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Research Article

The acceptability of blood spot screening and genome sequencing in newborn screening: a systematic review examining evidence and frameworks

Duncan Chambers[1*] Susan Baxter[1] Anastasios Bastounis[1] Katherine Jones[1] Burak Kundakci[1] Anna Cantrell[1] and Andrew Booth[1]

[1]School of Medicine and Population Health, University of Sheffield, Sheffield, UK

[*]Corresponding author d.chambers@sheffield.ac.uk

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Abstract

Background: Population-wide newborn blood spot screening programmes are a successful public health intervention used to detect whether the baby is at risk of certain rare conditions, with the aim of earlier diagnosis and provision of optimal care and treatment. Evaluating candidate conditions to include in newborn blood spot and genetic sequencing raises questions regarding acceptability to parents/carers.

Methods: In the context of the possible expansion of the newborn blood spot screening programme in the United Kingdom, this review aimed to systematically review research on the acceptability to parents of newborn blood spot screening and genetic sequencing. A protocol was developed prior to commencing the review and was registered on the PROSPERO database. A team of researchers carried out the review, with checking at all stages carried out by at least two individuals. We included research published after 2013 with participants who were pregnant or a recent parent of a newborn and were resident in a high-income country. We included quantitative and qualitative studies that investigated the acceptability to parents/carers of newborn blood spot screening or genetic sequencing. Quantitative studies were narratively synthesised, and theories/frameworks identified and evaluated. Qualitative studies were analysed for recurring themes, and a meta-synthesis was carried out to compare and contrast these two types of data. We quality appraised included articles using tools appropriate for their study design.

Results: Searches were carried out in September to November 2023 and screening identified 25 relevant research articles. Just over half were from North America, with four existing reviews and nine qualitative studies. Domains of acceptability described in the literature were: support for screening; level of anxiety, information and knowledge; consent; views of the procedure; and support after screening. The research indicated consensus support for blood spot screening, and for expanding to some other conditions, although some parental anxiety was reported. Parents/carers mostly perceived that they had received sufficient information, but the timing of this could be improved. While parents indicated interest in genomic screening, studies highlighted the need for clearer consent procedures and greater support for parents following genomic screening than for blood spot screening. Only three included studies reported using any kind of theoretical framework.

Discussion: Most parents/carers found newborn blood spot screening programmes to be acceptable and favoured their large-scale implementation. A minority of parents/carers expressed concerns regarding the acceptability of processes underpinning newborn blood spot screening, such as consent, the timing of receiving information and support available after testing. More research is needed regarding the acceptability of newborn genomic sequencing screening programmes, which are less established compared with newborn blood spot screening programmes.

Limitations: The over-representation of studies conducted in the United States has implications for the applicability of findings to other countries where testing is not typically mandatory and health systems differ considerably. Most studies were of cross-sectional design and there was limited representation of people from lower incomes and non-white ethnicity. While the inclusion of studies only in populations of future or very recent parents provided coherence to the findings, unclear reporting of participants may have resulted in under- or overinclusion of some studies.

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Background

Newborn screening in the UK includes a physical and hearing examination, and newborn blood spot (NBS) screening. Population-wide NBS screening programmes are used to detect whether a baby is at risk of or already has certain (often rare) conditions, with the aim of earlier diagnosis and provision of optimal care and treatment. NBS screening programmes have been described as one of the most significant public health achievements in the developed world.[1]

While the use of genomic sequencing (whole genome or exome) in newborn screening could expand the number of genetic conditions detected pre-symptomatically, it raises potential ethical concerns and highlights the importance of parental decision-making regarding screening for their newborn.[2] It has been argued that there needs to be a clear justification for additional screening of babies in terms of individual and public health benefit,[3] and studies have cautioned that parents and carers can have poor experiences of receiving the results of screening.[4]

Researchers have suggested that as more information becomes easily available, is available faster and is more affordable, a greater burden will be placed on individuals to decide if they want screening and what type of information they want.[5] A review of childhood screening in 2021 emphasised the need for considerations of acceptability to be properly evaluated when planning or refining screening programmes.[6] A 2021 study of stakeholder perspectives (including parents/carers) reported potential concerns regarding expanding screening. There may be an increase in results of uncertain significance, the diagnosis of conditions in asymptomatic mothers, the detection of disorders which are untreatable, together with increasingly complex consent procedures.[7] Authors have also identified a need for greater understanding of the extent to which preferences vary between individuals.[1]

Countries around the world differ in regard to the number of conditions that are included in NBS screening. Many are considering or have already expanded their list in recent years as diagnostic technology develops. The potential for further expansion of screening is also offered by new technologies such as whole-genome/exome sequencing. Researchers have highlighted that, while the clinical utility of these innovations is being investigated, there is a need for further exploration of parental perceptions.[8]

Aims and objectives

In the context of these developments, this review aimed to identify and synthesise available research on the acceptability to parents/carers of NBS screening and newborn genomic/exomic sequencing. We intended to examine both quantitative and qualitative data to gain an in-depth understanding of current research findings. We also aimed to explore theories and frameworks reported in the literature, to identify the extent to which the concept of acceptability has been adequately explored.

Methods

Protocol and registration

This study was reported adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist.[9] The protocol of this study was prospectively registered with PROSPERO (CRD42023463184).

Eligibility criteria

See *Table 1* for a summary of the criteria for inclusion/exclusion in the review. We sought studies on recent or forthcoming experiences of screening, rather than studies which collected data from parents some time later. This criterion was set on the basis that longer-term recollections are likely to differ from 'in the moment' views, and later experiences affect perceptions of screening. Studies that included populations of both recent and less-recent parents were eligible only if data for pregnant or recent parents were reported separately and could be extracted.

Any condition that is currently included in newborn screening programmes or whole-genome/exome sequencing of any eligible country was included. We included studies only from developed countries as being of most relevance to the UK. Studies reporting any outcome related to parental acceptability and of any design were included. Since the first human genome was sequenced in 2003, and given that views and technology change over time, we sought only studies published in the past 10 years.

TABLE 1 Parameters of the review (inclusion and exclusion criteria)

Categories	Inclusion criteria	Exclusion criteria
Population	Parents of newborns (first month of life) who were eligible for or who took part in bloodspot screening or genomic/exomic sequencing Future parents during their pregnancy (i.e. antenatal phase)	General population, adults who are not expecting a child, parents of children older than 1 month, healthcare staff or policy-makers
Intervention	NBS screening or primary whole-genome/exome sequencing	Screening other than NBS screening or genome/exome sequencing, secondary use of testing for identification or confirmation of specific conditions, storage of specimens
Control conditions	Any/none	
Outcomes	Any outcome related to acceptability of NBS screening or acceptability of genomic/exomic sequencing in newborns	Outcomes other than acceptability including the accuracy diagnostic performance of screening
Study design	RCTs, non-randomised trials, systematic reviews (including meta-analyses), rapid reviews, scoping reviews, prospective and retrospective cohort studies, case–control studies, cross-sectional studies (including surveys), qualitative studies	Diagnostic accuracy studies, laboratory studies, studies only for research rather than screening
Publication type	Articles published in peer-reviewed journals, governmental/public health guidelines/reports	Conference abstracts, case reports, theses, website pages with no associated report, commentaries, articles providing discursive information rather than data, protocols, studies where the full text is not retrievable
Setting (countries)	High-income countries (i.e. EU/EEA, UK, Switzerland, USA, Canada, Japan, Oceania) (according to OECD)	Countries other than those described as high-income (according to OECD)
Date; language	Published in English; published after 2013	Published in languages other than English; published before 2013

EEA, European Economic Area; EU, European Union; OECD, Organisation for Economic Co-operation and Development; RCT, randomised controlled trial.

Information sources

The following databases were searched in September 2023:

- MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to 13 September 2023> via Ovid
- APA PsycInfo <1806 to September Week 1 2023> via Ovid
- EMBASE <1974–2023 Week 36> via Ovid
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) 1981–2023 via EBSCO
- Cochrane Database of Systematic Reviews 2003–23 via WILEY
- Cochrane Central Register of Controlled Trials via Wiley
- Social Science Citation Index 1900–2023 via Web of Science.

Citation searches for included studies were conducted on Web of Science in November 2023. The following trials' registries, studies' repositories and 'grey literature' sources were also searched on 24 July 2023:

- ClinicalTrials.gov (www.clinicaltrials.gov)
- ELDIS (www.eldis.org)
- EThOS (ethos.bl.uk)
- EUnetHTA (www.eunethta.eu)
- National Academy of Medicine (https://nam.edu)
- Institute for Quality and Efficiency in Health Care (www.iqwig.de/en)
- ISRCTN Registry (www.isrctn.com)
- National Institute for Health and Care Excellence (www.nice.org.uk)
- National Institute for Health and Care Research (www.nihr.ac.uk)
- Open Access Theses and Dissertations (https://oatd.org)
- OAIster: Catalog of open access resources (www.oclc.org/en/oaister.html)
- OpenDOAR (https://v2.sherpa.ac.uk/opendoa/)
- OPENGREY.EU (https://opengrey.eu)
- Trip Medical Database (www.tripdatabase.com)
- International Clinical Trials Registry Platform (www.who.int/clinical-trials-registry-platform).

We also checked the Orphanet Newborn Screening Bibliographic Knowledgebase (28 November 2023) for any additional specialty publications.

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All potentially relevant citations were downloaded to EndNote X8 Reference Manager bibliographic software (version 8.0; Clarivate Analytics, Philadelphia, PA, USA).

Search strategy

The search strategy combined the concepts of newborn screening and acceptability. It was intentionally broad to attempt to retrieve all research on the acceptability of NBS screening and genome sequencing. The search used medical subject heading and free-text terms where appropriate. The search was then translated to the other databases. A combination of free keyword terms was used for searching trials' registries, studies' repositories and 'grey literature' sources. The only limit applied to the search was the date range '2013–current'. See *Appendix 1* for the MEDLINE search strategy.

Selection process

Selected studies were imported into Covidence (Melbourne, VIC, Australia) online software (www.covidence.org). A team of five reviewers screened studies for relevance based on titles/abstracts and, later, full texts. Disagreements were resolved through discussion and referral to a third reviewer.

Data collection process

A bespoke form was used to extract relevant data. This was developed and pilot-tested in two consecutive rounds before proceeding with the formal data extraction. All five reviewers participated in data extraction. Each reviewer extracted data from the selected records, with a second reviewer independently checking the extracted records. Data extraction was undertaken using Covidence.

Data items

Extracted data consisted of: (i) general information regarding the studies; (ii) characteristics of the methods (aims, study design, funding sources, any conflicts of interest) and participants (inclusion and exclusion criteria, method of participants' recruitment, number of participants); (iii) population characteristics (i.e. age, gender/sex, education level, socioeconomic status, ethnicity, religion, employment, time of data collection); (iv) any data regarding interventions and comparisons; (v) summary of the main findings; (vi) frameworks and theories; (vii) constructs of acceptability; and (viii) limitations and applicability.

Risk-of-bias assessment/quality appraisal

The methodological quality of the included primary studies was assessed by a single reviewer (AB), with a second reviewer (DC) independently checking all the judgements. Methodological quality was assessed using the Mixed Methods Appraisal Tool (MMAT).[10] This tool is a seven-item multidimensional checklist comprising two screening questions, then five questions evaluating different features according to the study design.[10] The methodological quality of systematic reviews was assessed using the Critical Appraisal Skills Programme (CASP) checklist.[11]

Synthesis methods

Owing to high heterogeneity in the study designs and outcomes, a meta-analysis was precluded. Data drawn from quantitative studies were narratively synthesised, providing textual, tabular and graphical presentations. Frameworks and theories were identified, summarised and evaluated. Data drawn from qualitative studies were thematically synthesised.[12] The extracted themes from each paper were tabulated and then examined across the studies to identify where themes were similar and could be merged or where new or different themes needed to be added. By this process of comparing and contrasting, a final list of themes was compiled. Data drawn from qualitative studies were compared with data drawn from quantitative studies by using the matrix method approach.[13]

Patient and public involvement

A patient and public involvement (PPI) group was established specifically for the study to provide advice and input at all stages of the work. We defined PPI as gaining contributions in an advisory capacity from people with lived experience of newborn screening.

We advertised for group members from across the UK and selected from those who responded to ensure that there was diversity in age, background and experience. Meetings were held online, with the agenda and slides to be used circulated in advance. The group comprised eight members who met three times: in the early stages to discuss the work and understandings of the term acceptability, during the process of synthesis to discuss emerging results and qualitative themes and towards the end of the project to provide input to producing study outputs and contribute to dissemination.

Patient and public involvement contributions informed study analysis, reporting and outputs. An emerging pathway for reporting results was discussed during the analysis phase and was found to be helpful and clear in guiding the write-up. Members highlighted the need to explore subpopulation differences, including country and ethnicity, which informed analysis and reporting. Members co-developed public-facing outputs including the plain language summary and a research briefing.

Results

Study selection

The database searches retrieved 3365 references, which were imported into EndNote X8 Reference Manager bibliographic software. Deduplication removed 672 references, leaving 2925 references to screen on title/abstract. Title/abstract screening excluded 2821 references, leaving 104 for full-text screening. A total of 79 references were excluded at this stage, with 25 sources being included in the review; see *Figure 1* for a flow chart illustrating the selection process. A moderate level of agreement was evident among the reviewers in title/abstract and full-text screening [Cohen's kappa coefficient (κ) ≈ 0.5]. Disagreements were mainly associated with unclear reporting of the interval between screening and assessment of acceptability and were resolved by consensus among the review team.

Characteristics of the literature

Of the 25 studies examined, just over half originated from the USA (14 studies), followed by 4 from the UK, 2 each from the Netherlands, Canada and Australia, and 1 from Switzerland (*Figure 2*).

The review included 21 primary studies and 4 systematic reviews. Almost half of the primary studies were cross-sectional (nine studies), with nine qualitative research studies, two using mixed methods and one randomised controlled trial (RCT) (*Figure 3*).

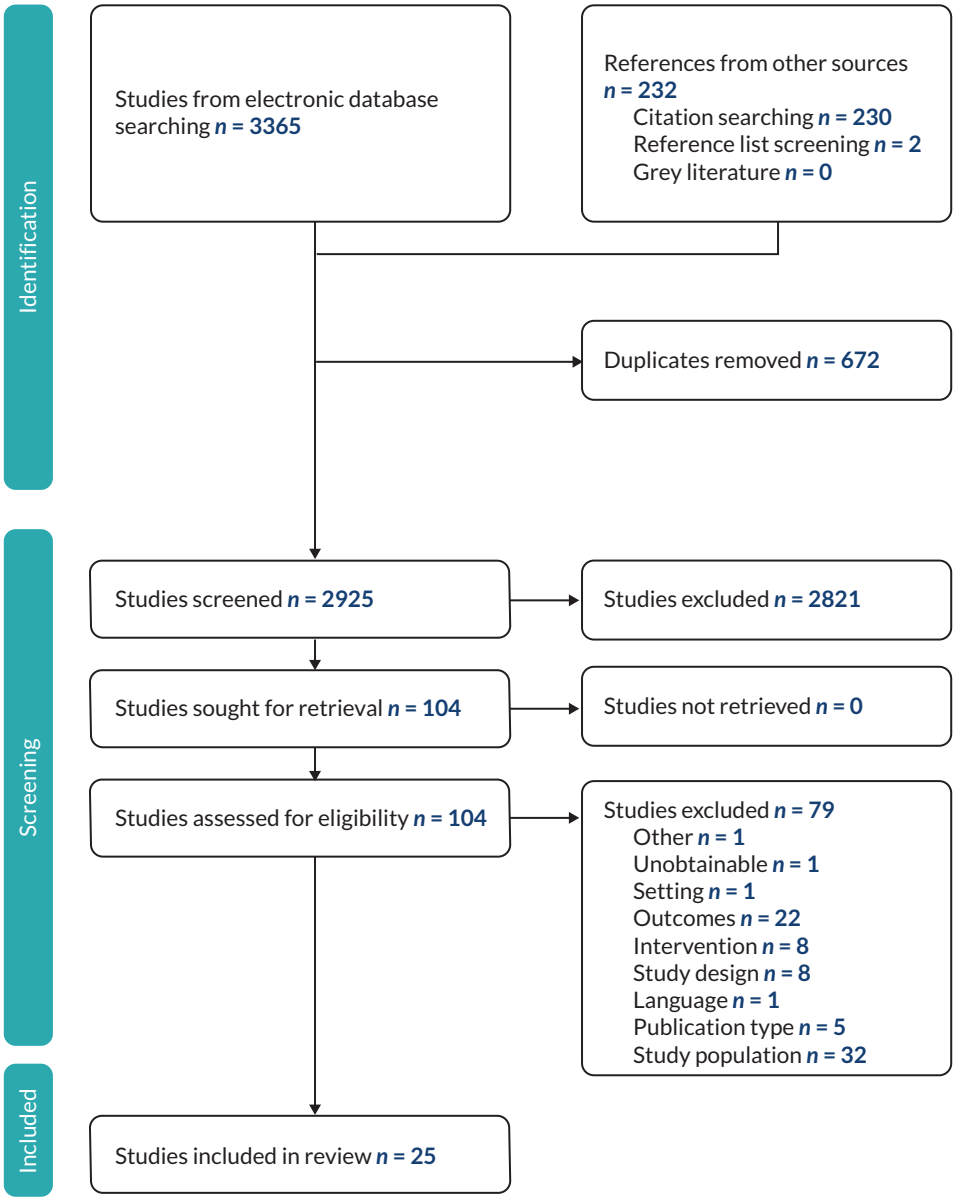

FIGURE 1 Flow diagram illustrating the process of study selection.

