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Policy Analysis

Bioethical Implications of Whole-Genome Sequencing in Newborn Screening Programs

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ABSTRACT

Whole-genome and whole-exome sequencing are increasingly proposed as extensions, or eventual replacements, for biochemical newborn screening, but the shift raises ethical questions that the sixty-year-old implied-consent framework for newborn screening was not designed to answer.

This review surveys the recent pilot literature -- including the BabySeq Project, the Early Check program, NICU-focused rapid genomic sequencing trials, and Genomics England's Generation Study -- and the bioethical debate these programs have generated.

It examines four unresolved fault lines: how parental proxy consent should function when the person sequenced cannot yet decide for themselves what they want to know; what a program owes families when it returns secondary findings unrelated to the screening indication; whether genomic newborn screening risks concentrating its benefits in already well-resourced health systems; and who retains interpretive authority over a genome retained long after the screening episode that generated it.

We find that no program reviewed here has resolved all four questions simultaneously, and that jurisdictions are currently working out genuinely different, defensible configurations rather than converging on one correct model.

We conclude that treating genomic newborn screening as a simple extension of biochemical screening understates how substantially its underlying ethical structure has changed.

Keywords: newborn screening; whole-genome sequencing; informed consent; secondary findings; genomic medicine ethics

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INTRODUCTION

Newborn screening has operated on a stable ethical settlement for more than sixty years: a heel-prick blood

spot, tested for a bounded and expanding list of conditions for which early treatment changes outcomes, offered to virtually every infant born in a given jurisdiction with parental consent treated as implied rather than actively solicited. Whole-genome and whole-exome sequencing unsettles that arrangement in ways that are not yet fully worked out. A genome does not test for a fixed panel of conditions; it is, in principle, a lifetime's worth of health information generated in the first days of life, only a fraction of which bears on anything actionable in infancy [1]. Several pilot and research programs have now moved this question from theoretical to operational: the BabySeq Project in the United States, the Early Check program in North Carolina, a NICU-focused rapid sequencing pilot led by Kingsmore and colleagues, and Genomics England's Generation Study, which aims to sequence the genomes of up to 100,000 newborns as both a screening and a research exercise [2,3,4,5].

The bioethical literature that has grown up around these programs is not really arguing about whether genomic newborn screening is coming — most participants in the debate now treat that as settled — but about which of its features are ethically load-bearing and which are merely operational choices that could be made differently. This review takes up four such fault lines: how consent should work when the person whose genome is sequenced cannot consent and may not benefit for decades; what a screening program owes a family when it finds something it was not looking for; whether genomic newborn screening is likely to narrow or widen existing disparities in access to genetic medicine; and how data generated at birth should be governed once a research pilot becomes durable clinical infrastructure. Table 1 sets these programs and their design choices against each other, and Figure 1 sketches, schematically, how the three broad screening modalities in current use trade off scope, consent burden, and secondary-finding risk against one another.

FROM BIOCHEMICAL PANELS TO GENOMIC SCREENING

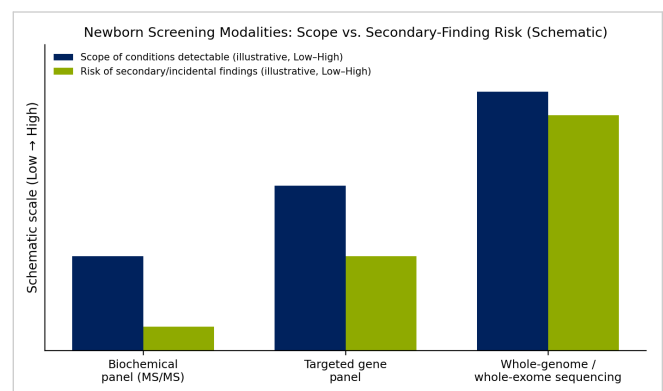
Classical newborn screening tests a dried blood spot for metabolite or enzyme markers of a defined set of conditions — phenylketonuria, congenital hypothyroidism, and, as tandem mass spectrometry became standard, several dozen additional metabolic and endocrine disorders. The ethical case for near-universal, minimally-consented screening rested on a specific conjunction: the conditions screened for were serious, the window for intervention was narrow, and a positive result led fairly directly to a confirmatory test and a treatment protocol. Botkin and Rothwell, reviewing the shift toward sequencing-based approaches, observed that genomic technology breaks this conjunction apart, because a genome sequence can flag genetic variants of uncertain significance,

