exacerbates inequities [4,5,269].
- Resource and policy challenges encompass chronically underfunded programs [26,29,194], regulatory frameworks lagging behind technology [38,79,287,289,394], and tension between standardization and innovation [187,194,287,289,323].

Arguments

- Proponents argue that policy-makers must be involved from earliest design stages [187,192,194,287,289], with coordinated federal-state partnerships [26,187] and clear governance structures [33,195,287,394].
- There is strong consensus that feasibility assessment and resource planning must be integrated into program design from the beginning [38,187,192,194,323], with sustainable funding mechanisms [26,29,190,194,268].
- Advocates emphasize that policy-maker involvement is essential for ensuring equitable program design [4,5,8,9,187,194,268,269] and enabling cross-jurisdictional coordination while respecting local autonomy [26,187,194,289].
- Critics note that programs dominated by disease-specific experts without policy-maker input may not reflect societal values [23,192,287], and that policy-makers must reconsider traditional evidence requirements in the genomic context [192,287,289].

Empirical Evidence

- Limited empirical evidence exists, with most studies being descriptive. Key findings include fragmented state programs with variation in panels, care, and funding due to inadequate policy coordination [26,187,194]; chronically underfunded programs slow to implement new

technologies [194]; screening without adequate follow-up care exacerbating health inequities [4,5]; resource constraints prioritizing other health needs in low-income settings [268,269]; and lacking explicit public policies on genomics [394].

Proposed Solutions

Governance/Coordination:
- Establish formal governance structures with policy-maker representation and advisory bodies [33,195,287,394]
- Create federal-state partnerships with funding and guidance [26,187]
- Develop transparent decision-making processes [287,289]

Feasibility/Resources:
- Conduct systematic feasibility assessments of infrastructure, workforce, and data governance [38,187,192,323]
- Develop sustainable funding models and phased implementation approaches [26,187,190,194]
- Assess follow-up care capacity across jurisdictions [4,5,187]

Policy Frameworks:
- Develop explicit public health genomics policies and data governance frameworks [38,79,394]
- Establish quality standards balancing rigor with feasibility [323]
- Create mechanisms for cross-jurisdictional coordination [26,187,194,289]

Equity/Implementation:
- Ensure adequate follow-up infrastructure before expansion [4,5]
- Address geographic disparities through policy interventions [187,269]
- Integrate genomic screening with existing health systems [4,5,190,394]
- Adapt programs to cultural contexts [67,287]

Implemented Solutions
- Arabian Peninsula: Government funding for premarital screening [67]
- Research programs: GUARDIAN [38], Newborn Genome Project [150]
- China: Facility requirements for genetic screening [323]

6: Should commercial/industry partners be involved in program design, and if so, how should conflicts be managed?

Two-Sentence Summary:
Commercial involvement in genomic newborn screening presents both opportunities (accelerating therapeutic development, addressing funding gaps) and significant risks (equity concerns, conflicts of interest, data privacy, technology-led rather than needs-led implementation, screening decisions driven by commercial imperatives). The literature emphasizes the need for careful oversight and governance structures, as well as the importance of transparency, to manage commercial partnerships while maintaining public health priorities and protecting against the creation of two-tier systems based on knowledge and ability to pay.

Extended Synthesis:

ELSI at stake:
- Balance between leveraging commercial resources/expertise and maintaining public health (particularly screening) priorities [27, 94, 169]
- Equity concerns regarding access to testing and creation of two-tier systems [269]
- Data privacy and ownership when sharing genetic information with commercial entities [415, 525]
- Conflicts of interest in program design (e.g. screening criteria) and implementation [27, 191]

Arguments:
Supportive:
- Partnerships with drug companies can help accelerate the development of drugs for rare diseases [120, 27]. This can be via addressing funding gaps, and via identifying patients who could potentially benefit from drugs in development or newly developed.
- Pre-competitive consortiums can enable beneficial collaboration while managing conflicts [120]

Critical:
- Commercial interests may drive premature adoption before clinical utility is established [94, 247]
- Commercial providers may fragment services and worsen health disparities [169, 269]

Empirical Evidence:
- European expert consensus supports public funding over out-of-pocket payments, with potential industry engagement [464]

Proposed Solutions:
- Assess and, where necessary, augment relevant regulatory frameworks for the use of gNBS [191]
- Establish public-private partnerships with proper oversight mechanisms [27, 120]
- Create pre-competitive consortiums with open membership [120]

- Maintain genomic NBS as public health intervention rather than as a commercial service [214]

Implemented Solutions:
- BeginNGS program created an open, public-private, pre-competitive consortium with academic, industry, and parent stakeholders [120]
- Historical example from France of successful public-private partnership with Evian in establishing newborn screening [279]

7: If the study is a research project, will there be a separate research and clinical consent?

Two-Sentence Summary:
The literature suggests significant tension between research and clinical care paradigms in genomic newborn screening, with different consent requirements traditionally applied to each domain. Key considerations include whether combining research and clinical consent could reduce participation rates and burden on parents, versus whether separate consent processes are needed to ensure clarity about different uses of genomic data and maintain public trust.

Extended Synthesis:

ELSI at stake:
- Tension between research and clinical uses of genomic data, raising questions about appropriate consent models [411, 469, 471]
- Privacy concerns and data protection for stored samples and genomic information [163, 396, 463]
- Risk of undermining public trust in newborn screening programs if research uses aren't clearly distinguished [411, 476]
- Administrative burden and potential reduction in participation rates with multiple consent processes [82, 144, 306]

Arguments:
Supporting separate consent:
- Research and clinical care have fundamentally different aims and ethical frameworks [147, 222]
- Clear separation helps maintain transparency and public trust [411, 476]
- Research consent requires more detailed information about future uses [282, 306]

Supporting combined consent:
- Reducing administrative burden and complexity for parents [144, 219]
- Maintaining high participation rates [308]
- Integration of research and clinical care may be inevitable for rare diseases [471]

Empirical Evidence:
- BabySeq Project faced challenges with parental enrollment when requiring extensive research consent [54, 136]
- Survey of genetic counselors showed concerns about obtaining proper informed consent for both purposes [205]
- Hong Kong study showed parents and healthcare providers have significant privacy concerns about research use of samples [396]

Solutions (Proposed):
- Multi-tiered consent processes separating mandatory screening from optional research participation [248, 308]

- Electronic consent platforms to streamline process while maintaining clarity [134, 141]
- Pre-birth education and consent to reduce burden during newborn period [349, 356]

Solutions (Implemented):
- BabySeq Project: Modified protocol to simplify consent requirements after low enrollment [441]
- SEQaBOO study: Offers separate enrollment options for clinical results versus research participation [198]
- Early Check program: Electronic education and consent platform for the research and clinical components as one, with options to get more information about each component [134]
- Danish Neonatal Screening Biobank: Uses passive consent for screening [235]
- BabyScreen+: Used an online digital platform for education and consent with research and clinical consent kept separate [391].

The synthesis reveals this as a complex issue without clear consensus, though there appears to be movement toward tiered or flexible consent processes that maintain distinction between clinical and research uses while minimizing burden on families.

8: When will consent be obtained?

Two Sentence Summary:
The timing of consent for genomic newborn screening (gNBS) presents a critical tension between obtaining truly informed parental decisions and maintaining program feasibility. Key considerations include balancing the emotional and practical challenges of the immediate postpartum period against the need for timely sample collection, with most literature suggesting that prenatal engagement about gNBS, with confirmation of consent after birth, may be optimal.

Extended Synthesis:

ELSI at Stake:
- Tension between parental autonomy (informed decision-making) and public health benefits (timely screening and high participation) [311, 244, 306]
- Challenge of ensuring parents can make genuinely informed decisions while managing time constraints around birth [149, 214]
- Balancing comprehensiveness of consent process with practical implementation feasibility [167, 391]
- Rights of the child who cannot directly consent [223, 486]
- The health rights of the asymptomatic but at-risk child to be screened and found [222]

Arguments:
Supporting prenatal consent:
- Parents are less stressed and have more capacity to process information [89, 349, 347]
- Allows time for questions and deliberation [56, 246]
- More conducive to thoughtful decision-making [304]

- Baby Beyond Hearing: approached parents mostly when their infant was between 3-9 months old, with lower uptake with additional findings for infants under 3 months.

Critical perspectives:
- The immediate postpartum period is problematic for complex decisions [144, 354]
- As children cannot consent themselves at the time of sequencing and parental consent is difficult with uncertain results, getting informed consent isn't ideal regardless [212]
- Current approaches often fail to achieve truly informed consent [393]

Empirical Evidence:
Studies showing challenges with postpartum timing:
- Parents report feeling overwhelmed and unable to process information [67, 89]
- Lower uptake of additional genomic information for parents of infants <3 months [159, 386]
- Poor recall of consent discussions in immediate postpartum period [507]

Studies supporting prenatal approach:
- Parents express preference for prenatal information [347, 402]
- Higher satisfaction with prenatal education [246]

- Better understanding when information provided during pregnancy [65]

Proposed Solutions:
- Two-stage consent process with prenatal education and postnatal confirmation [214, 246, 393]
- Online education modules during pregnancy [295]
- Extending timeframe for consent beyond immediate postpartum period [441]
- Multiple formats and channels for information delivery [56]

Implemented Solutions:
- BabySeq Project: Following a pPre-enrollment information session and consent-understanding survey with two-week period for consideration [441]
- BabyScreen+: Consent during third trimester with window extending to 2 weeks post-birth. Consent is done online following study invitation and a check in occurs 4 weeks prior to their due date [391]
- Baby Beyond Hearing: Consent obtained within 3 months of birth after genetic counseling [159]
- BabyDetect: Pre-delivery information with post-birth and pre-sample collection digital consent [371]

9: If conventional NBS uses a model of explicit consent, what are the considerations for making gNBS a separate versus combined consent?

TWO SENTENCE SUMMARY:
The literature suggests that implementing genomic newborn screening (gNBS) may require a different consent model than conventional NBS, with many authors advocating for separate and more explicit consent processes for genomic testing and long-term storage of genomic data. The key considerations – beyond legal requirements — include balancing the need for robust informed consent for generating and storing genomic information against maintaining program feasibility, with some authors proposing hybrid or tiered approaches that maintain current consent practices for traditional NBS while requiring explicit consent for additional genomic testing or screening. The literature focuses mostly on consent practices within research settings, so more research is needed for public health settings.

EXTENDED SYNTHESIS:

ELSI AT STAKE:
- The core ethical tension is between respecting parental autonomy through explicit consent for genomic testing versus maintaining the public health benefits of universal screening through simpler consent processes [26, 248, 390].
- There are also practical concerns about program implementation and efficiency if separate consent processes are required [360, 417].

ARGUMENTS:
Several authors argue that genomic testing requires more extensive consent than traditional NBS due to:
- The broader implications and complexity of genomic information [30, 35, 308]
- The need for greater transparency and parental understanding [142, 329]
- Privacy concerns specific to genetic data [324]

Counter-arguments include:
- The risk that separate consent processes could reduce participation rates and threaten universal screening [307, 324]
- Additional administrative burden and complexity [360]
- Potential confusion from having different consent processes [151]

EMPIRICAL EVIDENCE:
Studies show:
- Survey of healthcare professionals found varying opinions on consent approaches, with most supporting either opt-in or opt-out rather than mandatory screening for genomic testing [65]
- BabySeq Project found parents and clinicians felt differently about consent requirements for traditional NBS vs genomic sequencing [357]

- Lower acceptance rates observed for genomic screening compared to traditional NBS in some studies [491]

PROPOSED SOLUTIONS:
Several approaches have been suggested:
1. Two-tiered consent system:
- Maintain current consent practices for traditional NBS
- Require explicit consent for genomic testing [248, 329, 348]

2. Enhanced education and information provision:
- Digital decision aids [360]
- Standardized consent processes [417]
- Pre-test counseling [35]

IMPLEMENTED SOLUTIONS:
Few implementations are documented in these extracts, but:
- The NC NEXUS study implemented a tiered informed consent process [155]
- The Early Check program uses informed consent for additional screening beyond mandatory NBS [313]
- The BabyScreen+ had completely separate consent, conducted using an online platform in the participant's third trimester [391]

10: If conventional NBS is not explicitly consented, what are the considerations for making gNBS explicitly consented versus not?

Summary:
The literature reveals a fundamental tension between traditional newborn screening's opt-out approach (widely adopted, with the justification of clear and immediate benefit to the child) and arguments that genomic sequencing requires explicit informed consent due to its broader implications and uncertain benefits. Implementers must carefully weigh the justifications for implied consent against respecting parental autonomy through explicit consent, while considering that genomic information has different implications than traditional screening, including potential storage of data not relevant to screened for conditions.

Extended Synthesis:

ELSI at Stake:
- Tension between parental autonomy and public health benefits [26, 35, 56, 67, 148, 223, 244, 306]
- Privacy concerns and future implications of genetic data [35, 282, 324]
- Balance between universal screening coverage and informed decision-making [82, 282]
- Legal and ethical basis for mandatory screening vs. consent requirements [247, 463, 519]

Arguments:
Pro-Explicit Consent:
- Genomic information has broader implications beyond immediate health benefits [282, 463]
- Traditional justification for mandatory screening doesn't apply to genomic findings [514]
- Parents should have choice about receiving genetic information [247, 297]

Pro-Implied Consent:
- High participation rates are crucial for public health benefits [164, 241]
- Administrative burden of explicit consent could reduce access [166]
- Some conditions still warrant mandatory screening approach [248, 329]

Empirical Evidence:
- Studies show parents prefer explicit consent for genomic screening but support implied consent for traditional NBS [343, 403]
- California pilot program showed reduced participation with explicit consent requirement [164]
- BabySeq Project found different levels of support for mandatory traditional NBS versus genomic screening [357]
- Survey data indicates majority of public prefers opt-in consent for genomic screening [403, 404]

Proposed Solutions:

- Two-tiered approach: maintain implied consent for traditional screening while requiring explicit consent for genomic components [248, 329, 348]
- Digital consent tools to streamline process while maintaining informed choice [166]
- Obtaining consent during pregnancy rather than postpartum period [149]
- Standardized consent processes with comprehensive education [166, 417]

Implemented Solutions:
- NC NEXUS project implemented tiered informed consent process [155]
- BabySeq Project used explicit consent model [343, 357]
- Early Check program obtains informed consent for additional screening beyond mandatory panel [313]

The literature suggests that implementers should carefully consider hybrid approaches that preserve high participation rates for core conditions while allowing more parental choice for genomic findings.

11: What constitutes appropriate parent information resources for gNBS?

TWO SENTENCE SUMMARY:
The literature extensively discusses the need for engagement materials that balance the need for clear, informative and accessible information and decision aids, while avoiding information overload. Key considerations include the legal minimum requirements for informed consent, timing of information delivery (preferably during pregnancy), multiple formats and channels of delivery, accommodation of varying health literacy levels, and cultural sensitivity, with particular attention needed for complex genomic concepts and managing parental expectations about results.

EXTENDED SYNTHESIS:

ELSI AT STAKE:
- The primary ethical tension lies between providing sufficient information for truly informed consent versus maintaining program efficiency and high participation rates [438, 476]. This intersects with social justice concerns about ensuring equitable access to information across different educational, cultural, and socioeconomic backgrounds [240, 122, 174].
- There are also ethical considerations around managing parental expectations and anxiety, particularly regarding uncertain or unexpected results [213, 349].

ARGUMENTS:
- Several authors argue that traditional approaches to informed consent may be inadequate for genomic screening given the complexity of information [222, 466].
- There is debate about whether detailed technical information about genomic sequencing is necessary or if focusing on outcomes and implications is more appropriate [246].
- Some argue that digital tools and decision aids are essential for scaling programs [403], while others warn about potential disparities this could create [246].

EMPIRICAL EVIDENCE:
Multiple studies show parents have varying information needs and preferences:
- Studies find parents prefer receiving initial information from trusted healthcare providers [398, 396]
- Research shows timing is crucial, with many parents preferring prenatal education [261, 347]
- Studies demonstrate that greater understanding of genomic information can actually decrease participation willingness [404]
- Evidence indicates values clarification exercises in decision aids can improve decision-making, particularly for those with lower health literacy [502, 503]
- Research shows parents often have misconceptions about genomic information and tend to overestimate both actionability and severity [350]

PROPOSED SOLUTIONS:
Common recommendations include:
- Providing information through multiple channels and formats [134, 174]

- Using plain language principles while allowing access to more detailed information [432]
- Developing culturally sensitive materials in multiple languages [174]
- Implementing prenatal education programs [261, 347]
- Using values clarification exercises in decision aids [502, 503]

IMPLEMENTED SOLUTIONS:
Several programs have implemented specific approaches:
- BabySeq Project: Multi-step consent process including pre-enrollment information session with genetic counseling that discusses results, risk, and benefits, and consent understanding questions [441]
- Generation Study: Layered information delivery with digital consent platform provides leaflets, posters, decision aids, information sheets, letters, and a website for varied learning needs. [89]
- NC NEXUS: Interactive decision aid with values clarification exercises [432]
- Early Check: Electronic education and consent system with layered information using videos, infographics, and quizzes [134]
- BabyDetect: Multi-language materials and website with videos [174]
- BabyScreen+ used an online decision support tool ‘Genetics Adviser’ which incorporates education, values elicitation and consent [391]

The synthesis shows strong consensus on the need for comprehensive yet accessible materials, though specific approaches vary based on program context and population needs.

12: Will consent be obtained for secondary uses of the data, and if so, how should this be obtained?

Two-Sentence Summary:
The literature shows widespread agreement from parents and healthcare providers (supported by law in many jurisdictions) that explicit consent should be obtained for potential secondary uses of genomic data and dried bloodspots, including research, though there is debate about the feasibility of truly informed consent given the complexity and future uncertainty of potential uses. Key considerations include balancing research benefits with privacy protections, cost, maintaining public trust, respecting parental autonomy while preserving valuable research resources, and developing consent processes that are both meaningful and practical.

Extended Synthesis:

ELSI at stake:
- Privacy rights vs potential research benefits and medical knowledge advancement [116, 142, 148, 186, 525]
- Traditional one-time broad consent adequacy vs evolving/future research uses [82, 142]
- Research ethics and clinical care boundaries [106, 411, 515]
- Note that the ELSI will vary depending on whether the research is proposed on anonymized samples (including potentially legacy samples), versus participant recontact for future use

Arguments:
Supportive:
- Archived newborn screening samples represent valuable research resources that could advance medical knowledge [414, 186]
- Public health benefits from research using these samples could be substantial [466]

Critical:
- True informed consent may be impossible since future uses cannot be fully anticipated [142]
- Traditional "box-ticking" consent is inadequate given varied and dynamic participant motivations [82]
- Complex genomic data and future uncertainties make meaningful informed consent challenging [466, 519]
- Lack of transparency about secondary uses undermines public trust [411]

Empirical Evidence:
- Study in Belgium found 93% of parents consented to DNA storage and anonymous research use [174]
- Survey of Bulgarian healthcare providers showed 69.9% support requiring informed consent for research use [523]
- Studies indicate parents often willing to participate in research when informed consent obtained and privacy protected [244]

Solutions (Proposed):
- Dynamic/tiered consent approaches allowing participants to update preferences over time [82, 519]
- Online consent (e-Consent) systems that can be updated as participant views change [82]
- Classification of genetic conditions into "bins" to streamline consent process [519]
- Clear separation between research and clinical consent processes [282]

Solutions Implemented:
- Federal legislation (Newborn Screening Saves Lives Reauthorization Act 2014) requiring parental consent for research use of newborn blood spots [106, 148]
- Michigan Biobank model: IRB review, consent requirements, de-identification procedures [186]
- Texas and Minnesota now require parental consent for research use of residual dried blood spots after legal challenges [298, 306]
- Belgium's Baby Detect program implements separate consent for secondary research use and recontact [174]

13: How will withdrawals from the study be handled, particularly for screen positive findings where there might be a duty of clinical care?

Two-Sentence Summary:
The handling of withdrawals from genomic newborn screening, particularly for screen positive findings where there might be a duty of clinical care, requires careful consideration of the tension between respecting parental autonomy and ensuring appropriate clinical care. Empirical evidence suggests that parents frequently change their minds about genomic information choices after initial consent, highlighting the need for flexible consent processes with integrated check-ins that can accommodate such changes while maintaining clinical obligations.

Extended Synthesis:

ELSI at stake:
- The key ethical issues involve balancing respect for parental autonomy in decision-making with clinical obligations to act on potentially actionable findings, particularly when screen positive results are involved [159, 333].

Arguments:
- The literature emphasizes the need for clear boundaries between research and clinical care obligations regarding genomic findings [442]. There is recognition that established guidelines need to continue evolving as NGS techniques and ethical debates develop [333].
- Multiple check-ins during the Baby Beyond Hearing Project, but parents could withdraw at any time. Initial consent identified how much information parents wanted to receive, surveys checked parents' understanding, and a choice was given to opt-in to additional findings after initial results were returned [159].

Empirical Evidence:
- One study of 106 parents of infants with congenital deafness found that 14% of families changed their decision about genomic information choices after initial consent, with various patterns of opting in and out of additional findings [159]. This evidence highlights the "fragility of parents' decision-making" and emphasizes the importance of ongoing genetic counselor support.

Solutions (Proposed):
No hypothetical solutions were specifically proposed in these extracts.

