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(REVIEW ARTICLE)

FROM CARRIER SCREENING TO NEONATAL DIAGNOSIS: AN INTEGRATED GENOMIC APPROACH TO PREVENTING INHERITED DISORDERS

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ABSTRACT

Background: Inherited disorders still account for a significant proportion of infant illness and mortality globally and the ability to detect carrier status prior to conception and diagnose affected infants after birth has grown rapidly since the broad use of next generation sequencing (NGS). Carrier screening and newborn screening have been conducted separately, under separate professional accreditation bodies and funding mechanisms, even though they are both dealing with the same issue, albeit on opposite sides of the reproductive spectrum.

Aim: This review explores the potential for a new integrated genomic pathway, from preconception or prenatal carrier screening to whole genome sequencing based neonatal diagnosis, to enhance early detection of inherited disorders and considers the evidence relevant to this integration.

Method: A narrative review was conducted, which included publications published from January 2015 to December 2025 in English language on PubMed, Scopus, Google Scholar and the websites of the relevant professional organizations. The search terms used were a combination of carrier screening, non-invasive prenatal testing, newborn genomic screening, whole genome sequencing and cost-effectiveness. Studies, guidelines and programme reports that were directly relevant were included and synthesised according to themes.

Findings: Literature demonstrates consistent diagnostic yield from genomic newborn screening pilots, including BabySeq, GUARDIAN, the Belgian maternity ward pilot and the Generation Study, with guidance now available to support panethnic carrier screening, and cost, counselling skills capacity, variant interpretation and inequities in access remain barriers to implementation outside of high income contexts.

Conclusion: An integrated pathway is technically possible and clinically attractive, but is not likely to happen without a concerted investment in counselling support, evidence sharing and access, not sequencing.

Keywords: Carrier screening; Neonatal genomic screening; Whole genome sequencing; Non-invasive prenatal testing; Inherited disorders; Genetic counselling; Health equity.

1 INTRODUCTION

The total impact of inherited disorders is substantial and represents a significant proportion of all births within each population studied and their overall contribution to infant health-related services utilisation is greater than might be expected from the individual disease alone (Bick et al., 2022; Everett et al., 2025). Until the early twentieth century, there were two rather distinct activities to meet this burden. Carrier screening was on one side and offered to couples before or during pregnancy to inform them whether they were both carriers for one of the recessive conditions and what that meant for their reproductive options (American College of Obstetricians and Gynaecologists, 2017). Newborn screening was borne opposite to this on the public health side, which challenged blood sampling for a select group of treatable metabolic and endocrine disorders after birth, wherein the justifications were grounded in Wilson and Jungner's (1968) original criteria for population screening. While both activities had the same goal, to minimise or mitigate the impact of inherited disease, they did little to communicate in everyday practice.

These things have been drastically changed with the advent of next generation sequencing. While these carrier panels started with limited genes chosen for ethnic and racial groups, they are now more numerous with a panethnic format of a few hundred genes available for sequencing (Gregg et al., 2021). In the past, the same technology made it possible to derivativise the whole-genome or whole-exome sequencing to be used in newborns, either as a research pilot or, increasingly, as a first-tier testing tool in its own right (Ziegler et al., 2025; Boemer et al., 2025). Multiple large studies, including BabySeq in the USA (Holm et al., 2018; Smith et al., 2024), GUARDIAN in NY (Ziegler et al., 2025) and the Generation Study led by Genomics England (Genomics England, 2024), have found that by sequencing genomes, many more actionable disease cases can be identified in newborns than using conventional biochemical screening.

However, what has not been accomplished is a seamless integration of these two systems as one continuum in care. A woman could be screened for a pathogenic variant before becoming pregnant and find that she and her partner also both have a variant, and then several months later find out about a newborn screening testing regime that does not have a formal procedure for accessing her earlier genetic data for an informational way to guide the testing of her child. Similarly, a family with no known risk might have a child who has a serious recessive condition found during the child's initial birth testing and his sequencing may not have included one of the genes involved, which meant that carrier screening, had it been offered to the family, might have identified the child's risk earlier. This "missed connection" is not just an administrative hassle, but that is also an opportunity of earlier diagnosis, better informed reproductive planning, and potentially treatment that can begin before the occurrence of irreversible damage (Stark and Scott, 2023).