carrier status, adult-onset conditions, and findings unrelated to the reason for testing, none of which map onto the narrow window-for-intervention logic that justified the original public health mandate [6]. Woerner and colleagues, surveying the state of genomic newborn screening research more broadly, argue that whole-genome and whole-exome approaches genuinely expand the number of treatable conditions that can be caught before symptom onset, but that this benefit arrives bundled with categories of information — carrier status, non-actionable risk variants, and variants of uncertain significance — that biochemical screening never had to contend with [7].

Table 1. Newborn screening modalities compared by scope, consent model, and secondary-finding risk.

Modality	Scope of conditions detected	Typical consent model	Secondary/incidental finding risk
Biochemical panel (tandem mass spectrometry)	Dozens of well-characterized metabolic and endocrine disorders	Implied consent; opt-out in most jurisdictions	Minimal -- assay only reports the targeted analytes
Targeted gene panel	Hundreds of specific, pre-selected disease genes	Explicit consent, usually condition-focused	Low-to-moderate -- limited to genes on the panel
Whole-genome / whole-exome sequencing	Broad, effectively open-ended, including adult-onset and carrier findings	Explicit, often tiered consent specifying which result categories to return	Substantial -- variants of uncertain significance, carrier status, and unrelated findings are routinely generated

Figure 1. Schematic comparison of scope of detectable conditions and risk of secondary/incidental findings across three newborn screening modalities (illustrative, not derived from a single empirical study).



Pilot studies in the NICU setting illustrate the clinical upside most clearly. Kingsmore and colleagues report that genome-based screening for severe childhood genetic diseases achieved high positive predictive value and sensitivity in acutely ill newborns, a population where rapid genomic diagnosis can shorten a diagnostic odyssey that biochemical screening was never designed to address [4]. A pilot study of exome-based screening of several thousand

newborns in Russia similarly reported that sequencing-based approaches can be feasibly deployed at scale outside the small number of well-resourced academic centers where most published pilots have run [8]. Carli and colleagues make a related point about population-level implementation, arguing that a genomic sequencing approach to newborn mass screening opens opportunities that biochemical panels structurally cannot, particularly for ultra-rare conditions too numerous to screen for individually by metabolite testing [9]. None of this literature disputes that genomic screening can catch more; the disagreement is over what catching more costs in consent burden, false reassurance, and downstream findings nobody asked for.

Table 1 lays out how three screening modalities compare on the dimensions that recur across this literature — scope of conditions detected, consent model, and risk of secondary findings unrelated to the screening indication.

CONSENT FOR A PERSON WHO CANNOT YET CONSENT

Parental proxy consent for a minor is uncontroversial when the decision at hand is reversible, low-risk, and clearly in the child's near-term interest. Genomic sequencing complicates all three conditions at once. Joseph and colleagues, surveying parental attitudes toward expanded newborn screening using whole-genome sequencing, found that parents were broadly receptive to the idea in principle but drew sharp lines around what kinds of results they wanted returned, with substantially less enthusiasm for adult-onset or uncertain findings than for childhood-actionable ones [10]. This gap between openness to the technology and caution about its outputs recurs throughout the empirical literature and complicates any assumption that a single consent conversation at birth can capture what a family actually wants.

Faucett and colleagues, writing for a primary-care audience, note that the practical mechanics of consent and result disclosure for genetic and genomic testing already strain clinical workflows built around brief well-child visits, and that genomic newborn screening compounds this by asking a sleep-deprived family, often within days of delivery, to make choices about categories of genetic information most have never previously had to think about [11]. Ulph and Bennett go further, arguing that the psychological and ethical challenges of embedding whole-genome sequencing in routine screening are not fully answered by improving the consent conversation, because some of the harms in question — anxiety about a variant of uncertain significance, altered parental perception of an ostensibly healthy infant — are downstream of receiving results at all, not downstream of how well the results were explained beforehand [12]. Cao and

colleagues, interviewing Australian healthcare professionals actually delivering pilot genomic newborn screening, found that clinicians themselves are frequently unsure how to communicate the distinction between screening-positive findings requiring urgent follow-up and the much larger category of findings that are real but not immediately actionable, which suggests the consent problem here is not confined to what parents understand but extends to what the clinical workforce is prepared to explain [13].