Solutions Implemented:
The Baby Beyond Hearing project implemented a flexible consent process where:
- Parents could change their choice of gene list analysis at any time during the study period (before additional findings reports were issued)
- Only one parent's signature was required, though joint decision-making was encouraged
- Follow-up counseling was offered for undecided families or when a parent missed the initial session [159]

- The SEQaBOO program implemented a process requiring IRB approval for disclosure of incidental findings, with assessment of "need to know" determined by medical geneticists on staff [442].

14: What process (including who) is used to decide and update the condition list?

Two-Sentence Summary:
Deciding which conditions to include in genomic newborn screening requires balancing multiple stakeholder perspectives while maintaining transparent, evidence-based processes that prioritize the goals of screening. Programs must establish clear criteria for condition selection that considers factors like clinical actionability, age of onset, penetrance, and treatment availability, whilst also having mechanisms to regularly update these lists as evidence and technologies evolve — they can rely on existing frameworks to guide this process. Key considerations include establishing clear criteria for clinical validity and utility, developing mechanisms for regular review and updates as evidence evolves, and ensuring appropriate representation from medical experts, public health officials, and affected communities

Extended synthesis:

ELSI at Stake:

- The core ethical tension lies in balancing comprehensive screening capabilities against the need to maintain high standards for inclusion, involving questions of clinical utility vs. comprehensive information [203, 207, 272, 493]. This also includes weighing benefits of early detection against potential harms of overdiagnosis [221, 222], considering individual benefit vs. population benefit [469, 389], immediate medical benefit vs. future/broader utility [466, 309], and addressing tensions between advocacy pressures and evidence-based decision making [94, 298, 389].

- Additional concerns include ensuring equity in access [240] and balancing evidence requirements vs. advocacy pressure [282, 459, 324].

Arguments:

For structured, evidence-based approaches:
- Need for systematic, transparent frameworks to evaluate conditions [95, 182, 368, 494]
- Importance of maintaining public health screening principles [222]
- Value of standardized assessment criteria [108, 398, 496]
- Primary focus on child benefit over family/societal benefits [524, 411]
- Conditions should be early-onset and treatable in childhood [287, 508]

Against overly rigid frameworks:
- Risk of missing beneficial interventions for rare conditions [249, 381, 259]
- Challenge of applying traditional evidence standards to genomic conditions [146]
- Need for flexibility to accommodate emerging treatments [176]
- Difficulty in generating evidence base for rare conditions [294, 302]

Stakeholder involvement considerations:
- Need for transparent processes involving diverse perspectives [506, 391]
- Balance between expert guidance and public input [368, 483]
- Role of advocacy groups in decision-making [298, 389]

Empirical Evidence:
Studies have demonstrated:
Variation in current practices:
- Significant variation in gene selection across programs (only 74 genes included by >80% of programs) [108]
- Wide variation in condition selection criteria across jurisdictions [292, 519]
- Different approaches to evidence evaluation between programs [95]
- Different interpretations of screening criteria [323, 368]

Implementation challenges:
- Difficulty in establishing evidence base for rare conditions [294, 302]
- Technical limitations affecting condition selection [302, 499]
- Variable stakeholder preferences regarding condition selection [168]

Proposed Solutions:
Structured assessment approaches:
- Development of semi-quantitative metrics for evaluating conditions [155]
- Development of standardized evaluation frameworks [259, 511]
- Use of scoring systems for condition selection [293, 294]
- Implementation of structured Delphi processes [4]
- Development of a machine learning model to prioritise genes included for national genomic sequencing programmes [108]

Governance and stakeholder engagement:
- Creation of expert advisory committees [177]
- Multi-stakeholder advisory committees [368, 483]
- Public consultation processes [517, 506]
- Integration of multiple stakeholder perspectives [249]

Review and update mechanisms:
- Regular review cycles for included conditions [150]
- Systematic evidence review procedures [389, 481]
- Mechanisms for updating condition lists [482, 494]

Implemented Solutions:
Several programs have adopted specific approaches:
BabySeq Project [3, 253]:
- Used clinical validity classification framework for gene curation
- Focuses on conditions with clear medical actionability
- Uses expert panels for condition selection

BeginNGS [120]:
- Employed modified Delphi technique with expert panels

NC NEXUS [155]:
- Developed age-based semi-quantitative metric

UK Newborn Genomes Programme/UK Generation Study [112, 517]:

- Established working group of 28 experts for condition selection
- Four-principle framework for condition selection
- Extensive stakeholder consultation process

Early Check [24]:
- Created transparent framework with public engagement

GUARDIAN Study [491]:
- Systematic approach to gene curation
- Regular review and updates of condition list

Screen4Care TREAT Panel [483]:
- Combines automated scoring with expert curation
- Uses multiple selection criteria including treatability and clinical validity

BabyScreen+:
- Standard criteria developed
- Expert curation leveraging previous curations from multiple other projects
- Stakeholder engagement and review process
- Curations and opinions are publicly available on an open platform, PanelApp Australia [182]

15: How should advocacy influence be balanced with evidence-based decision making when it comes to condition selection?

Summary:
Patient advocacy has historically been a powerful force in expanding newborn screening programs, but there is ongoing tension between advocacy-driven expansion and evidence-based decision making. Implementers must balance the valuable perspectives and lived experiences that advocacy groups bring while ensuring that screening decisions remain grounded in scientific evidence of clinical benefit and careful consideration of potential program impacts.

Extended Synthesis:

ELSI at stake:
- The core ethical tension centers on how to appropriately weigh passionate advocacy from affected families and patient groups against the need for rigorous scientific evidence when deciding which conditions to include in screening programs [94, 247, 269]. This raises issues of distributive justice, as advocacy strength may not correlate with public health impact [2].
- There are also concerns about conflicts of interest when advocacy groups receive industry funding [94].

Arguments:
Supportive arguments emphasize that advocacy groups:
- Bring vital lived experience perspectives [293, 407]
- Help identify overlooked issues affecting patients [151]

Critical arguments highlight risks that advocacy can:
- Cloud critical thinking about benefits/harms [247]
- Lead to premature implementation without adequate evidence [307]
- Result in screening for conditions with disputed benefits [368]
- Undermine public trust if implemented without evidence base [241]

Several authors argue for a balanced approach that:
- Respects advocacy input while maintaining evidence-based standards [244]
- Uses advocacy to identify issues but relies on scientific review for decisions [164]
- Includes diverse stakeholder perspectives in structured decision processes [182]

Empirical Evidence:
Studies have found:
- Historical examples where advocacy led to implementation of screening without sufficient evidence validation (e.g., PKU in 1960s) [269]
- Cases where advocacy-driven expansion led to harms (e.g., Krabbe disease in NY) [172]
- Survey showing experts support advocacy involvement but want decisions grounded in evidence [363]
- Analysis showing wide variation in how states handle advocacy influence [519]

Proposed Solutions:
- Create structured, transparent frameworks for condition selection [368]
- Use expert advisory committees to balance various influences [26]
- Establish rigorous evidence review processes [151]
- Develop standardized assessment criteria [294]
- Include advocacy groups in discussions while maintaining evidence-based standards [507]

Implemented Solutions:
- Advisory Committee on Heritable Disorders establishment (US) [389]
- Evidence review process for RUSP recommendations [320]
- Screen4Care project's structured approach combining stakeholder input with evidence review, requiring that the advocacy community provide evidence for proposed gNBS programs [407]
- Generation Study's multi-stakeholder consultation process including the public, patients, and experts [517]
- SACHDNC's rigorous evidence review process requiring demonstrated benefits [244]

16: How are "actionability" and clinical utility defined for condition selection (including considerations of availability and accessibility)?

Brief Summary:
Defining actionability and clinical utility for genomic newborn screening is a complex challenge that requires balancing traditional screening criteria focused on immediate medical treatment benefits against broader conceptions of benefit that include factors like avoiding diagnostic odyssey, enabling family planning, and accessing early interventions. Implementers must carefully consider whether to maintain strict requirements for proven effective, available (which will vary by jurisdiction) treatments or adopt more flexible frameworks that recognize various forms of clinical and personal utility, while ensuring that selected conditions have sufficient evidence to justify population-level screening.

Extended Synthesis:

ELSI at Stake:
- The core ethical tension centers on how narrowly or broadly to define what makes a condition appropriate for inclusion in newborn screening when using genomic technologies [244, 295, 191]. The traditional focus on immediate medical treatment benefit is challenged by the expanded capabilities of genomic sequencing to detect many conditions that may not have proven treatments but could benefit from early intervention or family preparation [451, 453, 308]. This raises questions about balancing potential benefits against harms, resource allocation, and equity considerations [215, 207]. Critically, socioeconomic differences between countries lead to differences in availability of treatments, so “actionability” can be jurisdiction specific.

Arguments:
Traditional perspective advocates maintaining strict requirements for proven effective treatments and clear medical benefit to the child [272, 269, 451]. Counter-arguments suggest broader definitions of benefit including:
- Avoiding diagnostic odyssey
- Enabling informed reproductive decisions
- Early intervention opportunities
- Family preparation and support
- Access to clinical trials
[244, 294, 226, 479]

Some argue for considering both direct medical benefits and indirect benefits to families [146]. Others emphasize the need to maintain high evidence standards while acknowledging evolving treatment landscapes [310, 226].

Empirical Evidence:
Studies examining stakeholder perspectives show:
- Parents often value information beyond traditional medical actionability [347, 348]
- Healthcare professionals tend to favor more restrictive criteria [199]

- Different jurisdictions interpret actionability criteria differently [333, 294]

Clinical outcome studies demonstrate:
- Early intervention benefits for some conditions [461, 435]
- Improved outcomes with pre-symptomatic treatment [273, 271]
- Variable penetrance and expressivity challenges [227, 248]

Proposed Solutions:
- Develop standardized metrics for assessing clinical utility [272, 294]
- Create tiered systems for different types of actionability [332, 310]
- Establish regular review processes for updating condition lists as evidence evolves [215, 451]
- Include broader stakeholder input in defining actionability [347, 348]

Implemented Solutions:
Several programs have adopted specific approaches:
- BabySeq Project: Defined specific criteria based on evidence level, age of onset, and penetrance [3]
- NC NEXUS: Uses age-based framework for evaluating clinical actionability [34]
- UK Newborn Genomes Programme: Established four principles including evidence of causality and benefit of early intervention [517]
- BeginNGS: Developed systematic evaluation process for conditions with effective treatments [6]
- BabyScreen+, defined criteria including definition of treatability as treatment or intervention that alters the natural history of the condition (i.e. supportive measures not included) [182]

17: Should conditions with variable onset, penetrance, expressivity, or pleiotropy be included?

Two Sentence Summary:
The inclusion of conditions with variable onset, penetrance, expressivity, or pleiotropy in gNBS represents one of the most extensively debated ethical issues in the literature, with concerns centering on the balance between identifying actionable conditions early versus potential increased uncertainty creating "patients-in-waiting" and unnecessary anxiety. Key considerations include the psychological impact on families, healthcare resource allocation, and whether the benefits of early identification outweigh potential harms of uncertain prognoses at population or group level, with most current programs favoring a conservative approach that prioritizes conditions with high penetrance and clear childhood onset.

Extended Synthesis:

ELSI at stake:
- Ethical tension between potential benefits of early detection versus psychological burden of uncertain prognoses [269, 294, 371, 443]
- Social justice concerns about healthcare resource allocation and follow-up care burden [269, 308, 463]
- Privacy and autonomy considerations regarding future adult-onset conditions [444, 466]
- Responsibility to avoid creating "patients-in-waiting" and unnecessary medicalization [494, 151]

Arguments:
For inclusion:
- Early identification enables preventive interventions and family preparation [377, 299]
- Some variants with variable expression still have high enough penetrance to warrant screening [483]
- Knowledge allows for better clinical management and surveillance [498]

Against inclusion:
- Risk of overdiagnosis and unnecessary treatment [284, 443]
- Creation of anxiety about conditions that may never manifest [308, 347]
- Violation of child's right to an open future for adult-onset conditions [466]
- Challenge of interpreting variants without clinical context [515]

Empirical Evidence:
- BabySeq Project found that genomic sequencing identified variants associated with later-onset conditions in 9.4% of newborns [253]
- Studies of metabolic conditions show significant phenotypic variability, complicating treatment decisions [164, 294]
- Parent surveys indicate mixed preferences, with some wanting all possible information while others prefer only clearly actionable results [352, 505]
- Data from existing programs shows challenges in counseling families about conditions with variable expressivity [371, 498]

Proposed Solutions:
- Development of clear criteria for assessing penetrance and expressivity [483, 490]
- Tiered disclosure approaches based on certainty of manifestation [437]
- Enhanced genetic counseling and long-term follow-up protocols [434]
- Age-based framework for result disclosure [34]

Implemented Solutions:
- BabySeq Project: Limited reporting to highly penetrant childhood-onset conditions [441]
- BabyDetect: Excluded conditions with incomplete penetrance and adult onset [467]
- Dutch screening program: Excluded disorders like Pompe disease due to variable onset/penetrance [294]
- Screen4Care project: Focused on conditions with strong evidence of penetrance and early onset [483]
- BeginNGS program: Changed inheritance mode queries to focus on more severe forms of disease [382]

18: Should there be an age-of-actionability cut-off, and, if so, what should this be?

Two Sentence Summary:
The literature reflects significant debate about whether and when to disclose genetic information about conditions that manifest or require intervention at different life stages, with particular tension around adult-onset conditions. While traditional professional guidelines have recommended against testing children for adult-onset conditions for reasons including to preserve a child's future autonomy, emerging arguments suggest potential benefits of early identification for both the child and family members, leading some programs to adopt approaches including parental choice models and age-based disclosure frameworks.

Extended Synthesis:

ELSI at stake:
- Child's right to an open future vs. parental authority to make healthcare decisions [17, 34, 147, 466]
- Individual autonomy vs. family benefit [147, 353]
- Clinical utility vs. psychological burden [18, 30, 244]
- Privacy protection vs. comprehensive analysis [509]
- Direct vs. indirect benefits of early detection [453]
- Whether the option for "opportunistic screening" should be taken [147]

Arguments:
Pro early disclosure:
- Early identification enables preparation and life planning [347, 353]
- Family benefit can indirectly benefit child through parent health [3, 29]
- Traditional "right to an open future" arguments may be outdated given increased actionability of genetic information [376]

Against early disclosure:
- Violates child's future autonomy and right not to know [83, 220, 466]
- Creates "patients in waiting" with psychological burden [17, 30]
- May lead to overtreatment or unnecessary anxiety [294]
- Traditional NBS focuses on immediate childhood benefit [215]

Empirical Evidence:
- BabySeq study found 3.5% of infants had actionable adult-onset variants [253, 296]
- Survey of genetic counselors showed only 6.8% supported including adult-onset conditions vs. 37.2% of physicians [184]
- Australian healthcare professionals strongly opposed adult-onset condition disclosure [166]
- Parents generally express interest in receiving adult-onset information [343, 347]
- Young adults prefer limiting disclosure to childhood-onset conditions [505]

Proposed Solutions:
- Age-based frameworks for result disclosure [214, 472]

- Tiered disclosure approaches [259]
- Opt-in models for adult-onset condition disclosure [3]
- Life-course staged screening approach [311]

Implemented Solutions:
BabySeq Project:
- Initially did disclose adult-onset findings using an opt-out method of consent.
- Later changed to require participants to explicitly consent to adult-onset condition disclosure as to minimize moral distress [417]

NC NEXUS:
- Used age-based metric (ASQM) to evaluate and categorise the age of action for conditions
- Set cutoff at ≤2 years for primary panel [24]

BabyScreen+:
- Restricted to severe early-onset variants, age of actionability cut-off set as 5 years. [182]
- Considering future age-appropriate reanalysis which would require significantly more resources [182]

Early Check:
- Two-panel approach: Panel 1 for highly actionable conditions with early age of action (≤2 years)
- Panel 2 for conditions with emerging potential for high actionability [24]

19: Should carrier status for recessive conditions be reported?

Two Sentence Summary:
The reporting of carrier status in genomic newborn screening represents a complex balance between potential reproductive planning benefits for families and concerns about psychological harms, child autonomy, discrimination, and healthcare system burden. Key considerations include the very high prevalence of carrier variants, challenges in providing adequate genetic counseling at scale, and varying international approaches ranging from routine disclosure to opt-in models.

Extended Synthesis:

ELSI at Stake:
- Individual autonomy vs. family benefit: Tension between child's future autonomy/right not to know and parents' reproductive planning needs [155, 188, 195]
- Privacy vs. information access: Balancing privacy rights with parental right to genetic information [107, 326]
- Healthcare justice: Concerns about equitable access to genetic counseling and follow-up care [16, 151]
- Stigma and discrimination: Historical concerns about carrier status leading to discrimination, particularly in marginalized communities [266, 183]

Arguments:
Supporting disclosure:
- Information enables reproductive planning for parents and family members [3, 7]
- Some carrier states have health implications warranting early knowledge [459]
- Knowledge allows gradual integration of information into child's identity [85]

Against disclosure:
- Burdens healthcare systems with counseling needs [16]
- Violates child's future reproductive autonomy [195, 247]
- Creates unnecessary anxiety without immediate medical benefit [306, 442]
- May lead to stigmatization and discrimination [183, 393]

Empirical Evidence:
- BabySeq found 88% of infants carried recessive variants [253, 457]
- Healthcare provider surveys show mixed views on disclosure:
  - 74-77% of general providers support disclosure
  - Only 50% of genetics professionals support disclosure [266]
- Parents report varied preferences:
  - 70.8% very interested in carrier results [343]
  - Some value information for family planning [352]
  - Others concerned about psychological burden [393]
- Studies show persistent misunderstanding of carrier status even with counseling [151, 457]

Solutions Proposed:
- Opt-in model for carrier status disclosure [266]

- Staged disclosure based on age and relevance [214]
- Enhanced genetic counseling and education programs [317]
- Couple-based approach to carrier screening [191]
- Limiting disclosure to clinically actionable findings [307]

Solutions Implemented:
- Ontario Newborn Screening: Opt-in disclosure model where parents must request carrier results [266]
- BabySeq Project: Includes carrier status reporting with genetic counseling for future reproductive planning [3, 440]
- Dutch CF screening: Aims to minimize carrier detection for cost effectiveness [330]
- Danish NBS: Reports carriers only for CF, not other conditions [494]
- Early Check: Does not routinely report single heterozygous variants unless it is a special case [24]
- BabyScreen+: Carrier status excluded [182]

20: Should there be any parental choice in categories of results returned?

Two Sentence Summary:
The literature reveals significant debate around whether and how much choice parents should have in selecting which categories of genomic results they receive about their newborns, with considerations spanning clinical utility, future autonomy, psychological impact, practical implementation challenges (including cost). While there is broad agreement that parents should ideally have some degree of choice, there are differing views on the optimal approach - from highly granular choice to more structured "menu" options - with evidence suggesting parents generally want broad access to information but may benefit from guided decision-making frameworks.

Extended Synthesis:

ELSI at Stake:
- Tension between parental autonomy/right to information versus child's future autonomy and "right to an open future" [353, 466]
- Balance between providing valuable health information and avoiding information overload or psychological burden [386, 496]
- Clinical utility versus personal utility/value of information [326, 377]
- Privacy and discrimination concerns versus potential benefits to family health [163, 207]
- Standardization of screening versus individualization of choices [466, 478]

Arguments:
Supporting parental choice:
- Parents are responsible for children's healthcare decisions and should have access to information that could benefit their child [374, 376]
- Different families have different values and information preferences [350, 353]
- Information can enable early intervention and preparation [353, 377]

Against unlimited parental choice:
- Could violate child's future autonomy regarding adult-onset conditions [232, 450]
- Risk of psychological harm from too much uncertain information [307, 487]
- Practical challenges in implementing highly individualized choices [386, 466]
- May undermine public health benefits of standardized screening [404, 450]

Empirical Evidence:
- BabySeq Project found varying parental preferences regarding adult-onset conditions, with some wanting all information and others preferring limited disclosure [353]
- NC NEXUS study showed parents value choice but recognize challenges in making informed decisions [346, 350]
- Australian study found 90% of parents wanted choice in result categories [166]
- Studies show higher education/understanding associated with more selective preferences about receiving results [404]
- Focus groups reveal parents want some choice but also trust medical expertise [377, 396]

Proposed Solutions:
- Tiered consent models with mandatory core conditions and optional additional categories [450, 466]
- "Menu of options" approach with pre-structured choices [466, 478]
- Decision aids and genetic counseling to support informed choice [13, 432]
- Age-based disclosure framework [332]

Implemented Solutions:
- BabySeq Project: Required both parents to agree to receive adult-onset findings [412]
- NC NEXUS: Tiered approach with mandatory primary panel and optional secondary findings that allow parents to decide to receive non-actionable results. The “decision arm” had the option of “all, some, or none” [155, 432]
- Early Check: All babies screened with panel 1, parents choose panel 2 options [24]
- SEQaBOO: Different enrollment options with varying levels of information return [198]
- GUARDIAN study: Choice between basic and expanded condition lists. They receive results for 200 treatable conditions and can add 100 neurodevelopmental conditions that therapies could help [421]

21. Should major pharmacogenetics variants be included?

Two Sentence Summary:
The inclusion of pharmacogenetic variants in gNBS offers significant potential to prevent adverse drug reactions and optimize medication dosing throughout life, but raises complex questions about clinical actionability in the newborn period, variant interpretation across diverse populations, and appropriate timing of disclosure. While there is strong theoretical support for including well-validated pharmacogenetic variants, the literature reveals a notable gap between conceptual benefits and practical implementation, with no documented real-world newborn screening programs systematically including pharmacogenetic variants at the time of these publications.