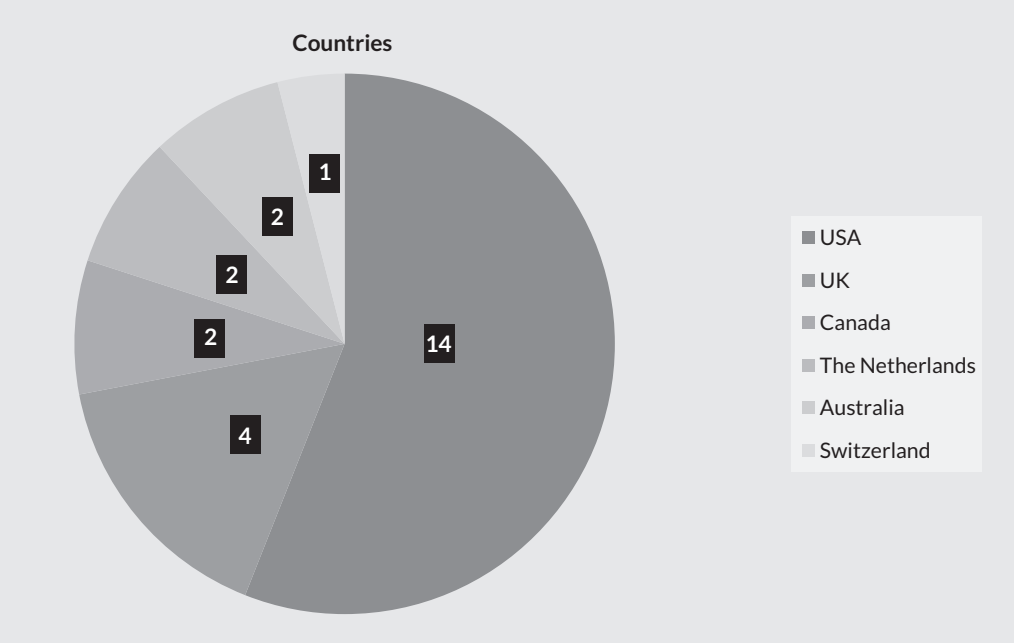

FIGURE 2 Countries of the included studies.

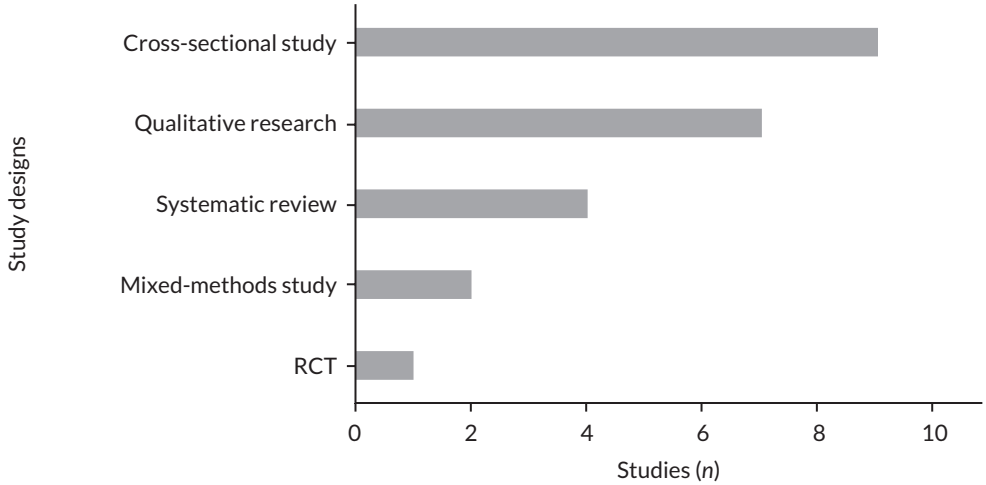

FIGURE 3 Study designs of the included studies.

Among these, 16 studies focused on NBS, 6 on genomic sequencing and 3 on both. Half the studies were published after 2020. Eighteen studies involved current or expectant parents, while two focused solely on mothers, and three specifically targeted pregnant individuals. The number of participants in primary studies ranged from 19 to 1971, while systematic reviews comprised 36–92 studies (*Table 2*).

Risk of bias and quality of the literature

The MMAT for primary qualitative studies was used in seven studies,[14–20] the MMAT for primary non-randomised studies was used in five studies,[21–25] the MMAT for primary descriptive quantitative studies was used in five studies[26–30] and the MMAT for mixed-methods studies was used in four studies.[31–34] All the studies received a positive rating in respect of the screening questions as all of them provided clear research questions and, in all cases, the collected data were applicable to address the research questions. Of note is that, in 16 of 21 studies, the research questions were not explicitly stated but rather derived from the reported aims and objectives. None of the studies or reviews were excluded on the basis of their appraisal.

TABLE 2 Summary of findings of the included studies

Author	Year	Screening type	Country	Study design	Population	Number of participants[a]	Summary of main findings
Armstrong *et al.*[21]	2022	NBS screening and GS	USA	Cohort	Parents	406	Parents generally favoured universal NBS screening over GS, with no notable change in GS support after experiencing GS results. Preference for informed consent in GS and a minority advocating for mandatory state implementation of GS
Bailey *et al.*[22]	2015	NBS	USA	Cohort	Mothers	20	Some mothers experienced notable anxiety and decision regret after accepting screening, with higher spousal support linked to better outcomes
Berrios *et al.*[31]	2020	GS	USA	Mixed methods	Parents	23	Most participants responded positively to GS for their infants. The majority acknowledged the psychological risks associated with genetic testing
Blackwell *et al.*[26]	2020	NBS	USA	Cross-sectional	Parents	20	Half of families supported nationwide NBS for Krabbe disease in the USA, opposition from others
Blom *et al.*[32]	2021	NBS	The Netherlands	Mixed methods	Parents	19	Parents largely supported SCID NBS, citing emotional impacts from abnormal results, highlighting the need for standardised follow-up procedures and comprehensive information provision to manage long-term stress and anxiety
Botkin *et al.*[23]	2016	NBS	USA	RCT	Pregnant women	901	Participants who received education about NBS and DBS retention exhibited higher knowledge regarding NBS, stronger support for screening, and minimal influence on declining screening
Cakici *et al.*[24]	2020	GS	USA	Cross-sectional	Parents or guardians	312	97% of parents reported perceiving that their child's genomic sequencing results were either useful or somewhat useful; 50.3% of parents reported no regret about undergoing screening
Carlton *et al.*[6]	2021	NBS	UK	Systematic review	Parents	46 studies	Acceptability commonly focused on affective attitude (parental emotions about the programme) and intervention coherence (understanding and consequences of a confirmed diagnosis)
Christie *et al.*[33]	2013	NBS	Australia	Cross-sectional	Mothers	1971	Almost all mothers wanted information, and supported testing due to convenience and recognising the benefits for preparation and reproductive planning
Downie *et al.*[35]	2021	GS	Australia	Systematic review	Parents	36 studies	There is a need for equitable access, transparent gene selection processes and informed consent in newborn GS
Etchegary *et al.*[14]	2016	NBS	Canada	Qualitative research	Parents	32	Parents generally expressed satisfaction, yet recommended early provision of NBS information before birth, accounts of declined screening emphasised the impact of parental experiences
Joseph *et al.*[15]	2016	NBS and GS	USA	Qualitative research	Pregnant women	31	Participants did not recall discussions about NBS during pregnancies, preferred information beforehand, valued increased knowledge, had varying views on formal consent and mistrust in the system, desired GS results related to immediate treatment and childhood
Moultrie *et al.*[16]	2020	GS	USA	Qualitative research	Current or expectant parents	66	A majority of parents showed strong interest in GS if offered, highlighting parental responsibility, early intervention benefits, preparedness, aiding children's future readiness and altruism. Concerns about quality of life, religious beliefs, child autonomy, outcomes of early intervention, and perceived lack of medical justification

continued

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TABLE 2 Summary of findings of the included studies (*continued*)

Author	Year	Screening type	Country	Study design	Population	Number of participants[a]	Summary of main findings
Newcomb *et al.*[25]	2013	NBS	USA	Cross-sectional	Mothers	548	Most respondents were unaware of NBS before their hospitalisation. While they generally understood NBS's ability to identify genetic disorders, disagreement more common among Hispanic women
Nicholls *et al.*[17]	2019	NBS	Canada	Qualitative research	Parents	32	Differing conceptions of consent terms based on decision-making and information attainment domains
Pereira *et al.*[34]	2019	NBS and GS	USA	Cross-sectional	Parents	493	Parents generally supported universal NBS over GS, with higher agreement for informed parental consent in GS, perceiving greater health benefits from NBS and higher risks, including discrimination and distress, associated with GS
Rueegg *et al.*[27]	2016	NBS	Switzerland	Cross-sectional	Parents	138	Parents found the information received at birth satisfactory, a small percentage remained unsure or unsatisfied
Tluczek *et al.*[36]	2022	NBS	USA	Systematic review	Parents	92 studies	Many new parents lack information about the purpose of NBS and the implications of positive results
Ulph *et al.*[18]	2020	NBS	UK	Qualitative research	Parents	45	Results after NBS initially causes anxiety but later allows understanding, with proper communication and support
Ulph *et al.*[19]	2015	NBS	UK	Qualitative research	Parents	67	Testing provided valuable information, concerns with delays and unaddressed concerns during the communication process leading to negative impacts, while explanations from well-informed professionals relieved concerns
van der Pal *et al.*[28]	2022	NBS	The Netherlands	Cross-sectional	Parents	852	Parents participating in NBS aimed to prevent adverse health issues, while those declining were more religious, valued alternative medicine, and expressed doubt, leading to lower informed choice, yet most supported NBS expansion
Waisbren *et al.*[29]	2015	GS	USA	Cross-sectional	Parents	514	Interest in NGS showed no significant association with demographics, with most parents interested. Those with child health concerns or married were less interested and marital status correlated with partner agreement
Wang *et al.*[20]	2022	GS	USA	Qualitative research	Pregnant women	32	Parents showed varying interest in newborn GS, with none refusing state-mandated NBS; however, married participants and those with infant health concerns exhibited lower interest, and around one quarter of couples had discordant interest levels between mothers and fathers
White *et al.*[37]	2021	NBS	UK	Systematic review	Parents	36 studies	Varying consent processes and information provision globally reveal parents' limited understanding of NBS implications, often perceiving it as a healthcare necessity rather than an active choice, leading to occasional uncertainty about refusal and instances of forgotten consent
Wood *et al.*[30]	2014	NBS	USA	Cross-sectional	Expectant parents	466	Both groups of parents showed strong support for NBS for genetic diseases

DBS, dried blood spot; GS, genomic sequencing; NBS, newborn screening; SCID, severe combined immunodeficiency.
a Number of studies for systematic reviews.

None of the qualitative studies received a negative rating in any of MMAT's categories. All five quantitative non-randomised studies received a negative rating in at least one of MMAT's categories, while in three studies there was an unclear rating.[21,23,25] Most of the negative ratings pertained to the observed dropout rates in outcomes' assessment. Four of five quantitative descriptive studies received a negative rating,[27,28,29,30] while in four studies there were unclear ratings. The negative ratings in quantitative descriptive studies pertained to the observed dropout rates in outcomes' assessment. Two of four mixed-methods studies received at least one negative and one unclear rating.[32,34] The negative ratings in mixed-methods studies generally pertained to the limited adherence to quality criteria in one of the two research components of the study. The CASP tool for systematic reviews was used in four studies.[6,35–37] All studies received a poor rating for critical appraisal. Categories related to meta-analysis were considered non-applicable due to the scope of research questions and type of synthesis in the included reviews.

Results of synthesis of the quantitative studies

Systematic reviews

The three included quantitative systematic reviews[6,20,36] were all published in 2021 or later. The range of coverage was diverse, with one focusing on acceptability of childhood screening in general,[6] one on 'psychosocial issues' around NBS,[36] and one on genomic NBS.[35] This meant that there was no overlap in included studies among the systematic reviews. Three primary studies[14,15,33] were included in both the present review and that by Carlton *et al.*[6] Findings of the reviews are summarised above (see *Table 2*) and quality assessment results (using the CASP checklist) in *Appendix 2*. None of the reviews included a formal quality/risk-of-bias assessment of the included studies; for example, Downie *et al.* only extracted data on 'strengths and limitations'.[35] Despite their diverse coverage, the three reviews showed considerable overlap in their conceptualisation of parental acceptability.

Constructs included parental knowledge and understanding, and attitudes and/or interest in screening. The importance of informed consent was emphasised, and one study used the term 'flexible' consent.[35,36] Reviews highlighted the need for high-quality information and/or parental education in securing consent and allowing parents to assess the risks and benefits of NBS. Risks were often framed in terms of anxiety about receiving a result suggesting a possible problem,[6] and parents valued certainty of prediction over the ability to take action based on the test results.[35] Stress caused by unexpected screening results (especially when accompanied by 'unsolicited genetic information') could threaten the acceptability of plans to expand NBS programmes.[36] In addition to effective parental education and communication, methods suggested in the literature to mitigate this threat included providing genetic counselling and information about what to expect following an unfavourable screening result.[36] The reviews found potential biases in the evidence base, particularly an over-representation of people of higher socioeconomic status.[35,36]

Primary research studies

The 13 primary quantitative studies typically used questionnaires/surveys to collect numerical data about parents' attitudes to screening, satisfaction with the process, information provided and communication of results. Some studies also used scales to measure outcomes like stress and anxiety. The largest group of studies were cross-sectional in design,[25–29,33,34] but there were also two cohort studies,[21,22] two mixed methods[31,32] and one study that recruited participants from a clinical trial.[23]

The studies involved populations of pregnant women, parents/carers of newborns and people who accepted or declined participation in screening, and evaluated NBS (overall and for specific conditions), genomic sequencing or both (see *Table 2*).

Table 3 summarises key findings using a simple vote-counting approach, with support for NBS programmes in general and NBS screening for specific conditions among actual or potential participants. Two studies reported that participants believed the benefits of NBS outweighed the risks.[31,34] Two publications from the same study (the BabySeq study) suggested varying attitudes towards genomic NBS and standard NBS, participants being more likely to support active consent for genomic NBS and seeing the sampling and screening procedure as more likely to involve risks.[21,34]

The evidence on provision of information was limited and inconsistent, two studies reporting that participants felt adequately informed,[24,27] while one concluded that new mothers' knowledge of NBS and dried blood spot retention was inadequate.[25] Two studies reported that participants felt adequately informed to consent to NBS screening.[24,28] The percentage reporting informed consent to NBS screening was higher than the percentage who felt they had made an informed decision to decline NBS screening for their child (83% vs. 44%).[28]

TABLE 3 Summary of key quantitative findings

Stage of NBS process	Key quantitative findings	Summary
Principle of NBS/GS programmes	Majority support for NBS programmes in general[28] High levels of interest in newborn genomic sequencing[29] Majority support for NBS for Krabbe disease in USA[26] Majority support for NBS for SCID in The Netherlands[32] High participation rates and reported attitudes indicated support for NBS for fragile X[33] Mandatory screening: stronger support for standard NBS than GS[21] Majority believed that benefits of NBS outweighed risks[31] Majority of parents believed there were health benefits associated with GS, but more parents felt there were risks associated with GS compared with standard NBS (71% vs. 19%)[34] Most NBS participants in The Netherlands (95%) favoured expanding the programme[28] Parents expressed high levels of interest in (hypothetical) newborn GS[29]	Consistent support for existing NBS; support for expanding to some other conditions; interest in genomic NBS but more emphasis on need for consent relative to standard NBS
Provision of information	Education increased knowledge of and support for NBS[23] Most parents felt adequately informed to consent[24] Researchers considered mothers' knowledge to be inadequate[25] Most parents were satisfied with the information provided on NBS for CF[27]	Limited evidence suggests parents felt adequately informed, but one study suggested that researchers did not agree
Consent	Stronger support for active consent for GS vs. standard NBS[21] Most parents felt adequately informed to consent[24] Most parents reported an informed choice to take part in NBS (83% vs. 44% for those who declined)[28]	Limited evidence suggests parents felt able to give informed consent; one study suggested consent was more important for GS
Procedure	Most parents (88%) were satisfied with NBS screening procedure for CF[27] Perceived harm to child from heel prick was the main reason for declining NBS[28]	Limited evidence
Communication of results	Minority of mothers in fragile X screening study experienced anxiety and/or decision regret[22] Early diagnosis considered beneficial for fragile X but some anxiety about receiving test results[33] Most parents denied regret or harm from undergoing genomic sequencing[24] Parents interested in knowing child's risk based on genomic sequencing[21] Most parents felt anxious when contacted about results and 38% remained anxious after a visit from CF centre[27]	Evidence from several studies of anxiety around receiving test results; one study identified decision regret in a minority of mothers

CF, cystic fibrosis; GS, genomic sequencing; NBS, newborn screening; SCID, severe combined immunodeficiency.

Evidence on the acceptability of the sampling procedure itself was very limited. Most participants in a study of NBS screening for cystic fibrosis (88%) were happy with the procedure[27] but an unrelated topic concern about pain to the baby while taking the sample was the most common reason reported for declining NBS screening.[28]

Participants in one study denied experiencing harm or regret following communication of genomic sequencing results,[24] but three others reported varying degrees of anxiety and/or regret.[22,33,27] In the case of NBS screening for cystic fibrosis, 38% of participants remained anxious after a visit from the cystic fibrosis centre.[27]

Synthesis of themes from the qualitative studies

Ten papers were included in the qualitative evidence synthesis. One of these[31] was a mixed-method study and included only limited qualitative data. Another was a review of 36 qualitative studies exploring parent experiences of newborn screening,[37] described as a meta-ethnography.