A further complication specific to genomic information is that the person whose genome is being interpreted cannot, in any meaningful sense, ratify or revoke that consent for years or decades. Findley and colleagues, reviewing challenges in the clinical understanding of genetic testing in pediatric disease, note that a newborn's genome will still be legible to interpretation long after the infant becomes an adult capable of deciding for themselves whether they want to know what it says — a temporal mismatch that parental proxy consent, structured around the infant's immediate medical interests, was never designed to resolve [14]. Iskrov and colleagues' survey of pediatricians' and geneticists' attitudes toward whole-genome newborn screening found that professional enthusiasm for the technology did not translate into confidence about how informed consent should actually be structured, with respondents divided over whether opt-in, opt-out, or tiered consent models were most appropriate [15].

SECONDARY FINDINGS AND THE LIMITS OF A DUTY TO DISCLOSE

Every genomic newborn screening pilot published so far has had to decide, in advance, what it will do with findings that fall outside the screening indication — carrier status for recessive conditions, pharmacogenomic variants, and pathogenic variants in adult-onset disease genes such as those associated with hereditary cancer syndromes. Ceyhan-Birsoy and colleagues, reporting results from the BabySeq Project, found that a meaningful proportion of both healthy and ill newborns in their cohort carried actionable findings unrelated to the reason for sequencing, and that interpreting and returning these findings required substantially more clinical and genetic-counseling infrastructure than the screening indication alone would have justified [2]. Kendir-Demirkol and Yeter, reporting on secondary findings in pediatric genomic testing more broadly, argue that the clinical significance of a secondary finding is frequently harder to establish in a child than the equivalent finding would be in an adult, because penetrance and expressivity data for many variants are drawn from adult cohorts and do not transfer cleanly to a pediatric population screened before symptom onset [16].

The Early Check program in North Carolina has

generated some of the most detailed evidence on how families actually experience secondary and negative findings once returned. Cope and colleagues, evaluating a web-based portal built to return normal individual research results, found that even a "nothing found" result required careful design to avoid either alarming parents unnecessarily or implying a false sense of complete reassurance about the child's genetic health [17]. A separate mixed-methods evaluation from the same program found that parents receiving normal genomic newborn screening results generally experienced relief, but a subset reported lingering uncertainty about exactly what a "normal" result had and had not ruled out, suggesting that the return-of-results problem in genomic screening is not confined to positive or ambiguous findings [18]. Cope and colleagues' broader report on the feasibility and clinical utility of expanded genomic newborn screening in Early Check likewise found that the program could scale sequencing and interpretation successfully, but that the operational cost of managing secondary findings responsibly, rather than the sequencing itself, was the more binding constraint on how far such a program could expand [3].

Chien and Hwu, reviewing what they term the modern face of newborn screening, situate this tension within the field's longer history, arguing that newborn screening programs have always had to draw a line between conditions serious and actionable enough to justify near-universal testing and conditions better left to voluntary, counseled genetic testing later in life — and that genomic sequencing does not eliminate this line so much as make drawing it explicitly, rather than implicitly through the choice of biochemical assay, unavoidable [19]. Duz and Chung, surveying the design, implementation, and outcomes of genomic newborn screening studies internationally, reach a similar conclusion: programs that have tried to specify their secondary-findings policy in detail before enrollment report fewer downstream disputes with families than programs that left the question to be resolved case by case as findings arose [20].

EQUITY, ACCESS, AND THE RISK OF A TWO-TIER SYSTEM

A screening technology that requires substantial genetic-counseling infrastructure, laboratory capacity, and sustained follow-up is not automatically a technology that reaches the same population a biochemical heel-prick test reaches. Ross and Ormond, reviewing the promise and perils of newborn sequencing, argue that the central policy risk of the current moment is not that genomic newborn screening will fail on clinical grounds, but that it will succeed unevenly — available first, and perhaps only, in health systems and countries with the genomic medicine infrastructure to support interpretation and follow-up, while jurisdictions that already have less developed newborn screening programs are left further behind

rather than allowed to leapfrog toward the newer technology [21]. This concern echoes a long-standing pattern in genomic medicine more broadly, where much of the reference data used to interpret variants of uncertain significance has been generated predominantly in populations of European ancestry, meaning families from underrepresented populations may face a higher rate of inconclusive results even where equitable access to the sequencing itself has been achieved.