Extended Synthesis

ELSI at Stake
- Balance between preventing future drug-related harm and adhering to traditional newborn screening principles of immediate actionability [18, 47, 242]
- Equity concerns regarding variant interpretation across diverse populations with different allele frequencies [2, 17, 18]
- Privacy and lifelong data management implications for pharmacogenetic information [408]
- Resource allocation tensions between immediate healthcare needs and future preventive benefits [12, 18]
- Child autonomy considerations for information with lifelong implications [185, 242]

Arguments
Supporting inclusion:
- Could prevent severe, potentially fatal adverse drug reactions (e.g., codeine toxicity in ultra-rapid metabolizers) [17, 18, 47]
- Lifetime utility provides value beyond newborn period [7, 18, 128]
- Efficient to obtain when genomic sequencing already being performed [176]
- Enables proactive medication management rather than trial-and-error prescribing [495]

Against broad inclusion:
- Limited immediate actionability conflicts with newborn screening principles [18, 242]
- Complexity of interpretation may lead to clinical errors [17, 49, 182]
- May divert resources from conditions requiring immediate intervention [12]
- Psychological burden of future-oriented information on families [47,185]

Empirical Evidence
- Studies demonstrate reduced hospitalization rates when pharmacogenetic information guides prescribing [17]
- Significant ethnic variation in drug metabolism genes documented across populations, which limits applicability for those on non-European ancestry [2,18]
- Parent surveys show variable interest in receiving pharmacogenetic information [47, 185, 242]
- Provider studies reveal knowledge gaps and need for education [244]

- Economic analyses suggest potential cost-effectiveness for preventing severe reactions, though results vary by variants included [12]
- Implementation studies highlight need for clinical decision support and EHR integration [7, 176]

Proposed Solutions
- Selective inclusion of only highly actionable, well-validated variants with clear guidelines [18, 62, 244]
- Tiered disclosure with storage of results until clinically relevant [128, 485]
- Standardized pharmacogenetic panels with continuous reanalysis protocols [62, 182]
- Comprehensive provider education and clinical decision support systems [7, 244, 495]
- Equity-focused approaches including wider research for diverse populations to ensure representation in databases [2, 27]
- Multidisciplinary implementation teams including genetic counselors and pharmacists [495]

Implemented Solutions
No documented real-world implementations of pharmacogenetic variant screening in actual newborn screening programs were identified in the reviewed literature. All solutions discussed were proposed, hypothetical, or in pilot/research phases, highlighting the gap between theoretical benefits and practical implementation in routine newborn genomic screening programs.

22: Should whole genome, whole exome, targeted panel sequencing or genotyping be adopted?

Two Sentence Summary:
The choice between whole genome sequencing (GS), whole exome sequencing (ES), or targeted gene panels represents a critical cost, technical and ethical trade-off between comprehensive detection capabilities and practical implementation challenges. While GS/ES may offer greater flexibility and future-proofing, targeted approaches may currently be more practical and cost-effective, with many gNBS research programs adopting hybrid or tiered approaches that combine targeted panels with more comprehensive sequencing in specific cases, though the evidence base is changing rapidly.

Extended Synthesis:

ELSI at stake:
- Clinical utility vs. information overload: Balancing comprehensive genetic information against the challenges of interpreting and managing vast amounts of data [457, 324, 466]
- Privacy and data management: Concerns about storing and protecting extensive genomic data [284, 311]
- Cost-effectiveness vs. accessibility: Ensuring equitable access while managing resource constraints [283, 364]
- Ethical implications of incidental findings: Managing secondary findings and variants of uncertain significance [404, 472]

Arguments:
For GS/ES:
- Provides more comprehensive coverage and future flexibility [516, 520]
- Enables detection of novel variants and complex structural changes [498, 484]
- Eliminates need for costly panel updates when new genes are discovered [509]

Against GS/ES:
- Generates excessive data requiring complex interpretation [457, 324]
- Higher costs and resource requirements [331, 482]
- May reveal unwanted information about adult-onset conditions [524]

For targeted panels:
- More focused and practical approach [483, 492]
- Better control over incidental findings [524]
- More cost-effective implementation [331]

Empirical Evidence:
Studies comparing approaches:
- NBSeq project showed ES had lower sensitivity (88%) than traditional screening (99%) for metabolic disorders [319, 472]
- BeginNGS study demonstrated feasibility of rapid GS with targeted analysis [320]
- Studies show variable coverage and accuracy across different genomic regions [338, 497]

Cost and implementation data:
- GS remains more expensive than targeted approaches [331, 482]
- Technical challenges with certain variant types and genomic regions [484, 497]

Solutions Proposed:
- Tiered approach using targeted panels first, followed by GS/ES when needed [484]
- Combined use of different technologies for comprehensive coverage [497]
- Virtual panels using GS data but analyzing only selected genes [509]

Solutions Implemented:
Programs adopting various approaches:
- BabySeq: Used ES with targeted analysis [119]
- Screen4Care: Implementing targeted gene panel approach [483]
- BeginNGS: Using rapid GS with targeted analysis [320]
- Danish NBS program: Using targeted panels as second-tier testing [494]
- UK Generation Study: GS [517]
- BabyScreen+: GS with targeted analysis [391]

This synthesis represents evidence from 23 articles in the dataset, showing the complexity and ongoing evolution of this decision point in gNBS implementation.

23: What sample collection methodology should be used?

Two Sentence Summary:
The choice of sample collection methodology for genomic newborn screening involves balancing technical feasibility (DNA quantity/quality) with practical and ethical considerations like minimizing infant discomfort and integrating with existing screening infrastructure. The literature strongly supports using dried blood spots (DBS) as they leverage existing collection procedures, provide sufficient DNA quality for sequencing, can be stored long-term, and minimize additional procedures for infants, though some programs are also exploring alternatives like cord blood or saliva samples for specific applications.

Extended Synthesis:

ELSI at stake:
- Minimizing physical harm and discomfort to newborns during sample collection [89, 104, 122]
- Preserving limited biological samples while enabling comprehensive testing [123, 276]
- Ensuring equitable access to screening, particularly in rural/remote areas [240, 245]
- Balancing sample quality requirements with practical implementation [413]
- Integration with existing screening infrastructure [330, 433]

Arguments:
- DBS offers advantages over venipuncture including less discomfort and higher participation rates [413]
- Earlier sample collection (e.g., cord blood) could enable faster diagnosis for time-sensitive conditions [295, 328]
- Different sample types may be optimal for different conditions (e.g., saliva for CMV detection) [498]
- Sample collection timing affects test validity and interpretation [318]
- Collection methods must be feasible for implementation at scale [330]

Empirical Evidence:
Multiple studies demonstrate:
- DBS provides sufficient DNA quality/quantity for genomic sequencing [204, 218, 238, 514, 520]
- Storage conditions affect sample integrity, with -20°C recommended [276, 413]
- High concordance between DBS and traditional blood samples for variant detection [481]
- Successful DNA extraction from archived DBS up to 20+ years old [512, 513]
- Variable DNA yields depending on collection/storage methods [514, 520]

Proposed Solutions:
- Using cord blood for earlier sample collection [295, 328]
- Implementing point-of-care testing (outside of hospitals) for remote areas [245]
- Optimizing DNA extraction protocols for limited sample material [512, 520]
- Alternative sample types (saliva, cord blood) for specific applications [498]
- Multi-tiered testing approaches combining different sample types [494]

Actually Implemented Solutions:
- California Biobank Program: PCR-free GS methods for DBS [512]
- Danish Newborn Screening Biobank: WGA of DBS samples [413]
- GUARDIAN and BabyDetect studies: Using DBS for traditional and genomic screening [163, 371] Also BabyScreen+, protocol paper [391]
- BabySeq Project: Validated microsampling (of capillary blood) methods using a heel prick kit from Neoteryx for DNA collection [440]
- Generation Study (UK): Using cord blood with optimized turnaround time [517]

24: How and when should test limitations be communicated?

Two Sentence Summary:
The literature emphasizes that test limitations must be clearly communicated to both healthcare providers and families due to significant technical and interpretive challenges in genomic sequencing, including limitations in detecting certain variant types, variable sensitivity across conditions, and challenges with interpretation. The timing and method of communication needs to balance providing large amounts of information against overwhelming parents during the sensitive peripartum period, while ensuring limitations are understood before testing to enable informed decision-making.

Extended Synthesis:

ELSI at stake:
- The core ethical tension centers on balancing the need for transparent communication about technical limitations against the risk of overwhelming or causing undue anxiety to parents during a sensitive time [349, 393]. This connects to broader ethical principles of informed consent, beneficence, and non-maleficence, particularly given that incomplete understanding of limitations could lead to false reassurance or unnecessary anxiety [390, 393].

Arguments:
- Several papers argue that comprehensive communication about limitations is essential for maintaining public trust and enabling truly informed decision-making [244, 349]. However, others caution that the complexity and volume of information about technical limitations may overwhelm parents and impede understanding [393].
- There are also arguments that healthcare providers need to fully understand limitations to appropriately counsel families [390].

Empirical Evidence:
- Focus group studies have found that parents generally do not grasp the uncertainty inherent in genomic data despite attempts at explanation, instead expressing optimistic expectations for clear, useful information [349].
Research has documented specific technical limitations that need to be communicated, including:
- Lower sensitivity compared to traditional screening for some conditions [35, 472]
- Challenges detecting certain variant types like structural variants [264, 521]
- Variable performance across different genes and conditions [299, 498]
- Issues with variant interpretation, especially for diverse populations [160]

Proposed Solutions:
Several approaches have been suggested:
- Developing targeted educational materials about genomic uncertainty [68, 349]
- Using multi-tiered communication strategies with different levels of detail [390]
- Providing ongoing education as knowledge evolves [244]

Implemented Solutions:

Few concrete implementations are described in the literature, but reported approaches include:
- The Early Check program incorporated test limitations into consent materials with interactive review questions [134]
- Some programs have requested improved quality samples from birth centers to enable better confirmatory testing [340]
- BabyScreen+ excluded certain genes with insufficient analytical validity despite clinical relevance, with this limitation communicated to families. This included diseases with a later onset. [182]

The literature suggests this remains an active challenge that most programs are still working to address effectively.

25: Should variants of uncertain significance ever be reported?

Two-Sentence Summary:
The reporting of variants of uncertain significance (VUS) in genomic newborn screening presents a critical tension between comprehensive detection of potentially clinically significant variants and returning information that does not fit a screening paradigm. Implementers must weigh the benefits of increased sensitivity from reporting VUS against the risks of false positives, psychological impacts on families, and healthcare system capacity for (potentially unnecessary) follow-up, while considering technical limitations in variant interpretation particularly for diverse populations.

Extended Synthesis:

ELSI at stake:
- Autonomy vs beneficence: balancing parents' right to information against potential psychological harms from uncertain results [142, 316, 492]
- Healthcare justice: equitable access to variant interpretation across diverse populations [160, 273, 336]
- Clinical utility vs uncertainty: managing uncertain results without clear clinical actionability [163, 273, 491]
- Resource allocation: healthcare system capacity to handle VUS follow-up [16, 142, 324]

Arguments:
For reporting VUS:
- Early identification could enable better preparation and monitoring [377]
- May help with future reclassification efforts [133]
- Parents may have a right to all available information [505]

Against reporting VUS:
- Creates unnecessary anxiety and medicalization [16, 323, 450]
- Risk of inappropriate clinical decisions based on uncertain information [273, 492]
- May overwhelm healthcare systems [142, 324]
- Could undermine public trust in screening programs [141]

Empirical Evidence:
Studies showing impacts:
- The BabySeq project found VUS reporting created significant counseling challenges [253]
- NC NEXUS study showed VUS reporting increased sensitivity from 80.3% to 89.4% but with increased false positives [139]
- Survey of genetic counselors showed 53.3% believed VUS should never be disclosed [199]
- Studies show parents often misunderstand implications of VUS [487]

Population preferences:
- Survey showing differences between clinicians and parents regarding VUS disclosure [396]
- Focus groups showing parents value certainty over comprehensive information [302]

Solutions (Proposed):

- Development of standardized VUS classification criteria for screening context [483, 491]
- Improved variant databases and interpretation tools [366, 477]
- Better education and counseling approaches [487]
- Multi-stakeholder engagement in developing reporting guidelines [483]

Solutions (Implemented):
- BabySeq Project: Only reported pathogenic/likely pathogenic variants in healthy infants; reported VUS for ill infants if relevant to clinical presentation [3]
- BeginNGS: Uses strict variant filtering to minimize VUS reports [120]
- BabyScreen+: Reports only pathogenic and likely pathogenic variants, explicitly excluding VUS [391]
- GUARDIAN study: Implemented specific algorithms for variant reporting balancing sensitivity and specificity [163]
- The literature emphasizes that this remains an active challenge requiring ongoing refinement of approaches as evidence and technologies evolve.

26: How should the challenges of variant interpretation across diverse populations be addressed?

:
Summary:
Genomic variant interpretation faces significant challenges due to the lack of diversity in reference databases, which primarily contain data from individuals of European ancestry. This creates potential for missed diagnoses, false positive results, and/or misclassification of variants in underrepresented populations, raising serious equity concerns that implementers must address. Newborn screening programs must balance the need for accurate variant interpretation across all populations against current technical limitations while working to expand representation in genomic databases.

Extended synthesis:

ELSI at stake:
The core ethical issue is ensuring equitable benefits from genomic newborn screening across diverse populations while maintaining screening accuracy. This involves:
- Healthcare access inequality and potential to exacerbate existing disparities [246, 269, 277, 488, 491]
- Risk of misdiagnosis or missed diagnoses in underrepresented populations [304, 335, 460, 491]
- Balance between expanding access and maintaining quality [269, 371, 477]
- Scientific validity vs equity considerations [488, 491]
- Privacy and discrimination concerns related to population-specific genetic data [143, 270]

Arguments:
Proponents argue:
- Genomic screening could reduce disparities in access to genetic testing [270, 364]
- Including diverse populations in screening would help build more representative databases [213, 215, 460]
- Early identification enables timely interventions [460, 470]

Critics argue:
- Current databases are too Eurocentric to ensure equitable benefits [215, 269, 304, 477, 488]
- Risk of exacerbating healthcare disparities [246, 269, 277, 488]
- Technical limitations disproportionately affect underrepresented groups [304, 335, 460]

EMPIRICAL EVIDENCE:
Empirical evidence:
Studies show:
- Lower diagnostic yield in non-European populations [269, 484, 488]

- Higher rates of variants of uncertain significance in underrepresented groups [335, 366, 484]
- Specific variants more common in certain populations [340, 341, 433]
- Evidence of population-specific mutation spectrums [275, 340, 433]

Proposed solutions:
- Development of population-specific variant databases [215, 340, 460, 470]
- Increased diversity in genomic research [213, 460, 470, 488]
- Enhanced variant interpretation tools [366, 482, 485]
- Multi-ethnic reference panels [340, 433, 460]
- International data sharing [215, 470, 521]
- Training in population-specific variant interpretation [201, 460]

Implemented solutions:
Several programs have adopted specific approaches:
- BabySeq Project: Counseling about limitations in variant interpretation for non-European ancestries. Aiming to analyze more non-European outcomes to improve knowledge and counseling [440]
- Guardian Study: Specific algorithms for variant reporting that consider ancestry and obtaining more data [315, 316]
- BeginNGS: Using population-specific data in variant interpretation [120]
- Screen4Care: Development of population-specific gene panels and datasets [407]
- Chinese newborn screening programs: Customized panels for Chinese population [433]

27: How should the process for disclosure of provisional results be managed?

Summary:
The disclosure of provisional results in genomic newborn screening (gNBS) requires carefully balancing the potential benefits of early detection against the risks of causing unnecessary anxiety and harm through false positives or uncertain findings. Programs must develop clear protocols and policies that address the timing, method, and content of result disclosure while ensuring appropriate support systems are in place for families receiving results and follow up care.

Extended synthesis:

ELSI at stake:
Key ethical tensions include:
- Balancing timely disclosure for actionable findings vs. avoiding unnecessary anxiety from uncertain results [15, 219, 282]
- Managing parental psychological impacts while ensuring clinical benefit [151, 244, 348]
- Protecting family privacy while enabling appropriate clinical follow-up [73, 143]
- Addressing healthcare access inequalities in result disclosure and follow-up [100]

Arguments:
Supporting earlier/broader disclosure:
- Early intervention opportunities could be missed by delaying disclosure [260, 341]
- Parents have a right to information about their child's health [146, 487]
- Transparency builds trust in screening programs [167]

Against earlier/broader disclosure:
- Risk of causing unnecessary anxiety with uncertain results [311, 393]
- Potential for misunderstanding or misuse of genetic information [487]
- Limited clinical utility of some findings [504]
- Resource burden on healthcare system [311]

Empirical evidence:
Studies show:
- Parents experience significant anxiety from uncertain results [244, 348]
- False positives create lasting psychological impacts [151, 189]
- Communication quality affects parental anxiety levels [151]
- Healthcare providers struggle with explaining complex genetic results [205]
- Different cultural contexts affect result disclosure preferences [378, 487]

Proposed solutions:
- Two-tier screening approaches to reduce false positives [451]
- Standardized protocols for result disclosure [86]

- Enhanced provider education and support [205]
- Improved parent education materials [244]
- Multi-disciplinary teams for result interpretation [508]
- Clear guidelines for what findings should be reported [46]

Implemented solutions:
BabySeq Project:
- Required genetic counseling for positive results [219]
- Used multidisciplinary approach to result disclosure [173]

NC NEXUS Project:
- Employed genetic counselors and clinical geneticists for result return [219]

GUARDIAN Study:
- Developed specific variant reporting algorithms to return results for treatable or likely treatable recessive conditions, and to minimize false positives [316]
- Used orthogonal testing before reporting positives [163]

Screen4Care Project:
- Implemented stakeholder engagement in developing reporting guidelines. Pathogenic or likely pathogenic variants are reported. [483]

BabyScreen+:
- Specific variant filtering algorithm developed
- Orthogonal validation of positive results using a separate sample; other confirmatory testing where available
- All screen positive results communicated by a genetic health professional to organise confirmatory testing and involve relevant other specialists as necessary

This synthesis suggests that while there is substantial literature on result disclosure challenges, there remains significant variation in how programs approach this critical aspect of implementation.

28: For positive results, who should deliver results?

Two-Sentence Summary:
The literature strongly suggests that result delivery should be tailored to the type of result and condition, with genetic counselors and clinical specialists generally preferred for complex genetic findings while maintaining involvement of primary care providers who have existing relationships with families. Key considerations include the limited availability of genetic specialists, the value of established provider-family relationships, and the need for providers to have sufficient genomic knowledge to effectively communicate results.

Extended Synthesis:

ELSI at stake:
- Balancing the need for genetic expertise in result communication against healthcare system capacity and resources [83, 138]
- Tension between maintaining established provider-family relationships and ensuring adequate genetic expertise [385]
- Equity concerns regarding access to genetic counseling services and timely delivery of results for treatment initiation [465]

Arguments:
- Clinical interpretation challenges require genetic expertise for complex results [61]
- Traditional genetic counseling models may not be feasible at population scale [138]
- Primary care physicians often lack confidence in discussing genetic results [244, 309]
- Provider-family relationships are valuable for sensitive communications [385]
- Non-genetic specialists may misinterpret results or provide insufficient support [465]

Empirical Evidence:
- Survey of 126 Australian parents found preferences varied by condition - GPs preferred for some conditions, specialists for others [66]
- Healthcare professionals agreed specialists should return results for current NBS conditions (41%) and childhood-onset actionable disorders (45%), while genetic counselors should handle carrier status (72%) [166]
- Parents with low health literacy rated primary care physicians unfavorably in explaining results [151]
- Interviews with PCPs revealed they value their role in result delivery despite concerns about expertise [385]

Solutions (Proposed):
- Development of alternative service delivery models including non-genetics professionals and educational media [138]
- Implementation of telegenetics to address limited availability of genetic counselors [465]
- Training programs to increase provider knowledge and communication skills [168, 194]
- Tailoring healthcare provider involvement based on condition type [66]

Solutions (Implemented):

- BabySeq Project: Results disclosed by genetic counselor and physician team during in-person session [441]
- GUARDIAN study: Negative results returned by phone/email, positive results by phone from medical geneticist and genetic counselor followed by in-person clinical visit [163]
- Generation Study (UK): Screening results passed to relevant specialist experienced in treating the condition [517]
- Baby Detect (Belgium): Disease specialists deliver positive results in face-to-face consultations and negative results are not delivered [174]
- BabyScreen+: screening results disclosed by genetic health professionals, specialists involved once result confirmed. Negative results returned via online platform [391]

29: For positive results, how should return be done (including what information should be provided, whether virtual or in person)?

Summary:
The return of positive results from genomic newborn screening requires careful consideration of both the mode of delivery (in-person vs remote) and the content/format of information provided. Implementation decisions must balance parents' strong preference for in-person result disclosure by genetic specialists against practical feasibility constraints in large-scale screening programs, while ensuring appropriate psychological support and follow-up care.