From comparing and contrasting the themes in the source papers (*Table 4*), five synthesised themes were developed describing acceptability in terms of the NBS screening pathway: choice and consent; information provision; weighing up risks and benefits; the procedure; and notification of results. Also one superordinate theme across the pathway: trust in the healthcare system (*Figure 4*).

Choice and consent

Five papers explored the concept of consent within newborn screening.[14,15,17,18,37] There were reports in all these of some parents perceiving that NBS was a necessity rather than them making an active decision or choice, while the experience of others was that consent

TABLE 4 Themes in the qualitative studies and contribution to the synthesis

First author, date	Themes in the source paper	Contribution to synthesised themes
Berrios *et al.* 2020[31]	Negative aspects of GS Positive aspects of GS	Risks and benefits
Blom *et al.* 2021[32]	Information provision Process of being informed of results	Information Results notification
Etchegary *et al.* 2016[14]	Offer Information provision Experiences	Information – timing and content, source Understandings of consent The procedure
Joseph *et al.* 2016[15]	Perspectives on NBS screening Return of results	Information provision and timing Knowledge and trust Understandings of consent Risks and benefits Results notification
Moultrie *et al.* 2020[16]	Benefits Negative aspects	Risks and benefits
Nicholls *et al.* 2019[17]	Lexical variation Domains of consent	Understandings of consent Information provision
Ulph *et al.* 2015[19]	Impact of learning result Effect of process of communication	Results notification
Ulph *et al.* 2020[18]	Consent preferences	Understandings of consent
Wang *et al.* 2022[20]	Attitudes towards GS Willingness to undergo test Negative consequences	Information provision Risks and benefits
White *et al.* 2021[37]	Screening pathways Assessing parent's absorptive capacities Uncertainty and the concertinaing of time	Understandings of consent Knowledge and trust Information provision – timing, content Results notification

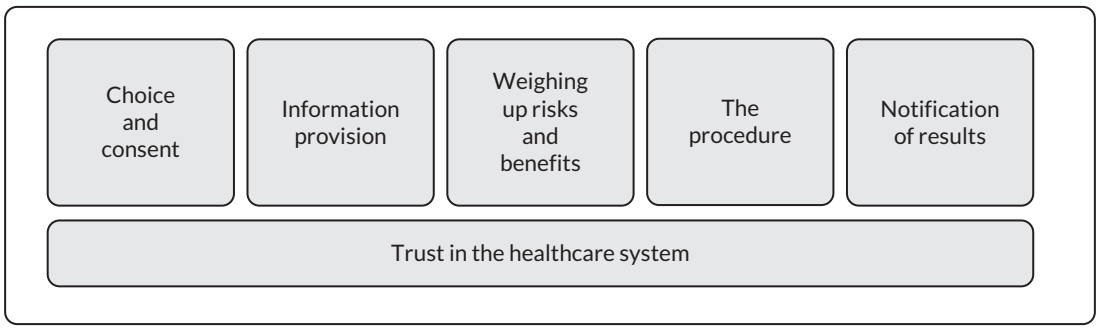

FIGURE 4 Domains of acceptability described in the qualitative literature.

had been fully informed. Different terminology, however, could lead to varying understandings of consent.[17] Choice could take different forms and was perceived to be linked to involvement in and a sense of control or empowerment over the process. Participants generally supported opt-out for current and potential future expanded NBS, but this needed to be linked to adequate information provision,[15,18] with consent constituting both parental decision-making and information ascertainment.[17]

Information provision

Aspects of information outlined in six studies were timing of the information, content of the information and the person (source) delivering the information.[14,15,17,20,32,37]

Primary studies and a review highlighted how some parents were unable to recall receiving information about NBS.[14,32,37] There was the recommendation that information should be provided prenatally, as the typical timing soon after birth was when parents were too busy with their newborn to fully take in information.[15,37] However, the possibility for lack of recall of information provided some time before was also noted.[14] Recommendations for information content included that it should be provided in different forms, should be accessible to all communities and varied by condition and context according to a parents 'absorptive capacity'.[37] A preference for a known healthcare professional to provide information verbally was noted.[14] One study described how the receipt only of a leaflet about screening was perceived to indicate a lack of engagement with parents.[18]

Weighing up risks and benefits

Views regarding acceptability was described as a process of weighing up pros and cons or the risks and benefits. Potential benefits might be the provision of new information, which would enable early action to be taken, and the ability to plan, but this was weighted against potential worry and anxiety (particularly for untreatable or unpreventable conditions), the adequacy/accuracy of test results and the explanation and support available. Individual variation when weighing up these factors can lead to variation in perceived acceptability and emphasises the need for choice.[20] One study highlighted that where testing was unable to provide knowledge or certainty this affected decision-making.[31]

The procedure

Two studies described how parent concerns or experiences of distress or pain to their child or poor handling of babies during the taking of the blood sample influenced their views regarding acceptability.[14,37]

Notification of results

Studies highlighted how there could be limited parental understanding of the conditions included in the screening and the terms 'positive' and 'negative'.[37] There were reports of parents receiving little or incorrect information following screening.[32] Following uncertain or positive results parents wished to be contacted by a specialist (rather than a general practitioner or other healthcare professional) so that they obtained correct and clear information and could ask questions.[32]

Trust in the healthcare system

The importance of trust across the screening pathway was emphasised across the included qualitative evidence. Studies reported that NBS could be seen just as routine and necessary, with trust placed in the system that it was required.[16] Trust in the healthcare system influenced perceptions that an assumed/opt-out system was acceptable.[22] There was some description of mistrust of medicine among parents who opted out of screening.[15] The authors of this study linked provision of sufficient information to trust.[15]

Meta-synthesis across the study types

Table 5 (based on the matrix method described by Candy *et al.*[13]) compares constructs of acceptability identified in the quantitative studies with those identified from the qualitative literature (see *Figure 4*). The overarching qualitative theme of trust in the healthcare system was only addressed to a limited extent in the quantitative studies; the predominant topic was overall support for and/or willingness to participate (although this could be a proxy for trust in the system).

The qualitative themes of 'choice and consent', 'information provision', 'weighing up risks and benefits' and 'notification of results' all featured prominently in the quantitative literature (see *Table 5*). Acceptability of the procedure itself was evaluated in three quantitative studies,[27–29] one of which focused on a hypothetical genomic sequencing scenario.[29] The qualitative and quantitative findings related to acceptability of notification of results were complementary, with the qualitative papers (or qualitative section of mixed-methods studies) focusing on source and quality of information[32,37] and the quantitative studies investigating the risk of stress or anxiety and the possible occurrence of 'decision regret' after receiving test results.[22,24,27,33]

Theories and frameworks

Only three studies reported using any kind of framework to support their analysis. Two of these studies were systematic reviews[6,35] and the third used a survey to investigate mothers' attitudes to and knowledge about NBS.[25] Key features are summarised in *Table 6*.

Evaluation of the utility and potential for bias in the tools (*Table 7*) revealed a mixture of strengths and limitations. The theoretical framework of acceptability[38] is a broadly based tool applicable to a wide range of complex interventions. It may be useful in the absence of more specific alternatives. The survey tool developed by Newcomb *et al.*[25] was carefully developed and underwent some testing but is not a comprehensive tool for assessing acceptability. Finally, the framework presented by Downie *et al.*[35] includes relevant constructs but has a slightly wider focus than acceptability and is specific to genomic sequencing programmes.

TABLE 5 Summary of correspondence between qualitative themes and quantitative studies

	Trust in healthcare system	Choice and consent	Information provision	Risks and benefits	Procedure	Notification of results
Reviews						
Carlton *et al.* 2021[6]		X	X	X		X
Downie *et al.* 2021[35]		X	X	X		
Tluczek *et al.* 2022[36]		X	X	X		X
Primary studies						
Armstrong *et al.* 2022[21]		X				X
Bailey *et al.* 2015[22]				X		X
Berrios *et al.* 2020[31]				X		
Blackwell *et al.* 2020[26]				X		
Blom *et al.* 2021[32]		X	X	X		X
Botkin *et al.* 2016[23]			X			
Cakici *et al.* 2020[23]		X	X	X		X
Christie *et al.* 2013[33]				X		X
Newcomb *et al.* 2013[25]	X	X	X			
Pereira *et al.* 2019[34]		X		X		
Rueegg *et al.* 2016[27]			X		X	X
van der Pal *et al.* 2022[28]		X	X		X	
Waisbren *et al.* 2015[20]		X				

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TABLE 6 Summary of frameworks used in included studies

Source of framework	Focus	Key constructs/components
Sekhon *et al.* 2017[38] via Carlton *et al.* 2021[6]	Healthcare interventions in general	Affective attitude; burden; ethicality; intervention coherence; opportunity costs; perceived effectiveness; self-efficacy
Newcomb *et al.*[25]	NBS and retention of DBS	Knowledge about NBS and genetic testing; attitudes to DBS retention and sharing; knowledge about inheritance
Downie *et al.*[35]	Genomic NBS	Ethical and legal considerations; validity and utility; gene selection and analysis; parental uptake and consent

DBS, dried blood spot; NBS, newborn screening.

TABLE 7 Evaluation of tools/frameworks used in included studies

Source of tool/framework	Sekhon *et al.* 2017[38] used in Carlton *et al.* 2021[6]	Newcomb *et al.* 2013[25]	Downie *et al.* 2021[35]
Name of tool/framework	Theoretical framework of acceptability	Maternal attitudes and knowledge about newborn screening	N/A
Type of approach	Mixed methods (can be applied qualitatively and quantitatively)	Quantitative	Qualitative
Is the tool specifically designed to measure acceptability?	Yes	Partly (focus on attitudes and dried blood spot retention and sharing)	No (includes additional considerations)
Is there potential for bias in the tool?	Yes (authors acknowledge possible bias in development of constructs)	Unclear (limited details provided)	Yes (authors acknowledge bias in underlying data)
Is development of the tool described?	Yes	Yes	Partly (developed from systematic review)
Is testing/validation of the tool reported?	No	Yes	No
Is the tool based on theory or an underlying empirical framework?	Partly (authors report combination of theory-driven and data-driven approaches)	Partly (includes three theoretically derived subscales)	No
How comprehensive is the tool?	Covers whole screening process	Covers multiple but not all aspects	Covers whole screening process

Equality diversity and inclusion

The Sex and Gender Equity in Research (SAGER) guidelines checklist was applied to all included studies (*Appendix 3*). This approach was chosen to better understand how the available evidence conceptualises and reflects 'parenthood' as the population of interest in this review.

Language and terminology

A total of 12 studies did not refer to the sex or gender of parents,[6,14,15,17,18,20,22,23,25,26,36,37] and 10 studies reported neither eligibility criteria for parents' sex/gender nor method of definition where either term was used.[16,19,21,27,28,29,30,31,32,34]

Participant representation

One study only included parents of the opposite sex who were married or in a committed relationship (and did not explain the rationale for this approach). The views of single parents, same-sex parents and guardians are likely under-represented. Cakici *et al.* 2020[24] was the only included study that specified either parent or guardian involvement as the population of interest, although this difference was not explored further in the study.

Three included studies specifically considered the acceptability of newborn screening among mothers,[22,25,33] and a fourth study explored the views of 'pregnant Latinas'.[20] One study highlighted that fathers can feel disempowered by their exclusion from communications.[19] Another study reported that fathers represented a higher proportion of parents declining newborn screening.[28] No included study focused on paternal acceptability alone, although return to work during follow-up tests of the infant was highlighted as a particular difficulty among fathers in one study.[19] Agreement was found to be higher among married couples, further emphasising the challenge of engaging and representing diverse voices.[29] Representation of men and women studied could be critical to understanding parental acceptability in relation to male–female disparity in the consequences of the condition. For example, one included study asked parents to share their perspectives on newborn screening for a condition that has large differences in manifestation and treatability between males and females.[28] In this way, the information communicated to parents about a condition screened for, and how parents receive this information, is expected to affect parental acceptability.

Twelve studies reported inclusion of parents able to communicate in two or more languages.[14,15,17–20,23–25,27,28,36] Interpreters or bilingual researchers were involved in four primary studies,[18–20,24] while four other studies included only parents who could speak English.[16,29,31,33] Despite consideration of educational attainment across most studies, none reported inclusion criteria for parents with learning difficulties or disabilities. Two primary studies excluded those who lacked capacity to consent or had an impaired decision-making capacity that was undefined.[18,28] Several studies involved only those aged 18 years or over, excluding young parents' views on newborn screening.[14–18,20,25] Together, these findings highlight a research gap in the views of parents who may have additional learning support needs.

Evidence of differential effects or impact on population subgroups

Wang *et al.* 2022[20] highlighted that studies of newborn screening have tended to focus on the views of non-Hispanic, white parents who have moderate to high socioeconomic status. Meanwhile, having minority status, lower income and lack of spousal and social support are associated with poorer mental health outcomes for parents after disclosure of a condition affecting their newborn.[35] Intersectional disparities reported for the uptake to newborn screening include the mother's ethnicity, the mother's income and the mother's prenatal information received on newborn screening. General knowledge about newborn screening, which may be a factor in parental acceptability, is also reported to exhibit disparities based on the postpartum woman's ethnicity and the mother's mental health.[37]

Generalisability and transferability of the evidence

Few studies detailed characteristics of parental participants. The language used for mothers and fathers appeared to relate to genetic parents, although this is not always clearly stated. This information could be critical to understanding parental acceptability beyond that of the genetic parents alone. The limited representation of fathers in the studies highlights that where informed consent is required to opt in or out of newborn screening, consideration needs to be given to 'whose' informed consent is required and indicates limited understanding of parental acceptability in relation to male–female disparity. The over-representation of people of higher socioeconomic status should be recognised when interpreting the evidence, and also the predominance of literature from the USA, where in many areas newborn testing is mandatory but follow-on care is not.

Reflections on research team and wider involvement

The research team comprised individuals with a mix of gender, level of experience in reviewing, and nationality. Our public advisory group had wide representation in terms of background and ethnicity but were majority female.

Discussion

Main findings

The evidence base encompasses a small number of diverse studies, in terms of conditions studied, research design, methodological quality and sample size. There was consistency however, in findings across the qualitative and quantitative literature. Most of the included studies were explorative and did not use any theoretical frameworks, and there was only one evaluation study. Qualitative studies were in general of high quality, while quantitative studies were judged to be of moderate methodological quality.

The review found that, in most studies, parents/carers of newborns and prospective parents perceived NBS programmes to be acceptable and beneficial, and supported the large-scale implementation of such screening programmes. Acceptability of NBS screening for parents was typically conceptualised in terms of being

able to make an informed choice and having sufficient information to make that choice being provided at the right time. While, for many parents, trust in the healthcare system and healthcare staff gave them confidence to take part in the screening programme with little hesitation, some perceived that they had been offered little choice, or that information provision was poorly timed, or that there could be greater transparency in the consent process. The review suggests that standardised processes and comprehensive information packages should be provided in advance of the screening procedure The review also suggests the need to further examine how NBS results are communicated to parents and by whom.

We did not detect differences in parental perceptions between the countries included in the review. Among the high-income countries included, the USA is unique in that NBS testing is mandatory in almost all states with only religious exemption. In the rest of the included countries, NBS screening is optional, although participation rates are very high. There is variability across the world in terms of the conditions tested (see *Appendix 4*). In studies which examined perceptions regarding the acceptability of expansion to additional conditions, most parents were in favour.

Similar findings were observed regarding parents' perceptions of genomic sequencing screening programmes. In general, parents favoured the implementation of genomic sequencing, and data suggested that most parents had sufficient knowledge and information regarding such screening. However, there were greater concerns regarding transparency in the processes underpinning genomic sequencing and informed consent.

Only two reviews and one primary study used or described any kind of theoretical framework. None of the frameworks were exclusively developed for assessing parents' perceptions regarding NBS programmes or based on robust empirical evidence Carlton *et al.* used a pre-existing framework adaptable for any type of health intervention.[6] This framework categorised studies using constructs such as attitude to screening, perceived burden and understanding of the intervention. This approach was helpful in classifying the broader literature on childhood screening (the review was not specific to NBS screening, although most included studies dealt with NBS screening). However, as noted by the authors, some of the constructs were not independent of one another and different constructs may be required for different populations. Downie *et al.*[35] presented a framework of factors to be considered in designing genomic NBS screening programmes, which included aspects of acceptability but also technical aspects of selecting genes for inclusion. The questionnaire developed by Newcomb *et al.*[25] was theory informed but assessed knowledge about NBS screening and attitudes to blood spot retention and use in research rather than attitudes to NBS screening as a whole. Overall, there is a need for additional theoretical work to improve understanding of constructs of acceptability to improve evaluation of this aspect of NBS and the development of interventions to support consent and uptake of NBS screening.

Our synthesis using a pathway model suggests a possible approach based on requirements for acceptability at each point in time from consent up to and beyond receipt of test results (see *Figure 4*). This approach differs from frameworks which we identified, although echoes the important constructs of knowledge, attitudes and consent within other acceptability frameworks.

