Parents' and children's views of wider genomic testing when used as part of newborn screening to identify cystic fibrosis

Chudleigh, J., Holder, P., Clark, C., Moody, L., Cowlard, J., Allen, L., Walter, C., Bonham, J. R. & Boardman, F.

DOI 10.1016/j.ssmqr.2024.100455
ISSN 2667-3215

Publisher: Elsevier

SSM - Qualitative Research in Health 6 (2024) 100455

Contents lists available at ScienceDirect

SSM - Qualitative Research in Health

journal homepage: www.journals.elsevier.com/ssm-qualitative-research-in-health

Parents' and childrens' views of wider genomic testing when used as part of newborn screening to identify cystic fibrosis

Jane Chudleigh [a,*], Pru Holder [a], Corinna Clark [b], Louise Moody [c], Jacqui Cowlard [d], Lorna Allen [e], Claire Walter [e], James R. Bonham [f], Felicity Boardman [b]

[a] King's College London, Bessemer Road, London, SE5 9PJ, UK
[b] University of Warwick, Coventry, CV4 7AL, UK
[c] Coventry University, Priory Street, Coventry, CV1 5FB, UK
[d] Barts Health NHS Trust, The Royal London Hospital, Whitechapel Rd, London, E1 1FR, UK
[e] Cystic Fibrosis Trust, 2nd Floor, One Aldgate, London, EC3N 1RE, UK
[f] Sheffield Children's NHS Foundation Trust, Clarkson Street, Sheffield, S10 2TH, UK

1. Introduction

Newborn bloodspot screening (NBS) is currently undergoing a 'revolution' (Spiekerkoetter et al., 2023). The development of new therapies (Vockley et al., 2023) and the piloting of whole genome sequencing in healthy newborns (e.g. Newborn Genomes Programme, UK, BabySeq USA) are challenging NBS practice and policy, as well as the Wilson & Jungner criteria (Wilson & Jungner, 1968) that underpin them (Andermann et al., 2008; Rahimzadeh et al., 2022; Vears et al., 2023). The capacity to screen for large numbers of variants simultaneously and generate data with potential relevance across the life course, and for family members beyond the screened infant, has prompted widespread discussion of the benefits (e.g., early identification and treatment of screened conditions) and harms (e.g., identification of variants of unknown clinical significance) that such high throughput screening programmes bring (Bick et al., 2022; Remec et al., 2021; Spiekerkoetter et al., 2023; Tluczek et al., 2022).

Screening programmes for CF vary internationally. A study which explored NBS programmes or CF in Europe found that while all (n = 16) used immunoreactive trypsinogen as a first line test, there was great variability in terms of second tier testing (Barben et al., 2017). Most programmes (n = 10) reported using a DNA panel as the second-tier test, but the panel size ranged from 4 to 644 mutations of the CF transmembrane conductance regulator (CFTR) gene (Barben et al., 2017). In addition, Canada and all states in Australia and the United States of America are using DNA-based NBS programmes. However, in other countries in Latin America such as Argentina, Chile, Uruguay, Brazil and Mexico, either IRT followed by pancreatitis-associated protein or IRT followed by a repeat IRT are used. And in Arab countries no NBS programmes for CF have been implemented (Scotet et al., 2020). The use of whole genome/exome sequencing as a second-tier screening test, or an adjunct to traditional NBS methods, is being considered in Europe and North America (Rahimzadeh et al., 2022). In the UK, the proposed introduction of next generation sequencing (NGS) techniques into existing cystic fibrosis (CF) NBS is a timely example. CF is an inherited condition caused by mutations of the CFTR gene, causing thick, sticky mucus build up throughout the body but notably in the lungs. People living with CF typically have reduced lung function, are susceptible to lung infections and require intensive physiotherapy and daily inhaled bronchodilators/corticosteroids. NBS for CF (Fig. 1) was introduced in the UK in 2007 and consists of measurement of immunoreactive trypsinogen (IRT) from dried bloodspot samples taken on day five of life, followed by a limited DNA analysis including the commonest CFTR mutations. Further IRT testing is undertaken on day 21 of life in babies for whom only one mutation of the CFTR gene has been identified but the initial IRT was very high. While NBS has improved outcomes for children with CF (Schlüter et al., 2020), one of the current difficulties of the programme include the false positive rate meaning some families being recalled for repeat testing. Most commonly, these infants are identified as 'probable carriers' (an outcome typically avoided by UK NBS programmes due to the lack of immediate benefit to the child and the adverse effects of a positive screen on parents). However, others within this recalled group will be infants given an inconclusive designation termed CRMS/CFSPID (CFTR-Related Metabolic Syndrome/-Cystic Fibrosis Screen Positive Inconclusive Diagnosis). CRMS/CFSPID is a designation assigned to infants who have changes identified in the CFTR gene (the gene associated with CF), but who do not otherwise fulfil criteria for a diagnosis of CF (e.g., negative sweat test). Most children with a CRMS/CFSPID designation will remain well. Research suggests that the proportion of children who convert from CRMS/CFSPID to a CF diagnosis varies from 2 to 48% (Castaldo et al., 2020; Groves et al.,

* Corresponding author.
E-mail address: jane.2.chudleigh@kcl.ac.uk (J. Chudleigh).

https://doi.org/10.1016/j.ssmqr.2024.100455
Received 11 January 2024; Received in revised form 3 June 2024; Accepted 22 June 2024
Available online 24 June 2024

Abbreviations

CF	Cystic fibrosis
CFSPID	Cystic Fibrosis Screen Positive Inconclusive Diagnosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CRMS	CFTR-Related Metabolic Syndrome
IRT	Immunoreactive trypsinogen
NBS	Newborn bloodspot screening
NGS	Next generation sequencing

2015; Gunnett et al., 2023; M. Kharrazi et al., 2015; Munck et al., 2020; C. Y. Ooi et al., 2015; Chee Y. Ooi et al., 2019; Ren et al., 2011; Terlizzi, Claut, Colombo, et al., 2021; Terlizzi, Claut, Tosco, et al., 2021; Terlizzi et al., 2020) - in most studies, this was below 10%. However, research suggests that the long-term emotional distress may be similar in parents of children with a CF diagnosis and a CRMS/CFSPID designation but lower in parents of children with a negative NBS result (Perobelli et al., 2009). There is a lack of international consensus on the clinical management of these children (Barben et al., 2021); one recent retrospective study recommended annual follow-up and review (Gunnett et al., 2023).