The objective of this study is to give a representative description of the integrated genomic approach, from preconception carrier screening to prenatal testing to neonatal diagnosis, and to provide evidence to support such an approach. The discussion is guided by three questions. First, from a literature perspective, what does the current literature say about the use of carrier screening alone versus newborn genomic screening alone for each of their respective indications? Secondly, where do these two pathways currently intersect; practically and/or organisationally, and where are the intersections thickest? Third, what would be the economic, ethical or infrastructural barriers to a truly joined up service, and how might they differ between well-resourced health systems and less well-resourced genomics ones? This study does not present new primary data but collates published data from trials, professional guidance and health economic evaluations and provides an evidence-based account of the current state of integration and what will be needed to push it forward.

2 MATERIAL AND METHODS

This research is in the form of a Narrative Review with described search strategy, not as systematic review because the aim was to gather and interpret the evidence from clinical trials, professional standards and health economic items, and not to answer one very specific question by exhaustive study identification. A systematic review protocol is a better fit for a question with a single measurable outcome than for a question of how two service pathways might be coupled together in real-world studies (Moosapour et al., 2021). A more flexible approach to the narrative style used here enabled information of varying types, such as randomised trial reports, professional practice guidelines, health economic evaluations and programme level updates to be considered together and read against each other, in a way that a harder-to-compress protocol within a single paper of this length would have made more difficult.

Literature was sourced using structured searches on PubMed, Scopus and Google Scholar, with website searches of relevant professional and government organisations including the American College of Medical Genetics and Genomics, the American College of Obstetricians and Gynecologists, the National Society of Genetic Counsellors and Genomics England. Boolean operators were used to merge keywords and carrier screen, expanded carrier screen, non-invasive prenatal testing, newborn screening, genomic newborn screening, whole genome sequencing infant, and cost-effectiveness genomic screening were used. Iterative searches were conducted instead of single search. An initial broad search on each term family was carried out to identify which named programmes, BabySeq, GUARDIAN, the Generation

Study, and similar pilots around the country, had most featured in the recent literature, from which more specific searches using a programme name and diagnostic yield, cost-effectiveness or ethics were conducted to find the most immediately relevant outputs from each. The search was limited to material published in an English language journal between January 2015 and December 2025 in order to include only work produced at a time when next generation sequencing had been enabled to be performed at a price low enough that a population level carrier and newborn screening programme could be piloted at scale with a view to launching, a period that also precludes the earlier and much more restricted phase of prenatal and neonatal genetic testing, which occurred before the advent of panel-based next generation sequencing approaches.

Records were examined and analysed (screened) in two steps. Titles and abstracts were initially screened against a broad term "relevance" against any source which related to either carrier screening or prenatal testing/services or neonatal screening or services, in a manner that carried into the conversation of integration between services. The sources that survived this initial screening were then read entirely and evaluated using a more limited rubric of criteria before they could be winnowed out for the purposes of synthesis. Peer-reviewed primary studies that reported diagnostic yield and/or clinical outcomes or cost data were preferred for programmes that had been named, instead of unnamed programmes, and clinical practice guidelines issued or updated since 2015 were added to the preference. Besides this, systematic reviews that included test accuracy or cost-effectiveness reports were included. These do not include the type of market analyses, opinion pieces that lack evidentiary basis, or the kind of information that may have been misattributed as independent studies because the material comes from an undocumented source (e.g., a webpage or un-named source). These analyses were determined not to be evidence-based, and were therefore not included for the same reason other articles may not be included in a bibliography. The older protocol papers were retained when the content had not been updated later in the year, such as methodological issues in the selection of genes for a panel or the process of consent; however, the most recently published report or the most complete one was preferred if such a full report was available from a large, national programme like Generation Study or GUARDIAN that had yielded multiple outputs over the course of the years.

Information extracted was clustered into the same general categories identified by the main questions asked in this paper: the areas of overlap between carrier genomic screening and neonatal genomic screening; and the financial, ethical and infrastructure constraints around greater integration. These results were then presented in a narrative synthesis instead of a pooled statistical synthesis, as there were differences in the designs of the analyses, the populations and the outcome measures of the studies included in the study, which would not have given much value in a formal meta-analysis anyway. There was no formal assessment of risk of bias as would be performed in a systematic review, but all sources, whether based on an article from a peer-reviewed trial report, a professional guideline, or the public update published by a programme, were assessed as to quality and source, and this determination informed the level of confidence placed in the source informing the discussion. This weighting was applied to each of the accounts, but not quantified and the authors regret this was not a feature of the narrative methodology adopted, and are aware any single claim made in the boxes below should be treated with equal precautions.