Limitations

We note the following limitations to this review. First, there was an over-representation of studies conducted in the USA compared with studies conducted in European Economic Area/European Union (81% of studies conducted in Northern America and the UK, with an overall 54% of studies conducted in USA). This will have implications for the applicability of findings to other countries where testing is not mandatory, and health systems vary substantially. However, as noted above, we did not detect any differences in findings when we scrutinised potential variability between countries. Second, the evidence is drawn from primary studies, which may have recruited parents with a generally positive stance towards NBS or genomic sequencing, and some studies were in parents of children with particular conditions. No studies directly compared the views of parents with healthy and affected newborns within the same screening programme, although support for NBS was generally high among parents of newborns with conditions detected by screening.[26,27,33] Third, parents' perceptions regarding NBS and genomic sequencing screening were also assessed retrospectively, something which might have affected the recall of certain events and the interpretation of those events through time. We believe that this potential was mitigated, however, as we deliberately included only studies carried out in parents of newborns within 1 month of birth. This narrow population inclusion criterion distinguishes the review from others in this area but proved challenging when screening studies for eligibility; unclear reporting of participants may have resulted in under- or overinclusion of some studies. The review highlights the need to consider that views of acceptability may vary depending

on which point in the process parents/carers are asked, further emphasising the challenges of the concept and its evaluation.

Future research

1. There is a need for further research to investigate how attitudes may change over time (possibly involving prospective parents and running from preconception to the early postnatal period, or parents at some distance from the moment of screening), including delivery of screening results and any regret about deciding to accept (or reject) screening.
2. There is a need for further research on constructs of acceptability and how they might vary in different populations. The review suggested that people from different faiths/cultures and socioeconomic backgrounds may have differing views on acceptability, which are important to consider in further developments/expansion.
3. The review identified varying experiences and views regarding the acceptability of the timing of information provision. Research to develop and evaluate appropriate interventions would help to clarify the optimal timing of information provision. The review also suggests the need to further examine how and by whom NBS results are communicated to parents.
4. The largest volume of studies identified by the review originated from North America, this highlights the need for research of direct relevance to the UK.
5. Although outside the scope of this review, there was some indication that attitudes towards assessing the risks and benefits of NBS may differ between parents and clinicians. This could be a topic for future evidence synthesis work.

Lessons learnt

1. Acceptability is a challenging concept which can be understood in varying ways and is likely to differ at different points in the process and by different experiences and outcomes. We anticipated that there would be a greater use of theoretical frameworks/concepts in the literature to inform our synthesis than we identified. Future reviews in this area should consider this during the protocol development stage, and it would be helpful for primary studies to more overtly draw on and develop theories and frameworks.
2. We found that reporting limitations made it challenging to identify the precise population criteria for data collection among parents of newborns. It would be valuable for future research in the area to more fully report their recruitment and data collection. There was also little reporting of the consent process and details of information provided to parents.
3. Tools designed to assess quality/risk of bias are primarily designed for effectiveness studies and additional considerations (e.g. sample size and representativeness, response rates to questionnaires) are needed in assessing the value of a study where the review question relates to acceptability. There may be a need to develop tools assessing these aspects of study quality.
4. The review identified a need to include more representative populations and to ensure equitable access to new screening programmes (specifically genomic sequencing), with a possible long-term benefit to equity. Some evidence identified during the review indicated that those who decline newborn screening are less likely to take up other healthcare services.
5. We have worked closely with stakeholders in designing the review. In addition to standard dissemination through academic publications, conference presentations and tailored evidence summaries, we will work with stakeholders and our public representatives to support dissemination to key audiences.

Implications for decision-makers

1. The evidence suggests that parents/carers and prospective parents of newborns generally regard NBS as an acceptable intervention conditional on acceptable consent procedures, availability of timely information and sufficient post-screening support, including communication of results by a knowledgeable source.
2. The review predominantly included studies from outside the UK, and while there was uniformity in evidence across countries and between qualitative and quantitative research, studies in healthcare settings substantially different to the UK influencing applicability of the evidence.
3. Acceptability is a challenging concept which can be understood in varying ways and is likely to differ at different points in the process and by different experiences and outcomes. Findings from this research indicate that assessments of attitudes towards NBS are rarely informed by theory and there is a lack of theoretical frameworks to inform both assessments of acceptability and design of appropriate information and support interventions.
4. Comparison of conventional NBS with NBS involving genomic sequencing suggests that people may have a more cautious attitude towards the latter, which highlights, for example, the need for enhanced and timely information provision, and appropriate consent processes.

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5. The review identified differences in views regarding acceptability between different population groups, highlighting a need to include more representative populations in future research studies.

Conclusions

Key learning points

1. The literature related to acceptability of NBS and genomic sequencing to parents and prospective parents is limited in both quantity and quality. In particular, many studies recruited small (< 100) and/or highly selected populations. Most included studies were performed in the USA, which should be taken into account when assessing transferability to the UK setting. However, we did not find significant variation in attitudes to NBS and genomic sequencing between countries.
2. In most studies, parents of newborns and prospective parents perceived NBS programmes to be acceptable and beneficial, and supported the large-scale implementation of such screening programmes. There was consistency in findings across the qualitative and quantitative literature. Findings for genomic sequencing screening programmes were similar to those for standard NBS.
3. Acceptability was typically described in terms of information provision, informed choice, acceptability of the collection procedure, and support provided. Many parents reported that trust in the healthcare system and healthcare staff gave them confidence to accept screening. However, some complained of limited choice, information offered at the wrong time or lack of transparency in the consent process.
4. Only two reviews and one primary study used or described any kind of theoretical framework. None of the reported frameworks were based on robust empirical evidence or developed specifically for assessing acceptability of NBS. Acceptability is a challenging concept which is likely to vary over time and experience and would benefit from greater theoretical underpinning.
5. Our synthesis of themes from the included qualitative studies, supported by data from included quantitative studies, suggested a possible approach to developing a framework based on requirements for acceptability at each stage of a pathway from consent up to and beyond receipt of test results. This could be developed and contrasted with perceptions at later points in time.

What this adds to existing knowledge

- To the best of our knowledge, this is the first systematic review specifically devoted to examining the acceptability of NBS and newborn genomic sequencing screening programmes among soon to be and recent parents/carers.
- We have identified key constructs of NBS acceptability, most of which were supported by both qualitative and quantitative evidence.
- The review includes a particular focus on use of frameworks to assess acceptability; we developed and piloted a tool to assess the robustness of such frameworks.
- The review highlights a clear need for further research, including in more diverse populations and studies in UK settings.

Additional information

CRediT contribution statement

Duncan Chambers (https://orcid.org/0000-0002-0154-0469): Conceptualisation, Formal analysis, Funding acquisition, Investigation, Methodology, Writing – original draft (lead), Writing – editing and reviewing (lead).

Susan Baxter (https://orcid.org/0000-0002-6034-5495): Conceptualisation, Formal analysis, Funding acquisition, Investigation, Methodology, Writing – original draft (lead), Writing – editing and reviewing (lead).

Anastasios Bastounis (https://orcid.org/0000-0001-5861-9373): Formal analysis, Investigation, Writing – original draft, Writing – editing and reviewing.

Katherine Jones (https://orcid.org/0009-0002-5166-6462): Formal analysis, Investigation, Writing – original draft, Writing – editing and reviewing.

Burak Kundakci (https://orcid.org/0000-0002-3507-1111): Formal analysis, Investigation, Writing – original draft, Writing – editing and reviewing.

Anna Cantrell (https://orcid.org/0000-0003-0040-9853): Data curation, Funding acquisition, Investigation, Methodology, Writing – original draft (supporting), Writing – editing and reviewing (supporting).

Andrew Booth (https://orcid.org/0000-0003-4808-3880): Conceptualisation, Funding acquisition, Methodology.

Katie Lewis: Project administration.

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Data-sharing statement

This study did not generate any new data as it used existing sources and all data are contained within the manuscript. Any queries should be addressed to the corresponding author.

Ethics statement

As secondary research with no human participants, ethical approval was not required.

Information governance statement

The study did not handle any personal information. The University of Sheffield is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org10.3310/RTPQ2268.

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Andrew Booth declares: Member of National Institute for Health Research Health Services and Delivery Research Funding Board (2019–22); Member of National Institute for Health Research Systematic Reviews Advisory Group (2019–22); Currently Co-director of NIHR EnSygN Evidence Synthesis Group (2023–); Co-director of NIHR HS&DR Evidence Synthesis Centre; and NIHR Public Health Evidence Synthesis Team. I am co-convenor of the Cochrane Qualitative and Implementation Methods Group and a core team member of the GRADE-CERQual group.

The other authors declare that they have no competing interests.

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List of abbreviations

CASP	Critical Appraisal Skills Programme
MMAT	Mixed Methods Appraisal Tool
NBS	newborn blood spot
NIHR	National Institute for Health and Care Research
PPI	patient and public involvement
RCT	randomised controlled trial
SAGER	Sex and Gender Equity in Research

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Appendix 1 MEDLINE search strategy

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review and Other Non-Indexed Citations and Daily, 1946 to 13 September 2023

Search strategy:

1 Neonatal Screening/ (11959)
2 Dried Blood Spot Testing/ (2090)
3 NBS.af. (7415)
4 "blood spot screen*".ab,ti. (85)
5 "blood spot test*".ab,ti. (174)
6 "bloodspot screen*".ab,ti. (117)
7 "bloodspot test*".ab,ti. (11)
8 or/1-7 (20420)
9 exp Infant, Newborn/ (676017)
10 (newborn* or new-born* or neonate* or neo-nate*).ab,ti. (272754)
11 9 or 10 (779034)
12 "screen*".ab,ti. (975959)
13 11 and 12 (41030)
14 8 or 13 (51412)
15 Genomics/ or Genetic Testing/ or High-Throughput Nucleotide Sequencing/ or Whole Genome Sequencing/ (156731)
16 Genetic Diseases, Inborn/ (14545)
17 (genom* adj3 screen*).ab,ti. (10688)
18 "whole genome sequencing".ab,ti. (23272)
19 or/15-18 (193464)
20 11 and 19 (5928)
21 "genom* newborn screening".ab,ti. (27)
22 GNBS.ab,ti. (88)
23 or/20-22 (6013)
24 14 or 23 (54922)
25 ((screen* or test* or diagnos*) adj2 (attitude* or knowledge or awareness or accept* or perspective* or perception* or participat* or consent or understanding or view*)).ab,ti. (37899)
26 attitude to health/ or health knowledge, attitudes, practice/ (205050)
27 25 or 26 (238610)
28 24 and 27 (924)
29 limit 28 to yr="2013 -Current" (457)

Appendix 2 Critical appraisal of included studies

Critical appraisal of the empirical (primary) studies included in the review using the MMAT tool																					Studies
Screening questions[a]		Qualitative[b]					Quantitative non-randomised[c]					Quantitative descriptive[d]					Mixed methods[e]					
S2		1.1	1.2	1.3	1.4	1.5	2.1	2.2	2.3	2.4	2.5	3.1	3.2	3.3	3.4	3.5	4.1	4.2	4.3	4.4	4.5	S1
Y							CT	Y	N	Y	Y											Armstrong *et al.*, 2022[21] Y
Y							Y	Y	N	Y	Y											Bailey *et al.*, 2015[22] Y
Y																	Y	Y	Y	Y	Y	Berrios *et al.*, 2020[31] Y
Y												Y	CT	Y	CT	CT						Blackwell *et al.*, 2020[26] Y
Y																	Y	Y	CT	Y	N	Blom *et al.*, 2021[32] Y
Y							Y	CT	N	N	Y											Botkin *et al.*, 2016[23] Y
Y							Y	Y	N	Y	Y											Cakici *et al.*, 2020[24] Y
Y																	Y	Y	Y	Y	Y	Christie *et al.*, 2013[33] Y
Y		Y	Y	Y	Y	Y																Etchegary *et al.*, 2016[14] Y
Y		Y	Y	Y	Y	Y																Joseph *et al.*, 2016[15] Y
Y		Y	Y	Y	Y	Y																Moultrie *et al.*, 2020[16] Y
Y							Y	Y	N	CT	Y											Newcomb *et al.*, 2013[25] Y
Y		Y	Y	Y	Y	Y																Nicholls *et al.*, 2019[17] Y
Y																	Y	CT	N	CT	N	Pereira *et al.*, 2019[34] Y
Y												Y	Y	Y	*N*	Y						Rueegg *et al.*, 2016[27] Y
Y		Y	Y	Y	Y	Y																Ulph *et al.*, 2020[18] Y
Y		Y	Y	Y	Y	Y																Ulph *et al.*, 2015[19] Y
Y												Y	Y	Y	N	Y						van der Pal *et al.*, 2022[28] Y
Y												Y	CT	CT	N	Y						Waisbren *et al.*, 2015[29] Y
Y		Y	Y	Y	Y	Y																Wang *et al.*, 2022[20] Y
Y												Y	Y	Y	CT	N						Wood *et al.*, 2014[30] Y

CT, cannot tell; N, no; Y, yes.

a S1: Are there clear research questions?; S2: Do the collected data allow the research questions to be addressed?

b 1.1: Is the qualitative approach appropriate to answer the research question?; 1.2: Are the qualitative data collection methods adequate to address the research question?; 1.3: Are the findings adequately derived from the data?; 1.4: Is the interpretation of results sufficiently substantiated by data?; 1.5: Is there coherence between qualitative data sources, collection, analysis and interpretation?

This article should be referenced as follows: Chambers D, Baxter S, Bastounis A, Jones K, Kundakci B, Cantrell A, Booth A. The acceptability of blood spot screening and genome sequencing in newborn screening: a systematic review examining evidence and frameworks [published online ahead of print March 12 2025]. *Health Technol Assess* 2025. https://doi.org/10.3310/RTPQ2268

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c 2.1: Are the participants representative of the target population?; 2.2: Are measurements appropriate regarding both the outcome and intervention (or exposure)?; 2.3: Are there complete outcome data?; 2.4: Are the confounders accounted for in the design and analysis?; 2.5: During the study period, is the intervention administered (or exposure occurred) as intended?
d 3.1: Is the sampling strategy relevant to address the research question?; 3.2: Is the sample representative of the target population?; 3.3: Are the measurements appropriate?; 3.4: Is the risk of nonresponse bias low?; 3.5: Is the statistical analysis appropriate to answer the research question?
e 4.1: Is there an adequate rationale for using a mixed-methods design to address the research question?; 4.2: Are the different components of the study effectively integrated to answer the research question?; 4.3: Are the outputs of the integration of qualitative and quantitative components adequately interpreted?; 4.4: Are divergences and inconsistencies between quantitative and qualitative results adequately addressed?; 4.5: Do the different components of the study adhere to the quality criteria of each tradition of the methods involved?

Critical appraisal of the systematic reviews included in the review using the CASP tool

Studies	Q1[a]	Q2[b]	Q3[c]	Q4[d]	Q5[e]	Q6[f]	Q7[g]	Q8[h]	Q9[i]	Q10[j]
Carlton *et al.*, 2021[6]	Y	Y	Y	N	NA	NA	NA	Y	Y	Y
Downie *et al.*, 2021[35]	Y	Y	Y	N	NA	NA	NA	Y	Y	Y
Tluczek *et al.*, 2022[36]	CT	Y	Y	N	NA	NA	NA	Y	CT	Y
White *et al.*, 2021[37]	Y	Y	Y	N	NA	NA	NA	Y	Y	Y

CT, cannot tell; N, no; NA, not applicable; Y, yes.
a Q1: Did the review address a clearly focused question?
b Q2: Did the authors look for the right type of papers?
c Q3: Do you think all the important, relevant studies were included?
d Q4: Did the review's authors do enough to assess quality of the included studies?
e Q5: If the results of the review have been combined, was it reasonable to do so?
f Q6: What are the overall results of the review?
g Q7: How precise are the results?
h Q8: Can the results be applied to the local population?
i Q9: Were all important outcomes considered?
j Q10: Are the benefits worth the harms and costs?