Extended Synthesis:

ELSI at Stake:
- Tension between comprehensive information disclosure and managing parental anxiety/psychological impact [13, 56, 248, 496]
- Balance between parental preferences for delivery method and healthcare system capacity/feasibility [403]
- Need to ensure effective communication while managing complex genomic information [13, 151, 168]
- Equity concerns regarding access to appropriate follow-up care and support [378]

Arguments:
Supporting in-person disclosure:
- Allows for immediate emotional support and clarification of questions [56, 168]
- Enables better assessment of family understanding and needs [150, 168]
- Maintains human connection for sensitive information [354]

Supporting alternative approaches:
- Resource constraints make universal in-person disclosure challenging [403]
- Video/telehealth options may provide acceptable compromise [122]

Empirical Evidence:
Studies supporting in-person disclosure:
- Interviews with 41/50 parents preferred in-person results delivery [122]
- Focus groups showed strong preference against online/electronic result delivery [354]
- Parents with low health literacy particularly value in-person communication [151]

Studies on content/format:
- Parents request visual aids and supplementary materials [122]
- Studies show primary care physicians often provide inadequate or misleading information [151]
- Qualitative research reveals parents expect comprehensive explanation and support [361]

Solutions Proposed:

- Tiered approach based on result type (in-person for positives, electronic for negatives) [403]
- Development of standardized communication protocols with visual aids [122]
- Integration of genetic counseling with primary care delivery [244]
- Comprehensive follow-up support system including specialists [378]

Solutions Implemented:
BabySeq Project:
- In-person disclosure by genetic counselor and physician [441]
- Written reports mailed to parents and faxed to providers [441]

Ontario NBS Program:
- Primary care providers deliver positive results and value points-of-care information with specialist support [385]

Baby Detect:
- Disease specialists deliver positive results in face-to-face consultations [174]

Generation Study:
- Specialist-led result disclosure and follow-up [517]

BabyScreen+:
- Different processes for low vs high chance results (online platform vs genetic counselor phone call) [391]

30: For positive results, how can the psychological impacts on families be assessed, addressed and minimised, and with what role for advocacy and patient community input?

Summary:
Psychological impacts of positive gNBS results on families represent a major concern requiring careful management, with evidence indicating risks of anxiety, depression, parent-child bonding disruption, and relationship strain, particularly for uncertain or untreatable conditions. However, studies also show that with appropriate support systems including genetic counseling, clear result communication, and access to specialist care and peer support groups, these negative impacts can be minimized while preserving the benefits of early detection; consumer involvement in program design would help to this end.

Synthesis:

ELSI at stake:
The core ethical tension centers on balancing the benefits of early detection against potential psychological harms to families receiving positive results [63, 144, 332]. Key concerns include:
- Parental anxiety, depression and distress [56, 63, 373]
- Impact on parent-child bonding and relationship dynamics [67, 232, 394]
- Family strain and partner blame [373, 394]
- Stigmatization of affected families [12]
- Additional burden during already stressful postpartum period [138, 178]
- Additional uncertainty and challenges with uncertain results or untreatable conditions [31, 149, 220]

Arguments:
Supportive arguments:
- Early identification allows families to prepare practically and emotionally [358, 394]
- Knowledge can provide relief from uncertainty and guilt [361]
- Benefits of early intervention outweigh temporary psychological impacts [25, 480]

Critical arguments:
- Risk of creating "patients-in-waiting" with unclear prognosis [415, 416]
- Potential disruption of parent-child bonding [228, 394]
- Unnecessary anxiety for conditions that may never manifest [141, 142]
- Particular burden in resource-limited settings [315]

Empirical Evidence:
Major studies:
- BabySeq Project found no persistent negative psychosocial effects in families receiving genomic results [394, 449]
- However, study population was self-selected and well-resourced [449]
- Studies show varying levels of anxiety and stress following positive results [172, 358]
- Higher distress reported with uncertain results vs definitive findings [348]

- Evidence that effective communication and support can mitigate negative impacts [352]

Proposed Solutions:
1. Educational/Communication:
- Clear communication protocols [244, 442]
- Improved provider education [144, 168]
- Age-appropriate information [505]

2. Support Systems:
- Comprehensive genetic counseling [416, 523]
- Psychological support services [210, 391]
- Peer support networks [168, 352]

3. Procedural:
- Structured follow-up protocols [56, 391]
- Rapid confirmatory testing [289]
- Regular assessment of psychological impacts [441]

Implemented Solutions:
Several programs have implemented specific approaches:
- NC NEXUS: Structured joint parental decision-making process and monitoring of psychological impacts [110]
- BabySeq: Standardized assessment measures and safety protocols for identifying parents needing additional support. The study psychologist will contact parents who score above the cut-off for depression or anxiety. [441]
- Baby Beyond Hearing Project: Integrated genetic counseling and follow-up support system [352]
- NESTS program: Comprehensive genetic counseling achieving 71.6% counseling rate with 95.2% reporting reduced anxiety [434]

31: For negative results, will results be returned, and if so, using what model?

Two-Sentence Summary:
The literature shows varying approaches to returning negative results in gNBS, with some programs actively communicating these results while others only provide them upon request. Key considerations include balancing psychological benefits (such as providing peace of mind to parents) against healthcare system resource constraints, while also ensuring effective documentation and communication methods.

Extended Synthesis:

ELSI at stake:
- Balance between providing complete information to parents and healthcare system resources [403, 391]
- Psychological impact of result communication on parents [174, 361]
- Documentation and awareness challenges [480]
- Information access patterns in the digital age [13]

Arguments:
- Technical concerns about false negatives and the need to communicate test limitations [288]
- The importance of adapting communication strategies to accommodate public preferences towards digital information [13]

Empirical Evidence:
- Studies indicate that negative results can provide psychological benefits to parents, allowing them peace of mind and the ability to focus on their child's specific conditions [361]
- Public preference studies in Australia show that even for negative results, in-person communication is preferred over electronic methods [403]
- Evidence from Russia shows challenges in result documentation and awareness, with 58% of participants lacking verified results [480]
- Low follow-up rates observed in some programs, suggesting challenges in result communication systems [508]

Proposed Solutions:
- Development of multi-channel communication strategies incorporating digital platforms where parents already seek information [13]
- Balancing in-person result delivery preferences with feasibility through selective application [403]

Solutions Actually Adopted:
Different programs have implemented varying approaches:
- BabyScreen+ (Australia): Low chance results communicated via online platform with email/SMS notification and optional genetic counseling [391]
- Belgian Baby Detect: No communication of negative results [174]

- GUARDIAN study (US): Negative results returned by phone and encrypted email [163]
- SEQaBOO (US): All negative results communicated directly to parents via telephone [419]
- EXAMEN project (Russia): Negative results only issued upon parents' request [508]

32: How to build sufficient genomics expertise in the healthcare provider workforce, particularly pregnancy providers and pediatricians?

Two Sentence Summary:
Healthcare providers often lack sufficient knowledge and confidence to effectively discuss and action genomic newborn screening results, with studies showing widespread discomfort in interpreting and communicating genomic results. A multi-faceted approach combining professional education, supportive infrastructure, and potentially new service delivery models is needed to build adequate workforce capacity, as the current genetics workforce is insufficient to handle population-wide genomic screening.

Extended Synthesis:

ELSI at stake:
- The core ethical-social issue is the tension between the rapid advancement of genomic technologies and the limited capacity of the healthcare workforce to effectively implement them [13, 30, 138, 242]. This raises concerns about potential harm from misinterpretation of results [184] and inequitable access to genetic expertise and follow up care [288].
- There are also social justice considerations regarding workforce diversity [472] and cultural competence in genetic counseling and related follow-up care [487].

Arguments:
Supportive arguments emphasize:
- The essential role of healthcare provider education in successful genomic medicine implementation [7, 201, 229]
- The potential for healthcare systems to adapt to and incorporate new genomic technologies and their subsequent needs as they have with other advances [423]
- The importance of nurses and other non-genetic professionals in translating genomic information [201]

Critical arguments highlight:
- Current shortage of genetics professionals [138, 160, 298]
- Risk of inappropriate clinical management from result misinterpretation by non-specialists [184]
- Inadequate genetics education in medical training [30]
- Concerns about overwhelming primary care providers [297]

Empirical Evidence:
Multiple studies document workforce challenges:
- Survey showing 76.1% of genetic counselors concerned about result misinterpretation by non-specialists [184]
- Cross-sectional survey showing only 44% of family physicians feel up-to-date on newborn screening compared to 85% of pediatricians [385]
- Studies showing limited genetics knowledge among nurses [306]

- Delphi study identifying workforce limitations as a key barrier to implementing genomic newborn screening [464]

Proposed Solutions:
Educational approaches:
- Comprehensive genomics education throughout medical training [13]
- Development of core competencies for healthcare providers [400]
- Training programs for non-genetics providers [472]
- Cultural competency training [487]

Structural approaches:
- Alternative service delivery models [138]
- Digital decision support tools [13]
- Regional centers of excellence [26]
- Telegenetics services [465]

Implemented Solutions:
- Master of Science in Genetic Counseling program established at University of the Philippines Manila to reduce genetics-trained staff shortages [250]
- BabySeq project implemented genomics education program for healthcare providers [440]
- GUARDIAN study provided navigator support and healthcare provider training [163]
- Healthy Nevada Program developed educational support for providers to learn more about consenting parents, decision-making, returning results, and clinical action. [132]

33: What should be done if a newborn dies before or soon after result return (including what should happen to their data)?

Two-Sentence Summary:
There is very little literature on this topic. When a newborn dies before or soon after result return, programs need to consider both the immediate handling of genetic/metabolic data for any post-mortem analysis (if applicable) and the broader implications for family members who might benefit from this information

Extended Synthesis:

ELSI at stake:
- Researcher obligations versus protocol restrictions [412]
- Family rights to genetic information after infant death [137, 412]
- Duty to warn versus regulatory compliance [412]

Arguments:
- After infant death, the ethical focus shifts from the infant's best interests to the family's interests [412]

Empirical Evidence:
No empirical evidence was presented in the extracted literature.

Proposed Solutions:
None discussed

Implemented Solutions:
None discussed

34: What standards should be established for clinical follow-up after screening (including resources provided for healthcare providers, and the role of advocacy groups)?

Two-Sentence Summary:
Implementing genomic newborn screening requires establishing comprehensive standards for clinical follow-up that address both immediate and long-term care needs, including genetic counseling, specialist referrals, and ongoing monitoring. The literature emphasizes that follow-up systems must integrate multiple stakeholders (healthcare providers, genetic specialists, advocacy groups) while ensuring equitable access to necessary treatments and support services, with particular attention to preventing healthcare disparities and maintaining adequate workforce capacity.

Extended Synthesis:

ELSI at Stake:
- Ethical obligation to provide comprehensive follow-up care after screening identifies conditions [2, 269, 314]
- Tension between expanding screening capabilities and limited healthcare system capacity [274, 283]
- Equity concerns regarding access to follow-up services and treatments [2, 269, 380]
- Need to balance comprehensive care with resource constraints [352, 385]

Arguments:
- Healthcare systems must ensure adequate follow-up infrastructure before implementing expanded screening [451, 478]
- Follow-up standards should include both immediate clinical care and long-term monitoring [244, 447]
- Comprehensive support systems needed, including specialists, multidisciplinary teams, and local contacts [437]
- Clinical follow-up must address both medical and psychosocial needs of families [352]

Empirical Evidence:
- Studies show high dropout rates in follow-up despite comprehensive counseling being offered [416]
- Research indicates limited genetic counseling resources are already strained [443]
- Evidence that early intervention can improve long-term outcomes but requires robust follow-up systems [460]
- Data shows healthcare providers often feel unprepared to manage positive results [320]

Proposed Solutions:
- Development of standardized follow-up protocols and clinical pathways [317, 385]
- Creation of specialized reference centers for coordinated care [268]
- Implementation of comprehensive support networks including genetic counseling [378]
- Establishment of long-term monitoring systems and registries [478]

Implemented Solutions:
- BabySeq Project: Structured disclosure process with integration into medical records [441]
- NewSTEPs data repository: Tracking and improving follow-up processes [320]
- Generation Study: Confirmation of clinical pathway capacity before implementation [517] and development of information sheets for clinicians and for families for all conditions [89]
- NESTS program: Comprehensive post-screening management system [434]

The literature reflects strong consensus that establishing robust follow-up standards is critical for successful gNBS implementation, with multiple programs developing various approaches to address this challenge. However, significant gaps remain in ensuring adequate resources and healthcare system capacity to meet these standards.

35: How should referral networks and other follow-up care infrastructure be developed to support families after positive genomic findings?

Summary:
Healthcare systems currently lack sufficient infrastructure and workforce capacity to handle the increased demands that would come from genomic newborn screening, particularly for coordinating follow-up care across multiple specialists and providing genetic counseling services. The literature emphasizes that comprehensive support systems that integrate specialized expertise are needed, as are multidisciplinary care teams, and mechanisms to ensure equitable access to follow-up services, especially for geographically dispersed and underserved populations.

Extended synthesis:

ELSI at stake:
- The core ethical tension is between the potential benefits of early identification through genomic screening and the healthcare system's current limitations in providing appropriate follow-up care [13, 26, 28, 34, 138]. This raises justice concerns about implementing screening without adequate infrastructure to support diagnosed families [168, 172, 213].
- There are also issues around equitable access to specialized care, particularly for rural and underserved populations [168, 305, 406].

Arguments:
- Proponents argue that comprehensive follow-up systems are essential for realizing the benefits of genomic screening [153, 293, 447]. This includes not just medical care but also genetic counseling, educational resources, and psychosocial support [145, 393].

Critics highlight several challenges:
- Limited genetic counseling workforce [13, 288, 298]
- Geographic barriers to accessing specialists [168, 305]
- Risk of overwhelming existing medical genetics services [390, 414]
- Concerns about healthcare system capacity [141, 274, 282]
- Need for coordination across multiple specialties [274]

Empirical evidence:
Several studies document implementation challenges:
- Survey showing 77.3% of genetic counselors felt unprepared for increased clinical volume [184]
- Data on geographic disparities in genetic specialist distribution [305]
- Evidence of socioeconomic disparities in follow-up care access [229]
- Reports of families struggling to access appropriate specialists [168]
- Parent interviews revealing barriers including financial, work, and childcare challenges [377]

Proposed solutions:

The literature suggests several approaches:
- Development of regional centers of excellence [26]
- Use of telemedicine to overcome geographic barriers [213, 250]
- Digital decision aids and alternative communication channels [13]
- Standardized follow-up protocols [262, 264]
- Multidisciplinary care team models [254, 268]
- Patient navigation services [491]

Implemented solutions:
Several programs have implemented specific approaches:
- BabySeq established a Genomic Resource Center to assist with referrals [173]
- Philippine Newborn Screening Program created network of strategically located screening centers [250]
- GUARDIAN study provided patient navigators and social workers [491]
- NESTS program in China implemented comprehensive post-screening management system [434]

36: Should the program plan for surveillance and follow up of positive findings, including those with later-onset conditions?

Two sentence summary:
The literature extensively discusses the need for long-term follow-up of positive findings from genomic newborn screening, particularly for later-onset conditions, with broad agreement that comprehensive follow-up systems are essential but challenging to implement. Key considerations include the resource implications of lifelong surveillance, the need for standardized protocols, data collection for understanding natural disease progression, and ensuring equitable access to follow-up care across healthcare systems.

Extended synthesis:

ELSI at stake:
- Tension between early identification benefits and healthcare system burden of long-term follow-up [16, 18, 31, 48, 60]
- Ethical and biopsychosocial concerns about diagnostic accuracy, decision-making, and medicalizing otherwise healthy individuals identified with later-onset conditions [274]
- Resource allocation challenges for comprehensive follow-up systems [68, 157, 244]
- Healthcare access inequality and disparities in follow-up care [48, 98, 327]
- Data management and privacy considerations for long-term surveillance [107]

Arguments:
Supportive:
- Early identification enables timely interventions and improved outcomes [48, 299]
- Long-term follow-up necessary for understanding natural disease progression [320]
- Comprehensive follow-up essential for maximizing screening benefits [194]

Critical:
- Creates substantial ongoing burden for follow-up centers without immediate benefit [311]
- Resource limitations may prevent adequate long-term follow-up [244]
- Risk of overwhelming healthcare systems with volume of cases requiring monitoring [107]

Empirical evidence:
- Studies show improved intervention rates when genetic screening combined with clinical follow-up [98]
- Data from multiple centers demonstrates need for long-term monitoring of asymptomatic carriers [60, 100]
- Evidence that some conditions have variable onset requiring extended surveillance [97, 135]
- Research shows gaps in current follow-up systems and specialist shortages [244]

Proposed solutions:
- Establishment of standardized follow-up protocols [262]
- Creation of patient registries for long-term monitoring [16]
- Development of comprehensive referral networks [98]

- Implementation of data management systems for tracking outcomes [370]
- Multi-stakeholder planning for long-term care needs [157]

Implemented solutions:
- Beijing Newborn Screening Program: Established referral networks with designated hospitals for follow-up [98]
- NBSTRN LPDR: Developed longitudinal data resource with common data elements [370]
- Qingdao cohort study: Implemented regular follow-up testing protocols [18]
- Multi-center deafness gene screening in Zhejiang: Combined hearing and genetic screening with follow-up protocols [275]
- Nanjing NBGS program: Created personalized follow-up plans based on disease type [135]

37: To what extent should the program coordinate cascade testing, and if so to what degree relatives?

Two Sentence Summary:
Cascade testing following genomic newborn screening raises complex ethical tensions between potential benefits to family members and issues of privacy, autonomy (e.g. right not to know), and healthcare access barriers. Programs must carefully balance the opportunity to identify and prevent serious conditions in relatives against challenges including consent processes, healthcare system fragmentation, and equitable access to follow-up testing and care.

Extended Synthesis:

ELSI at stake:
- Privacy rights (and right not to know) vs duty to warn relatives about genetic findings [17]
- Individual autonomy vs family/community health benefits [254, 487]
- Child's best interests vs benefits to extended family [313, 514]
- Healthcare access inequalities and cost barriers [504]
- Family dynamics and psychological impacts [77]
- Implementation challenges in fragmented healthcare systems [400]
- Complexities and inefficiencies of family communication, including direct vs family-mediated contact
- NOTE: Cascade testing will have the greatest value for X-linked and autosomal dominant conditions (see e.g. PMC1235308/).

Arguments:
Supportive:
- Cascade testing can prevent early mortality in parents, benefiting children by avoiding loss of a parent [17]
- Identifying carriers (beyond the parents) may enable informed reproductive choices for future pregnancies [7, 50, 509]
- Family-wide screening can have public health benefits beyond individual patients [58, 254]

Critical:
- Raises privacy concerns when contacting relatives about genetic risks [400]
- May create financial barriers for families when parents lack insurance coverage (depending on the jurisdiction and funding for health care) [504]
- Shifts focus from child's benefit to family benefit, conflicting with traditional NBS principles [514]

Empirical Evidence:
- BabySeq Project found actionable findings in 3.6% of family members [29, 73]
- Study showing 76.5% of cases led to specialist evaluations/procedures for family members [29]
- Survey showing 93% of participants felt duty to inform relatives but 78% opposed direct healthcare provider disclosure [487]

- Low uptake of cascade testing despite potential benefits - fewer than half of at-risk relatives get tested in US [82]

Solutions Proposed:
- Develop partnerships between public health departments and healthcare providers [400]
- Create standardized protocols using electronic medical records [400]
- Provide options for patient-controlled vs provider-assisted disclosure [358]
- Expand insurance coverage for parental testing [504]
- Implement systematic family-wide screening approaches [53]

Solutions Implemented:
BabySeq Project:
- Offers cascade testing for up to two first/second-degree relatives at no cost [440]
- Does not collect parental DNA at baseline but offers targeted testing when needed [440]
- Does not offer cascade testing for adult-onset conditions to minor siblings [440]

Note: Many articles discuss cascade testing but few document actual implemented solutions, suggesting this remains an area where programs are still developing approaches. There may also be variation between programs as to whether cascade testing is considered part of NBS, or as a separate activity.

38: How should healthcare system disparities that affect follow-up care be addressed?

Two Sentence Summary:
Health equity gaps in follow-up care represent a critical challenge for genomic newborn screening (gNBS) implementation, with concerns that without careful planning, gNBS could exacerbate existing inequities in healthcare access and outcomes. Key considerations include ensuring adequate infrastructure and resources for follow-up care, addressing financial barriers to access treatments and services, developing support systems for underserved populations, and creating mechanisms to ensure equitable access to genetic expertise and specialized care across different geographic and socioeconomic contexts, especially for communities with pre-existing healthcare disparities.

Extended Synthesis:

ELSI at stake:
- Equity in access to follow-up care and treatment after positive screening results [2,16,271,327]
- Fair distribution of benefits from genomic screening across different populations [167,270]
- Social justice implications of universal screening without equitable follow-up capability [77,461]
- Resource allocation and healthcare system capacity to handle increased demand [284,472]

Arguments:
- Universal gNBS could either reduce or exacerbate existing healthcare disparities depending on implementation [157,167,270]
- Current fragmented healthcare systems create barriers to comprehensive follow-up care [400,461]
- High costs of treatments for rare diseases may limit access despite early detection [2,161,278]
- Geographic disparities in access to specialist expertise and treatment centers [437]
- Need to balance technological advancement with ensuring equitable access [473]

Empirical Evidence:
- Studies show current disparities in access to genetic services across socioeconomic groups [347]
- Evidence of differential follow-up rates based on race/ethnicity and socioeconomic status [305,327]
- Research demonstrates geographic barriers to accessing specialized care [437]
- Data shows higher rates of lost to follow-up in underserved populations [198,472]
- Cost barriers prevent complete diagnostic workup including parental testing [504]

Proposed Solutions:
- Development of telemedicine and remote care options [485]
- Implementation of patient navigator programs [491]
- Universal healthcare coverage for identified conditions [472]

- Standardized protocols for follow-up care [309]

Implemented Solutions:
- UK's National Generation Study includes infrastructure planning for equitable access [515]
- GUARDIAN study implemented patient navigators and social workers [491]
- Some states have adopted RUSP alignment legislation requiring coverage [471]
- BabySeq project established Genomic Resource Center for referral support [173]
- European Reference Network created to support equitable access [470]

This synthesis represents the key themes from the literature regarding healthcare system disparities in follow-up care for gNBS. The evidence suggests that careful attention to equity in implementation planning is crucial for success.