The identification of children with a CRMS/CFSPID designation via NBS and the uncertainty surrounding their prognosis and management has formed part of the argument for the inclusion of NGS within CF NBS protocols. A 'sensitive' use of NGS would miss fewer cases of true CF but *increase* the number of babies assigned the inconclusive CRMS/CFSPID designation while a 'specific' use of NGS would miss more cases of true CF but *reduce* the number of CRMS/CFSPID designations.

Due to the complexity and nuances of these decisions, policy makers frequently consult with relevant stakeholders. These include: the population that screening is aimed at (parents of newborns) (Blackwell et al., 2020), charities and advocacy groups, but also families living with the screened conditions. In recent years the literature has grown showcasing the wide range of conditions and views held by this group (Boardman et al., 2019; Freeman et al., 2022; Quinn et al., 2023; Redgrave & McNeill, 2022). Despite the complexities of views espoused by affected families and individuals, they remain the group of stakeholders best positioned to describe the impacts of screening (or not) on their lives (Rueegg et al., 2016), the consequences of early (Morton et al., 2022; Prakash et al., 2022) or late diagnosis (Martin Kharrazi & Kharrazi, 2005) and to outline the daily realities of life with a genetic condition or inconclusive designation (Castellanos et al., 2018).

Studying the views of the general public towards screening programmes, however, has many challenges-not least because the public often don't have a personal connection or interest in the screening programme or the condition and/or don't see it as relevant to them (Beard et al., 2016). Views may also be condition specific and depend on the perceived immediate or longer-term outcomes and benefits to the child (Tluczek et al., 2022). However, recent public dialogues including those on this CF question (Kinsella et al., 2022), and others about genomics more broadly with appropriate engagement and information provision, demonstrate members of the public can offer insightful and unique contributions to complex scenarios in genomics when provided with appropriate information and engagement strategies (Etchegary et al., 2015, 2021; Hassan et al., 2020).

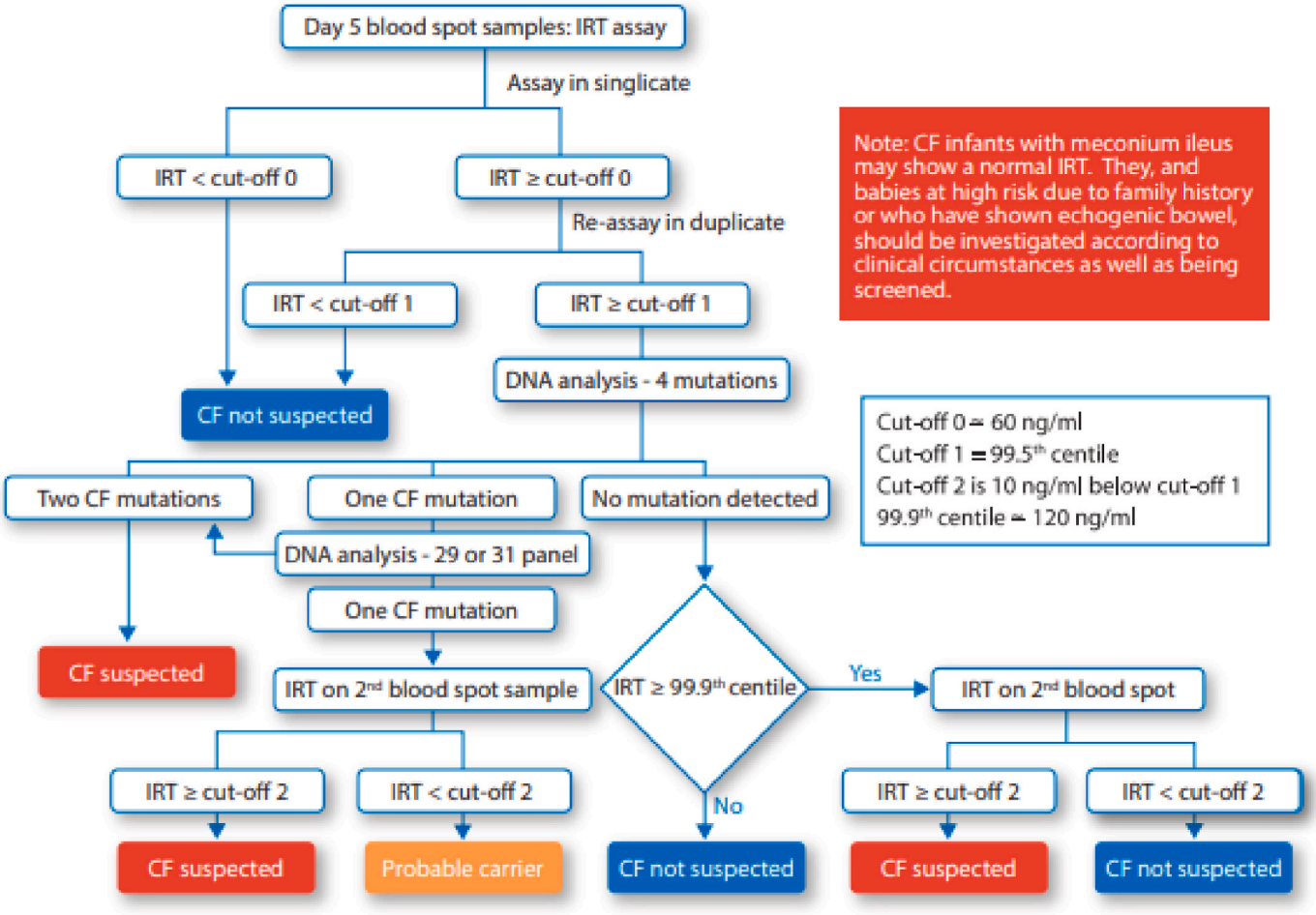

Fig. 1. CF screening algorithm.

This study aimed to gather, analyse and compare the views of a range of stakeholders with experience of CF on the proposed CF NBS protocol incorporating NGS. By exploring the views of stakeholders, the epistemological implications of stakeholder engagement and the authority of contrasting knowledge claims will be discussed to highlight the complexities of policy decisions, especially as these are likely to occur more frequently with expanding genomic screening.