3 RESULTS

The results of the studies that were included in this review can be categorized into three areas: carrier screening performance, neonatal genomic screening performance, and areas of overlap of the two pathways.

Carrier screening has come a long way from ethnicity-driven screening for disorders like Tay-Sachs and sickle cell disease. The American College of Medical Genetics and Genomics (ACMGG) recommends a tiered, panethnic approach, with Tier 3 screening, which are conditions with a carrier frequency of 1 in 200 or more in any represented population group, offered to all patients who are pregnant or planning a pregnancy (Gregg et al., 2021). In the context of expanded carrier screening, the National Society of Genetic Counselors made a similarly broad recommendation in its evidence-based guideline to offer expanded carrier screening to "all people who are considering reproduction," not just those with ancestry (Sagaser et al., 2023). This change is partly because there are some couples who are considered carrier couples as a result of screening but are not carriers, due to the fact that screening based on self-reported ethnicity often fails to detect mixed ancestry or poor representation of ethnicity. This has been specifically identified within the professional literature (Gregg et al., 2021). The same guideline acknowledges that providing panethnic screening to all reproductive age patients puts a strain on an under-resourced genetic counselling workforce, and it suggests other approaches to delivering pre-test genetic counselling, such as the use of short educational videos and even illustrated comic style materials, to support pre-test genetic counselling when a face-to-face session with a genetic counsellor is not an option (Sagaser et al., 2023). It does not specify whether these lower intensity formats can provide an appropriate substitution for individual counselling once a result is positive.

In constrast, non-invasive prenatal testing based on cell free fetal (cf) DNA has emerged as a well-established screening tool for common aneuploidies over approximately the same time period.During the same timeframe however, non-

invasive fetal DNA testing has become a well-established screening tool for common aneuploidies. A meta-analysis and systematic review of data from dozens of studies showed that cell free DNA testing had a sensitivity greater than 97% for trisomies 21, 18 and 13 (Taylor-Phillips et al., 2016) and more recent studies have continued to expand the use of cell free DNA to copy number variants, microdeletions and many other applications, with increasingly high analytical performance. Outside of the context of a known familial mutation, what prenatal testing has not done generally, in contrast to other single gene recessive conditions, is test the fetus directly for the specific gene mutation present in the parents.

The early promoters of neonatal genomic screening have been pleasantly surprised by the results. A few years ago, the BabySeq Project identified an unexpected risk of childhood onset disease in nearly 1 in 10 newborns, all of which had not been suggested by clinical or family history (Ceyhan-Birsoy et al., 2019, Holm et al., 2018). A later and larger version of the same project recruited over 500 babies, from a more varied population (Smith et al., 2024). The GUARDIAN study screened the first four thousand babies in New York, and a positive genomic result was returned for 3.7 per cent of them, most of which would not have been detected by traditional biochemical newborn screening (Ziegler et al., 2025). In Belgium, a population based, first tier genomic newborn screening pilot directly integrated into the maternity ward yielded broadly similar results and illustrated the potential for using sequencing as a primary test instead of a confirmatory test (Boemer et al., 2025). The Generation Study initiated by Genomics England is currently sequencing the genomes of one hundred thousand newborns in the United Kingdom for more than two hundred treatable conditions, with early pilot testing showing that whole genome sequencing led to the identification of an entirely new diagnosis for about 1% of the children screened (Genomics England, 2024). Table 1 below collates the diagnostic yield reported by four key programmes included in this review.

Table 1: Diagnostic yield reported by major carrier and neonatal genomic screening programmes

Programme	Country	Sequencing approach	Positive finding rate	Source
BabySeq (pilot phase)	United States	Exome sequencing of well and NICU infants (n = 159)	9.4% childhood-onset disease risk	Ceyhan-Birsoy et al. (2019)
GUARDIAN	United States (New York)	First-tier genome sequencing, first 4,000 newborns	3.7% (120/4,000); ~92% missed by standard NBS	Ziegler et al. (2025)
Generation Study	United Kingdom	First-tier whole genome sequencing, target n = 100,000	Approx. 1 in 200 babies screened	Genomics England (2024)
Maternity-ward pilot	Belgium	Population-based, first-tier genomic screening embedded in maternity care	Broadly comparable to GUARDIAN/BabySeq range	Boemer et al. (2025)

There are two observations to make regarding Table 1. A positive rate of between one and four per cent, as seen in most of the programmes, implies that the benefit of a diagnostic test from genetic screening of newborns is not a product of any single health system. The percentage of positive results that would have been missed with conventional screening (typically > 90 per cent) suggests that the tests are complementary, at least when they are used with the current panel design (Chen et al., 2023).