Appendix 3 Sex and Gender Equity in Research guidelines checklist (primary studies)

Section/topic		Checklist item	Study
Armstrong et al., 2022[21]			
General	1	The terms sex/gender used appropriately	Unclear (study eligibility criteria do not relate to a specific sex/gender; the method of definition of gender is not reported)
Title	2	Title specifies the sex/gender of participants if only one included	Not applicable (title refers to parental attitudes; demographic characteristics refer to parents' gender as male or female)
Abstract	3a	Abstract specifies the sex/gender of participants if only one included	Not applicable
	3b	Study population described with gender/sex breakdown[a]	No
Introduction	4a	If relevant, previous studies that show presence or lack of sex/gender differences or similarities are cited	No
	4b	Mention of whether sex/gender might be an important variant and if differences might be expected	No
	4c	The demographics of the study population with regard to sex/gender (e.g. disease prevalence among male/female study participants) are outlined[a]	No
Methods	5a	Method of definition of sex/gender (e.g. self-report, genetic testing)	No
	5b	Description of how sex/gender was considered in the design, whether authors ensured adequate representation of male and female study participants, justification of the reasons for any exclusion of male or female participants, or explanation if not considered. Justification of other sex/gender-specific interventions of study designs (i.e. mandating contraception for women).[a] Explicit reporting of the scientific rationale for contraception requirements and exclusions for pregnancy and lactation should be required[a]	No
Results	6a	Study population description with complete gender/sex breakdown for all categories considered[a]	No (results presented for parents and with a breakdown for self-reported liberal, moderate or conservative beliefs)
	6b	Where appropriate, data presented disaggregated by sex/gender, and sex/gender differences and similarities are described	No
	6c	Sex- and gender-based analyses reported regardless of outcome (in main paper if pre-specified; otherwise in appendix)[a]	No
	6d	For clinical trials, adverse event data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6e	Patient-reported outcome data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	No
	6f	For epidemiological studies, the effects of other exposures on health problems examined for all genders and analysed critically from a gender perspective	Not applicable
	6g	Table 1 includes separate rows for male sex/gender, female sex/gender and other categories if collected[a]	Yes (demographic characteristics report gender as male or female for each arm of the study)
Discussion	7a	Potential implications of sex/gender on the study results and analyses, including the extent to which the findings can be generalised to all sexes/genders in a population	No
	7b	If a sex/gender analysis not done, a rationale is given and implications of the lack of such analysis on the interpretation of the results are discussed	No

Section/topic		Checklist item	Study
Bailey et al., 2015[22]			
General	1	The terms sex/gender used appropriately	Not applicable (terms not used)
Title	2	Title specifies the sex/gender of participants if only one included	Partial (title refers to maternal consequences; demographic characteristics refer to mothers)
Abstract	3a	Abstract specifies the sex/gender of participants if only one included	Partial (abstract refers to mothers)
	3b	Study population described with gender/sex breakdown[a]	Partial (abstract describes study population of mothers)
Introduction	4a	If relevant, previous studies that show presence or lack of sex/gender differences or similarities are cited	No
	4b	Mention of whether sex/gender might be an important variant and if differences might be expected	No (introduction refers to lower income, minority status and absence of social support as factors found to be associated with poor mental health outcomes among parents following disclosure of a disorder affecting the newborn)
	4c	The demographics of the study population with regard to sex/gender (e.g. disease prevalence among male/female study participants) are outlined[a]	No
Methods	5a	Method of definition of sex/gender (e.g. self-report, genetic testing)	No
	5b	Description of how sex/gender was considered in the design, whether authors ensured adequate representation of male and female study participants, justification of the reasons for any exclusion of male or female participants, or explanation if not considered. Justification of other sex/gender-specific interventions of study designs (i.e. mandating contraception for women).[a] Explicit reporting of the scientific rationale for contraception requirements and exclusions for pregnancy and lactation should be required[a]	No (methods refer to comparison of screen-positive participants and non-participants in relation to the following characteristics: maternal age and education, marital status and race/ethnicity. Screen-positive and screen-negative participants were matched for language and income as well as ethnicity and education)
Results	6a	Study population description with complete gender/sex breakdown for all categories considered[a]	No (mothers only; no data presented for gender/sex)
	6b	Where appropriate, data presented disaggregated by sex/gender, and sex/gender differences and similarities are described	Not applicable (association presented for maternal outcomes and spousal support)
	6c	Sex- and gender-based analyses reported regardless of outcome (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6d	For clinical trials, adverse event data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6e	Patient-reported outcome data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6f	For epidemiological studies, the effects of other exposures on health problems examined for all genders and analysed critically from a gender perspective	Not applicable
	6g	Table 1 includes separate rows for male sex/gender, female sex/gender and other categories if collected[a]	Not applicable
Discussion	7a	Potential implications of sex/gender on the study results and analyses, including the extent to which the findings can be generalised to all sexes/genders in a population	No
	7b	If a sex/gender analysis not done, a rationale is given and implications of the lack of such analysis on the interpretation of the results are discussed	No

Section/topic		Checklist item	Study
Berrios et al., 2020[31]			
General	1	The terms sex/gender used appropriately	Unclear (study eligibility criteria do not relate to a specific sex/gender; the method of definition of gender is not reported)
Title	2	Title specifies the sex/gender of participants if only one included	Not applicable (title refers to parents; demographic characteristics refer to participants' gender as male or female)
Abstract	3a	Abstract specifies the sex/gender of participants if only one included	Not applicable
	3b	Study population described with gender/sex breakdown[a]	No
Introduction	4a	If relevant, previous studies that show presence or lack of sex/gender differences or similarities are cited	No
	4b	Mention of whether sex/gender might be an important variant and if differences might be expected	No
	4c	The demographics of the study population with regard to sex/gender (e.g. disease prevalence among male/female study participants) are outlined[a]	No
Methods	5a	Method of definition of sex/gender (e.g. self-report, genetic testing)	No
	5b	Description of how sex/gender was considered in the design, whether authors ensured adequate representation of male and female study participants, justification of the reasons for any exclusion of male or female participants, or explanation if not considered. Justification of other sex/gender-specific interventions of study designs (i.e. mandating contraception for women).[a] Explicit reporting of the scientific rationale for contraception requirements and exclusions for pregnancy and lactation should be required[a]	No
Results	6a	Study population description with complete gender/sex breakdown for all categories considered[a]	No
	6b	Where appropriate, data presented disaggregated by sex/gender, and sex/gender differences and similarities are described	No
	6c	Sex- and gender-based analyses reported regardless of outcome (in main paper if pre-specified; otherwise in appendix)[a]	No
	6d	For clinical trials, adverse event data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6e	Patient-reported outcome data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	No
	6f	For epidemiological studies, the effects of other exposures on health problems examined for all genders and analysed critically from a gender perspective	Not applicable
	6g	Table 1 includes separate rows for male sex/gender, female sex/gender and other categories if collected[a]	Yes (demographic characteristics report gender as male or female for each arm of the study)
Discussion	7a	Potential implications of sex/gender on the study results and analyses, including the extent to which the findings can be generalised to all sexes/genders in a population	No
	7b	If a sex/gender analysis not done, a rationale is given and implications of the lack of such analysis on the interpretation of the results are discussed	No

Section/topic		Checklist item	Study
Blackwell et al., 2020[26]			
General	1	The terms sex/gender used appropriately	Not applicable (terms not used)
Title	2	Title specifies the sex/gender of participants if only one included	Not applicable (title refers to family attitudes; demographic characteristics are not reported for sex/gender)
Abstract	3a	Abstract specifies the sex/gender of participants if only one included	Not applicable
	3b	Study population described with gender/sex breakdown[a]	No
Introduction	4a	If relevant, previous studies that show presence or lack of sex/gender differences or similarities are cited	No
	4b	Mention of whether sex/gender might be an important variant and if differences might be expected	No
	4c	The demographics of the study population with regard to sex/gender (e.g. disease prevalence among male/female study participants) are outlined[a]	No
Methods	5a	Method of definition of sex/gender (e.g. self-report, genetic testing)	No
	5b	Description of how sex/gender was considered in the design, whether authors ensured adequate representation of male and female study participants, justification of the reasons for any exclusion of male or female participants, or explanation if not considered. Justification of other sex/gender-specific interventions of study designs (i.e. mandating contraception for women).[a] Explicit reporting of the scientific rationale for contraception requirements and exclusions for pregnancy and lactation should be required[a]	No
Results	6a	Study population description with complete gender/sex breakdown for all categories considered[a]	No
	6b	Where appropriate, data presented disaggregated by sex/gender, and sex/gender differences and similarities are described	No
	6c	Sex- and gender-based analyses reported regardless of outcome (in main paper if pre-specified; otherwise in appendix)[a]	No
	6d	For clinical trials, adverse event data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6e	Patient-reported outcome data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	No
	6f	For epidemiological studies, the effects of other exposures on health problems examined for all genders and analysed critically from a gender perspective	Not applicable
	6g	Table 1 includes separate rows for male sex/gender, female sex/gender and other categories if collected[a]	No (demographic characteristics for newborn screening report the proportion of fathers only)
Discussion	7a	Potential implications of sex/gender on the study results and analyses, including the extent to which the findings can be generalised to all sexes/genders in a population	No
	7b	If a sex/gender analysis not done, a rationale is given and implications of the lack of such analysis on the interpretation of the results are discussed	No

Section/topic		Checklist item	Study
Blom et al., 2021[32]			
General	1	The terms sex/gender used appropriately	Unclear (study eligibility criteria do not relate to a specific sex/gender; the method of definition of gender is not reported)
Title	2	Title specifies the sex/gender of participants if only one included	Not applicable (title refers to parents' perspectives; demographic characteristics refer to the population gender as male or female in relation to screening, and surveyed or interviewed population as mother, father or both)
Abstract	3a	Abstract specifies the sex/gender of participants if only one included	Not applicable
	3b	Study population described with gender/sex breakdown[a]	No
Introduction	4a	If relevant, previous studies that show presence or lack of sex/gender differences or similarities are cited	No
	4b	Mention of whether sex/gender might be an important variant and if differences might be expected	No
	4c	The demographics of the study population with regard to sex/gender (e.g. disease prevalence among male/female study participants) are outlined[a]	No
Methods	5a	Method of definition of sex/gender (e.g. self-report, genetic testing)	No
	5b	Description of how sex/gender was considered in the design, whether authors ensured adequate representation of male and female study participants, justification of the reasons for any exclusion of male or female participants, or explanation if not considered. Justification of other sex/gender-specific interventions of study designs (i.e. mandating contraception for women).[a] Explicit reporting of the scientific rationale for contraception requirements and exclusions for pregnancy and lactation should be required[a]	No
Results	6a	Study population description with complete gender/sex breakdown for all categories considered[a]	No
	6b	Where appropriate, data presented disaggregated by sex/gender, and sex/gender differences and similarities are described	No
	6c	Sex- and gender-based analyses reported regardless of outcome (in main paper if pre-specified; otherwise in appendix)[a]	No
	6d	For clinical trials, adverse event data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6e	Patient-reported outcome data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	No
	6f	For epidemiological studies, the effects of other exposures on health problems examined for all genders and analysed critically from a gender perspective	Not applicable
	6g	Table 1 includes separate rows for male sex/gender, female sex/gender and other categories if collected[a]	Partial (demographic characteristics report gender as male or female for survey and mother, father or both parents for interview)

Section/topic		Checklist item	Study
Discussion	7a	Potential implications of sex/gender on the study results and analyses, including the extent to which the findings can be generalised to all sexes/genders in a population	No
	7b	If a sex/gender analysis not done, a rationale is given and implications of the lack of such analysis on the interpretation of the results are discussed	No
Botkin et al., 2016[23]			
General	1	The terms sex/gender used appropriately	Not applicable (terms not used)
Title	2	Title specifies the sex/gender of participants if only one included	No (title refers to parents; inclusion criteria refer to pregnant women; results refer to women recruited (plus partner responses) and demographic characteristics of those who completed follow-up (not randomised) refer to whether participants had given birth previously or not)
Abstract	3a	Abstract specifies the sex/gender of participants if only one included	Yes (abstract refers to women)
	3b	Study population described with gender/sex breakdown[a]	Yes (abstract describes eligible women)
Introduction	4a	If relevant, previous studies that show presence or lack of sex/gender differences or similarities are cited	No
	4b	Mention of whether sex/gender might be an important variant and if differences might be expected	No
	4c	The demographics of the study population with regard to sex/gender (e.g. disease prevalence among male/female study participants) are outlined[a]	No
Methods	5a	Method of definition of sex/gender (e.g. self-report, genetic testing)	No
	5b	Description of how sex/gender was considered in the design, whether authors ensured adequate representation of male and female study participants, justification of the reasons for any exclusion of male or female participants, or explanation if not considered. Justification of other sex/gender-specific interventions of study designs (i.e. mandating contraception for women).[a] Explicit reporting of the scientific rationale for contraception requirements and exclusions for pregnancy and lactation should be required[a]	No
Results	6a	Study population description with complete gender/sex breakdown for all categories considered[a]	No
	6b	Where appropriate, data presented disaggregated by sex/gender, and sex/gender differences and similarities are described	No
	6c	Sex- and gender-based analyses reported regardless of outcome (in main paper if pre-specified; otherwise in appendix)[a]	No
	6d	For clinical trials, adverse event data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6e	Patient-reported outcome data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	No
	6f	For epidemiological studies, the effects of other exposures on health problems examined for all genders and analysed critically from a gender perspective	Not applicable
	6g	Table 1 includes separate rows for male sex/gender, female sex/gender and other categories if collected[a]	No (demographic characteristics report whether participants had given birth previously or not)

Section/topic		Checklist item	Study
Discussion	7a	Potential implications of sex/gender on the study results and analyses, including the extent to which the findings can be generalised to all sexes/genders in a population	No
	7b	If a sex/gender analysis not done, a rationale is given and implications of the lack of such analysis on the interpretation of the results are discussed	No
Cakici et al., 2020[24]			
General	1	The terms sex/gender used appropriately	Not applicable (terms not used)
Title	2	Title specifies the sex/gender of participants if only one included	Not applicable (title refers to parental perceptions; inclusion criteria refer to parents or guardians; results refer to the proportion of father responses to an enrolment survey; demographic characteristics unreported for sex/gender for follow-up survey)
Abstract	3a	Abstract specifies the sex/gender of participants if only one included	Not applicable
	3b	Study population described with gender/sex breakdown[a]	No
Introduction	4a	If relevant, previous studies that show presence or lack of sex/gender differences or similarities are cited	No
	4b	Mention of whether sex/gender might be an important variant and if differences might be expected	No
	4c	The demographics of the study population with regard to sex/gender (e.g. disease prevalence among male/female study participants) are outlined[a]	No
Methods	5a	Method of definition of sex/gender (e.g. self-report, genetic testing)	No
	5b	Description of how sex/gender was considered in the design, whether authors ensured adequate representation of male and female study participants, justification of the reasons for any exclusion of male or female participants, or explanation if not considered. Justification of other sex/gender-specific interventions of study designs (i.e. mandating contraception for women).[a] Explicit reporting of the scientific rationale for contraception requirements and exclusions for pregnancy and lactation should be required[a]	No
Results	6a	Study population description with complete gender/sex breakdown for all categories considered[a]	No
	6b	Where appropriate, data presented disaggregated by sex/gender, and sex/gender differences and similarities are described	No
	6c	Sex- and gender-based analyses reported regardless of outcome (in main paper if pre-specified; otherwise in appendix)[a]	No
	6d	For clinical trials, adverse event data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6e	Patient-reported outcome data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	No
	6f	For epidemiological studies, the effects of other exposures on health problems examined for all genders and analysed critically from a gender perspective	Not applicable
	6g	Table 1 includes separate rows for male sex/gender, female sex/gender and other categories if collected[a]	No (demographic characteristics refer to parents only)

Section/topic		Checklist item	Study
Discussion	7a	Potential implications of sex/gender on the study results and analyses, including the extent to which the findings can be generalised to all sexes/genders in a population	No
	7b	If a sex/gender analysis not done, a rationale is given and implications of the lack of such analysis on the interpretation of the results are discussed	No
Carlton et al., 2021[6]			
General	1	The terms sex/gender used appropriately	Not applicable (terms not used)
Title	2	Title specifies the sex/gender of participants if only one included	Not applicable (population unspecified in title; demographic characteristics are not reported for sex/gender)
Abstract	3a	Abstract specifies the sex/gender of participants if only one included	Not applicable
	3b	Study population described with gender/sex breakdown[a]	No
Introduction	4a	If relevant, previous studies that show presence or lack of sex/gender differences or similarities are cited	No
	4b	Mention of whether sex/gender might be an important variant and if differences might be expected	No
	4c	The demographics of the study population with regard to sex/gender (e.g. disease prevalence among male/female study participants) are outlined[a]	No
Methods	5a	Method of definition of sex/gender (e.g. self-report, genetic testing)	No
	5b	Description of how sex/gender was considered in the design, whether authors ensured adequate representation of male and female study participants, justification of the reasons for any exclusion of male or female participants, or explanation if not considered. Justification of other sex/gender-specific interventions of study designs (i.e. mandating contraception for women).[a] Explicit reporting of the scientific rationale for contraception requirements and exclusions for pregnancy and lactation should be required[a]	No
Results	6a	Study population description with complete gender/sex breakdown for all categories considered[a]	No
	6b	Where appropriate, data presented disaggregated by sex/gender, and sex/gender differences and similarities are described	No
	6c	Sex- and gender-based analyses reported regardless of outcome (in main paper if pre-specified; otherwise in appendix)[a]	No
	6d	For clinical trials, adverse event data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6e	Patient-reported outcome data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	No
	6f	For epidemiological studies, the effects of other exposures on health problems examined for all genders and analysed critically from a gender perspective	Not applicable
	6g	Table 1 includes separate rows for male sex/gender, female sex/gender and other categories if collected[a]	No

Section/topic		Checklist item	Study
Discussion	7a	Potential implications of sex/gender on the study results and analyses, including the extent to which the findings can be generalised to all sexes/genders in a population	No
	7b	If a sex/gender analysis not done, a rationale is given and implications of the lack of such analysis on the interpretation of the results are discussed	No
Christie et al., 2013[33]			
General	1	The terms sex/gender used appropriately	Not applicable (terms not used)
Title	2	Title specifies the sex/gender of participants if only one included	Not applicable (title refers to maternal attitudes; demographic characteristics refer to 'mothers')
Abstract	3a	Abstract specifies the sex/gender of participants if only one included	Partial (abstract refers to mothers)
	3b	Study population described with gender/sex breakdown[a]	No
Introduction	4a	If relevant, previous studies that show presence or lack of sex/gender differences or similarities are cited	No
	4b	Mention of whether sex/gender might be an important variant and if differences might be expected	No
	4c	The demographics of the study population with regard to sex/gender (e.g. disease prevalence among male/female study participants) are outlined[a]	No
Methods	5a	Method of definition of sex/gender (e.g. self-report, genetic testing)	No
	5b	Description of how sex/gender was considered in the design, whether authors ensured adequate representation of male and female study participants, justification of the reasons for any exclusion of male or female participants, or explanation if not considered. Justification of other sex/gender-specific interventions of study designs (i.e. mandating contraception for women).[a] Explicit reporting of the scientific rationale for contraception requirements and exclusions for pregnancy and lactation should be required[a]	No
Results	6a	Study population description with complete gender/sex breakdown for all categories considered[a]	No (mothers only; no data presented for gender/sex)
	6b	Where appropriate, data presented disaggregated by sex/gender, and sex/gender differences and similarities are described	Not applicable
	6c	Sex- and gender-based analyses reported regardless of outcome (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6d	For clinical trials, adverse event data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6e	Patient-reported outcome data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6f	For epidemiological studies, the effects of other exposures on health problems examined for all genders and analysed critically from a gender perspective	Not applicable
	6g	Table 1 includes separate rows for male sex/gender, female sex/gender and other categories if collected[a]	Not applicable