2. Materials and methods

2.1. Research methods

This study adopted a qualitative design using semi structured interviews (children) and focus groups (adults). Interviews and focus groups were audio recorded and transcribed with identifiers removed for analysis. Specific information materials were designed for use with people with experience of CF (defined as adults with CF, parents of children with CF, a CRMS/CFSPID designation or who had received a false negative CF NBS result for their child) in this study that acknowledged their existing knowledge of CF and NBS. These were not the same materials that were used with the general public (Kinsella et al., 2022).

Individual interviews were conducted with children diagnosed with CF via NBS. Children were given the choice of being interviewed alone or with their parent(s) present. Where parents were present, they did not contribute to the responses. Prior to the interview, the researchers had a telephone conversation with the parent(s) of each child interviewed to discuss the topics that would be covered and to ask if there was any specific information, they did not wish the researchers to discuss with their child e.g., life expectancy or fertility. This approach was taken to ensure the research team could respect parents' wishes regarding information sharing with their child and prevent oversharing of information. The interview questions were designed with the child's existing knowledge of CF in mind (obtained prior to interview from parents) to prevent inappropriate questioning or disclosure of previously unknown facts about CF (see Appendix 1 for the children's interview guide).

Online focus groups (Barbour, 2018) were conducted via Microsoft Teams (with an option to dial in) with adults with CF, parents of children with CF, a CRMS/CFSPID designation or who had received a false negative CF NBS result for their child. The decision was taken to conduct the focus groups online in order to eliminate the risk of cross-infection for people with CF/CRMS/CFSPID (Chudleigh et al., 2019, 2022), and emerging evidence suggests equivalence in data quality when compared to face-to-face methods (Jones et al., 2022). Vignettes developed with our oversight group were shared with adults prior to the online focus groups and used as a springboard for engagement during the focus groups to gather views on the proposed CF NBS protocol incorporating NGS, alongside encouraging participants to talk about their own experiences (see Appendix 2 for the adult focus group prompts).

2.2. Study location and dates

Participants were recruited via CF doctors and nurses at twelve CF centres throughout England. CF doctors and nurses approached potential participants during routine clinic appointments, provided them with an information sheet about the study and asked if they would be willing to be contacted by the research team to discuss the study and their potential involvement. In addition, the study was advertised via social media and the CF Trust using their various patient/parent facing forums. Data were collected between August 2022–February 2023. 101 potential participants were approached; 17 (17%) declined to be involved and 37 (37%) were not contactable (i.e., they did not answer our calls/return our messages/respond to emails despite the best efforts of the research team).

2.3. Sampling procedures

We purposefully sampled people with personal experience of CF (defined as adults with CF, parents of children with CF, a CRMS/CFSPID designation or who had received a false negative CF NBS result for their child), making particular effort to ensure inclusion of people whose first language was not English, BAME communities (to reflect ethnic diversity of the CF population (Cystic Fibrosis Trust, 2020, pp. 1–47)), different socio-economic groups (to ensure inclusion of underserved populations) and men (as male perspectives are under-represented in NBS research - particularly fathers).

2.4. Data collection

Focus groups were facilitated by members of the research team who consisted of a registered children's nurse, medics, psychologists, and sociologists who have extensive experience of working with families with children with CF and conducting qualitative research, including interviews and focus groups specifically with parents and children who have received positive and negative NBS results. Individual interviews were undertaken with children $\geq$10 years of age with CF and focus groups were undertaken with adults. Adults and children with experience of CF (defined as adults with CF, parents of children with CF, a CRMS/CFSPID designation or who had received a false negative CF NBS result for their child) were presented with information about the proposed changes to the CF NBS protocol to include NGS, the differences between a sensitive and a specific approach and an explanation of CRMS/CFSPID before being asked their opinions about whether and how NGS should be incorporated into the existing CF NBS protocol using the interview and focus group guides in Appendices 1 and 2 respectively.

2.4.1. Reflexivity and positionality

Members of the study team (JC, JCo, LA, CW, JRB) have been involved in or continue to undertake a variety of roles and activities associated with the NBS programme in the UK. This had the potential to lead to bias during data collection and analysis. However, this was balanced by other members of the research team whose NBS role had been solely for academic purposes (PH, CC, LM, FB). Data collection and analysis was mainly undertaken by JC, PH, CC, LM and FB who fall within both camps; none of whom were employed in the organisations where data collection was undertaken.

2.5. Data analysis

Credibility was achieved by conducting eight focus groups with adults with similar but different experiences and outcomes following NBS. Data generated during the focus groups with adults and interviews with children were analysed using a reflexive thematic analysis using both inductive and deductive approaches (Fereday & Muir-Cochrane, 2006) was adopted to ensure it was data driven to enhance confirmability. Five members of the research team with extensive experience of analysing qualitative data specifically with adults and children who have received various outcomes following NBS, met regularly to discuss initial codes, develop the initial code book and ensure consistency in coding by comparing assigned codes to interview transcripts to ensure dependability of data analysis. An iterative process was adopted to ensure codes and categories were consistent and accurately represented data collected to enhance transferability. Memo writing enabled researchers to remain reflexive throughout the process (Charmaz, 2014) to further enhance confirmability.

2.6. Stakeholder oversight group

Collaborative research, working with relevant stakeholders, is vital to bridge the gap between research and practice and assist with knowledge translation (Nyström et al., 2018). The scope, structure and

data collection tools for the project were developed in collaboration with patient representatives (three parents of children with CF and one adult with a late CF diagnosis), a CF clinical nurse specialist and CF physician through involvement activities at the outset and at key stages of progress. Patient representatives met with the research team and other members of the Oversight Group prior to the start of the project to review and provide feedback on proposed data collection approaches and techniques. Vignettes were constructed using interview data from a previous study (Boardman & Clark, 2022) and were shared with members of the oversight group who provided feedback and suggestions that were incorporated into the final documents.

2.7. Ethical approval and funding

Ethical approval was granted from Tyne and Wear South Ethics Committee 22/NE/0024. Informed written consent (adults) and assent (children) was obtained from all participants prior to their involvement in the focus groups or interviews respectively. The project was funded by the UK Department of Health and Social Care.

3. Results

3.1. Sample

47 (47% of those approached) participants with experience of CF (including 6 children with CF) from 12 CF centres were recruited. Of the 41 adults recruited, 35 (85%) (four adults with CF, 20 parents of children with CF, seven parents whose child had received an inconclusive outcome following NBS (termed CRMS/CFSPID and four parents who had received a false negative CF NBS result for their child as well as six children with CF)) took part in eight focus groups: three with parents of children with CF (who are also therefore adult carriers of CF), two with parents of children with CRMS/CFSPID, two with adults with CF and one with parents who had received a false negative result. Three parents of children with CF did not take part as the times were not convenient, one adult with CF and one parent of a child with CF did not attend the focus groups but attended the workshop. Despite varied attempts, only one adult carrier of CF (a niece of a parent who had a child with CF) was recruited who did not take part in a focus group. Six individual interviews were undertaken with children ≥10 years of age with CF. Length of focus groups and interviews can be seen in Table 1.