In practice, there is not a great deal of overlap with carrier and neonatal genomic pathways, and the extent of overlap, if there is any, is limited in principle. Full disclosure of recessive carrier status is part of the results of the BabySeq reporting protocol, and carrier status is disclosed in the same test that is used to screen for disease affecting the infant (Holm et al., 2018). In principle, this mingling of carrier and diagnostic information in a single sequencing run is the most obvious diagnostic/technical connection made in this review. Cost-effectiveness modelling of genome-based newborn screening, however, has traditionally considered the newborn test without any prior carrier test result, a topic that has only recently been explored with the consideration of an adaptive trial comparing genome-based with standard newborn screening, but not yet fully resolved (Reimers et al., 2025). The economic evaluation of screening for the most experienced childhood and adult disease for which newborn screening is practiced, namely severe combined immunodeficiency (SCID), has produced acceptable incremental cost-effectiveness ratios (ICERs) within health systems that use quality adjusted life year (QALY) thresholds ranging from about thirty thousand to fifty four thousand US dollars per quality adjusted life year gained (Bessey et al., 2019), a ratio that other expanded genomic panels have not yet matched with the same level of certainty.

Outside of high-income contexts, access to both pathways is highly skewed. Successful pilot programmes, mostly donor or research-funded, have been implemented in diverse countries, including Chile and Iran, while trained genetic

counsellors remain scarce and databases with locally relevant variants are lacking, as described in a themed collection on genomic testing in low-and-middle-income countries (Girisha and Moosa, 2024). In addition, non-European populations are underrepresented in reference databases used to classify carrier and diagnostic variants, which can lead to a diagnostic variant reported as being of uncertain significance in a patient of a different ancestral background because there is a lack of similar information. (Gregg et al. 2021).

The main barriers to a fully integrated pathway are summarised in Table 2, based on the literature reviewed.

Table 2: Barriers to a fully integrated genomic pathway

Dimension	Description	Illustrative evidence
Economic	Cost-effectiveness established for single treatable conditions but not yet for full genomic panels	Bessey et al. (2019); Reimers et al. (2025)
Workforce	Shortage of genetic counsellors to manage pre- and post-test counselling for expanded panels	Sagaser et al. (2023)
Variant interpretation	Underrepresentation of non-European populations in reference databases raises misclassification risk	Gregg et al. (2021)
Data infrastructure	No routine mechanism links parental carrier results to infant genomic screening	Holm et al. (2018)
Equity of access	Programmes remain concentrated in high-income settings; pilots elsewhere largely donor-funded	Girisha and Moosa (2024)
Ethics and consent	Parental consent for a child who cannot yet decide; some findings carry adult-onset or reproductive implications	Genomics England (2024); Kariyawasam et al. (2024)

4 DISCUSSION

The evidence analysed here leads to three broad conclusions. Although genomic testing enhances detection ability at both ends of the reproductive and neonatal pathway, a formal linkage between carrier and neonatal tests is present in only a few programmes, with progress towards the next steps being hampered more by workforce and data infrastructure issues than the sequencing technology itself.

The demonstration of diagnostic benefit of the genomic newborn screening results is hard to ignore (Friedman, 2024). Continuously higher positive rates than biochemical screening and the fact that the vast majority of positive findings would not have been noted otherwise suggest that newborn screening has the potential to do much more than merely more expensive biochemical screening, but actually expand baby screening programs (Stark and Scott, 2023; Ziegler et al., 2025). Of course, biochemical screening should not be disregarded. There are decades of population-level data supporting the biochemical detection of these conditions, with the biochemical markers currently employed still being more scalable and economical to process at a population level than genome sequencing for the time being (Chen et al., 2023; Bodaghi, Fattahi, and Ramazani, 2023). The better way to interpret what the evidence is saying is that, for the time being at least, genomic and biochemical newborn screening should be used simultaneously, each picking up on something the other is not well at identifying, not by one doing away with the other as sequencing technologies get cheaper.