Section/topic		Checklist item	Study
Discussion	7a	Potential implications of sex/gender on the study results and analyses, including the extent to which the findings can be generalised to all sexes/genders in a population	No
	7b	If a sex/gender analysis not done, a rationale is given and implications of the lack of such analysis on the interpretation of the results are discussed	No
Downie et al., 2021[35]			
General	1	The terms sex/gender used appropriately	Not applicable (terms not used)
Title	2	Title specifies the sex/gender of participants if only one included	Not applicable (population unspecified in title; demographic characteristics include families, parents, pregnant women, couples)
Abstract	3a	Abstract specifies the sex/gender of participants if only one included	Not applicable
	3b	Study population described with gender/sex breakdown[a]	No
Introduction	4a	If relevant, previous studies that show presence or lack of sex/gender differences or similarities are cited	No
	4b	Mention of whether sex/gender might be an important variant and if differences might be expected	No
	4c	The demographics of the study population with regard to sex/gender (e.g. disease prevalence among male/female study participants) are outlined[a]	No
Methods	5a	Method of definition of sex/gender (e.g. self-report, genetic testing)	No
	5b	Description of how sex/gender was considered in the design, whether authors ensured adequate representation of male and female study participants, justification of the reasons for any exclusion of male or female participants, or explanation if not considered. Justification of other sex/gender-specific interventions of study designs (i.e. mandating contraception for women).[a] Explicit reporting of the scientific rationale for contraception requirements and exclusions for pregnancy and lactation should be required[a]	No
Results	6a	Study population description with complete gender/sex breakdown for all categories considered[a]	No
	6b	Where appropriate, data presented disaggregated by sex/gender, and sex/gender differences and similarities are described	No
	6c	Sex- and gender-based analyses reported regardless of outcome (in main paper if pre-specified; otherwise in appendix)[a]	No
	6d	For clinical trials, adverse event data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6e	Patient-reported outcome data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	No
	6f	For epidemiological studies, the effects of other exposures on health problems examined for all genders and analysed critically from a gender perspective	Not applicable
	6g	Table 1 includes separate rows for male sex/gender, female sex/gender and other categories if collected[a]	No

Section/topic		Checklist item	Study
Discussion	7a	Potential implications of sex/gender on the study results and analyses, including the extent to which the findings can be generalised to all sexes/genders in a population	No
	7b	If a sex/gender analysis not done, a rationale is given and implications of the lack of such analysis on the interpretation of the results are discussed	No
Etchegary et al., 2016[14]			
General	1	The terms sex/gender used appropriately	Not applicable (terms not used)
Title	2	Title specifies the sex/gender of participants if only one included	Not applicable (title refers to parents; demographic characteristics are not reported for sex/gender)
Abstract	3a	Abstract specifies the sex/gender of participants if only one included	Not applicable
	3b	Study population described with gender/sex breakdown[a]	No
Introduction	4a	If relevant, previous studies that show presence or lack of sex/gender differences or similarities are cited	No
	4b	Mention of whether sex/gender might be an important variant and if differences might be expected	No
	4c	The demographics of the study population with regard to sex/gender (e.g. disease prevalence among male/female study participants) are outlined[a]	No
Methods	5a	Method of definition of sex/gender (e.g. self-report, genetic testing)	No
	5b	Description of how sex/gender was considered in the design, whether authors ensured adequate representation of male and female study participants, justification of the reasons for any exclusion of male or female participants, or explanation if not considered. Justification of other sex/gender-specific interventions of study designs (i.e. mandating contraception for women).[a] Explicit reporting of the scientific rationale for contraception requirements and exclusions for pregnancy and lactation should be required[a]	No
Results	6a	Study population description with complete gender/sex breakdown for all categories considered[a]	No
	6b	Where appropriate, data presented disaggregated by sex/gender, and sex/gender differences and similarities are described	No
	6c	Sex- and gender-based analyses reported regardless of outcome (in main paper if pre-specified; otherwise in appendix)[a]	No
	6d	For clinical trials, adverse event data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6e	Patient-reported outcome data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	No
	6f	For epidemiological studies, the effects of other exposures on health problems examined for all genders and analysed critically from a gender perspective	Not applicable
	6g	Table 1 includes separate rows for male sex/gender, female sex/gender and other categories if collected[a]	No

Section/topic		Checklist item	Study
Discussion	7a	Potential implications of sex/gender on the study results and analyses, including the extent to which the findings can be generalised to all sexes/genders in a population	No
	7b	If a sex/gender analysis not done, a rationale is given and implications of the lack of such analysis on the interpretation of the results are discussed	No
Joseph et al., 2016[15]			
General	1	The terms sex/gender used appropriately	Not applicable (terms not used)
Title	2	Title specifies the sex/gender of participants if only one included	No (title refers to parental views; inclusion criteria refer to pregnant women, and a comparator group of parents; demographic characteristics refer to pregnant women)
Abstract	3a	Abstract specifies the sex/gender of participants if only one included	Partial (abstract refers to healthy pregnant women and parents of children diagnosed with a primary immunodeficiency disorder)
	3b	Study population described with gender/sex breakdown[a]	Partial (abstract describes a pregnant women study population and a parental population)
Introduction	4a	If relevant, previous studies that show presence or lack of sex/gender differences or similarities are cited	No
	4b	Mention of whether sex/gender might be an important variant and if differences might be expected	No
	4c	The demographics of the study population with regard to sex/gender (e.g. disease prevalence among male/female study participants) are outlined[a]	No
Methods	5a	Method of definition of sex/gender (e.g. self-report, genetic testing)	No
	5b	Description of how sex/gender was considered in the design, whether authors ensured adequate representation of male and female study participants, justification of the reasons for any exclusion of male or female participants, or explanation if not considered. Justification of other sex/gender-specific interventions of study designs (i.e. mandating contraception for women).[a] Explicit reporting of the scientific rationale for contraception requirements and exclusions for pregnancy and lactation should be required[a]	No
Results	6a	Study population description with complete gender/sex breakdown for all categories considered[a]	No
	6b	Where appropriate, data presented disaggregated by sex/gender, and sex/gender differences and similarities are described	No
	6c	Sex- and gender-based analyses reported regardless of outcome (in main paper if pre-specified; otherwise in appendix)[a]	No
	6d	For clinical trials, adverse event data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6e	Patient-reported outcome data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	No
	6f	For epidemiological studies, the effects of other exposures on health problems examined for all genders and analysed critically from a gender perspective	Not applicable
	6g	Table 1 includes separate rows for male sex/gender, female sex/gender and other categories if collected[a]	No (demographic characteristics refer to pregnant women; unclear if comparator group of parents of children with primary immunodeficiency disorders are also pregnant women)

Section/topic		Checklist item	Study
Discussion	7a	Potential implications of sex/gender on the study results and analyses, including the extent to which the findings can be generalised to all sexes/genders in a population	No
	7b	If a sex/gender analysis not done, a rationale is given and implications of the lack of such analysis on the interpretation of the results are discussed	No
Moultrie et al., 2020[16]			
General	1	The terms sex/gender used appropriately	Unclear (only parents of the opposite sex who were married or in a committed relationship met study eligibility criteria without rationale given)
Title	2	Title specifies the sex/gender of participants if only one included	Not applicable (title refers to parental views; inclusion criteria refer to current or expecting parents who were with a partner of the opposite sex; participant characteristics not reported for sex/gender)
Abstract	3a	Abstract specifies the sex/gender of participants if only one included	Not applicable
	3b	Study population described with gender/sex breakdown[a]	No
Introduction	4a	If relevant, previous studies that show presence or lack of sex/gender differences or similarities are cited	No
	4b	Mention of whether sex/gender might be an important variant and if differences might be expected	No
	4c	The demographics of the study population with regard to sex/gender (e.g. disease prevalence among male/female study participants) are outlined[a]	No
Methods	5a	Method of definition of sex/gender (e.g. self-report, genetic testing)	No
	5b	Description of how sex/gender was considered in the design, whether authors ensured adequate representation of male and female study participants, justification of the reasons for any exclusion of male or female participants, or explanation if not considered. Justification of other sex/gender-specific interventions of study designs (i.e. mandating contraception for women).[a] Explicit reporting of the scientific rationale for contraception requirements and exclusions for pregnancy and lactation should be required[a]	Partial [methods refer to the selection of participants who were married or in a committed relationship with a partner of the opposite sex, and efforts to recruit equal numbers of females from three major race/ethnicity groups (white, black and Hispanic)]
Results	6a	Study population description with complete gender/sex breakdown for all categories considered[a]	No
	6b	Where appropriate, data presented disaggregated by sex/gender, and sex/gender differences and similarities are described	No
	6c	Sex- and gender-based analyses reported regardless of outcome (in main paper if pre-specified; otherwise in appendix)[a]	No
	6d	For clinical trials, adverse event data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6e	Patient-reported outcome data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	No
	6f	For epidemiological studies, the effects of other exposures on health problems examined for all genders and analysed critically from a gender perspective	Not applicable
	6g	Table 1 includes separate rows for male sex/gender, female sex/gender and other categories if collected[a]	No (demographic characteristics refer to time married or in a committed relationship (specified in eligibility criteria as opposite sex) and to mother's race/ethnicity but not parents' sex/gender)

Section/topic		Checklist item	Study
Discussion	7a	Potential implications of sex/gender on the study results and analyses, including the extent to which the findings can be generalised to all sexes/genders in a population	No
	7b	If a sex/gender analysis not done, a rationale is given and implications of the lack of such analysis on the interpretation of the results are discussed	No
Newcomb et al., 2013[25]			
General	1	The terms sex/gender used appropriately	Not applicable (terms not used)
Title	2	Title specifies the sex/gender of participants if only one included	Partial (title refers to maternal attitudes; inclusion criteria refer to mothers; results refer to postpartum women)
Abstract	3a	Abstract specifies the sex/gender of participants if only one included	Partial (abstract refers to mothers)
	3b	Study population described with gender/sex breakdown[a]	Partial (abstract describes study population of mothers)
Introduction	4a	If relevant, previous studies that show presence or lack of sex/gender differences or similarities are cited	No
	4b	Mention of whether sex/gender might be an important variant and if differences might be expected	No
	4c	The demographics of the study population with regard to sex/gender (e.g. disease prevalence among male/female study participants) are outlined[a]	No
Methods	5a	Method of definition of sex/gender (e.g. self-report, genetic testing)	No
	5b	Description of how sex/gender was considered in the design, whether authors ensured adequate representation of male and female study participants, justification of the reasons for any exclusion of male or female participants, or explanation if not considered. Justification of other sex/gender-specific interventions of study designs (i.e. mandating contraception for women).[a] Explicit reporting of the scientific rationale for contraception requirements and exclusions for pregnancy and lactation should be required[a]	No. Methods report representative numbers of females from three major ethnic groups (African American, Caucasian and Hispanic)
Results	6a	Study population description with complete gender/sex breakdown for all categories considered[a]	No (mothers only; no data presented for gender/sex)
	6b	Where appropriate, data presented disaggregated by sex/gender, and sex/gender differences and similarities are described	Not applicable
	6c	Sex- and gender-based analyses reported regardless of outcome (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6d	For clinical trials, adverse event data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6e	Patient-reported outcome data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6f	For epidemiological studies, the effects of other exposures on health problems examined for all genders and analysed critically from a gender perspective	Not applicable
	6g	Table 1 includes separate rows for male sex/gender, female sex/gender and other categories if collected[a]	Not applicable
Discussion	7a	Potential implications of sex/gender on the study results and analyses, including the extent to which the findings can be generalised to all sexes/genders in a population	No
	7b	If a sex/gender analysis not done, a rationale is given and implications of the lack of such analysis on the interpretation of the results are discussed	No

Section/topic		Checklist item	Study
Nicholls et al., 2019[17]			
General	1	The terms sex/gender used appropriately	Not applicable (terms not used)
Title	2	Title specifies the sex/gender of participants if only one included	Not applicable (title refers to parent; demographic characteristics are not reported for sex/gender)
Abstract	3a	Abstract specifies the sex/gender of participants if only one included	Not applicable
	3b	Study population described with gender/sex breakdown[a]	No
Introduction	4a	If relevant, previous studies that show presence or lack of sex/gender differences or similarities are cited	No
	4b	Mention of whether sex/gender might be an important variant and if differences might be expected	No
	4c	The demographics of the study population with regard to sex/gender (e.g. disease prevalence among male/female study participants) are outlined[a]	No
Methods	5a	Method of definition of sex/gender (e.g. self-report, genetic testing)	No
	5b	Description of how sex/gender was considered in the design, whether authors ensured adequate representation of male and female study participants, justification of the reasons for any exclusion of male or female participants, or explanation if not considered. Justification of other sex/gender-specific interventions of study designs (i.e. mandating contraception for women).[a] Explicit reporting of the scientific rationale for contraception requirements and exclusions for pregnancy and lactation should be required[a]	No (methods refer to one study site's postal recruitment of parents as addressed only to the mother based on contact information in clinical records)
Results	6a	Study population description with complete gender/sex breakdown for all categories considered[a]	No
	6b	Where appropriate, data presented disaggregated by sex/gender, and sex/gender differences and similarities are described	No
	6c	Sex- and gender-based analyses reported regardless of outcome (in main paper if pre-specified; otherwise in appendix)[a]	No
	6d	For clinical trials, adverse event data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6e	Patient-reported outcome data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	No
	6f	For epidemiological studies, the effects of other exposures on health problems examined for all genders and analysed critically from a gender perspective	Not applicable
	6g	Table 1 includes separate rows for male sex/gender, female sex/gender and other categories if collected[a]	No
Discussion	7a	Potential implications of sex/gender on the study results and analyses, including the extent to which the findings can be generalised to all sexes/genders in a population	No
	7b	If a sex/gender analysis not done, a rationale is given and implications of the lack of such analysis on the interpretation of the results are discussed	No
Pereira et al., 2019[34]			
General	1	The terms sex/gender used appropriately	Unclear (study methods do not relate to a specific sex/gender; the method of definition of sex is not reported)

Section/topic		Checklist item	Study
Title	2	Title specifies the sex/gender of participants if only one included	Not applicable (population unspecified in title; demographic characteristics refer to participant sex as male or female)
Abstract	3a	Abstract specifies the sex/gender of participants if only one included	Not applicable
	3b	Study population described with gender/sex breakdown[a]	No
Introduction	4a	If relevant, previous studies that show presence or lack of sex/gender differences or similarities are cited	No
	4b	Mention of whether sex/gender might be an important variant and if differences might be expected	No
	4c	The demographics of the study population with regard to sex/gender (e.g. disease prevalence among male/female study participants) are outlined[a]	No
Methods	5a	Method of definition of sex/gender (e.g. self-report, genetic testing)	No
	5b	Description of how sex/gender was considered in the design, whether authors ensured adequate representation of male and female study participants, justification of the reasons for any exclusion of male or female participants, or explanation if not considered. Justification of other sex/gender-specific interventions of study designs (i.e. mandating contraception for women).[a] Explicit reporting of the scientific rationale for contraception requirements and exclusions for pregnancy and lactation should be required[a]	No
Results	6a	Study population description with complete gender/sex breakdown for all categories considered[a]	No
	6b	Where appropriate, data presented disaggregated by sex/gender, and sex/gender differences and similarities are described	No
	6c	Sex- and gender-based analyses reported regardless of outcome (in main paper if pre-specified; otherwise in appendix)[a]	No
	6d	For clinical trials, adverse event data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6e	Patient-reported outcome data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	No
	6f	For epidemiological studies, the effects of other exposures on health problems examined for all genders and analysed critically from a gender perspective	Not applicable
	6g	Table 1 includes separate rows for male sex/gender, female sex/gender and other categories if collected[a]	Yes (demographic characteristics report sex as male or female)
Discussion	7a	Potential implications of sex/gender on the study results and analyses, including the extent to which the findings can be generalised to all sexes/genders in a population	No
	7b	If a sex/gender analysis not done, a rationale is given and implications of the lack of such analysis on the interpretation of the results are discussed	No
Ruegg et al., 2016[27]			
General	1	The terms sex/gender used appropriately	Unclear (sex of the child but not parents reported)
Title	2	Title specifies the sex/gender of participants if only one included	Not applicable (title refers to parent perspective; results refer to parents but demographic characteristics reported for child not parents)