39: What aggregate outcomes data should the program plan to collect?

Summary (2 sentences):
The literature emphasizes the critical importance of collecting comprehensive outcomes data to evaluate program effectiveness, advance scientific understanding of rare diseases, and support evidence-based policy decisions. Key considerations include: the need to balance data collection for research purposes with the primary public health mandate, ensure standardization across jurisdictions, and develop adequate infrastructure for long-term follow-up while protecting privacy.

Extended Synthesis:

ELSI at stake:
- Tension between research needs and public health mandate: collecting data beyond direct clinical benefit raises ethical questions [269]
- Equity concerns regarding access to follow-up care and outcomes across populations [2]
- Privacy and data sharing considerations when aggregating health information [229]
- Social justice implications of healthcare system disparities affecting follow-up care [2, 270]

Arguments:
Pro:
- Comprehensive data collection enables evaluation of program effectiveness and improvement [467, 478]
- Population-wide screening provides unique opportunity to advance understanding of rare diseases [427]
- Standardized data collection across jurisdictions allows comparison and assessment of disparities [400]
- Data collection supports evidence-based policy decisions [467, 524]

Con:
- May exceed explicit public health mandate of protecting individual children's health [269]
- Resource constraints and implementation challenges [370]
- Privacy concerns with data sharing across systems [229]

Empirical Evidence:
- Study showing earlier intervention for children identified through screening vs those not screened [461]
- Implementation challenges documented in pilot programs, including limited duration affecting ability to assess long-term outcomes [370]
- Evidence of fragmented data systems hampering outcome assessment [27, 30]

Solutions (Proposed):
- Development of standardized data infrastructure and collection protocols [400]
- Creation of integrated health data systems and registries [406, 493]
- Implementation of learning healthcare systems [229]

- Establishment of longitudinal follow-up programs [427]
- Development of common data collection modules across states [400]

Solutions (Implemented):
- Longitudinal Pediatric Data Resource (LPDR) with common data elements to collect data from clinicians, health educators, and others who care for the individuals [370]
- BabySeq Project's longitudinal follow-up protocol to determine the economic, medical, and behavioral impact of whole-exome sequencing [73]
- National Cancer Institute Childhood Cancer Data Initiative for surveillance following sequencing [490]
- Ontario's expanded newborn screening program with outcome tracking [461]
- NBSTRN partners with Longitudinal Pediatric Data Resource and Ethical, Legal, and Social Implications Advantage for data sharing infrastructure [427]
- Southwest Germany's national registries for metabolic diseases [478]

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)?

Two Sentence Summary:
This decision presents trade-offs between maximizing future clinical utility through comprehensive data retention and managing practical constraints including storage costs, privacy risks, and data governance complexities. While storing raw sequence data (.fastq, .bam files) enables future reanalysis as knowledge advances, implementers must balance this potential against substantial infrastructure requirements and environmental impacts, consent implications for lifelong data storage, and the need for robust security measures to protect sensitive genomic information that could impact both the child and their biological relatives.

Extended Synthesis

ELSI at Stake

- Privacy and security risks from storing comprehensive genomic data with lifelong implications: [31, 116, 301]
- Balance between future diagnostic utility and current storage/computational burdens: [16, 36, 56]
- Consent complexities for long-term data retention and potential secondary uses: [164, 306, 336]
- Equity issues regarding who can afford long-term data storage and reanalysis services: [194, 211, 384]
- Questions of data ownership, control, and access rights over time: [241, 308, 493]
- Intergenerational impacts as stored data affects biological family members: [207, 309, 522]

Arguments

- Supporting comprehensive storage (raw files):
- Enables reanalysis as genomic knowledge rapidly expands: [16, 32, 121]
- Could provide diagnostic answers for children who develop symptoms later: [36, 84, 160] - though whether this would be faster and more efficient than conventional clinical diagnostic sequencing remains to be determined and will likely vary with several factors
- Maximizes research potential and public health benefits: [65, 124, 337]
- Preserves option value for future technologies and interpretations: [191, 316, 471]
- Cost-efficient in long term as resequencing avoided: [191, 420, 241]

Supporting minimal storage (results only):
- Reduces privacy and security risks from data breaches: [30, 67, 77]
- Minimizes storage costs and computational infrastructure needs: [194, 450]
- Simplifies consent and governance requirements: [164, 306, 336]

- Aligns with traditional NBS practice of storing minimal data: [241, 380, 486]
- Reduces computational burden on health systems: [92, 157, 430]

Empirical Evidence
- Technical assessments project exponential growth in storage requirements, with costs potentially exceeding screening itself: [44, 58, 157]
- Security vulnerability analyses document significant breach risks for genomic databases: [31, 116, 301]
- Reanalysis studies demonstrate an improvement in diagnostic yield over time: [32, 121, 160]
- Cost analyses reveal ongoing expenses of $50-200 per genome per year for storage and curation: [194, 415]
- Parent preference studies identify privacy as primary concern, with many preferring limited retention: [164, 206, 289]
- Health system assessments reveal current infrastructure inadequate for population-scale genomic data: [92, 180, 430]
- Studies show data sharing barriers between institutions limiting utility of stored data: [276, 516]

Proposed Solutions
- Hybrid storage models: raw data retained short-term (1-2 years), processed data long-term: [36, 107, 316]
- Centralized secure repositories with standardized access controls and audit trails: [67, 77, 297]
- Tiered opt-in/opt-out frameworks for different storage durations and data types: [164, 306, 463]
- Cloud-based solutions with encryption and privacy-preserving technologies: [95, 179, 392]
- Clear data governance policies specifying use limitations, access rights, and deletion timelines: [241, 308, 493]
- Automated reanalysis pipelines triggered by knowledge updates: [16, 84, 121]
- Interoperable systems enabling data portability while maintaining security: [276, 414, 516]
- Cost-sharing models between healthcare systems, insurers, and families: [194, 384, 450]
- Blockchain-based systems for maintaining data provenance and access logs: [392, 493]
- Federated learning approaches allowing analysis without data sharing: [517]

Implemented Solutions
No specific real-world implementations documenting actual data storage decisions and outcomes in operational newborn genomic screening programs were identified in the reviewed literature. All solutions discussed remain in proposal or pilot phases.

41: For how long should sequence data be maintained (legal minimum or longer)?

Two-Sentence Summary:
Long-term data storage (beyond what is legally required) is not an essential component of gNBS but may have profound implications for a project's/program's costs, consent protocols, risks, and public acceptance. The duration of genomic data storage from newborn screening presents a fundamental tension between potential future clinical benefits and risks to privacy and public acceptance, with considerations including costs of storage, data security, potential for reanalysis as knowledge advances (versus the possible need to re-test using new technology), the rights of the parents to withdraw from data storage rights of the child to make decisions about their data when they reach majority. Implementers must carefully weigh the trade-offs between destroying data to protect privacy versus maintaining it for future clinical use, while considering practical constraints like storage costs, feasibility in a screening paradigm, technological evolution, and regulatory requirements.

Extended Synthesis:

ELSI at Stake:
- Privacy and data protection vs. clinical utility and research benefits [7, 13, 16, 30, 32, 59, 241, 321, 493]
- Child's future autonomy rights vs. current parental decisions [32, 349, 519]
- Cost and environmental impact of long-term data storage [84, 191, 223]
- Data ownership and control transitions from parents to child [179, 332, 486]
- Balancing public health benefits against individual privacy rights [311, 390]
- Storage of data, including dried bloodspots, and a lack of transparency around this, has been a key driver of public mistrust of newborn screening [430]

Arguments:
Pro longer storage:
- Enables reanalysis as genetic knowledge advances [16, 223, 332]
- Valuable for future diagnostic purposes if symptoms develop and if gNBS data is sufficient for diagnostic purposes [16, 510]
- Could reduce diagnostic delays and healthcare costs [16, 332]
- One-time sequencing could provide lifetime value [332, 510]

Against longer storage:
- Privacy risks increase with storage duration [13, 241, 390]
- Technological advances may make stored data obsolete [241, 515]
- Storage costs may outweigh benefits [191, 241]
- May erode public trust in screening programs [311, 390]
- Future discrimination risks [206, 463]

Empirical Evidence:

- Survey of parents and healthcare providers in Hong Kong showed 72.3% support storing data beyond current 6-month practice (396)
- Study of dried blood spots showed DNA quality decreases with storage time but remains usable for up to 20 years with proper storage conditions [500]
- Parent interviews revealed mixed views on data storage, with desire for control over data use [349, 377]

Solutions Proposed:
- Age-adjusted communication of results [95]
- Encrypted cloud-based storage systems [56]
- Variant call file storage instead of raw data to reduce size [465]
- Giving parents control over storage decisions [278]
- Obtaining new consent at age of majority [191]
- Periodic reanalysis protocols [223]

Solutions Implemented:
- Michigan Biobank: indefinite storage with research access [186, 204]
- German law: 10-year mandatory destruction [528]
- Denmark: storage with multiple approval requirements for access [204]
- UK Newborn Genomes Programme: approaching participants at age of majority for decisions about their data [486]
- Belgian pilot: 5-year secure storage requirement [371]

42: Who will store the data and where will it be stored?

Two-Sentence Summary:
The storage of genomic data from newborn screening raises significant technical, ethical, and legal challenges around data security, privacy protection, and long-term accessibility. Implementers must balance the clinical and research utility of maintaining genomic data—and making it accessible when and where needed—against privacy risks, storage costs, and infrastructure requirements, while ensuring appropriate governance frameworks for data access, management, and interoperability.

Extended Synthesis:

ELSI at stake:
- Privacy and data security concerns vs. clinical utility and research value [6, 13, 30, 144, 177, 306]
- Data ownership rights and transfer between parents and children [6, 179, 267]
- Infrastructure and cost burden of storing massive genomic datasets [7, 58, 336]
- Long-term accessibility and reanalysis capabilities [56, 144, 329]
- Integration with healthcare systems and electronic health records [242, 455]

Arguments:
Supportive:
- Genomic data has lifetime value for healthcare and should be maintained in medical records [332, 423]
- Secure data platforms with parent-controlled access can protect privacy while enabling beneficial use [6]

Critical:
- Government control of sensitive genetic information raises privacy concerns [306, 308]
- Current healthcare systems lack adequate infrastructure for secure long-term storage [455]
- Storage costs and environmental impact may be prohibitive [191]
- Privacy risks may outweigh benefits as sequencing becomes cheaper [241]

Empirical Evidence:
- Survey of genetic counselors identified data storage infrastructure as key practical concern [184]
- BeginNGS study developed cloud-based system reducing computational costs by 33-fold [6]
- Danish study showed successful storage and use of dried blood spots for 27-29 years [51]
- Parent focus groups revealed concerns about healthcare system's ability to manage data [349]
- Pilot study generating 3.5 terabytes of data from 3,847 babies highlighted scaling challenges [371]

Proposed Solutions:
Technical:
- Cloud-based storage with encryption and access controls [6, 371]

- Store variant call files only to reduce data volume [336]
- Integration with electronic health records to improve diagnostic and treatment accuracy and efficiency [242]

Policy:
- Parent-controlled data platforms with transparent rights [6]
- Clear governance frameworks for data access [277]
- Strict legislative protection against unauthorized access [482]

Implemented Solutions:
- BeginNGS: Cloud-based system using multi-dimensional arrays (TileDB). Secure platforms house the data and allow parents and patients access. Data is encrypted and isolated between trusted environments, which are tested and updated. [6]
- Danish Newborn Screening Biobank: Long-term storage of dried blood spots [51]
- California Biobank Program: Local server storage of raw clinical and genetic data [392]
- Luna PBC platform: Parent-controlled data access system [6]

43: What security and privacy measures should be implemented to protect genomic data?

Two Sentence Summary:
Implementing genomic newborn screening requires robust privacy and security measures to protect sensitive genetic data from unauthorized access, discrimination, and potential misuse by third parties including insurers, employers, and law enforcement. Key considerations include data storage infrastructure, access controls, encryption, consent processes for data sharing, and legal frameworks to prevent genetic discrimination, with particular attention needed for marginalized communities who may be more vulnerable to privacy breaches and discrimination.

Extended Synthesis:

ELSI at stake:
The primary ethical-legal-social issues concern protecting sensitive genomic data while enabling appropriate clinical and research use [6, 7, 13, 31, 207, 467].
Key concerns include:
- Privacy and confidentiality of genetic information [132, 134, 144, 211]
- Risk of genetic discrimination in insurance and employment [164, 239, 523]
- Potential misuse by law enforcement or other third parties [306, 472, 486]
- Special vulnerabilities of marginalized communities [277]
- Data ownership and control rights [223, 277, 347]
- Balancing privacy protection with research benefits [384, 470]

Arguments:
Pro stronger privacy protection:
- Genomic data is uniquely sensitive and identifiable [179, 223, 515]
- Current legal protections are insufficient [463, 477]
- Privacy breaches could have lifelong consequences [306, 523]
- Risk of creating genetic surveillance infrastructure [447, 486]

Pro data sharing/access:
- Clinical benefits of data availability for future diagnosis [16, 124, 521]
- Research benefits from aggregated data [132, 167]
- Cost-effectiveness of reanalysis vs. repeat sequencing [191, 241]

Empirical Evidence:
Studies document:
- Public concerns about privacy and data security [347, 349, 357, 360]
- Healthcare provider concerns about discrimination [357, 523]
- Differential privacy concerns across populations [167, 277]
- Examples of unauthorized access attempts [306, 390]

Solutions (Proposed):
Technical:

- Secure cloud-based storage systems with provisions for hybrid or federated systems [6, 371]
- Data encryption and access controls, alerts and provenance tracking [187, 474]
- Standardised de-identification protocols [409]

Policy:
- Legal protections against discrimination [164, 384]
- Clear governance frameworks for data access [167, 482]
- Transparent consent processes with sufficient informational engagement [144, 515]

Solutions Implemented:
Programs reporting implemented solutions include:
- GUARDIAN study: Certificate of confidentiality, restricted data release [315, 316]
- BeginNGS: Multi-dimensional array system for data management [6]
- UK Newborn Genomes Programme: Non-identifiable data publication policy [392]
- Virtual Repository of Dried Blood Spots (VRDBS): Web-based tool with privacy protections [320]

44: How will requests to delete data be managed?

Two-Sentence Summary:
The management of data deletion requests in gNBS programs involves balancing parental rights, future autonomy of the child, and public health benefits against privacy concerns and potential misuse of genetic information. Programs must consider whether to allow parents and/or children to request data deletion, at what age control transfers from parents to children, and how to balance these requests against the potential future clinical and research utility of the data, along with regional legal requirements.

Extended Synthesis:

ELSI at Stake:
- Individual privacy rights and autonomy vs. public health benefits and research utility [74, 86, 107, 124, 142, 194, 215, 241]
- Future autonomy of the child vs. parental decision-making authority [309, 377]
- Trust in public health institutions vs. data retention [220, 447]
- Protection against potential discrimination and misuse [124, 206]

Arguments:
Non-empirical assessments largely focus on three main perspectives:
1. Pro-deletion rights:
- Individuals should have control over their genetic information [220, 221]
- Privacy risks may outweigh benefits of long-term storage [241, 524]
- Risk of discrimination and misuse justifies deletion rights [124, 206]

2. Against broad deletion rights:
- Potential future clinical benefits of retained data [124]
- Research value of comprehensive datasets [194]
- Cost-effectiveness of maintaining data vs. resequencing [241]

3. Nuanced positions:
- Need to balance privacy concerns with clinical utility [124, 223]
- Consider tiered approaches to data retention and deletion [194]

Empirical Evidence:
Limited empirical evidence in the extracts, but two relevant findings:
- Parents express desire for control over their children's genetic information [377]
- Legal challenges in multiple states have led to requirements for deletion options [306]

Solutions (Proposed):
Several approaches suggested:
1. Time-limited storage with automatic deletion [194]
2. Tiered consent system allowing different levels of data retention [377]

4. Resequencing when needed rather than long-term storage [241]

Solutions (Implemented):
Several implemented solutions reported:
- Texas: Required parental option to request destruction of residual dried blood spots [309, 321]
- Minnesota: Written consent required for long-term storage [309]
- Some states allow parents to opt out of storage, though many parents are unaware of this option [306]

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?

Two-Sentence Summary:
The literature highlights a fundamental tension between parents' rights to access their children's genomic data and the child's future autonomy, with additional considerations around data privacy, clinical utility, and potential discrimination. Implementers must balance providing appropriate parental access for healthcare decisions while protecting the child's future interests and right to privacy, with particular attention to consent processes, data ownership transfer mechanisms, and clear protocols for data access and protection.

Extended Synthesis:

ELSI at stake:
- Parental rights vs. child's future autonomy [84, 36]
- Data privacy and protection vs. clinical utility/access [178, 135, 160]
- Control and ownership of genomic information over time [179, 181, 188]
- Questions of data transparency vs. privacy protection [447]

Arguments:
Supporting parental access:
- Parents need access to make informed healthcare decisions [332]
- Data has lifetime clinical value and utility [332, 423]
- Restricting access could lead to mistrust in public health programs [220]

Against unrestricted parental access:
- Could violate child's future privacy rights and autonomy [84, 188]
- Risk of genetic discrimination in insurance/employment [178]
- Concerns about maintaining confidentiality throughout child's life [188]

Empirical Evidence:
- Parents generally want access to their child's genomic data but express concerns about privacy and data security [349, 377]
- Focus groups reveal mixed views on data storage, with most supporting inclusion in medical records while wanting control over data use [377]
- Privacy concerns particularly acute among participants of color [160]
- Parents want transparency about how data will be used [160]

Proposed Solutions:
Technical/Policy:
- Secure, parent-controlled data platforms with transparent rights that transfer to child [6]
- Integration with electronic medical records with appropriate access controls [521]
- Clear protocols for data access and ownership transfer [179]

Institutional:

- High data protection standards with clear regulation of data access [437]
- Extreme transparency in data handling to maintain public trust [447]

Solutions Actually Adopted:
- The literature extracts do not report specific examples of implemented solutions by existing programs, though article [6] mentions that Luna PBC has developed such a system for natural history studies in childhood genetic diseases. The system allows for secure access to the parents, which transfers to the child and can be integrated into other medical care.

46: Will there be a process of transferring data ownership from the parents to the child?

Two Sentence Summary:
The literature extensively discusses the ethical tension between parental proxy decision-making for newborn genomic screening and preserving the child's future autonomy to make decisions about their genetic information. A key consideration for implementers is developing mechanisms to transition control of genomic data from parents to children as they mature, while ensuring appropriate data storage, privacy protections, and clear policies for accessing and managing the information throughout the individual's lifetime.

Extended Synthesis:

ELSI at stake:
- The core ethical issue involves balancing parental authority to make healthcare decisions for their children against protecting the child's future autonomy regarding their genetic information [36, 84, 142, 192, 277, 282, 505]. This raises questions about privacy protection, data ownership, and the right of individuals to control access to their genetic information throughout their lifetime [6, 179, 232, 248, 460].

Arguments:
- Proponents of establishing transfer processes argue that since genomic information has lifelong implications, individuals should have control over their genetic data when they reach maturity [6, 181, 460].
- Critics argue that collecting comprehensive genetic information at birth without the person's consent fundamentally violates their future autonomy [84, 393].
- Some suggest a middle ground where certain information is held "in trust" until the child reaches an appropriate age [473].

Empirical Evidence:
- Focus groups with young adults revealed concerns about parents making decisions about genomic screening that would impact them as adults, potentially removing their right to choose what information they want to know about themselves [505].
- A survey of healthcare providers in Bulgaria showed concerns about children's future autonomy regarding genetic information [523].
- Studies involving parents indicated support for their children having control over their genetic information when they reach adulthood [377].

Solutions (Proposed):
Several approaches have been suggested:
- Secure, parent-controlled data platforms with transparent rights that transfer to the child at the age of consent [6]
- Staged disclosure of genomic information based on age and clinical actionability [288]
- Systems for re-consent at adolescent/adult age for storage and future use of data [191]
- Age-appropriate transfer of genomic information control with clear protocols [505]
- Holding information "in trust" until the child reaches maturity [473]

Solutions Implemented:
- The UK Generation Study reports that they plan to approach participants when they come of age to ask them what they would like done with their data [486].
- Luna PBC has developed a system for natural history studies in childhood genetic diseases that includes transfer of rights to the child [6].

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?