Genomics England's Generation Study, discussed by Etheredge and colleagues, has tried to build equity considerations into its ethics governance from the outset, embedding an ethics advisory function directly into program design rather than treating equity as an issue to be addressed once the pilot phase is complete [5]. Whether that approach generalizes to programs without comparable public funding and centralized health-system infrastructure is an open question the broader literature has not yet answered. Woerner and colleagues note that the population-health case for genomic newborn screening — catching more treatable conditions than biochemical panels can — is strongest precisely in settings with the laboratory and counseling capacity to act on what sequencing finds, which risks a self-reinforcing pattern in which the benefits of genomic screening accrue fastest to systems that already have the most genomic-medicine infrastructure [7].

DATA GOVERNANCE AND THE GENOME AS DURABLE INFRASTRUCTURE

A newborn's genome, once sequenced for a screening pilot framed as research, does not stop existing when the pilot ends. Findley and colleagues note that data generated in infancy may be retained, reanalyzed as variant interpretation improves, and potentially reused for purposes the original consent process never contemplated, which raises the same durability problem that has occupied the broader genomic-biobanking literature, but with the added complication that the person whose data is being retained had no say in the matter at all [14]. Faucett and colleagues observe that primary care clinicians, who are often the ones fielding a family's questions years later about what a newborn genomic screen actually stored and who can access it, are rarely equipped with clear institutional answers, which leaves an accountability gap between the research infrastructure that generated the data and the clinical relationships expected to explain it [11].

The Generation Study's approach — sequencing newborns as part of an explicitly dual screening-and-research program — makes this tension unusually visible rather than resolving it. Etheredge and colleagues describe deliberate efforts to separate the screening return-of-results pathway from the research use of retained genomic data, with

distinct consent and governance tracks for each, precisely because conflating the two risks obscuring from families that a screening test has quietly become a long-term research relationship [5]. Knoppers and colleagues, writing when whole-genome newborn screening was still a largely prospective proposal, anticipated much of this governance debate, arguing that any program combining screening with data retention needs to specify at the outset who owns interpretive authority over a genome years after the fact, since new pathogenic reclassifications will inevitably occur and someone must decide whether, and how, families are recontacted [1]. Recent program evaluations suggest this remains unsettled in practice rather than merely in theory: Cope and colleagues note that even a program built around returning individual results has had to develop its recontact and reinterpretation policy iteratively, rather than having resolved it definitively at launch [3].

CONCLUSION

The bioethical literature on genomic newborn screening has moved past the question of whether the technology belongs in newborn screening programs at all and toward the harder work of specifying its terms: what parents can meaningfully consent to on behalf of an infant who cannot yet speak for themselves, what a program owes a family when it finds something unrelated to what it was looking for, how the benefits of a technology with a real infrastructure cost can be distributed rather than concentrated, and who retains interpretive authority over a genome that will still be legible decades after the screening test that generated it. None of the pilot programs reviewed here — BabySeq, Early Check, the NICU-focused rapid sequencing efforts, or Genomics England's Generation Study — has resolved all four questions simultaneously, and the honest conclusion the literature currently supports is that they are being worked out differently in different jurisdictions, with genuine trade-offs rather than a single correct configuration. What does look settled is that treating genomic newborn screening as a simple extension of biochemical newborn screening, governed by the same implied-consent logic that has served the field for sixty years, understates how much the underlying ethical structure has actually changed.

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Conflict of Interest

The authors declare no conflicts of interest relevant to

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Author Contributions

Zsafia Georgiou conceived the review, coordinated the literature search, and drafted the initial manuscript. Lieve Papadopoulos led the analysis of consent and return-of-results literature and critically revised the manuscript. Laura Kowalczyk contributed the sections on equity and data governance and provided final approval of the submitted version. All authors read and approved the final manuscript.

Ethics Statement

As a literature review synthesizing previously published, publicly available research and policy analysis, this article did not involve new data collection from human participants and did not require institutional ethics committee approval.

Data Availability

No new data were generated or analyzed for this review. All sources discussed are cited in the reference list and are publicly available through their respective publishers.

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