Section/topic		Checklist item	Study
Abstract	3a	Abstract specifies the sex/gender of participants if only one included	Not applicable
	3b	Study population described with gender/sex breakdown[a]	No
Introduction	4a	If relevant, previous studies that show presence or lack of sex/gender differences or similarities are cited	No
	4b	Mention of whether sex/gender might be an important variant and if differences might be expected	No
	4c	The demographics of the study population with regard to sex/gender (e.g. disease prevalence among male/female study participants) are outlined[a]	No
Methods	5a	Method of definition of sex/gender (e.g. self-report, genetic testing)	No
	5b	Description of how sex/gender was considered in the design, whether authors ensured adequate representation of male and female study participants, justification of the reasons for any exclusion of male or female participants, or explanation if not considered. Justification of other sex/gender-specific interventions of study designs (i.e. mandating contraception for women).[a] Explicit reporting of the scientific rationale for contraception requirements and exclusions for pregnancy and lactation should be required[a]	No
Results	6a	Study population description with complete gender/sex breakdown for all categories considered[a]	No
	6b	Where appropriate, data presented disaggregated by sex/gender, and sex/gender differences and similarities are described	No
	6c	Sex- and gender-based analyses reported regardless of outcome (in main paper if pre-specified; otherwise in appendix)[a]	No
	6d	For clinical trials, adverse event data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6e	Patient-reported outcome data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	No
	6f	For epidemiological studies, the effects of other exposures on health problems examined for all genders and analysed critically from a gender perspective	Not applicable
	6g	Table 1 includes separate rows for male sex/gender, female sex/gender and other categories if collected[a]	No (demographic characteristics refer to the sex of the child not parents)
Discussion	7a	Potential implications of sex/gender on the study results and analyses, including the extent to which the findings can be generalised to all sexes/genders in a population	No
	7b	If a sex/gender analysis not done, a rationale is given and implications of the lack of such analysis on the interpretation of the results are discussed	No
Tluczek et al., 2022[36]			
General	1	The terms sex/gender used appropriately	Not applicable (terms not used)
Title	2	Title specifies the sex/gender of participants if only one included	Not applicable (population unspecified in title; demographic characteristics not reported for sex/gender)
Abstract	3a	Abstract specifies the sex/gender of participants if only one included	Not applicable
	3b	Study population described with gender/sex breakdown[a]	No

Section/topic		Checklist item	Study
Introduction	4a	If relevant, previous studies that show presence or lack of sex/gender differences or similarities are cited	No
	4b	Mention of whether sex/gender might be an important variant and if differences might be expected	No
	4c	The demographics of the study population with regard to sex/gender (e.g. disease prevalence among male/female study participants) are outlined[a]	No
Methods	5a	Method of definition of sex/gender (e.g. self-report, genetic testing)	No
	5b	Description of how sex/gender was considered in the design, whether authors ensured adequate representation of male and female study participants, justification of the reasons for any exclusion of male or female participants, or explanation if not considered. Justification of other sex/gender-specific interventions of study designs (i.e. mandating contraception for women).[a] Explicit reporting of the scientific rationale for contraception requirements and exclusions for pregnancy and lactation should be required[a]	No
Results	6a	Study population description with complete gender/sex breakdown for all categories considered[a]	No
	6b	Where appropriate, data presented disaggregated by sex/gender, and sex/gender differences and similarities are described	No (sex/gender differences incompletely reported. One included study comparing mothers and fathers found that fewer fathers were informed about newborn screening. Narrative reporting of disparities in relation to newborn screening uptake and the mother's ethnicity, mother's income and mother's prenatal information about newborn screening; also, general knowledge of newborn screening and the postpartum woman's ethnicity and the mother's mental health)
	6c	Sex- and gender-based analyses reported regardless of outcome (in main paper if pre-specified; otherwise in appendix)[a]	No
	6d	For clinical trials, adverse event data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6e	Patient-reported outcome data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	No
	6f	For epidemiological studies, the effects of other exposures on health problems examined for all genders and analysed critically from a gender perspective	Not applicable
	6g	Table 1 includes separate rows for male sex/gender, female sex/gender and other categories if collected[a]	No
Discussion	7a	Potential implications of sex/gender on the study results and analyses, including the extent to which the findings can be generalised to all sexes/genders in a population	No
	7b	If a sex/gender analysis not done, a rationale is given and implications of the lack of such analysis on the interpretation of the results are discussed	No
Ulph et al., 2015[19]			
General	1	The terms sex/gender used appropriately	Unclear (gender of the child reported as male or female; parents' gender not reported)
Title	2	Title specifies the sex/gender of participants if only one included	Not applicable (title refers to parents' responses; results refer to parents or family members; demographic characteristics refer to gender of infant not parents)

Section/topic		Checklist item	Study
Abstract	3a	Abstract specifies the sex/gender of participants if only one included	Not applicable
	3b	Study population described with gender/sex breakdown[a]	No
Introduction	4a	If relevant, previous studies that show presence or lack of sex/gender differences or similarities are cited	No
	4b	Mention of whether sex/gender might be an important variant and if differences might be expected	No
	4c	The demographics of the study population with regard to sex/gender (e.g. disease prevalence among male/female study participants) are outlined[a]	No
Methods	5a	Method of definition of sex/gender (e.g. self-report, genetic testing)	No
	5b	Description of how sex/gender was considered in the design, whether authors ensured adequate representation of male and female study participants, justification of the reasons for any exclusion of male or female participants, or explanation if not considered. Justification of other sex/gender-specific interventions of study designs (i.e. mandating contraception for women).[a] Explicit reporting of the scientific rationale for contraception requirements and exclusions for pregnancy and lactation should be required[a]	No
Results	6a	Study population description with complete gender/sex breakdown for all categories considered[a]	No
	6b	Where appropriate, data presented disaggregated by sex/gender, and sex/gender differences and similarities are described	No (narrative reporting of fathers also appearing to struggle, which is considered in the context of them waiting for further test results once they have returned to work)
	6c	Sex- and gender-based analyses reported regardless of outcome (in main paper if pre-specified; otherwise in appendix)[a]	No
	6d	For clinical trials, adverse event data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6e	Patient-reported outcome data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	No
	6f	For epidemiological studies, the effects of other exposures on health problems examined for all genders and analysed critically from a gender perspective	Not applicable
	6g	Table 1 includes separate rows for male sex/gender, female sex/gender and other categories if collected[a]	No (demographic characteristics report gender of infant as male or female but not parents)
Discussion	7a	Potential implications of sex/gender on the study results and analyses, including the extent to which the findings can be generalised to all sexes/genders in a population	Partial (disempowerment of fathers when communication of results solely with mothers; possibility of non-paternity disclosure through screening raised but not a major theme among respondents)
	7b	If a sex/gender analysis not done, a rationale is given and implications of the lack of such analysis on the interpretation of the results are discussed	No
Ulph et al., 2020[18]			
General	1	The terms sex/gender used appropriately	Not applicable (terms not used)
Title	2	Title specifies the sex/gender of participants if only one included	Not applicable (title refers to parents' views; demographic characteristics not reported for sex/gender)

Section/topic		Checklist item	Study
Abstract	3a	Abstract specifies the sex/gender of participants if only one included	Not applicable
	3b	Study population described with gender/sex breakdown[a]	No
Introduction	4a	If relevant, previous studies that show presence or lack of sex/gender differences or similarities are cited	No
	4b	Mention of whether sex/gender might be an important variant and if differences might be expected	No
	4c	The demographics of the study population with regard to sex/gender (e.g. disease prevalence among male/female study participants) are outlined[a]	No
Methods	5a	Method of definition of sex/gender (e.g. self-report, genetic testing)	No
	5b	Description of how sex/gender was considered in the design, whether authors ensured adequate representation of male and female study participants, justification of the reasons for any exclusion of male or female participants, or explanation if not considered. Justification of other sex/gender-specific interventions of study designs (i.e. mandating contraception for women).[a] Explicit reporting of the scientific rationale for contraception requirements and exclusions for pregnancy and lactation should be required[a]	No
Results	6a	Study population description with complete gender/sex breakdown for all categories considered[a]	No
	6b	Where appropriate, data presented disaggregated by sex/gender, and sex/gender differences and similarities are described	No (narrative reporting of the need for couples to be informed not just the mother)
	6c	Sex- and gender-based analyses reported regardless of outcome (in main paper if pre-specified; otherwise in appendix)[a]	No
	6d	For clinical trials, adverse event data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6e	Patient-reported outcome data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	No
	6f	For epidemiological studies, the effects of other exposures on health problems examined for all genders and analysed critically from a gender perspective	Not applicable
	6g	Table 1 includes separate rows for male sex/gender, female sex/gender and other categories if collected[a]	Yes (demographic characteristics not reported for sex/gender)
Discussion	7a	Potential implications of sex/gender on the study results and analyses, including the extent to which the findings can be generalised to all sexes/genders in a population	No
	7b	If a sex/gender analysis not done, a rationale is given and implications of the lack of such analysis on the interpretation of the results are discussed	No
van der Pal et al., 2022[28]			
General	1	The terms sex/gender used appropriately	Unclear (sex of the child as male or female reported; parents' sex not reported)
Title	2	Title specifies the sex/gender of participants if only one included	Not applicable (title refers to parents' views; demographic characteristics refer to mothers and fathers/ partners)
Abstract	3a	Abstract specifies the sex/gender of participants if only one included	Not applicable
	3b	Study population described with gender/sex breakdown[a]	No

Section/topic		Checklist item	Study
Introduction	4a	If relevant, previous studies that show presence or lack of sex/gender differences or similarities are cited	No
	4b	Mention of whether sex/gender might be an important variant and if differences might be expected	No
	4c	The demographics of the study population with regard to sex/gender (e.g. disease prevalence among male/female study participants) are outlined[a]	No
Methods	5a	Method of definition of sex/gender (e.g. self-report, genetic testing)	No
	5b	Description of how sex/gender was considered in the design, whether authors ensured adequate representation of male and female study participants, justification of the reasons for any exclusion of male or female participants, or explanation if not considered. Justification of other sex/gender-specific interventions of study designs (i.e. mandating contraception for women).[a] Explicit reporting of the scientific rationale for contraception requirements and exclusions for pregnancy and lactation should be required[a]	No
Results	6a	Study population description with complete gender/sex breakdown for all categories considered[a]	No
	6b	Where appropriate, data presented disaggregated by sex/gender, and sex/gender differences and similarities are described	Partial (data presented for a higher proportion of respondents declining newborn screening being fathers)
	6c	Sex- and gender-based analyses reported regardless of outcome (in main paper if pre-specified; otherwise in appendix)[a]	Partial (sex- and gender-based analyses not presented for parental acceptability but for respondents' perspectives on screening for a condition that has large differences in manifestation and treatability between males and females)
	6d	For clinical trials, adverse event data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6e	Patient-reported outcome data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	No
	6f	For epidemiological studies, the effects of other exposures on health problems examined for all genders and analysed critically from a gender perspective	Not applicable
	6g	Table 1 includes separate rows for male sex/gender, female sex/gender and other categories if collected[a]	No (demographic characteristics report respondents as mothers or fathers/partners or both)
Discussion	7a	Potential implications of sex/gender on the study results and analyses, including the extent to which the findings can be generalised to all sexes/genders in a population	No
	7b	If a sex/gender analysis not done, a rationale is given and implications of the lack of such analysis on the interpretation of the results are discussed	No
Waisbren et al., 2015[29]			
General	1	The terms sex/gender used appropriately	Unclear (study methods do not relate to a specific sex/gender; the method of definition of gender is not reported)
Title	2	Title specifies the sex/gender of participants if only one included	Not applicable (title refers to parents; demographic characteristics report gender as the proportion of female parents)

Section/topic		Checklist item	Study
Abstract	3a	Abstract specifies the sex/gender of participants if only one included	Not applicable
	3b	Study population described with gender/sex breakdown[a]	No
Introduction	4a	If relevant, previous studies that show presence or lack of sex/gender differences or similarities are cited	No
	4b	Mention of whether sex/gender might be an important variant and if differences might be expected	No
	4c	The demographics of the study population with regard to sex/gender (e.g. disease prevalence among male/female study participants) are outlined[a]	No
Methods	5a	Method of definition of sex/gender (e.g. self-report, genetic testing)	No
	5b	Description of how sex/gender was considered in the design, whether authors ensured adequate representation of male and female study participants, justification of the reasons for any exclusion of male or female participants, or explanation if not considered. Justification of other sex/gender-specific interventions of study designs (i.e. mandating contraception for women).[a] Explicit reporting of the scientific rationale for contraception requirements and exclusions for pregnancy and lactation should be required[a]	No
Results	6a	Study population description with complete gender/sex breakdown for all categories considered[a]	No
	6b	Where appropriate, data presented disaggregated by sex/gender, and sex/gender differences and similarities are described	Partial (concordance on genomic newborn testing between mothers and fathers reported to be higher if married. Those married also found to express less interest in newborn genomic testing)
	6c	Sex- and gender-based analyses reported regardless of outcome (in main paper if pre-specified; otherwise in appendix)[a]	Partial (concordance analysis reported for mothers and fathers in the same family unit regarding attitudes on newborn genomic testing)
	6d	For clinical trials, adverse event data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6e	Patient-reported outcome data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	No
	6f	For epidemiological studies, the effects of other exposures on health problems examined for all genders and analysed critically from a gender perspective	Not applicable
	6g	Table 1 includes separate rows for male sex/gender, female sex/gender and other categories if collected[a]	No (demographic characteristics report gender as the proportion of females)
Discussion	7a	Potential implications of sex/gender on the study results and analyses, including the extent to which the findings can be generalised to all sexes/genders in a population	Partial (mostly similar interest between both parents towards newborn genomic screening reported but need for processes in place to support informed consent of both parents also)
	7b	If a sex/gender analysis not done, a rationale is given and implications of the lack of such analysis on the interpretation of the results are discussed	No
Wang et al., 2022[20]			
General	1	The terms sex/gender used appropriately	Not applicable (terms not used)
Title	2	Title specifies the sex/gender of participants if only one included	Partial (title refers to pregnant Latinas; demographic characteristics not reported for sex/gender but as pregnant Latinas)

Section/topic		Checklist item	Study
Abstract	3a	Abstract specifies the sex/gender of participants if only one included	Partial (abstract refers to pregnant Latinas)
	3b	Study population described with gender/sex breakdown[a]	Partial (abstract describes study population of pregnant Latinas)
Introduction	4a	If relevant, previous studies that show presence or lack of sex/gender differences or similarities are cited	No
	4b	Mention of whether sex/gender might be an important variant and if differences might be expected	No (introduction refers to previous studies focusing on the perspectives of non-Hispanic white people of moderate to high socioeconomic status)
	4c	The demographics of the study population with regard to sex/gender (e.g. disease prevalence among male/female study participants) are outlined[a]	No
Methods	5a	Method of definition of sex/gender (e.g. self-report, genetic testing)	No
	5b	Description of how sex/gender was considered in the design, whether authors ensured adequate representation of male and female study participants, justification of the reasons for any exclusion of male or female participants, or explanation if not considered. Justification of other sex/gender-specific interventions of study designs (i.e. mandating contraception for women).[a] Explicit reporting of the scientific rationale for contraception requirements and exclusions for pregnancy and lactation should be required[a]	Partial (methods refer to participating prenatal clinics mainly serving Latina patients in the region)
Results	6a	Study population description with complete gender/sex breakdown for all categories considered[a]	No (pregnant Latinas/mothers only; no data presented for gender/sex)
	6b	Where appropriate, data presented disaggregated by sex/gender, and sex/gender differences and similarities are described	Not applicable
	6c	Sex- and gender-based analyses reported regardless of outcome (in main paper if pre-specified; otherwise in appendix)[a]	No
	6d	For clinical trials, adverse event data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6e	Patient-reported outcome data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	No
	6f	For epidemiological studies, the effects of other exposures on health problems examined for all genders and analysed critically from a gender perspective	Not applicable
	6g	Table 1 includes separate rows for male sex/gender, female sex/gender and other categories if collected[a]	No
Discussion	7a	Potential implications of sex/gender on the study results and analyses, including the extent to which the findings can be generalised to all sexes/genders in a population	No
	7b	If a sex/gender analysis not done, a rationale is given and implications of the lack of such analysis on the interpretation of the results are discussed	No
White et al., 2021[37]			
General	1	The terms sex/gender used appropriately	Not applicable (terms not used)
Title	2	Title specifies the sex/gender of participants if only one included	Not applicable (title refers to parents; demographic characteristics include parent study populations)

Section/topic		Checklist item	Study
Abstract	3a	Abstract specifies the sex/gender of participants if only one included	Not applicable
	3b	Study population described with gender/sex breakdown[a]	No
Introduction	4a	If relevant, previous studies that show presence or lack of sex/gender differences or similarities are cited	No
	4b	Mention of whether sex/gender might be an important variant and if differences might be expected	No
	4c	The demographics of the study population with regard to sex/gender (e.g. disease prevalence among male/female study participants) are outlined[a]	No
Methods	5a	Method of definition of sex/gender (e.g. self-report, genetic testing)	No
	5b	Description of how sex/gender was considered in the design, whether authors ensured adequate representation of male and female study participants, justification of the reasons for any exclusion of male or female participants, or explanation if not considered. Justification of other sex/gender-specific interventions of study designs (i.e. mandating contraception for women).[a] Explicit reporting of the scientific rationale for contraception requirements and exclusions for pregnancy and lactation should be required[a]	No
Results	6a	Study population description with complete gender/sex breakdown for all categories considered[a]	No
	6b	Where appropriate, data presented disaggregated by sex/gender, and sex/gender differences and similarities are described	No
	6c	Sex- and gender-based analyses reported regardless of outcome (in main paper if pre-specified; otherwise in appendix)[a]	No
	6d	For clinical trials, adverse event data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6e	Patient-reported outcome data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	No
	6f	For epidemiological studies, the effects of other exposures on health problems examined for all genders and analysed critically from a gender perspective	Not applicable
	6g	Table 1 includes separate rows for male sex/gender, female sex/gender and other categories if collected[a]	No
Discussion	7a	Potential implications of sex/gender on the study results and analyses, including the extent to which the findings can be generalised to all sexes/genders in a population	No
	7b	If a sex/gender analysis not done, a rationale is given and implications of the lack of such analysis on the interpretation of the results are discussed	No
Wood et al., 2014[30]			
General	1	The terms sex/gender used appropriately	Unclear (study methods do not relate to a specific sex/gender; the method of definition of gender is not reported)
Title	2	Title specifies the sex/gender of participants if only one included	Not applicable (title refers to parental attitudes; demographic characteristics refer to gender as men or women; results refer to expectant parents)

Section/topic		Checklist item	Study
Abstract	3a	Abstract specifies the sex/gender of participants if only one included	Not applicable
	3b	Study population described with gender/sex breakdown[a]	No
Introduction	4a	If relevant, previous studies that show presence or lack of sex/gender differences or similarities are cited	No
	4b	Mention of whether sex/gender might be an important variant and if differences might be expected	No
	4c	The demographics of the study population with regard to sex/gender (e.g. disease prevalence among male/female study participants) are outlined[a]	No
Methods	5a	Method of definition of sex/gender (e.g. self-report, genetic testing)	No
	5b	Description of how sex/gender was considered in the design, whether authors ensured adequate representation of male and female study participants, justification of the reasons for any exclusion of male or female participants, or explanation if not considered. Justification of other sex/gender-specific interventions of study designs (i.e. mandating contraception for women).[a] Explicit reporting of the scientific rationale for contraception requirements and exclusions for pregnancy and lactation should be required[a]	No
Results	6a	Study population description with complete gender/sex breakdown for all categories considered[a]	No
	6b	Where appropriate, data presented disaggregated by sex/gender, and sex/gender differences and similarities are described	No
	6c	Sex- and gender-based analyses reported regardless of outcome (in main paper if pre-specified; otherwise in appendix)[a]	No
	6d	For clinical trials, adverse event data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	Not applicable
	6e	Patient-reported outcome data disaggregated by sex/gender (in main paper if pre-specified; otherwise in appendix)[a]	No
	6f	For epidemiological studies, the effects of other exposures on health problems examined for all genders and analysed critically from a gender perspective	Not applicable
	6g	Table 1 includes separate rows for male sex/gender, female sex/gender and other categories if collected[a]	Partial (demographic characteristics report gender as men or women)
Discussion	7a	Potential implications of sex/gender on the study results and analyses, including the extent to which the findings can be generalised to all sexes/genders in a population	No
	7b	If a sex/gender analysis not done, a rationale is given and implications of the lack of such analysis on the interpretation of the results are discussed	No

a These points extend beyond the original SAGER table.
Source: Adapted from Van Epps H, Astudillo O, Maretin YDP, Marsh J. The Sex and Gender Equity in Research (SAGER) guidelines: implementation and checklist development. *Eur Sci Edit* 2022;**48**:e86910. https://doi.org/10.3897/ese.2022.e86910. Reproduced under the terms of Creative Commons Attribution License (CC BY 4.0).