3.2. Demographic data

Demographic data can be seen in Table 2. Eleven of the 35 adult participants (31%) who took part in the focus groups were male. Thirty-two out of the 35 participants (91%) aged over 18 years completed the demographic questionnaire. Of the six children with CF who were interviewed, five were girls (aged 15, 13, 12 and two 10-year-olds) and one was a boy (aged 10 years). No other demographic data about children were collected.

Table 1
Length of focus groups and interviews.

Focus group/interview	Duration range	Median duration
All focus groups	33.16–80.3 min	72.54 min
Adult focus groups	33.16–62.57 min	47.87 min
Parent of Child with CF focus groups	71.59–80.3 min	79.55 min
Parent of Child with CRMS/CFSPID focus groups	73.48–79.26 min	76.37 min
False negative Parent focus Group	56.49 min	N/A
Child interviews	17.5–36.41 min	28.76 min

Table 2
Demographic data.

Sex (n = 35)[a]	Male	Male = 11 (31%)
Age (n = 32)[a]		
	20–29 years	3 (9%)
	30–39 years	17 (54%)
	40–49 years	10 (31%)
	50–59years	1 (3%)
	60–69 years	1 (3%)
Marital status (n = 32)[a]		
	Married/in partnership with co-parent	28 (88%)
	Separated	2 (6%)
	Widowed	1 (3%)
	Prefer not to say	1 (3%)
Religion (n = 32)[a]		
	Christian	11 (34%)
	Muslim	2 (6%)
	No religion	19 (60%)
Ethnicity (n = 32)[a]		
	White British	24 (76%)
	Any other White background	3 (9%)
	Pakistani	2 (6%)
	White and Black African	1 (3%)
	Any other Black British or Caribbean background	1 (3%)
	Any other Mixed or Multiple background	1 (3%)
Education (n = 32)[a]		
	PhD	2 (6%)
	MSc	5 (15%)
	BSc	12 (38%)
	GSCE-Foundation Level degree	12 (38%)
	No qualifications	1 (3%)
Dependents (n = 32)[a]		
	One child	18 (57%)
	Two children	10 (31%)
	Three children	3 (9%)
	Four children	1 (3%)
CF status of dependents (n = 51)[b]	CF	26 (50%)
	CRMS/CRMS/CFSPID	7 (14%)
	Carrier	3 (6%)
	Unaffected	6 (12%)
	Unknown	9 (18%)

[a] Of 35 participants, n = 32 completed the demographic questionnaire.
[b] The 32 participants who completed the demographic questionnaire had 51 dependents.

3.3. Duration of interviews and focus groups

The interviews and focus groups were held in the evenings to accommodate participant schedules and treatment regimens and lasted between 33.16 and 80.3 min (median 72.54 min) for the focus groups, and 17.5–36.41 min (median 28.76 min) for the interviews.

3.4. Themes

When views of stakeholders with experience of CF were explored regarding whether a sensitive or specific approach should be adopted if NGS were incorporated into the CF NBS protocol, three main themes were identified; information provision and communication; importance of NBS and harms of NBS.

3.4.1. Information provision and communication

Parents felt if NGS were to be introduced into the NBS protocol for CF, it would be vital that the rationale and possible outcomes were explained at the time of the heel prick test. This was felt to be particularly relevant if the sensitive approach were to be adopted and more children with CRMS/CFSPID were identified.

"… if we were to be educated on the heel prick more, so if we were to be aware that CRMS/CFSPID … you know it's a possibility … when it comes back as a potential CF gene that if they're a carrier or they're full-

on CF or if they're CRMS/CFSPID then at least we've got those options in our mind … It doesn't have to be 100% CF." Parent of Child with CRMS/CFSPID.

Given these experiences regarding the lack of information provision at the time of NBS, many parents commented that even though communication of their child's positive NBS result had been done as well as it could have been and the wait to see the CF team was minimal, they still felt it was a traumatic experience that had resulted in both physical and psychological sequelae.

"… that 24 h when you first get that call to the next stage when you go in, even 24 h, I mean you do not sleep, you do not think about anything else, you do Google, you do speak to people, you do start looking on the Internet at other people with CF and you start, your mind is just going crazy." Parent of Child with CF.

After visiting the CF team for the diagnostic appointment following the NBS result, the uncertainty associated with a CRMS/CFSPID designation was viewed as having the potential to cause ongoing angst. Parents discussed the guilt associated with the genetic origin of the condition as well as the impact this has had on their lives in terms if their (lack of) understanding of the implications of the outcome and how this had affected their lives and their relationship.

"It turned our lives upside down and the reality is, I think it's, that, well, I think it's my gene … to hear your wife crying while you're stood at work was horrible and to not understand it was even worse" Parent of Child with CRMS/CFSPID.

The importance of ensuring staff are appropriately trained in communicating the CRMS/CFSPID designation sensitively to reduce resultant distress was therefore highlighted by parents.

In addition, if the sensitive route for NGS were to be adopted and therefore more children with CRMS/CFSPID were to be identified, it was felt that appropriate support for families would be vital. The reasons for this were multifaceted and included enabling children to understand their designation, being able to confidently share information with family and friends and ensuring parents were adequately supported within the CF community.

"… some groups where we could all meet and chat … because it's a really weird position to be in like do we need to worry? Don't we need to worry? And … how you tell your family how you tell your friends." Parent of Child with CRMS/CFSPID.

Although communication of the CRMS/CFSPID designation was viewed as potentially anxiety provoking due to the associated uncertainty, it was recognised that if ongoing support were provided by a knowledgeable team, this could be alleviated.

"… after the CRMS/CFSPID I've noticed we, we relaxed as well … and they [CF Team] were very relaxed with their communications with us … As soon as the CF Team said to remain positive and not to worry too much, then from that day onwards I was positive, and we haven't worried since then." Parent of Child with CRMS/CFSPID.

The importance of obtaining timely and appropriate help, support and answers, particularly in the face of uncertainty, was reiterated by parents of children with experience of CF, and adults with CF who had received a diagnosis of CF in adulthood.