Two-Sentence Summary:
Data sharing decisions for genomic newborn screening programs must balance the critical need for international collaboration to advance rare disease research and variant interpretation against privacy concerns, potential misuse, and discrimination risks. Implementers must carefully consider multiple stakeholder perspectives on who should have access to the data (e.g., clinicians, researchers, industry partners, law enforcement), establish robust governance frameworks for data protection, and determine appropriate consent processes for secondary uses while ensuring compliance with relevant regulations.

Extended Synthesis:

ELSI at Stake:
- Privacy protection vs research benefits and public health utility [63,179, 186, 221, 423, 450, 467, 472]
- Data federation needs vs privacy regulations [187, 470]
- Equitable access vs potential discrimination [179, 521]
- Individual control over genetic information vs societal benefit [251]
- Law enforcement access concerns [179, 472, 486]

Arguments:
Supportive:
- International data sharing is essential for rare disease research and variant interpretation [105, 467]
- Shared resources can standardize and accelerate genomic interpretation [3]
- Biobanking valuable for future research [329]

Critical:
- Risk of genetic discrimination by insurers [179, 423]
- Concerns about law enforcement access disproportionately affecting minorities [472]
- Privacy risks from centralized data repositories [486]
- Need to protect unconsented children's future privacy rights [418]

Empirical Evidence:
- Survey of UK medical students (n=116) showed strong support for clinician access (97%) and NHS-affiliated research (75%) but limited support for external research groups (18%) [360]
- Interviews with Australian healthcare professionals revealed concerns about access by law enforcement, population databases, researchers, and clinical staff [65]
- Workshops with 148 participants showed consistent concerns about third-party access across different screening contexts [63]

Solutions Proposed:

- Development of federated data sharing systems [467]
- Creation of secure platforms for genetic data sharing [470]
- Implementation of comprehensive privacy frameworks [187]

Solutions Implemented:
- Michigan Biobank's model includes IRB review, consent requirements, and de-identification to allow left over blood spots for scientific use [186]
- Virtual Repository of Dried Blood Spots (VRDBS) facilitates researcher with IRB permission access while maintaining privacy protections [320]
- California Department of Public Health restricts genotype data sharing to approved research teams [234]
- International Consortium on Newborn Sequencing (ICoNS) formed for harmonizing resources and scientific evidence [218]

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?

Summary:
Secondary use of newborn screening genomic data presents a fundamental tension between advancing scientific knowledge/improving healthcare and protecting individual privacy/autonomy. Implementers must carefully consider governance structures that balance research benefits with privacy protections, while maintaining public trust through transparency and appropriate consent mechanisms.

Extended Synthesis:

ELSI at stake:
- Privacy protection vs research benefits/scientific advancement [6, 31, 77, 274, 282]
- Individual autonomy vs collective knowledge generation [229, 467]
- Research-clinical care boundaries and distinctions [269, 282, 515]
- Data ownership and control rights [65, 486]
- Public trust in newborn screening programs [244, 321]

Arguments:
Supportive:
- Genomic data sharing is essential for advancing understanding of rare diseases and improving variant interpretation [206, 218, 469]
- Population-level data could accelerate therapy development [415]
- Research use of archived samples represents an invaluable resource [235, 329]

Critical:
- Privacy concerns about long-term storage and potential misuse [220, 423]
- Risk of genetic discrimination and unauthorized access [309, 467]
- Research uses may exceed public health mandate [269]
- Could undermine trust in screening programs [450]

Empirical Evidence:
- Survey of 1,539 US parents showed decreased interest in GS when told data might be stored/used for research [355]
- Survey of Bulgarian healthcare providers (n=72) found 69.9% support research use only with informed consent [523]
- Survey of UK medical students showed strong support for clinician/NHS researcher access (97%/75%) but limited support for external research access (18%) [360]
- Parents of children with hearing loss valued contributing to research through data sharing [361]

Solutions Proposed:

- Developing clear governance frameworks distinguishing clinical and research uses [282, 321]
- Implementing dynamic consent models [228]
- Creating federated data sharing systems [187, 467]
- Increasing transparency about benefits of data storage/use [321]

Solutions Implemented:
- Michigan Biobank: IRB review requirements and de-identification procedures for research access [186]
- California Department of Public Health: Restricts genotype data sharing beyond approved research team. One must reach out to the research team at Stanford to obtain access. [234]
- BeginNGS: Created ELSI workgroup to provide guidance [120]
- UK Generation Study: Making de-identified data available as a research resource and approaching participants at age of consent for the majority of long-term data management decisions [486]

49: Should genomic data be periodically reanalyzed as knowledge that impacts variant interpretation advances (and if so, with what time limit)?

Summary:
Periodic reanalysis of genomic data for symptomatic individuals is widely recognized as crucial due to the rapidly evolving nature of genetic knowledge, with studies showing significant changes in variant interpretations within just 1-2 years. However, implementers must carefully weigh the potential benefits of reanalysis against substantial resource requirements and challenges in determining responsibility for updates, storage, and recontact procedures.

Extended Synthesis:

ELSI at Stake:
The core ethical-social issues involve balancing the potential benefits of reanalysis against practical and resource limitations [102, 160, 329], including:
- Duty to recontact vs practical feasibility [504]
- Long-term data storage and privacy concerns [56, 329]
- Resource allocation and cost implications [160]
- Equitable access to reanalysis benefits [423]
- Responsibility for updates and recontact [297]

Arguments:
Supportive arguments:
- Reanalysis allows genomic data to serve as a "resource for life" [289, 516]
- Enables rapid response to new genomic advances [58]
- More efficient than repeated testing [364]
- Maximizes value of initial sequencing investment [510]

Critical arguments:
- Creates overwhelming burden on healthcare systems [297]
- Raises questions about long-term storage costs and security [56]
- Lack of standardization in reanalysis procedures [408]
- Uncertainty about responsibility for updates [329]

Empirical Evidence:
- MedSeq Project found 22% of reports had updates/changes in variant interpretations after 1-2 years [376]
- BabySeq Project found 5% of well-baby nursery infants developed indications prompting reanalysis during study period [253]
- Study of postmortem genetic analysis highlighted limitations of interpretation without ongoing clinical correlation [372]

Proposed Solutions:

- Development of sophisticated systems to integrate functional data, variant penetrance, and clinical data [20]
- Creating centralized variant repositories [142]
- Implementing AI tools with regular updates [388]
- Establishing clear policies for reanalysis timing and responsibility [376]
- Cloud-based storage with appropriate security measures [56]

Implemented Solutions:
- BabySeq Project: Real-time variant assessment and gene curation updates as new variants are found [441]
- Early Check: Regular re-evaluation of gene-condition pairs at 6-12 month intervals. They plan to recheck panel 2 when new therapies emerge to see if patients are candidates for panel 1 (actionable arm). [24]
- Magic Bison system: Built-in capabilities for periodic data reanalysis for actionable conditions during follow-ups, in addition to periodic checks. [47]
- BeginNGS: Panel inquiry approach allowing updates over time, with annual updates ideally [120]
- AUDIOME: Targeted analysis followed by full exome analysis as needed [299]

50: Should genomic data be periodically reanalyzed as the gene list changes (and if so, with what time limit)?

Two-Sentence Summary:
The literature related to symptomatic individuals strongly suggests that genomic data should be periodically reanalyzed as gene lists evolve, given the rapid pace of discovery in genetic medicine and emergence of new treatments that could make conditions actionable. However, implementers must carefully consider whether this literature is relevant in the screening setting, as well as the resource implications, legal obligations, and infrastructure requirements for long-term data storage and reanalysis processes.

Extended Synthesis:

ELSI at stake:
- The key ethical issues center on balancing the potential benefits of reanalysis against resource constraints and system capabilities [3, 24, 56]. This involves technical-ethical considerations about data management and storage [107], questions of intergenerational equity and future health benefits [186], and responsibilities regarding ongoing surveillance and updates [160].
- Social justice considerations arise regarding healthcare access and the potential reduction of health disparities through expanded detection capabilities [363].

Arguments:
Supportive arguments emphasize:
- The cumulative benefits of having genomic data available for reanalysis as knowledge advances [58, 62, 160]
- Greater efficiency compared to repeated targeted testing [364]
- Potential for improving diagnostic yield over time as new genes are discovered [299]
- Ability to adapt to emerging treatments and evidence [294, 108]

Critical perspectives highlight:
- Resource implications of storing and reanalyzing data long-term [160]
- Questions about legal obligations if reanalysis isn't performed [160]
- Potential strain on healthcare systems and providers [244]
- Concerns about technological obsolescence [515]

Empirical Evidence:
Limited empirical evidence is presented in the literature, but includes:
- The BabySeq Project found that 5% of well-baby nursery infants developed indications requiring reanalysis during the study period [253]
- Regression analysis showing that improved knowledge of gene-disease relationships increased likelihood of inclusion in newborn screening programs by 14.8% [108]

Solutions (Proposed):
- Create adaptable gene panels with regular re-evaluation schedules [294]
- Develop data systems supporting longitudinal follow-up [471]

- Implement cloud-based storage with appropriate security measures [56]
- Limit data storage and reanalysis to clinically indicated cases [160]
- Use whole genome sequencing with bioinformatic filtering rather than fixed panels [482]

Solutions Actually Adopted:
Several programs have implemented solutions:
- BabySeq Project: Periodic updates to gene classifications as new evidence emerges [3]
- Early Check: Regular re-evaluation of gene-condition pairs at 6-12 month intervals [24]
- Magic Bison: System with built-in capabilities for periodic data reanalysis [47]
- BeginNGS: Using whole genome sequencing but only returning results for conditions on a predefined panel that can be updated [120]
- UK Generation Study: Working group focused on consent processes for research and reanalysis [112]

51: Should there be any planned disclosures of information that is relevant later in life?

Two Sentence Summary:
The literature extensively discusses the ethical tension between providing potentially beneficial health information throughout life versus protecting the child's future autonomy and right not to know. A key consideration is whether and how to implement systems for staged disclosure of genetic information at developmentally and clinically appropriate times, balancing the benefits of early knowledge against the challenges of storing and managing genomic data long-term. A further key consideration is the extent to which information relevant later in life is ‘core business’ of NBS.

Extended Synthesis:

ELSI at Stake:
The core ethical issues involve:
- Tension between child autonomy and parental authority regarding access to genetic information [3,34,46,282,466]
- Right to an open future vs. potential health benefits throughout life [207,393,521]
- Privacy and control of genetic information across the lifespan [178,465,473]
- Financial and capacity challenges of managing and storing genomic data long-term [297,510]
- Intergenerational equity and future health benefits [186]

Arguments:
Supporting planned disclosure:
- Genomic data could provide lifelong health benefits through periodic reanalysis [207,213,259]
- Early knowledge allows for preventive interventions and better health outcomes [7,85,229]
- Sequential analysis could improve cost-effectiveness [56]

Against planned disclosure:
- Violates child's future autonomy and right not to know [141,309,336]
- Creates burden of knowledge years before clinical relevance [213]
- May cause unnecessary anxiety or psychological harm [320]

Empirical Evidence:
Studies show:
- Parents prefer early return of results regardless of age of onset [66]
- Young adults express concerns about parents making decisions that impact their adult lives [505]
- Healthcare providers worry about patients being lost to follow-up after receiving complex genomic information [205]
- All newborns carry some actionable variants relevant to future health [18]

Proposed Solutions:

- Age-based tiered disclosure systems [34,214,223]
- Electronic health records and data linkages for lifetime coordination [225]
- Regular reanalysis protocols with appropriate resourcing [465]
- Opt-in approaches for parents to receive adult-onset information [3]
- Holding information "in trust" until appropriate age [473]

Implemented Solutions:
Several programs have adopted specific approaches:
- NC NEXUS created age-based categories separating childhood from adult-onset conditions [34]
- Magic Bison system incorporates future disease risk assessment [47]
- BabySeq allows parents to opt-in to receiving adult-onset information [182]

The literature suggests most programs are still working to develop comprehensive approaches to managing disclosure of genetic information across the lifespan, with ongoing debate about optimal strategies.

52: Should the data be available for diagnostic purposes, if the child develops a phenotype?

Two-Sentence Summary:
The literature predominantly supports making genomic data available for future diagnostic purposes, citing benefits like reduced diagnostic delays and cost-effectiveness of reanalyzing existing data versus new testing. However, this raises important considerations around data provenance, data quality, storage infrastructure, privacy protections, and consent processes that need to be carefully addressed in implementation. Additionally, implementers should also consider the ease with which (newer) genome sequencing can be done for diagnostic purposes.

Extended Synthesis:

ELSI at stake:
- Tension between potential clinical benefits and privacy/data protection concerns [16, 232]
- Questions of data ownership and transfer from parents to child [121]
- Balance between immediate versus lifetime utility of genomic data [253, 516]

Arguments:
Supporting:
- Could reduce diagnostic delays for rare diseases [16]
- More economical than repeat testing [7, 253]
- Provides lifelong health resource for families [465]
- Enables rapid response to new genomic advances [423]

Critical:
- Raises privacy and discrimination concerns [232, 491]

Empirical Evidence:
- BabySeq Project found 5% of well-baby nursery infants developed indications requiring genomic analysis during study period [253]
- Interview study with parents showed support for storing data for future clinical use [121]
- Study of healthcare professionals in Australia revealed support for long-term storage with option for individual choice [65]

Solutions (Proposed):
- Optional secondary uses with parental consent and eventual transfer to child [6]
- Secure long-term storage with controlled access [16]
- Quality assessment protocols to determine if reanalysis needed [289]
- Tiered disclosure system based on clinical relevance and timing [329]
- Legislation to protect confidentiality while enabling appropriate clinical access [491]

Solutions (Implemented):

- Wisconsin project exploring use of stored genomic data for diagnosis and treatment optimization in cystic fibrosis (CF) patients. The previously masked data that didn't focus on CF was kept and able to be revisited. [459]
- Luna PBC developed a system to securely store genetic data for parents and children, which could have the option of phenotype-informed secondary diagnostics when physicians order re-evaluation of genetic data previously collected. [6]
- BabyScreen+: performed clinically accredited testing, and data is available for diagnostic reuse. Participating families are made aware of this as part of education/consent and at the return of results.

Note: The literature emphasizes careful consideration of governance structures and consent processes, suggesting implementers should develop clear policies around data access, privacy protection, and transfer of control to the individual when they reach adulthood.

53: Should the ability to recontact parents, and eventually the child, be maintained, and if so, how?

Two-Sentence Summary:
The ability to recontact parents and eventually the child is viewed as crucial for multiple purposes including research participation, variant reclassification, disclosure of adult-onset conditions, and transfer of genetic information when the child reaches maturity. The main challenges involve establishing robust systems for maintaining contact over long periods, determining responsibility for recontact, and creating clear procedures for transferring information control from parents to children.

Extended Synthesis:

ELSI at stake:
- Ethical responsibility to communicate updated genetic information vs practical limitations of maintaining long-term contact [82, 504]
- Child autonomy and right to access their genetic information vs parental control [142]
- Privacy and confidentiality in maintaining long-term contact information [26]
- Responsibility for ensuring appropriate transfer of information between healthcare providers, parents, and eventually children [85]

Arguments:
- Support for recontact: Facilitates development of treatments for rare disorders [26], enables sequential interrogation of genomic data [56], allows staged disclosure of genetic information at appropriate life stages [223]
- Concerns: Lack of binding regulations creates gaps in follow-up [82], challenges in maintaining accurate information transfer over long periods [85], uncertainty about responsibility for ensuring disclosure [85]
- Debate over whether parental consent for minors' participation should require reconsent at majority [142]

Empirical Evidence:
- Study showing poor documentation and parental awareness of screening results in Russia, highlighting importance of robust documentation systems [480]
- Limited research on how parents explain genetic risks to children, though evidence suggests communication often occurs before majority age [232]

Proposed Solutions:
- Creation of privacy-protected registries with opt-in consent for research participation [26]
- Robust process of recontact and reconsent at age of majority [142]
- Electronic health records and record linkages for lifetime coordination of genetic information [225]
- Development of support systems for parents in communicating genetic information to children [232]
- Implementation of database systems to track variants and generate updates when classifications change [504]

Implemented Solutions:
- Laboratory system for tracking variant reclassifications and generating lists of cases requiring updated reports. An internal database flags cases with reclassifications. The research team can let the patient's provider know about the reclassifications that are not benign so that the provider can let patients know [504]
- No other specific implemented solutions were described in the extracted literature

54: How should project success be defined and measured?

Summary:
The literature emphasizes that defining and measuring success in genomic newborn screening (gNBS) requires balancing multiple dimensions including clinical utility, cost-effectiveness, equity of access, and psychosocial impacts on families. Attention is also needed to the effect on competing public health priorities, the need to evaluate public participation or public buy-in, the effect on existing newborn screening programs, or access to appropriate followup. The literature emphasizes the need for comprehensive evaluation frameworks that go beyond traditional clinical outcomes to include both quantitative metrics and qualitative assessments of program impacts across stakeholder groups

Extended Synthesis:

ELSI at stake:
- Tension between measuring narrow clinical outcomes versus broader societal impacts [272, 431], including competing public health priorities, how successful public education has been, how much public buy in there is
- Challenge of balancing individual benefits against population-level outcomes [169, 526], including impact on traditional newborn screening
- Need to consider both short-term and long-term impacts [373, 437]
- Equity considerations in how success is defined and measured [2, 270]

Arguments:
- Success metrics should include both clinical and social outcomes [229, 392, 472]
- Need to move beyond traditional cost-effectiveness measures to include quality of life impacts [272, 502]
- Programs should be evaluated on their ability to reduce health disparities [2, 169]
- Importance of considering both benefits and potential harms [319, 320]
- Need for transparency in how success is defined and measured [26, 319]
- Impact on the broader NBS ecosystem should be considered, including whether there is any change to uptake of traditional NBS, and whether connections to followup care continue to function well

Empirical Evidence:
Existing empirical evidence is focused on individual and not public health outcomes:
- BabySeq Project showing both clinical utility and psychological impacts [394, 449]
- Studies showing cost savings from early diagnosis [191]
- Research on parental perspectives and decision-making [502, 503]
- Evidence on diagnostic yield and clinical management changes [253, 434]
- Limited long-term outcome data available [320, 373]

Proposed Solutions:
- Development of comprehensive evaluation frameworks [272, 432]
- Implementation of standardized metrics across programs [105]
- Regular stakeholder engagement in defining success metrics [272, 392]
- Longitudinal follow-up systems [270, 373]

- Integration of both quantitative and qualitative measures [232, 392]

Implemented Solutions:
Existing implemented solutions are focused on individual and not public health outcomes.
- BabySeq Project's multi-dimensional evaluation framework including clinical, behavioral, and economic impacts [441]
- NC NEXUS project's approach to measuring decisional outcomes [502, 503]
- BeginNGS program's staged implementation with iterative evaluation [120]
- Generation Study's systematic feedback collection from participants and healthcare providers [517]
- Screen4Care EU-IMI project's comprehensive evaluation approach [407]
- BabyScreen+: participant surveys [391]

This synthesis demonstrates the complexity of defining and measuring success in gNBS programs, with a clear trend toward more comprehensive evaluation frameworks that consider multiple stakeholder perspectives and outcomes. The literature suggests that successful implementation requires careful attention to both clinical and social impacts, with regular evaluation and adjustment based on evidence.

55: What governance system should be put in place for managing emerging issues?

Two Sentence Summary:
The literature emphasizes that implementing genomic newborn screening requires comprehensive governance systems that can address multiple challenges including ethical oversight, stakeholder engagement, data sharing, quality assurance, and cross-jurisdictional coordination. A key consideration is the need to balance rapid technological advancement with careful ethical implementation while ensuring programs maintain public participation and protect their core public health mission, likely involving advisory boards and governing agencies.

Extended Synthesis:

ELSI at Stake:
- Tension between technological advancement and ethical implementation [220]
- Balance between research value and protecting public health mission [411]
- Need to coordinate across jurisdictions with varying governance models [228]
- Privacy protection vs public health benefit [401]
- Program integrity vs technological adoption [220]
- Professional responsibility vs technological delegation [388]

Arguments:
Supportive:
- Expert advisory groups at international level needed to support policy development [105]
- Implementation science frameworks can guide implementation [32]

Critical:
- Current fragmented governance structures hamper coordination [471]
- Siloed approaches fail to account for how genomic data moves between domains [251]
- Premature adoption could undermine program integrity [220]

Empirical Evidence:
- Survey of genetic counselors found advocacy for caution in implementation and need for additional education [205]
- Q methodology study with 30 healthcare professionals identified need for clear responsibility frameworks [388]
- Review of pilot studies found lack of coordination in data analysis and consensus development [370]

Proposed Solutions:
- Create European Commission-recognized expert advisory groups [105]
- Implement high reliability organization principles [314]
- Create multidisciplinary oversight committees [388]
- Establish research ethics consultation services [86]
- Develop formal dissemination plans for pilot study data [370]

Implemented Solutions:
- PERIGENOMED Project in France established comprehensive pilot project to assess feasibility and implementation dimensions [208]
- BabySeq Project underwent IRB and FDA review with determination of "greater than minimal risk with potential for benefit." There is also an External Advisory Board containing various types of experts. [441]

56: How can transparency be assured in decision-making processes?

Two-Sentence Summary:
The literature emphasizes that transparency in decision-making processes is fundamental for maintaining public trust in genomic newborn screening programs and should encompass clear documentation of criteria for condition selection, program financing, and benefit distribution. Implementers should focus on establishing formal mechanisms for transparent documentation and communication of decisions, while ensuring meaningful engagement with multiple stakeholders including medical professionals, researchers, patient advocacy groups, and the general public.