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Appendix 4 List of conditions tested in newborn blood spot programmes by country (included studies)

USA[a] (CA)[b]	USA (IL)[b]	USA (MA)[b]	USA (MO)[b]	USA (NY)[b]	USA (NC)[b]	USA (PA)[b]	USA (SC)[b]	USA (TX)[b]	USA (UT)[b]	Australia[c]	Canada[d]	The Netherlands[e]	Switzerland[f]	UK[g]
ARG	ARG	ARG	ARG	ARG	ASA	ARG	ASA	ARG	ARG	CAH	BIOT	HbH	PKU	SCD
ASA	ASA	ASA	ASA	ASA	H-PHE	ASA	H-PHE	ASA	ASA	CH	CUD	Hb S/βTh	BIOT	CF
H-PHE	H-PHE	H-PHE	H-PHE	H-PHE	CIT	H-PHE	BIOPT-BS	H-PHE	H-PHE	ASA	CIT	BIOT	CF	CH
BIOPT-BS	CIT	BIOPT-BS	BIOPT-BS	CIT	PKU	BIOPT-BS	BIOPT-REG	BIOPT-BS	BIOPT-BS	CIT I	GA-1	CPT1	GA-1	PKU
BIOPT-REG	CIT II	BIOPT-REG	BIOPT-REG	CIT II	HCY	BIOPT-REG	CIT	BIOPT-REG	CIT	HCY	GALT	CAH	MSUD	MCADD
CPS	PKU	CPS	CIT	PKU	MSUD	CIT	CIT II	CIT	CIT II	MSUD	HMG	CH	SCID	MSUD
CIT	HCY	CIT	CIT II	HCY	TYR I	CIT II	PKU	CIT II	PKU	PKU (plus hyperpheny-lalinemias and pterin enzyme deficiencies)	IVA	CF	Severe T-cell lymphopenia	IVA
CIT II	MET	CIT II	PKU	MET	TYR II	PKU	HCY	PKU	HCY	TYR II	LCHAD	GAL	MCADD	GA-1
PKU	MSUD	PKU	HCY	MSUD	TYR III	HCY	MET	HCY	MSUD	TYR III	MCAD	GALK	CAH	HCY
HCY	TYR I	HCY	MET	TYR I	CAH	MET	MSUD	MET	PRO	CACT	MMA	GA-1	GALT	
MET	CAH	MET	MSUD	TYR II	CH	MSUD	TYR I	MSUD	TYR I	CPT-IA	MSUD	HMG	CH	
Hyper ORN	CH	Hyper ORN	TYR I	TYR III	CACT	TYR I	TYR II	TYR I	TYR II	CPT-II	PROP	IVA		
MSUD	CACT	MSUD	TYR II	CAH	CPT-II	TYR II	TYR III	TYR II	TYR III	CUD	PKU	LCHAD		
OTC	CPT-IA	OTC	TYR III	CH	CUD	TYR III	CAH	TYR III	CAH	LCHAD	TFP	MCD		
PRO	CPT-II	TYR I	CAH	DE RED	GA-2	CAH	CH	CAH	CH	MCAD	TYR1	MSUD		
TYR I	CUD	TYR II	CH	CACT	LCHAD	CH	DE RED	CH	CACT	TFP	VLCAD	MCADD		
TYR II	GA-2	TYR III	DE RED	CPT-IA	MCAD	DE RED	CACT	DE RED	CPT-IA	VLCHAD	CAH	3-MCC		
TYR III	LCHAD	CAH	CACT	CPT-II	SCAD	CACT	CPT-IA	CACT	CPT-II	HMG	CH	MMA		
CAH	MCAD	CH	CPT-IA	CUD	TFP	CPT-IA	CPT-II	CPT-IA	CUD	BKT	CF	PKU		
CH	M/SCHAD	DE RED	CPT-II	GA-2	VLCAD	CPT-II	CUD	CPT-II	GA-2	GA-1	Hb SS	PROP		
CACT	SCAD	CACT	CUD	LCHAD	Var Hb	CUD	GA-2	CUD	LCHAD	GA-2	SCID	SCID		

USA[a] (CA)[b]	USA (IL)[b]	USA (MA)[b]	USA (MO)[b]	USA (NY)[b]	USA (NC)[b]	USA (PA)[b]	USA (SC)[b]	USA (TX)[b]	USA (UT)[b]	Australia[c]	Canada[d]	The Netherlands[e]	Switzerland[f]	UK[g]
CPT-IA	TFP	CPT-IA	GA-2	MCAD	Hb S/βTh	GA-2	LCHAD	GA-2	MCAD	MCD	SMA	Hb SS		
CPT-II	VLCAD	CPT-II	LCHAD	MCAT	Hb S/C	LCHAD	MCAD	LCHAD	SCAD	IVA		TYR-1		
CUD	Var Hb	CUD	MCAD	M/SCHAD	Hb SS	MCAD	MCAT	MCAD	TFP	Cbl A,B		VLCAD		
GA-2	Hb S/βTh	GA-2	MCAT	SCAD	MPS I	MCAT	M/SCHAD	MCAT	VLCAD	Cbl C, D, v2		CACT		
LCHAD	Hb S/C	LCHAD	M/SCHAD	TFP	POMPE	M/SCHAD	TFP	M/SCHAD	Var Hb	MUT		CPT2		
MCAD	Hb SS	MCAD	SCAD	VLCAD	2MBG	SCAD	VLCAD	SCAD	Hb S/βTh	PROP		GAMT		
M/SCHAD	FABRY	MCAT	TFP	Var Hb	HMG	TFP	Var Hb	TFP	Hb S/C	CF		BKT		
SCAD	GBA	M/SCHAD	VLCAD	Hb S/βTh	3-MCC	VLCAD	Hb S/βTh	VLCAD	Hb SS			MPS I		
TFP	Krabbe	SCAD	Var Hb	Hb S/C	BKT	Var Hb	Hb S/C	Var Hb	2M3HBA			SMA		
VLCAD	MPS I	TFP	Hb S/βTh	Hb SS	GA-1	Hb S/βTh	Hb SS	Hb S/βTh	2MBG			ALD		
Var Hb	MPS II	VLCAD	Hb S/C	Krabbe	MCD	Hb S/C	MPS I	Hb S/C	HMG			OCTN 2		
Hb S/βTh	NPD	Var Hb	Hb SS	MPS I	IBG	Hb SS	POMPE	Hb SS	3-MCC					
Hb S/C	POMPE	Hb S/βTh	FABRY	POMPE	IVA	Krabbe	2M3HBA	2M3HBA	3MGA					
Hb SS	2MBG	Hb S/C	GBA	2M3HBA	Cbl A,B	MPS I	2MBG	2MBG	BKT					
MPS I	HMG	Hb SS	Krabbe	2MBG	MUT	POMPE	HMG	HMG	GA-1					
POMPE	3-MCC	MPS I	MPS I	HMG	Cbl C, D, F	2M3HBA	3-MCC	3-MCC	MCD					
2M3HBA	3MGA	POMPE	MPS II	3-MCC	PROP	2MBG	3MGA	3MGA	IBG					
2MBG	BKT	2M3HBA	POMPE	3MGA	ALD	HMG	BKT	BKT	IVA					
HMG	GA-1	2MBG	2M3HBA	BKT	BIOT	3-MCC	GA-1	GA-1	MAL					
3-MCC	MCD	HMG	2MBG	GA-1	GALT	3MGA	MCD	MCD	Cbl A,B					
3MGA	IBG	3-MCC	HMG	MCD	CCHD	BKT	IVA	IBG	MUT					
BKT	IVA	3MGA	3-MCC	IBG	CF	GA-1	MAL	IVA	Cbl C, D, F					
EME	MAL	BKT	3MGA	IVA	HEAR	MCD	Cbl A,B	MAL	PROP					
GA-1	Cbl A,B	GA-1	BKT	MAL	SCID	IBG	MUT	Cbl A,B	ALD					

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USA[a] (CA)[b]	USA (IL)[b]	USA (MA)[b]	USA (MO)[b]	USA (NY)[b]	USA (NC)[b]	USA (PA)[b]	USA (SC)[b]	USA (TX)[b]	USA (UT)[b]	Australia[c]	Canada[d]	The Netherlands[e]	Switzerland[f]	UK[g]
MCD	MUT	MCD	GA-1	Cbl A,B	SMA	IVA	Cbl C, D, F	MUT	BIOT					
IBG	Cbl C, D, F	IBG	MCD	MUT		MAL	PROP	Cbl C, D, F	GALT					
IVA	PROP	IVA	IBG	Cbl C, D, F		Cbl A,B	BIOT	PROP	Congenital cytomegal-ovirus					
MAL	ALD	MAL	IVA	PROP		MUT	GALT	ALD	CCHD					
Cbl A,B	BIOT	Cbl A,B	MAL	ALD		Cbl C, D, F	CCHD	BIOT	CF					
MUT	GALT	MUT	Cbl A,B	BIOT		PROP	CF	GALT	GAMT					
Cbl C, D, F	CCHD	Cbl C, D, F	MUT	GALT		ALD	GALE	CCHD	HEAR					
PROP	CF	PROP	Cbl C, D, F	CCHD		BIOT	GALK	CF	SCID					
ALD	HEAR	ALD	PROP	CF		GALT	HEAR	HEAR	SMA					
BIOT	5-OXO	BIOT	ALD	GAMT		CCHD	SCID	SCID						
GALT	SCID	GALT	BIOT	HEAR		CF		SMA						
CCHD	SMA	TOXO	GALT	HIV		GALE		T-cell-related lymphocyte deficiencies						
CF		CCHD	CCHD	SCID		GALK								
FIGLU		CF	CF	SMA		HEAR								
HEAR		FIGLU	HEAR	T-cell related lymphocyte deficiencies		SCID								
HHH		GALE	SCID			SMA								
SCID		GALK	SMA			T-cell related lymphocyte deficiencies								
SMA		HEAR												

USA[a] (CA)[b]	USA (IL)[b]	USA (MA)[b]	USA (MO)[b]	USA (NY)[b]	USA (NC)[b]	USA (PA)[b]	USA (SC)[b]	USA (TX)[b]	USA (UT)[b]	Australia[c]	Canada[d]	The Netherlands[e]	Switzerland[f]	UK[g]
T-cell related lymphocyte deficiencies		HHH												
		SCID												
		SMA												

CA, California; IL, Illinois; MA, Massachusetts; MO, Missouri; NC, North Carolina; NY, New York; PA, Pennsylvania; SC, South Carolina; TX, Texas; UT, Utah.
Amino acid disorders: ARG, argininaemia; ASA, argininosuccinic aciduria; BIOPT-BS, biopterin defect in cofactor biosynthesis; BIOPT-REG, biopterin defect in cofactor regeneration; CIT I, citrullinemia, type I; CIT II, citrullinemia, type II; CPS, carbamoyl phosphate synthetase I deficiency; HCY, homocystinuria; H-PHE, benign hyperphenylalaninaemia; Hyper ORN, hyperornithine with gyrate deficiency; MET, hypermethioninaemia; MSUD, maple syrup urine disease; OTC, ornithine transcarbamylase deficiency; PKU, classic phenylketonuria; PRO, prolinaemia; TYR I, tyrosinaemia, type I; TYR II, tyrosinaemia, type II; TYR III, tyrosinaemia, type III.
Endocrine disorders: CAH, congenital adrenal hyperplasia; CH, primary congenital hypothyroidism.
Fatty acid oxidation disorders: CACT, carnitine acylcarnitine translocase deficiency; CPT-IA, carnitine palmitoyltransferase i deficiency; CPT-II, carnitine palmitoyltransferase type II deficiency; CUD, carnitine uptake defect; DE RED, 2,4 dienoyl-CoA reductase deficiency; GA-2, glutaric acidaemia, type II; DE RED, 2,4 dienoyl-CoA reductase deficiency; LCHAD, long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency; MCAD, medium-chain acyl-CoA dehydrogenase deficiency; MCAT, medium-chain ketoacyl-CoA thiolase deficiency; M/SCHAD, medium/short-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency; SCAD, short-chain acyl-CoA dehydrogenase deficiency; TFP, trifunctional protein deficiency; VLCAD, very long-chain acyl-CoA dehydrogenase deficiency.
Haemoglobin disorders: HbH, haemoglobin H disease (alpha-thalassaemia); Hb S/βTh, S, beta-thalassemia; Hb S/C, haemoglobin SC disease; Hb SS, sickle cell anaemia; SCD, sickle-cell disease; Var Hb, haemoglobinopathies.
Lysosomal storage disorders: GBA, Gaucher disease; MPS I, mucopolysaccharidosis type-I; NPD, Niemann–Pick disease; POMPE, Pompe disease.
Organic acid conditions: 2M3HBA, 2-methyl-3-hydroxybutyric acidaemia; 2MBG, 2-methylbutyrylglycinuria; 3-MCC, 3-methylcrotonyl-CoA carboxylase deficiency; 3MGA, 3-methylglutaconic aciduria; BKT, beta-ketothiolase deficiency; Cbl A,B, methylmalonic acidaemia (cobalamin disorders); Cbl C, D, F, methylmalonic acidaemia with homocystinuria; EME, ethylmalonic encephalopathy; GA-1, glutaric acidaemia, type I; HMG, 3-hydroxy-3-methylglutaric aciduria; IBG, isobutyrylglycinuria; IVA, isovaleric acidaemia; MAL, malonic acidaemia; MCD, holocarboxylase synthetase deficiency; MMA, methylmalonic acidaemia; MUT, methylmalonic acidaemia (methymalonyl-CoA mutase deficiency); PROP, propionic acidaemia
Other disorders: 5-OXO, pyroglutamic acidaemia (5-oxoprolinemia); ALD, adrenoleukodystrophy; BIOT, biotinidase deficiency; CCHD, critical congenital heart disease; CF, cystic fibrosis; FIGLU, formiminoglutamic acidaemia; GALE, galactoepimerase deficiency; GALK, galactokinase deficiency; GALT, classic galactosaemia; GAMT, guanidinoacetate methyltransferase deficiency; HEAR, hearing loss; HHH, hyperornithinaemia–hyperammonaemia–homocitrullinuria syndrome; HIV, human immunodeficiency virus; OCTN 2, organic cation transporter 2 deficiency; SCID, severe combined immunodeficiency; SMA, spinal muscular atrophy; T-cell-related lymphocyte deficiencies; TOXO, congenital toxoplasmosis
b NBS conditions reported by USA and retrieved from:www.babysfirsttest.org/newborn-screening/states.
c NBS conditions in Australia retrieved from: www.health.gov.au/our-work/newborn-bloodspot-screening/what-is-screened.
d NBS conditions in Canada retrieved from: www.alberta.ca/newborn-metabolic-screening.
e NBS conditions in the Netherlands retrieved from: www.ncbi.nlm.nih.gov/pmc/articles/PMC7938310/.
f NBS conditions in Switzerland retrieved from: www.neoscreening.ch/en/diseases/.
g NBS conditions in the UK retrieved from: www.gov.uk/guidance/newborn-blood-spot-screening-programme-overview#conditions-screened-for.

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