"… if you're going to pick up more babies with [CRMS/CFSPID], there's just got to be a very clear and kind of supportive way of going forward with those parents. I think that's, that will be the key." Parent of Child with CRMS/CFSPID.

In addition, the worry associated with a CRMS/CFSPID designation was considered to subside over time if annual reviews with the CF Team did not highlight any concerns about the child converting to a CF diagnosis or developing CFTR related symptoms.

"… as the years have gone by, it's kind of, it gives you reassurance, but it's always in the back of your mind." Parent of Child with CRMS/CFSPID.

However, parents could still be left with residual worry that their child may become unwell and therefore find themselves living in a state of constant uncertainty.

3.4.2. Importance of screening

Parents and children felt CF should be identified as early as possible following NBS to enable them to access appropriate treatment and ensure better health outcomes for the child. This was particularly evident during the interviews that were undertaken with children with CF.

"I think people could live for longer if you found out that they had it sooner … Because you could treat them like before they got too like sick … because I want people to live longer, so we have like as much like life as we can to enjoy the things that we do." Child with CF.

Furthermore, adults with CF who had been diagnosed in adulthood felt that an earlier diagnosis for them could have been life changing. For these reasons, after listening to other's stories and experiences, all focus group participants agreed on the sensitive approach as their preferred method. Participants also commented on the psychological impact of a false negative NBS result and the diagnostic odyssey they experienced which also influenced their preference for the sensitive approach to NGS for CF NBS. For some this could lead to various lifestyle changes in a bid to achieve answers for the symptoms they were experiencing for which they had not been able to achieve a satisfactory explanation despite numerous encounters with various different health care professionals and specialities.

"… there was still that … psychological impact in my life because there was, it was, it was just a different type because I didn't know what was wrong with me. And it was like a search for like, what could it be, you know, trying all different things and thinking, what am I allergic to? Is it this food? Is it this food having different diets, trying to eliminate foods from my diet to work out what was causing it. And you know, I went through, I got I think I got to like about 15 or 16 and I was just like, I just gave up trying. I was just like; I'll live with it. It wasn't fun, but I didn't really know what else to do … it definitely changed my life quality for sure. Like digestive wise I've just like, it was almost like having an eating disorder as a child. I was too scared to eat. That kind of a mental impact of it" Adult with CF.

Even when it was explained that if a child with CF were missed at the time of NBS, it would be likely that they would be identified clinically by the age of two years, most participants felt this would be too late and vital treatment opportunities could have been missed.

As well as clinical implications, parents who had experienced a false negative CF NBS result, described the multidimensional impacts of a missed diagnosis in terms of for instance employment, childcare arrangements and parent/child relationships.

"… those 6 months it was, you know where we didn't know where we stood or what it was that we had, you know obviously we knew something wasn't right … I was fortunate and extended my maternity leave because … those first six months were just ruined by looking and analysing and worrying." Parent of Child with a False Negative Result.

While the emphasis was on not missing children with CF, many participants commented on the concept of additional knowledge about a child CF status equating to power and therefore providing them with the ability to make informed decisions about their child's care. Therefore, participants felt that while identifying all children with CF was crucial, identifying children with CRMS/CFSPID was also important:

"I think pick up everyone with CF and some people with CRMS/CFSPID … if your child has like a condition … you should know about it and if your child might have a condition then you should also know about it and have the option and opportunity to get them tested again so that you can find out if they do or do not have the condition." Child with CF.

Being aware of their child's CRMS/CFSPID designation was also seen as being potentially advantageous by parents and children as they felt they could be prepared should CFTR-related symptoms start to develop in the future.

Informing children of their CRMS/CFSPID designation was also viewed as important in terms of providing reassurance to children and involving them in decision-making and the rationale for their care.

"… you could also tell them and be honest from the start and say, look, you're completely healthy, you're fine. And when you was [sic] born, the doctors picked this up and what we're going to do is we're going to check regularly just to make sure that you stay as you are now, which is healthy." Parent of Child with CF.

Children also felt that being aware of a CRMS/CFSPID designation could be advantageous in terms of preparing them for the potential of a conversion to CF in the future and therefore enabling them to keep themselves as healthy as possible in the interim and access care if and when required.

"It could also get them prepared for the future [knowing about CRMS/CFSPID] … whatever, like they've got told in the past, they can use it to keep themselves healthy and do nebulizers and tablets in the future." Child with CF.

This view was also shared by adults who had been diagnosed in adulthood who felt they may have received a CRMS/CFSPID designation when they were children if the knowledge and resources were available to enable this.

"… had I had all of that information at a younger age I would have been able to manage it and not necessarily be scared by it but be prepared. You can't live your life in denial of what might happen. At least if you have knowledge of, you know, what could happen, you could be prepared" Adult with CF.

Parents and children with CF described how if a child had not received a CRMS/CFSPID designation or had received a false negative CF NBS result, seeking help from health professionals if their child were to become symptomatic could be particularly problematic.

"… if you don't pick them up by three months, and if there is something wrong with the baby, like they're having like breathing problems or something, or they're always hungry because they like, just can't keep food in then. That's just a lot of worrying for the parent, and if they go to the clinic in their town and the doctors there are just like don't think about CF or they just like don't know about it and then they just say 'ohh, just try, maybe they're like lactose intolerant or something, maybe stop giving them dairy or … ' then that's just even more worrying because you stop giving them dairy, but then they're still like sick. So, then you just don't know what to do." Child with CF.

This was also reflected in the experience of an adult with CF who was not diagnosed until adulthood who felt that having a CRMS/CFSPID designation could help parents to have their concerns taken seriously by health professionals while also leading to better health outcomes for the child.

"… if there's something that's not quite right and you know, instead of being fobbed off and whatever by people you've, you've got something to say. Look, this is what it is and that this is what I need treating for. And so, we're not being pushed under the carpet for any reason. You can get the help as soon as things start, you know … as soon as you get the symptoms and then you've got you better outcomes for all those people as well." Adult with CF.

Parents of children with a CRMS/CFSPID designation also felt that if parents were aware of their child's CRMS/CFSPID designation, it would be easier to have their concerns taken seriously by health professionals, gain access to a CF Team if needed in the future and obtain any required treatments in order to ensure the child remained healthy.