Where the links from carrier screening to neonatal diagnosis are truly overlapping, it often seems that carrier testing is a facet of study design (Van Steijvoort and Borry, 2025). Technically, a joined up report may look something like the BabySeq report, which reports the newborn's own carrier status in addition to his or her disease risk results, but this model came into being as a research protocol and not one intended to report back to parents' own carrier screening results, speaking to the myriad issues of direct-to-consumer carrier testing, let alone to prospective reproduction future choices this baby might make. One more ambitious integration model would be to have a shared record that reflects a positive parental carrier result for a condition in the neonatal screen, which will then trigger a higher level of screening on the infant, not simply an infant screen, but a more comprehensive evaluation, such as for testing for the rare, costly, advanced genetic disorders that you might not see in labor at delivery. There is no programme identified in this review that currently operates in this context, although the technical infrastructure, shared sequencing platforms, the shared, standardised classification of variants, and the presence of electronic health records that store genomic information are largely present in the health systems running the larger pilots.

Yet, of course, the price factor is still a serious hurdle and one may assume a more binding one than it in fact is. Cost-effectiveness thresholds typically employed by health technology assessment bodies (HTABs) would support targeted genomic screening for a specific and well characterised, treatable disease, such as that for severe combined immunodeficiency (SCID), before embarking on a genomic panel (Bessey et al., 2019). The greater challenge from the economic perspective is to have a panel that expands to include hundreds of conditions of differing severity, treatability and penetrance, such as those of the genome-based screening of newborns, where the marginal cost of detecting every additional case increases as increasingly rare and less actionable conditions are included, but which has only recently started to be quantifiable (Reimers et al., 2025).

Economic, social, ethical and equity concerns permeate most of the barriers mentioned in this review and shouldn't be glossed over as an afterthought. Parents consent for their child's sequencing because the child is too young to express their opinion, and some of the conditions screened for may have an adult onset or reproductive impact that the child, once grown, may not have wanted to hear about, or wanted to not know about (Genomics England, 2024). The tension can be sensibly met by the approach taken by Genomics England itself, limiting its panel to conditions which can present to children and which have clear clinical actionability, though as highlighted other approaches could be taken too, and other programmes have drawn the boundary differently, at least partly in line with public preference research conducted in Australia (Lynch et al., 2024), and other programmes have incorporated stakeholder informed protocols that discuss the ethics and equity of the broader concept of genomic newborn screening (Kariyawasam et al., 2024). Equity issues and concerns are keener than ever. The bias of reference databases towards European ancestry populations may result in miss-classification of a carrier or finding something as a variant of uncertain significance in underrepresented population backgrounds (Gregg et al., 2021). Findings across low-and-middle income countries highlight that while genomic carrier testing and newborn screening has a donor-funded pathway outside of high income health systems the program is still not seen as a routine service and risks widening this ever-expanding gap in access to genomic preventive medicine if not intentionally acted on (Girisha and Moosa, 2024).

5 CONCLUSION

The findings gathered for this review suggest a more intelligible pathway for inherited disease prevention on a genomic level than currently exists practice-wise. Carrier screening is now more comprehensive and increasingly more precise than the use of ethnicity-based selection to panethnic, tiered screening panels based on professional consensus. Routine neonatal genomic screening has detected serious and often treatable disease, which would not have been detected by standard biochemical screening and is proven to have been detected in pilot programmes in the United States, the United Kingdom and on the continent of Europe. What has been missing is the intentional integration of these two activities into a pathway that follows the family from preconception counselling to the diagnosis and management of their child.

Filling this gap will not only call for a further advancement in the technology of sequencing, but also necessitate new protein structures capable of decoding the information carried by the magnetic code. It will need a capacity investment in genetic counselling skills to enable the ability to explain and act on the results of both the parent and the child; a system to allow a parent's carrier result to inform and contribute to the diagnostic process for the newborn, rather than be an isolated result; ongoing expansion of reference variant databases to include populations that are not well represented within the database; and a conscious effort to roll out further pilot programmes beyond their current small number of high income health systems. None of these steps is on its own difficult to do.

These collectively constitute authentic integration efforts, and the evidence presented here indicates that health systems prepared to do those integration efforts will reap a significant share of the benefits of reducing or, at the very least, significantly mitigating some of the burdens of inherited disorders on their infants and their families.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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