Extended Synthesis:

ELSI at Stake:
- The primary ethical issues concern balancing the need for transparent decision-making with the complexity of genomic screening programs [425, 471], maintaining public trust while implementing innovations [447], and ensuring equitable representation in decision-making processes [279].
- Social implications include the need to maintain public confidence in established screening programs while introducing new technologies [447], and addressing potential disparities in program benefits [264].
- An issue is that transparent decision making tends to take longer, add costs, and thus be less efficient.

Arguments:
Supportive arguments emphasize that transparency is essential for:
- Building and maintaining public trust [225]
- Ensuring accountability in program performance [314]
- Facilitating international cooperation and standardization [48]
- Supporting informed decision-making by stakeholders [294]

Critical perspectives highlight:
- Risks of eroding public trust through lack of transparency [228]
- Challenges of maintaining transparency across complex, multi-jurisdictional systems [251]
- Concerns about political polarization affecting public trust [311]

Empirical Evidence:
Limited empirical evidence exists specifically addressing transparency in decision-making:
- A study of genetic counselors found support for increased transparency before implementing whole genome sequencing [205]
- Analysis of the UK Generation Study revealed lack of transparency in condition selection criteria [476]
- Survey research showed varying levels of trust in screening program information across demographic groups [134]

Solutions (Proposed):
Multiple approaches have been suggested:
- Creating standardized documentation systems for decision-making processes [294]
- Establishing multi-stakeholder advisory bodies [105]
- Developing formal dissemination plans for sharing pilot study data [370]
- Implementing regular self-assessment and review processes [431]
- Creating centralized offices for program coordination [471]

Solutions Actually Implemented:
Several programs have adopted specific transparency measures:
- Early Check pilot study: Included collaborating institutions and provided transparent information to build trust [134]
- Netherlands PNPNL: Centralized laboratory system with standardized processes [153]
- BeginNGS: Created an open, pre-competitive consortium with academic, industry, and parent stakeholders [120]

57: What are the priorities for cross-jurisdiction policy consistency, both across regions and internationally?

Two Sentence Summary:
The literature strongly emphasizes that significant variation exists in newborn screening programs across jurisdictions, both within countries and internationally, creating inequities in screening access and healthcare outcomes based solely on geography. A key tension exists between respecting local/state autonomy in healthcare decision-making and the need for standardization to ensure equitable access to screening, with most authors advocating for increased harmonization while acknowledging the need to account for regional differences in healthcare systems, resources, and priorities.

Extended Synthesis:

ELSI at stake:
- Equity in healthcare access vs. jurisdictional autonomy [4, 26, 27, 77, 144, 151, 282]
- Standardization vs. local implementation flexibility [48, 98, 105]
- Global responsibility vs. national sovereignty [161, 478]
- Healthcare system differences vs. evidence generalizability [169, 464]

Arguments:
Pro-standardization:
- Current fragmentation leads to preventable harm when children aren't screened for conditions that neighboring jurisdictions include [323]
- International collaboration necessary for rare diseases due to limited data in any single jurisdiction [105]

Pro-local autonomy:
- Different healthcare systems and resources require flexibility [77, 169]
- Local context and priorities must be considered [77, 478]
- State/regional authority over healthcare decisions is legally established [27, 282]

Empirical Evidence:
- Study of 27 genetic newborn screening programs found number of genes analyzed ranged from 134 to 4,299, with only 74 genes included by >80% of programs [483]
- Analysis of US state screening panels found variation from 32 to 71 conditions [370]
- Successful expansion of concurrent screening from Beijing to 21 cities in 16 provinces demonstrates potential for regional scaling [98]
- European Delphi study found consensus on barriers to genomic screening implementation despite heterogeneous national systems [464]

Proposed Solutions:
- Develop international consensus on core genes/conditions while allowing for regional expansion [182, 294]
- Create expert advisory groups at international level to support policy development [105]
- Focus on principles-based rather than rules-based approaches to regulation [228]

- Create central offices for coordination at national level [471]

Implemented Solutions:
- US Recommended Uniform Screening Panel (RUSP) provides federal guidance while maintaining state autonomy, which have worked cooperatively [320]
- Michigan Biobank established standardized policies for blood spot retention and research use, but each state varies regarding duration and condition [186]
- Screen4Care project in EU working to develop standardized approaches while respecting national autonomy [478]
- UK Generation Study testing implementation in public healthcare system context [169]

58: How should sustainability of any ongoing implementation be planned for, including expansion of downstream capacity?

Two Sentence Summary:
Implementing genomic newborn screening requires careful consideration of long-term financial sustainability and system capacity for expanded screening, including costs beyond just sequencing (like interpretation, follow-up care, and data management). Programs must balance the decreasing costs of sequencing technology against the substantial infrastructure and workforce requirements needed for comprehensive screening programs, while ensuring adequate resources for both existing and expanded screening capabilities.

Extended Synthesis:

ELSI at Stake:
- Economic sustainability vs comprehensive screening implementation [463, 464, 471]
- Resource allocation between existing and new screening programs [293, 324]
- Healthcare system capacity and infrastructure development [164, 200, 206]
- Equity in access to screening and follow-up care [141, 149, 363]

Arguments:
Supportive:
- Decreasing sequencing costs will make implementation more feasible over time [202, 332]
- Early identification through genomic screening could reduce long-term healthcare costs [223, 400]
- When amortized over a lifetime, the cost per year becomes minimal [510]

Critical:
- Current costs are prohibitively expensive compared to traditional screening [149, 307, 514]
- Implementation requires significant infrastructure beyond just sequencing costs [492, 450]
- Resources might be better spent on other public health priorities [472, 526]
- May create unsustainable burden on healthcare systems [317, 371]

Empirical Evidence:
Cost Analyses:
- BabySeq project collecting comprehensive economic data comparing sequenced vs control groups [441]
- GUARDIAN study found implementation would require infrastructure for 3.5 million sequences annually [491]
- Belgian pilot reported €365/sample vs €42 for conventional screening [371]
- UK analysis estimated £735 million annual cost vs £413,000 for expanded biochemical screening [476]

Healthcare System Impact:
- Study of 7,501 newborns in China showed need for robust data quality control and interpretation capabilities [434]
- Survey of Bulgarian healthcare providers indicated concerns about system readiness [523]

- Analysis of US state programs showed average 9.5 years for nationwide adoption of new conditions [370]

Proposed Solutions:
- Phased implementation approach with pilot studies before full-scale adoption [120, 464]
- Regional centralization of testing and analysis [176, 313]
- Public-private partnerships to support funding [313, 464]
- Developing automated technologies to reduce costs [56, 163]
- Building collaborative networks between institutions [240, 400]

Implemented Solutions:
- BeginNGS program implementing staged rollout with annual expansion cycles [120]
- UK Newborn Genomes Programme using pilot study approach to broaden insight for developing future studies and wider implementation [112]
- French PERIGENOMED project implementing two-phase approach with feasibility study followed by regional implementation [90]
- Australian BabyScreen+ conducting comprehensive health economic analyses [391]

59: How should closing the project be managed?

Two Sentence Summary:
Managing project closure in genomic newborn screening implementations requires careful consideration of both sustaining established screening programs and planning for future capacity. Key considerations include maintaining public trust in traditional newborn screening programs while managing the transition or expansion of genomic screening capabilities.

Extended Synthesis:

ELSI at stake [141]:
- Risk to traditional newborn screening programs and public trust
- Sustainability of screening infrastructure and capabilities

Arguments [141]:
- There is concern that implementing genomic NBS could potentially undermine public trust in all newborn screening, including well-established traditional screening programs
- The benefits of traditional NBS programs for thousands of children and families worldwide need to be protected during any transition or closure

Empirical Evidence [434]:
- Evidence from implementation in China suggests consideration must be given to maintaining data quality control and report interpretation capabilities
- Cost considerations and healthcare system capacity need to be factored into closure planning

Proposed Solutions [434]:
- Development of robust infrastructure for data quality control and interpretation
- Planning for technological advancement and database growth to support long-term sustainability
- Consideration of cost-effectiveness and scalability in different populations

Implemented Solutions:
- No implemented solutions are described in the provided extracts

Note: The literature coverage of this specific decision point is relatively limited in the provided extracts, focusing mainly on considerations around maintaining existing screening program integrity and planning for sustained capacity. Additional literature may provide more specific guidance on project closure management.

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33	Alternative DNA-based newborn screening for glucose-6-phosphate dehydrogenase deficiency	Lin, Z.; Fontaine, J. M.; Freer, D. E.; Naylor, E. W.	2005	https://dx.doi.org/10.1016/j.ymgme.2005.05.008
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38	An Opportunity to Fill a Gap for Newborn Screening of Neurodevelopmental Disorders	Chung, Wendy K; Kanne, Stephen M; Hu, Zhanzhi	2024	https://dx.doi.org/10.3390/ijns10020033
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53	Are the new genetic tools for diagnosis of Wilson disease helpful in clinical practice?	Espinos, Carmen; Ferenci, Peter	2020	https://dx.doi.org/10.1016/j.jhepr.2020.100114

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67	Australian Public Perspectives on Genomic Newborn Screening: Risks, Benefits, and Preferences for Implementation	Lynch, Fiona; Best, Stephanie; Gaff, Clara; Downie, Lilian; Archibald, Alison D; Gyngell, Christopher; Goranitis, Ilias; Peters, Riccarda; Savulescu, Julian; Lunke, Sebastian; Stark, Zornitza; Vears, Danya F	2024	https://dx.doi.org/10.3390/ijns10010006
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95	Comparative Analysis of Gene and Disease Selection in Genomic Newborn Screening Studies	Betzler, I. R.; Hempel, M.; M√ºtze, U.	2025	10.1002/jimd.70022
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114	Development and validation of a carnitine cycle and transport disorders (CCD) panel: an ONT-compatible multi-gene diagnostic kit for newborn and selective	Akan, G.; Balcƒ±, M. C.; Tuncel, G.; Karaca, M.; Kazan, H. H.; √ñzketen, A. √á; √ñzgen, √ñ; G√∂k√ßay, G. F.; Atalar, F.	2025	10.1186/s13023-025-03775-4

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119	Discordant results between conventional newborn screening and genomic sequencing in the BabySeq Project	Wojcik, Monica H; Zhang, Tian; Ceyhan-Birsoy, Ozge; Genetti, Casie A; Lebo, Matthew S; Yu, Timothy W; Parad, Richard B; Holm, Ingrid A; Rehm, Heidi L; Beggs, Alan H; Green, Robert C; Agrawal, Pankaj B	2021	https://d x.doi.org /10.1038 /s41436- 021-011 46-5
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121	Diverse Parental Perspectives of the Social and Educational Needs for Expanding Newborn Screening through Genomic Sequencing	Timmins, George Thomas; Wynn, Julia; Saami, Akilan Murugesan; Espinal, Aileen; Chung, Wendy K	2022	https://d x.doi.org /10.1159 /000526 382
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143	Ethical and social implications of genetic testing for communication disorders	Arnos, Kathleen S	2008	https://dx.doi.org/10.1016/j.jcomdis.2008.03.001
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155	Evaluating parents' decisions about next-generation sequencing for their child in the NC NEXUS (North Carolina Newborn Exome Sequencing for Universal Screening) study: a randomized controlled trial protocol	Milko, Laura V; Rini, Christine; Lewis, Megan A; Butterfield, Rita M; Lin, Feng-Chang; Paquin, Ryan S; Powell, Bradford C; Roche, Myra I; Souris, Katherine J; Bailey, Donald B Jr; Berg, Jonathan S; Powell, Cynthia M	2018	https://dx.doi.org/10.1186/s13063-018-2686-4
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174	Feasibility and Acceptability of a Newborn Screening Program Using Targeted Next-Generation Sequencing in One Maternity Hospital in Southern Belgium	Dangouloff, T.; Hovhannesyan, K.; Mashhadizadeh, D.; Minner, F.; Mni, M.; Helou, L.; Piazzon, F.; Palmeira, L.; Boemer, F.; Servais, L.	2024	10.3390/children11080926
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214	Genomic newborn screening: Proposal of a two-stage approach	Schaaf, Christian P; Kolker, Stefan; Hoffmann, Georg F	2021	https://dx.doi.org/10.1002/jimd.12381
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226	Genomics and proteomics of retinopathy of prematurity: DNA-based prevention and treatment	Good, W V; Gendron, R L	29-6	https://dx.doi.org/10.1136/bjo.2007.124404
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232	Growing Up in the Genomic Era: Implications of Whole-Genome Sequencing for Children, Families, and Pediatric Practice	Wade, CH; Tarini, BA; Wilfond, BS	2013	10.1146/annurev-genom-091212-153425
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238	Identification of Clinically Significant Genetic Variants by Exome Sequencing of DNA Extracted from Dried Blood Spots: A Model for Newborn Screening	Guettouche, T.; Rantus, J.; Hulme, W.; Diaz, A.; Andersen, A.; Gonzalez, M.; Zuchner, S.; Bodamer, O.	2013	
239	Implementation of Genetics to Personalize Medicine	Chung, W.K.	2007	10.1016/S1550-8579(07)80044-1
240	Implementation of public health genomics in Pakistan	Riaz, Moeen; Tiller, Jane; Ajmal, Muhammad; Azam, Maleeha; Qamar, Raheel; Lacaze, Paul	2019	https://dx.doi.org/10.1038/s41431-019-0428-z
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244	Implications of newborn screening for nurses	DeLuca, Jane; Zanni, Karen L; Bonhomme, Natasha; Kemper, Alex R	2013	https://dx.doi.org/10.1111/jnu.12005
245	Improving newborn screening in India: Disease gaps and quality control	Panchbudhe, S. A.; Shivkar, R. R.; Banerjee, A.; Deshmukh, P.; Maji, B. K.; Kadam, C. Y.	2024	10.1016/j.cca.2024.117881
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252	International Perspectives of Extended Genetic Sequencing When Used as Part of Newborn Screening to Identify Cystic Fibrosis	Clark, C.C.A.; Holder, P.; Boardman, F.K.; Moody, L.; Cowlard, J.; Allen, L.; Walter, C.; Bonham, J.R.; Chudleigh, J.	2024	10.3390/ijns10020031
253	Interpretation of Genomic Sequencing Results in Healthy and Ill Newborns: Results from the BabySeq Project	Ceyhan-Birsoy, Ozge; Murry, Jaclyn B; Machini, Kalotina; Lebo, Matthew S; Yu, Timothy W; Fayer, Shawn; Genetti, Casie A; Schwartz, Talia S; Agrawal, Pankaj B; Parad, Richard B; Holm, Ingrid A; McGuire, Amy L; Green, Robert C; Rehm, Heidi L; Beggs, Alan H	2019	https://dx.doi.org/10.1016/j.ajhg.2018.11.016
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257	Introduction to the Special Issue: Public Health Genetics and Genomics	McWalter, Kirsty; Gaviglio, Amy	2015	https://dx.doi.org/10.1007/s10897-015-9825-9
258	Key informant perspectives on implementing genomic newborn screening: a qualitative study guided by the Action, Actor, Context, Target, Time framework	Tutty, Erin; Archibald, Alison D; Downie, Lilian; Gaff, Clara; Lunke, Sebastian; Vears, Danya F; Stark, Zornitza; Best, Stephanie	16-7	https://dx.doi.org/10.1038/s41431-024-01650-7

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268	Metabolic Myopathies in the Era of Next-Generation Sequencing	Urtizberea, Jon Andoni; Severa, Gianmarco; Malfatti, Edoardo	2023	https://dx.doi.org/10.3390/genes14050954
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282	New tools and approaches to newborn screening: ready to open Pandora's box?	Ficicioglu, Can	2017	https://dx.doi.org/10.1101/mcs.a001842
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292	Newborn screening and the era of medical genomics	Francescatto, Ludmila; Katsanis, Nicholas	2015	https://dx.doi.org/10.1053/j.semperi.2015.09.010
293	Newborn screening as a model for population screening	McCabe, L. L.; McCabe, E. R. B.	2002	10.1016/S1096-7192(02)00005-7
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298	Newborn screening controversy: past, present, and future	Lewis, Michelle Huckaby	2014	https://dx.doi.org/10.1001/jamapediatrics.2013.4980
299	Newborn Screening for Deafness/Hard of Hearing in the Genomic Era	Giersch, Anne B S; Morton, Cynthia C	2025	https://dx.doi.org/10.1093/clinchem/hvae193
301	Newborn screening for genetic disorders: Current status and prospects for the future	Ding, Si; Han, Lianshu	2022	https://dx.doi.org/10.1002/ped4.12343
302	Newborn Screening for Inborn Errors of Metabolism by Next-Generation Sequencing Combined with Tandem Mass Spectrometry	Tang, C.; Li, L.; Chen, T.; Li, Y.; Zhu, B.; Zhang, Y.; Yin, Y.; Liu, X.; Huang, C.; Miao, J.; Wang, X.; Zou, H.; Han, L.; Feng, J.; Huang, Y.	2024	10.3390/ijns10020028
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319	Newborn screening: adapting to advancements in whole-genome sequencing	Meade, Caroline; Bonhomme, Natasha F	2014	https://dx.doi.org/10.1089/gtmb.2014.1558
320	Newborn Screening: Beyond the Spot	Urv, Tiina K; Parisi, Melissa A	2017	https://dx.doi.org/10.1007/978-3-319-67144-4_19
321	Newborn Screening: From Guthrie to Whole Genome Sequencing	Caggana, M; Jones, EA; Shahied, SI; Tanksley, S; Hermerath, CA; Lubin, IM	2013	10.1177/00333549131280S204
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332	Next-Generation Newborn Hearing Screening	Shen, J.; Morton, C. C.	2016	10.1159/000444598
333	Next-generation sequencing (NGS) techniques for pre-symptomatic identification of genetic diseases in newborns	Pessano, Sara; Boldor, Maria; Faravelli, Francesca; Fiander, Michelle; Jorgensen, Karsten Juhl; Soll, Roger F; Bruschettini, Matteo	2025	https://dx.doi.org/10.1002/14651858.CD016118
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335	Next-generation sequencing improves precision medicine in hearing loss	Imizcoz, T.; Prieto-Matos, C.; Manrique-Huarte, R.; Calavia, D.; Huarte, A.; Pruneda, P. C.; Ordo√±ez, G. R.; Ca√±ada-Higueras, E.; Pati√±o-Garc√≠a, A.; Alkorta-Aranburu, G.; Manrique Rodr√≠guez, M.	2023	10.3389/fgene.2023.1264899
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340	One-step NGS molecular analysis of the CFTR gene on newborn dried blood spots gives a higher diagnostic sensitivity in affected and carrier subjects: A pilot study	Nunziato, M.; Starnone, F.; Giordano, S.; D'Antonio, M.; Scognamiglio, D.; Esposito, M. V.; Correra, A.; Di Maggio, F.; D'Argenio, V.; Luca Scaglione, G.; Castaldo, G.; Salvatore, F.	2024	10.1016/j.cca.2023.117625
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343	Parental Attitudes Toward Standard Newborn Screening and Newborn Genomic Sequencing: Findings From the BabySeq Study	Armstrong, Brittan; Christensen, Kurt D; Genetti, Casie A; Parad, Richard B; Robinson, Jill Oliver; Blout Zawatsky, Carrie L; Zettler, Bethany; Beggs, Alan H; Holm, Ingrid A; Green, Robert C; McGuire, Amy L; Smith, Hadley Stevens; Pereira, Stacey	2022	https://dx.doi.org/10.3389/fgene.2022.867371
344	Parental Depression and Anxiety Associated with Newborn Bloodspot Screening for Rare and Variable-Onset Disorders	Boychuk, Natalie A; Mulrooney, Niamh S; Kelly, Nicole R; Goldenberg, Aaron J; Silver, Ellen J; Wasserstein, Melissa P	2022	https://dx.doi.org/10.3390/ijns8040059
345	Parental Guidance Suggested: Engaging Parents as Partners in Research Studies of Genomic Screening for a Pediatric Population	Powell, Sabrina N; Byfield, Grace; Bennetone, Ashley; Frantz, Annabelle M; Harrison, Langston K; James-Crook, Erin R; Osborne, Heather; Owens, Thomas H; Shaw, Jonathan L; O'Daniel, Julianne; Milko, Laura V	2022	https://dx.doi.org/10.3389/fgene.2022.867030
346	Parental interest in genomic sequencing of newborns: enrollment experience from the BabySeq Project	Genetti, Casie A; Schwartz, Talia S; Robinson, Jill O; VanNoy, Grace E; Petersen, Devan; Pereira, Stacey; Fayer, Shawn; Peoples, Hayley A; Agrawal, Pankaj B; Betting, Wendi N; Holm, Ingrid A; McGuire, Amy L; Waisbren, Susan E; Yu, Timothy W; Green, Robert C; Beggs, Alan H; Parad, Richard B	2019	https://dx.doi.org/10.1038/s41436-018-0105-6