"I feel like having that diagnosis of a CRMS/CFSPID, you can kind of fight your corner a bit and with the help of our consultant, she's got antibiotics sooner. Rather than waiting until she's really, really poorly." Parent of Child with CRMS/CFSPID.

Adults diagnosed with CF in adulthood, and parents who had experienced a delayed diagnosis of CF following a false negative NBS result, described the period until diagnosis as being particularly distressing. Consequently, obtaining the CF diagnosis was felt to be a relief as it ensured they received the required and correct treatments to maintain their health.

"… there was a slight relief when he was diagnosed because finally, we had identified what the problem was and at least you could kind of then have the kind of the correct treatment and the care that he needed … had he been picked up with the heel prick test I feel, well, he could have been saved of probably 2 procedures and started to recover sooner and come home sooner." Parent of Child with a False Negative Result.

When balancing the possible outcomes of the sensitive versus specific approach to NGS for CF NBS, many participants considered that the uncertainty associated with CRMS/CFSPID was less harmful than a missed CF diagnosis and therefore identifying more children with CRMS/CFSPID to ensure children with CF were not missed was an acceptable risk.

"… the prospect of someone else having that [a missed diagnosis of CF] for months and months because they were missed, I think that would be … that is more torturous than some people having a carrier diagnosis, or a non-disease causing [mutation]." Parent of Child with CF.

Participants also expressed the view that as CRMS/CFSPID is a relatively new designation, identifying more children with this outcome following NBS could help to improve clinical and scientific knowledge about the pathogenicity of different mutations of the CFTR gene.

3.4.3. Harms of screening

It was acknowledged that receiving either a CF diagnosis or a CRMS/CFSPID designation for their child was unexpected and therefore could cause additional anxiety and worry for parents.

"… those first 48 h … were literally the worst hours of my life. I was literally just crying. Thinking like you have this idea that you're going to have this child and you're going to go on lovely beach holidays and do this and do that. And then for someone to just whip that carpet out … you have this baby and they're healthy as far as you can see. And then six weeks later, someone comes up to you and says, actually they might not be, and I think that was hard." Parent of Child with CRMS/CFSPID.

However, the uncertainty associated with a CRMS/CFSPID designation seemed particularly worrisome and confusing for parents.

"Maybe we didn't have quite as a sort of clear cut different, you know, clear cut. This is the diagnosis. I think … it was the unknown" Parent of Child with CRMS/CFSPID.

Parental concern about a CRMS/CFSPID designation was also seen as something that could be transferred to the child as they grew into adulthood and also have potential negative psychological consequences.

".will he worry about it [CRMS/CFSPID] as he gets older? I don't know. You know, as he moves into adulthood, is he going to think 'oh potentially this is when I could get ill' and you know, is that going to affect him mentally? I guess it's more of a sort of mental load for them as they get older … Is that going to become their worries?" Parent of Child with CRMS/CFSPID.

However, children with CF did not think that being aware of a CRMS/CFSPID designation would cause undue worry for a child.

Many parents spoke about how finding out their child's CRMS/CFSPID designation had affected many aspects of their lives including returning to employment, childcare decisions and had the potential to lead to social isolation for both the parents ad the child.

"I was told 'keep your child away from all germs' and, you know, I actually gave up my job because I didn't want her to go into nursery because we were told you need to keep her well, you need to keep her away from others, you know, so it's had a massive impact on our life." Parent of Child with CRMS/CFSPID.

Inconsistency of information provision could be similarly confusing for parents and contribute to their ongoing anxiety.

"… some doctors like to be, you know, much more cautious than others. So again it depends who you see …" Parent of Child with CRMS/CFSPID.

Some parents described being made to feel like they were bad parents, neurotic or hypochondriacs when they sought help for their child if they became symptomatic.

"It got to the point where I think they thought I was mental for repeatedly taking her back because they wasn't [sic] doing anything." Parent of Child with CRMS/CFSPID.

It was also felt that both missing children with CF and having a CRMS/CFSPID designation could potentially impact on the child/parent relationship and lead to parents becoming overprotective in an attempt to prevent their child becoming unwell.

"… it's made us much, much more protective over her. Yeah, feel like we wrap her in bubble wrap, don't we?" Parent of Child with CRMS/CFSPID.

Another issue identified by parents of children with a CRMS/CFSPID designation was not knowing where they fitted into the CF world, and this impacting on the support perceived to be available to them. This in turn made them question their 'right' to be part of the CF world.

"… you sort of feel like you don't have the right to worry that much when there are obviously, you know, parents with children, with classic CF. So, it's, you know, it's quite a difficult place to be really, because I'm quite a worrier but then I sort of feel like I shouldn't be worrying when compared to these people, I don't have the right to." Parent of Child with CRMS/CFSPID.

There were mixed views from both adult and child participants about the non-identification of carriers of CF as part of the proposed introduction of NGS in the CF NBS protocol. Children did not appear to feel the information would be relevant in childhood but felt it would be important in terms of reproductive decision making in adulthood and demonstrated an impressive knowledge of autosomal recessive inheritance patterns.

"… if you were to like marry another carrier, but then you didn't know [about carrier status] then that would cause like it. It could cause like the baby to have CF. But it's obviously like a one in four chance … I think it's better that you do identify them." Child with CF.

This was also reflected in the parental discussions; some parents felt they would have wanted to have known about their own carrier status prior to having their children. Others felt that carrier identification was not important as children who are carriers are considered healthy and therefore, they did not believe the information to be useful. Some felt that knowing your own carrier status could be unnecessarily burdensome and therefore CF NBS should only focus on clinically significant outcomes.

"I wouldn't say it's necessary to pick up carriers … that is really making you worry for no reason at all at that stage … I don't think I'd need to know about just a carrier if they've got one CF gene. Yeah, that potentially they could have a child down the line with someone else that has a CF gene. I don't think that's as important." Parent of Child with CRMS/CFSPID.

Discussions around reproductive decision making in relation to knowing their own carrier status was complex and included the perceived impact of having two children with CF and the associated infection risks.

"We did have a second pregnancy when my daughter was four. We decided to take a roll of the dice, but 75%, right? If you play poker, it's not bad. The baby was … Had CF Delta F508 and we made a decision to terminate the pregnancy." Parent of Child with CF.

Parents unknowingly being carriers of CF also had the potential to lead to guilt in terms of passing on the condition to their child.

"… my mum has spoken about, 'oh gosh, I didn't know, and I didn't know your dad did'. And I was like, 'no, of course you didn't know because you were both carriers.' But that really, that really did bother her in hindsight. Not knowing. That's information that she didn't know. And therefore, it's impacted my life." Adult with CF.