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348	Parental Preferences for Expanded Newborn Screening: What Are the Limits?	Liang, Nicole S Y; Watts-Dickens, Abby; Chitayat, David; Babul-Hirji, Riyana; Chakraborty, Pranesh; Hayeems, Robin Z	2023	https://dx.doi.org/10.3390/children10081362
349	Parental Views on Expanded Newborn Screening Using Whole-Genome Sequencing	Joseph, Galen; Chen, Flavia; Harris-Wai, Julie; Puck, Jennifer M; Young, Charlotte; Koenig, Barbara A	2016	https://dx.doi.org/10.1542/peds.2015-3731H
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352	Parents' and childrens‚Äô views of wider genomic testing when used as part of newborn screening to identify cystic fibrosis	Chudleigh, J.; Holder, P.; Clark, C.; Moody, L.; Cowlard, J.; Allen, L.; Walter, C.; Bonham, J.R.; Boardman, F.	2024	10.1016/j.ssmqr.2024.100455
353	Parents' decision-making regarding whether to receive adult-onset only genetic findings for their children: Findings from the BabySeq Project	Pereira, Stacey; Gutierrez, Amanda M; Robinson, Jill Oliver; Christensen, Kurt D; Genetti, Casie A; Blout Zawatsky, Carrie L; Hsu, Rebecca L; Zettler, Bethany; Uveges, Melissa Kurtz; Parad, Richard B; Beggs, Alan H; Holm, Ingrid A; Green, Robert C; McGuire, Amy L	2023	https://dx.doi.org/10.1016/j.gim.2022.100002
354	Parents' experiences 12 years after newborn screening for genetic susceptibility to type 1 diabetes and their attitudes to whole-genome sequencing in newborns	Kerruish, Nicola	2016	https://dx.doi.org/10.1038/gim.2015.73
355	Parents' interest in whole-genome sequencing	Goldenberg, Aaron J; Dodson, Daniel S; Davis, Matthew M; Tarini, Beth A	2014	https://dx.doi.org

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356	Parents' perspectives on expanded newborn genomic screening in Abu Dhabi, United Arab Emirates	Elhadi, Y. A. M.; Alkatheeri, M.; Alktifan, M.; Alhammadi, F.; Sultan, T.; Alqumboz, Y. M. A.; Jihad, A.; Shaidul, M. I.; Al Saadi, M.; Alkaabi, M. S. N.; Almaamari, K.; Alseiari, K.; Alshamsi, N.; Alzaabi, O.; Al Tamimi, S.; Alameri, M. S.; Masuadi, E.; Rahma, A. T.	2025	https://dx.doi.org/10.1186/s40246-025-00766-1
357	Perceived Benefits, Risks, and Utility of Newborn Genomic Sequencing in the BabySeq Project	Pereira, Stacey; Robinson, Jill Oliver; Gutierrez, Amanda M; Petersen, Devan K; Hsu, Rebecca L; Lee, Caroline H; Schwartz, Talia S; Holm, Ingrid A; Beggs, Alan H; Green, Robert C; McGuire, Amy L	2019	https://dx.doi.org/10.1542/peds.2018-1099C
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360	Perceptions of genomic newborn screening: a cross-sectional survey conducted with UK medical students	Seed, Lydia; Scott, Anna; Pichini, Amanda; Peter, Michelle; Tadros, Shereen; Sortica da Costa, Cristine; Hill, Melissa	2024	https://dx.doi.org/10.1136/bmjopen-2024-089108
361	Personal utility of genomic sequencing for infants with congenital deafness	Tutty, Erin; Amor, David J; Jarmolowicz, Anna; Paton, Kate; Downie, Lilian	2021	https://dx.doi.org/10.1002/ajmg.a.62411
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363	Perspectives of Rare Disease Experts on Newborn Genome Sequencing	Gold, Nina B; Adelson, Sophia M; Shah, Nidhi; Williams, Shardae; Bick, Sarah L; Zoltick, Emilie S; Gold, Jessica I; Strong, Alanna; Ganetzky, Rebecca; Roberts, Amy E; Walker, Melissa; Holtz, Alexander M; Sankaran, Vijay G; Delmonte,	2023	https://dx.doi.org/10.1001/jamanetworkopen.2023.12231

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365	Pilot project: Neonatal screening using genomic methods	Valovicov√°, K.; Val√°skov√°, I.	2024	
366	PirePred: An Accurate Online Consensus Tool to Interpret Newborn Screening-Related Genetic Variants in Structural Context	Galano-Frutos, Juan Jose; Garcia-Cebollada, Helena; Lopez, Alfonso; Rosell, Mireia; de la Cruz, Xavier; Fernandez-Recio, Juan; Sancho, Javier	2022	https://dx.doi.org/10.1016/j.jmoldx.2022.01.005
367	Point of Care Exome Sequencing Reveals Allelic and Phenotypic Heterogeneity Underlying Mendelian disease in Qatar	Fakhro, Khalid A; Robay, Amal; Rodrigues-Flores, Juan L; Mezey, Jason G; Al-Shakaki, Alya A; Chidiac, Omar; Stadler, Dora; Malek, Joel A; Imam, Abu Bakr; Sheikh, Arwa; Azzam, Asmaa; Janahi, Ibrahim; Khanjar, Izzat; Osman, Kamal; Ziki, Maen Abu; Mahmah, Mohamed Adnan; Selim, Mohamed; Numeiri, Nuha; Ali, Rehab; Lakhani, Shenela; Butt, Fizza; Omran, Tawfeg Ben; Crystal, Ronald G	2019	https://dx.doi.org/10.1093/hmg/ddz134
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373	Potential Psychosocial Risks of Sequencing Newborns	Frankel, Leslie Ann; Pereira, Stacey; McGuire, Amy L	2016	https://dx.doi.org/10.1542/peds.2015-3731F
374	Potential Uses and Inherent Challenges of Using Genome-Scale Sequencing to Augment Current Newborn Screening	Berg, Jonathan S; Powell, Cynthia M	2015	https://dx.doi.org/10.1101/cshperspect.a023150
375	Predicting clinical phenotypes of metachromatic leukodystrophy based on the arylsulfatase A activity and the ARSA genotype? ‚Äì Chances and challenges	Santhanakumaran, V.; Groeschel, S.; Harzer, K.; Kehrer, C.; Elg√ºn, S.; Beck-W√∂dl, S.; Hengel, H.; Sch√∂ls, L.; Haack, T. B.; Kr√§geloh-Mann, I.; Laugwitz, L.	2022	10.1016/j.ymgme.2022.09.009
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377	Preferences of parents from diverse backgrounds on genomic screening of apparently healthy newborns	Gold, Nina B; Omorodion, Jacklyn O; Del Rosario, Maya C; Rivera-Cruz, Greysha; Hsu, Celeste Y; Ziniel, Sonja I; Holm, Ingrid A	2025	https://dx.doi.org/10.1002/jgc4.1994
378	Pregnant Latinas‚Äô views of adopting exome sequencing into newborn screening: A qualitative study	Wang, H.; Page, R.; Lopez, D.; Arkatkar, S.; Young, C.; Martinez, D.; Robbins-Furman, P.; Montalvo-Liendo, N.; Chen, L.-S.	2022	10.1016/j.gim.2022.04.012

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381	Preparing for Genomic Newborn Screening in Germany: lesson learned from comparative analysis of existing initiatives	Betzler, I.; Hempel, M.; K√∂lker, S.; Winkler, E.; Garbade, S.; Schaaf, C.; Brennenstuhl, H.	2024	
382	Prequalification of genome-based newborn screening for severe childhood genetic diseases through federated training based on purifying hyperselection	Kingsmore, Stephen F; Wright, Meredith; Smith, Laurie D; Liang, Yupu; Mowrey, William R; Protopsaltis, Liana; Bainbridge, Matthew; Baker, Mei; Batalov, Sergey; Blincow, Eric; Cao, Bryant; Caylor, Sara; Chambers, Christina; Ellsworth, Katarzyna; Feigenbaum, Annette; Frise, Erwin; Guidugli, Lucia; Hall, Kevin P; Hansen, Christian; Kiel, Mark; Van Der Kraan, Lucita; Krilow, Chad; Kwon, Hugh; Madhavrao, Lakshminarasimha; Lefebvre, Sebastien; Leipzig, Jeremy; Mardach, Rebecca; Moore, Barry; Oh, Danny; Olsen, Lauren; Ontiveros, Eric; Owen, Mallory J; Reimers, Rebecca; Scharer, Gunter; Schleit, Jennifer; Shelnutt, Seth; Mehtalia, Shyamal S; Oriol, Albert; Sanford, Erica; Schwartz, Steve; Wigby, Kristen; Willis, Mary J; Yandell, Mark; Kunard, Chris M; Defay, Thomas	2024	https://dx.doi.org/10.1016/j.ajhg.2024.10.021
383	Presymptomatic diagnosis: a first step toward genetic health care	Caskey, C T	1993	https://dx.doi.org/10.1126/science.8211129
384	Preventive and predictive genetics: A perspective	Grech, G.; Scerri, C.; Scerri, J.; Cesuroglu, T.	2015	10.1007/978-3-319-15344-5_2

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386	Principles of Genomic Newborn Screening Programs: A Systematic Review	Downie, Lilian; Halliday, Jane; Lewis, Sharon; Amor, David J.	2021	10.1001/ jamanet workope n.2021.1 4336
388	Professional perspectives towards implementing artificial intelligence in next generation sequencing‚Äìbased newborn screening: A Q methodology study	Soriano Longar√≥n, S.; Johansson, L.; Christiaans, I.; Birnie, E.; van Gijn, M.; Ranchor, A.V.; Plantinga, M.	2025	10.1016/ j.hlpt.20 25.1009 82
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391	Prospective cohort study of genomic newborn screening: BabyScreen+ pilot study protocol	Lunke, Sebastian; Bouffler, Sophie E; Downie, Lilian; Caruana, Jade; Amor, David J; Archibald, Alison; Bombard, Yvonne; Christodoulou, John; Clausen, Marc; De Fazio, Paul; Greaves, Ronda F; Hollizeck, Sebastian; Kanga-Parabia, Anaita; Lang, Nitzan; Lynch, Fiona; Peters, Riccarda; Sadedin, Simon; Tutty, Erin; Eggers, Stefanie; Lee, Crystle; Wall, Meaghan; Yeung, Alison; Gaff, Clara; Gyngell, Christopher; Vears, Danya F; Best, Stephanie; Goranitis, Ilias; Stark, Zornitza	2024	https://d x.doi.org /10.1136 /bmjope n-2023- 081426
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	Challenges of Introducing Whole Genome Sequencing into Routine Newborn Screening: Lessons Learned from Existing Newborn Screening			x.doi.org/10.1080/20502877.2022.2124582
394	Psychosocial Effect of Newborn Genomic Sequencing on Families in the BabySeq Project: A Randomized Clinical Trial	Pereira, Stacey; Smith, Hadley Stevens; Frankel, Leslie A; Christensen, Kurt D; Islam, Rubaiya; Robinson, Jill Oliver; Genetti, Casie A; Blout Zawatsky, Carrie L; Zettler, Bethany; Parad, Richard B; Waisbren, Susan E; Beggs, Alan H; Green, Robert C; Holm, Ingrid A; McGuire, Amy L	2021	https://dx.doi.org/10.1001/jamapediatrics.2021.2829
395	Psychosocial Factors Influencing Parental Interest in Genomic Sequencing of Newborns	Waisbren, S. E.; Weipert, C. M.; Walsh, R. C.; Petty, C. R.; Green, R. C.	2016	https://dx.doi.org/10.1542/peds.2015-3731G
396	Public and Healthcare Provider Receptivity toward the Retention of Dried Blood Spot Cards and Their Usage for Extended Genetic Testing in Hong Kong	Belaramani, K.M.; Fung, C.W.; Kwok, A.M.K.; Lee, S.Y.R.; Yau, E.K.C.; Luk, H.M.; Mak, C.M.; Yeung, M.C.W.; Ngan, O.M.Y.	2023	10.3390/ijns9030045
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401	Public health policy forum. From genes to public health: the applications of genetic technology in disease prevention	Khoury MJ; Genetics Working Group	1996	10.2105/AJPH.86.12.1717
402	Public perspectives on genomic newborn screening: a qualitative approach	Vears, D.; Lynch, F.; Gyngell, C.; Best, S.; Goranitis, I.; Archibald, A.; Gaff, C.; Downie, L.; Lunke, S.; Stark, Z.	2024	
403	Public preferences for the value and implementation of genomic newborn screening:	Peters, Riccarda; Best, Stephanie; Lynch, Fiona; Vears, Danya F; Downie, Lilian; Archibald, Alison D;	2025	https://dx.doi.org/10.1016

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404	Public views on participating in newborn screening using genome sequencing	Bombard, Yvonne; Miller, Fiona A; Hayeems, Robin Z; Barg, Carolyn; Cressman, Celine; Carroll, June C; Wilson, Brenda J; Little, Julian; Avard, Denise; Painter-Main, Michael; Allanson, Judith; Giguere, Yves; Chakraborty, Pranesh	2014	https://dx.doi.org/10.1038/ejhg.2014.22
405	Rapid Detection and Treatment of Inborn Errors of Metabolism in the Newborn Period: Beginning of a New Trend	Bijarnia-Mahay, S.; Mishra, R.	2021	10.1007/s12098-021-03739-z
406	Rare diseases research and policy in Australia: On the journey to equitable care	Bhattacharya, K.; Millis, N.; Jaffe, A.; Zurynski, Y.	2021	10.1111/jpc.15507
407	Rare diseases' genetic newborn screening as the gateway to future genomic medicine: the Screen4Care EU-IMI project	Ferlini, A.; Gross, E. S.; Garnier, N.	2023	https://dx.doi.org/10.1186/s13023-023-02916-x
408	Recent updates and challenges on the regulation of precision medicine: The United States in perspective	Chang, LC; Colonna, TE	2018	10.1016/j.yrtph.2018.04.021
409	Recommendations for patient screening in ultra-rare inherited metabolic diseases: What have we learned from Niemann-Pick disease type C?	Sobrido, M. J.; Bauer, P.; De Koning, T.; Klopstock, T.; Nadjar, Y.; Patterson, M. C.; Synofzik, M.; Hendriksz, C. J.	2019	10.1186/s13023-018-0985-1
410	Reconciling newborn screening and a novel splice variant in BTD associated with partial biotinidase deficiency: a BabySeq Project case report	Murry, Jaclyn B; Machini, Kalotina; Ceyhan-Birsoy, Ozge; Kritzer, Amy; Krier, Joel B; Lebo, Matthew S; Fayer, Shawn; Genetti, Casie A; VanNoy, Grace E; Yu, Timothy W; Agrawal, Pankaj B; Parad, Richard B; Holm, Ingrid A; McGuire, Amy L; Green, Robert C; Beggs, Alan H; Rehm, Heidi L	2018	https://dx.doi.org/10.1101/mcs.a002873
411	Return of Results from Research Using Newborn Screening Dried Blood Samples	Lewis, Michelle Huckaby; Goldenberg, Aaron J.	2015	10.1111/jlme.12299
412	Returning a Genomic Result for an Adult-Onset Condition	Holm, Ingrid A; McGuire, Amy; Pereira, Stacey; Rehm, Heidi; Green,	2019	https://dx.doi.org

	to the Parents of a Newborn: Insights From the BabySeq Project	Robert C; Beggs, Alan H		/10.1542/peds.2018-1099H
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419	SEQuencing a baby for an optimal outcome: a genomic future for newborn screening	Giersch, A.; Shen, J.; Booth, K.; Chekaluk, Y.; Cohen, M.; Gregory, K.; Hochschild, J.; Johnson, L.; Kenna, M.; Krier, J.; Lorenzo, A.; McGrath, L.;	2021	

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	data for sequential interrogation across the lifespan	Vears, Danya; Bowman-Smart, Hilary; Savulescu, Julian; Christodoulou, John		x.doi.org/10.1136/jme-2022-108471
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445	The cost-effectiveness of	Landfeldt, E.	2023	10.1111/

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471	The Progress and Future of US Newborn Screening	Watson, Michael S.; Lloyd-Puryear, Michele A.; Howell, R. Rodney	2022	10.3390/ijns8030041
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479	Towards an evidence-based neonatal genomic screening panel	Zimani, AN; Bergant, G; Podbregar, P; Harej, N; Kovanda, A; Maver, A; Peterlin, B	2024	
480	Towards Comprehensive Newborn Hearing and Genetic Screening in Russia: Perspectives of Implementation	Chibisova, Svetlana; Markova, Tatiana; Tsigankova, Evgenia; Tavartkiladze, George	2024	10.3390/ohbm5010006
481	Towards genomic-Newborn Screening: Technical feasibility of Exome Sequencing starting from dried blood spots	Mauri, Alessia; Berardo, Clarissa; Biganzoli, Davide; Meta, Andrea; Benedetti, Sara; Rey, Federica; Messa, Letizia; Zuccotti, Gian Vincenzo; Carelli, Stephana; Alberti, Luisella; Cereda, Cristina	2024	https://dx.doi.org/10.1016/j.ymgmr.2024.101074
482	Towards Next-Generation Sequencing (NGS)-Based Newborn Screening: A Technical Study to Prepare for the Challenges Ahead	Veldman, A.; Kiewiet, M.B.G.; Heiner-Fokkema, M.R.; Nelen, M.R.; Sinke, R.J.; Sikkema-Raddatz, B.; Voorhoeve, E.; Westra, D.; Doll√©, M.E.T.; Schielen, P.C.J.I.; van Spronsen, F.J.	2022	10.3390/ijns8010017
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	hearing loss: a scoping review of gene panels, exome and genome sequencing	Gallego-Martinez, Alvaro; Perez-Carpena, Patricia		x.doi.org/10.1080/14992027.2024.2435564
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486	UK explores whole-genome sequencing for newborn babies	Burki, Talha	2022	https://dx.doi.org/10.1016/S0140-6736(22)01378-2
487	Understanding and issues related to next-generation sequencing among educated laypersons in India	Shambhavi, Arya; Moirangthem, Amita; Mishra, Prabhaker; Phadke, Shubha R	2025	https://dx.doi.org/10.1002/jgc4.2008
488	Unequal global implementation of genomic newborn screening	Abou Tayoun, Ahmad N	2023	https://dx.doi.org/10.1038/s41576-023-00654-1
489	Universal genomic newborn screening for early, treatable, and severe conditions-including 33 genes of NMD: Baby Detect	Dangouloff, T.; Hovhannesyan, K.; Piazzon, F.; Mashhadizadeh, D.; Helou, L.; Palmeira, L.; Boemer, F.; Servais, L.	2023	10.1016/j.nmd.2023.07.259
490	Universal newborn genetic screening for pediatric cancer predisposition syndromes: model-based insights	Yeh, J.M.; Stout, N.K.; Chaudhry, A.; Christensen, K.D.; Gooch, M.; McMahon, P.M.; O,ÄôBrien, G.; Rehman, N.; Blout Zawatsky, C.L.; Green, R.C.; Lu, C.Y.; Rehm, H.L.; Williams, M.S.; Diller, L.; Wu, A.C.	2021	10.1038/s41436-021-01124-x
491	Universal newborn screening using genome sequencing: early experience from the GUARDIAN study	Ziegler, Alban; Chung, Wendy K	17-7	https://dx.doi.org/10.1038/s41390-024-03647-w
492	Universal screening for inherited metabolic diseases in the neonate (and the	Scala, Iris; Parenti, Giancarlo; Andria, Generoso	2012	https://dx.doi.org/10.3109

	fetus)			/14767058.2012.716983
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494	Use of molecular genetic analyses in danish routine newborn screening	Lund, A.M.; Wibrand, F.; Skogstrand, K.; B√¶kvad-Hansen, M.; Gregersen, N.; Andresen, B.S.; Hougaard, D.M.; Dun√∏, M.; Olsen, R.K.J.	2021	10.3390/IJNS7030050
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496	Utility before business	Teutsch, S. M.; Fielding, J. E.; Khoury, M. J.; Evans, J. P.	2014	10.1038/gim.2014.71
497	Utility of NIST Whole-Genome Reference Materials for the Technical Validation of a Multigene Next-Generation Sequencing Test	Shum, Bennett O V; Henner, Ilya; Belluoccio, Daniele; Hinchcliffe, Marcus J	2017	https://dx.doi.org/10.1016/j.jmoldx.2017.04.004
498	Utility of Whole Genome Sequencing for Population Screening of Deafness-Related Genetic Variants and Cytomegalovirus Infection in Newborns	Xiang, Jiale; Zhang, Hongfu; Sun, Xiangzhong; Zhang, Junqing; Xu, Zhenpeng; Sun, Jun; Peng, Zhiyu	2022	https://dx.doi.org/10.3389/fgene.2022.883617
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500	Utilization of archived neonatal dried blood spots for genome-wide genotyping	Sok, Pagna; Lupo, Philip J; Richard, Melissa A; Rabin, Karen R; Ehli, Erik A; Kallsen, Noah A; Davies, Gareth E; Scheurer, Michael E; Brown, Austin L	2020	https://dx.doi.org/10.1371/journal.pone.0229352

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504	Variants of uncertain significance in newborn screening disorders: implications for large-scale genomic sequencing	Narravula, Alekhya; Garber, Kathryn B; Askree, S Hussain; Hegde, Madhuri; Hall, Patricia L	2017	https://dx.doi.org/10.1038/gim.2016.67
505	Views of children and young adults about Whole Genome Sequencing in newborn screening: a qualitative study	Parfett, Molly; Johnson, Faye; Bennett, Rebecca; Ulph, Fiona	2024	https://dx.doi.org/10.1038/s41431-024-01614-x
506	We screen newborns, don't we?: realizing the promise of public health genomics	Evans, James P; Berg, Jonathan S; Olshan, Andrew F; Magnuson, Terry; Rimer, Barbara K	2013	https://dx.doi.org/10.1038/gim.2013.11
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