Parents also considered the relevance of knowing their carrier status to provide other family members with options in terms of reproductive decision making. However, in reality, this did not mean that siblings always chose cascade testing; this seemed to be a very personal choice.

"I just think people should deserve the right to sort of, it's sort of the knowledge, that knowledge is power. Obviously, a lot of people that would have known they were carriers previously would have gone about having children a different way, some might not have been able to, but at least they've had the choice." Parent of Child with CF.

Finally, participants recognised the potential burden of detecting more children with a CRMS/CFSPID designation in terms of NHS resources.

"… in terms of staffing and might just stretch resources. I guess that really depends on the department and whether they're able to cope in terms of numbers." Parent of Child with a False Negative Result.

However, it was felt that if those with CRMS/CFSPID were followed less frequently than children with CF, it may alleviate some of the burden. Furthermore, consideration was given to the potential monetary costs associated with the diagnostic journey parents could find themselves experiencing while seeking answers for their child's symptoms following a false negative result. This could result in referrals to a range of health professionals leading to further tests. It was therefore felt that it would make more economical sense to ensure all children with CF were picked up as early as possible.

4. Discussion

The purpose of this work was to gather, analyse and compare the views of a range of stakeholders with a connection to the 'CF world' on the proposed CF NBS protocol incorporating NGS.

It is notable that the importance of not missing *any* children with 'true CF' was a driving force behind favouring a sensitive approach to CF NGS. Key reasons for this view were that routes to diagnosis were often protracted and difficult. Within the focus group setting, hearing others' stories also brought feelings of distress from this time to the surface. Recent data demonstrates the excellent performance of the existing UK NBS protocol for CF (Driscoll et al., 2024) in terms of sensitivity (children correctly identified as having CF) and positive predictive value (the proportion of children who with a positive screening result who actually have CF)(Monaghan et al., 2021). However, this is dependent on the screening protocol used which may be negatively impacted by the date of sample (age of the baby), whether high cut-off values are used and whether DNA is used during second-tier testing (Lumertz et al., 2019). Therefore, the use of NGS by countries demonstrating lower performance data in terms of false negative results would need careful additional consideration.

Adults who were not diagnosed with CF in childhood, reflected on both psychological and physical impacts of their prolonged diagnostic journeys which usually included multiple referrals to different specialists as well as hospital admissions in childhood. Negative impacts on the parent/child relationship, as well as the wider extended family were also mentioned. These participants also described their own parents' guilt at not being more persistent and proactive and obtaining their child's diagnosis sooner. While previous research has explored the immediate and childhood impacts of delayed and/or missed diagnoses, this study has highlighted the potential life-long negative psychosocial negative sequalae particularly associated with a diagnostic odyssey.

A final component of the participants' support for a sensitive approach related to the meaning they assigned to a CRMS/CFSPID designation. Previous work with parents of children with CRMS/CFSPID demonstrates the distress and sense of displacement the designation can cause (Boardman & Clark, 2022), and how it can be as traumatic as a CF diagnosis in the short-term (Ginsburg et al., 2023; Perobelli et al., 2009) but may offer benefits related to improved clinical monitoring (Tluczek et al., 2022). Indeed, participants in this study viewed the designation in more positive ways. These included: having a 'foot in the door' should CF develop with easier access to CF clinics and a cutting out of the diagnostic odyssey. Parents in the present project indicated that it might be important to identify children with CRMS/CFSPID so that if they did become symptomatic, they could seek support and/or have direct access to a CF team who they felt would be more likely to take their concerns seriously; a common phrase used by parents being 'knowledge is power'. This was reflected in a systematic review of psychosocial issues related to NBS which determined parents and the public may view genomic information as empowering (Tluczek et al., 2022). Parents in this study

also indicated that health information about their child is useful, and initial anxiety would likely subside over time as the child continued to be well. The findings of this study suggest the updated guidance on the management of children with CRMS/CFSPID has improved management of this NBS outcome and the confidence with which clinicians are able to reassure families about their child's 'risk' of conversion to, for instance a CF diagnosis. Whilst it was acknowledged that increasing the number of children identified with a CFPISD designation had the potential to result in additional burden to the NHS, parents in this project argued that costs associated with appointments, referrals, tests and treatments undertaken while trying to reclassify a missed CF diagnosis, or if a CRMS/CFSPID was not identified at the time of NBS and the child became symptomatic, could outweigh the costs associated with additional CRMS/CFSPID cases being identified via a sensitive approach to NGS.

This contrast between the views of families and individuals in the 'CF world' (who favoured a sensitive approach to NBS) and those of the general public (who preferred a specific approach that would reduce the number of families living with this inconclusive outcome) (Kinsella et al., 2022), raises important questions about the way that stakeholder views are incorporated into policy decisions, particularly when there is conflict in views. As has been found by other studies, the general public often has differently calibrated barometers of condition severity when compared to people with direct lived experience (Boardman et al., 2018; Paul, 2021). Members of the public are comparing a healthy newborn to one with a CRMS/CFSPID designation, whereas families with experience of CF are more likely to see CRMS/CFSPID as much less serious, and they emphasised it as a gateway to early diagnosis and intervention. This difficulty with contrasting levels of lived experience is particularly pronounced in screening research where the public often have little or no prior knowledge or experience of the condition being screened for.

The current UK CF NBS protocol was designed to minimise the number of CF carriers unavoidably detected (NHS England, 2022). Despite this, currently approximately 200 families per year are informed that their child is a 'probable carrier'. The introduction of NGS into the CF NBS protocol using either the sensitive or specific approach would mean that carriers were no longer reported. While some parents in this study felt it would be advantageous to identify carriers to enable sharing of information with close family to assist with reproductive decision making, most parents felt this information would not have changed anything about their first pregnancy – this was related to them feeling that CF was part of the child they knew. However, others felt that knowledge of their carrier status was important to inform decisions regarding future pregnancies as well as being important information for their child to be aware of in the future. This has been reflected in previous research conducted with families following a CF carrier result for their child (Ulph et al., 2014, 2015) and a systematic review which found carrier status being viewed as critical for future reproductive decisions but conversely could pose challenges in terms of information sharing with children and extended family (Tluczek et al., 2022). Views related to avoiding the identification of carriers when using either the sensitive or specific approach for CF NGS, were not explored with the general public (Kinsella et al., 2022).

Whilst Kinsella (Kinsella et al., 2022) have argued that members of the public can make meaningful and significant contributions to complex policy questions when provided with appropriate support and information, communicating lived realities of people with conditions is challenging and can lead to polarised views between the public and families for whom the condition is a daily reality, as occurred in this case. This work highlights the importance of valuing both group's perspectives where binary policy decisions (specific or sensitive approach) need to be made that incorporate stakeholders' views. Further research is indicated to explore methods to reconcile, or further interrogate differing views based on personal experience.

Limitations of this study include difficulties encountered in terms of recruiting parents of children who were carriers of CF (without a sibling with CF) as well as children who were carriers of CF and/or had a CRMS/CFSPID designation who may have had different views about the potential of identifying more children with a CRMS/CFSPID designation of a sensitive approach were to be adopted or not identifying carriers if either approach were to be adopted. Undertaking research with the CF population can be challenging due to it being an emotive topic (Allen et al., 2023). However, those who participated in the current study were engaged and readily committed their time to the project. In addition, participants' potential bias in favour of early CF diagnosis, regardless of methods used. Finally, all members of the research team have extensive experience of working with children and families with various outcomes following NBS which may have influenced data collection and analysis. However, they included several disciplines (nurse, psychologist, sociologist, medic, PPI expert) which enhanced the multidisciplinarity of the team.

5. Conclusions

In contrast to previous research with the general public (Kinsella et al., 2022), most participants in the present study indicated a preference for the sensitive approach to NGS. This was due to the perceived importance of identifying all children with CF as early as possible following NBS, to enable them to access appropriate treatment and ensure better health outcomes. Adopting a sensitive approach would lead to more children being identified with a CRMS/CFSPID outcome and therefore the importance of ensuring information provision at the time of NBS included an explanation of CRMSCFSPID and appropriate support being made available afterwards should be emphasised. Identifying more children with CFSPID was thought to be potentially beneficial as the child would get access to appropriate and timely healthcare if they were to become symptomatic. However, further research is needed to inform definitive written guidelines for health professionals regarding the clinical management of children with a CRMS/CFSPID designation to avoid over-medicalisation.

While it was acknowledged that identifying more cases of CFSPID may have implications for clinical practice in terms of resources needed, it was felt this could be mitigated by (i) the additional scientific knowledge gained to inform the management of these children and potentially reduce overmedicalisation (ii) the reduction in resources associated with a diagnostic odyssey in those cases where a child with CFSPID child converts to a CF diagnosis or develops a CFTR related disorder (in terms of the various appointments, referrals, tests, hospital admissions etc.) (iii) the reduction in clinical and psychological impacts on the child and family of a missed diagnosis of CF. Therefore, if a sensitive approach were to be adopted, further research should include a health economic analysis of the actual costs associated with managing a CRMS/CFSPID designation as well as identifying a missed case of CF or CRMS/CFSPID.

Data statement

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to ethical constraints.

CRediT authorship contribution statement

Jane Chudleigh: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Pru Holder:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Formal analysis, Data curation. **Corinna Clark:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Formal analysis, Data curation. **Louise Moody:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Funding

acquisition, Formal analysis, Data curation, Conceptualization. **Jacqui Cowlard:** Writing – review & editing, Writing – original draft, Methodology. **Lorna Allen:** Writing – review & editing, Writing – original draft, Methodology. **Claire Walter:** Writing – review & editing, Writing – original draft, Methodology. **James R. Bonham:** Writing – review & editing, Writing – original draft, Methodology, Funding acquisition, Conceptualization. **Felicity Boardman:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was funded by NHS England/Department of Health and Social Care Ref: CFNGS.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ssmqr.2024.100455.

References

Allen, L., Allen, L., Carr, S. B., Davies, G., Downey, D., Egan, M., et al. (2023). Future therapies for cystic fibrosis. *Nature Communications, 14*, 693.
Andermann, A., Blancquaert, I., Beauchamp, S., & Déry, V. (2008). Revisiting Wilson and jungner in the genomic age: A review of screening criteria over the past 40 years. *Bulletin of the World Health Organization, 86*, 317–319.
Barben, J., Castellani, C., Dankert-Roelse, J., Gartner, S., Kashirskaya, N., Linnane, B., et al. (2017). The expansion and performance of national newborn screening programmes for cystic fibrosis in Europe. *Journal of Cystic Fibrosis: Official Journal of the European Cystic Fibrosis Society, 16*, 207–213.
Barben, J., Castellani, C., Munck, A., Davies, J. C., de Winter-de Groot, K. M., Gartner, S., et al. (2021). Updated guidance on the management of children with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome/cystic fibrosis screen positive, inconclusive diagnosis (CRMS/CFSPID). *Journal of Cystic Fibrosis, 20*, 810–819.
Barbour, R. (2018). *Doing focus groups*. London: Sage.
Beard, C. A., Amor, D. J., Di Pietro, L., & Archibald, A. D. (2016). "I'm Healthy, It's Not Going to Be Me": Exploring experiences of carriers identified through a population reproductive genetic carrier screening panel in Australia. *American Journal of Medical Genetics, 170*, 2052–2059.
Bick, D., Ahmed, A., Deen, D., Ferlini, A., Garnier, N., Kasperaviciute, D., et al. (2022). Newborn screening by genomic sequencing: Opportunities and challenges. *International Journal of Neonatal Screening, 8*, 40.
Blackwell, K., Gelb, M. H., Grantham, A., Spencer, N., Webb, C., & West, T. (2020). Family attitudes regarding newborn screening for krabbe disease: Results from a survey of leukodystrophy registries. *Int J Neonatal Screen, 6*.
Boardman, F., & Clark, C. (2022). 'We're kind of like genetic nomads': Parents' experiences of biographical disruption and uncertainty following in/conclusive results from newborn cystic fibrosis screening. *Social Science & Medicine, 301*, Article 114972.
Boardman, F., Hale, R., Gohel, R., & Young, P. J. (2019). Preventing lives affected by hemophilia: A mixed methods study of the views of adults with hemophilia and their families toward genetic screening. *Molecular Genetics & Genomic Medicine, 7*, Article e618.
Boardman, F., Young, P. J., Warren, O., & Griffiths, F. E. (2018). The role of experiential knowledge within attitudes towards genetic carrier screening: A comparison of people with and without experience of spinal muscular atrophy. *Health Expectations, 21*, 201–211.
Castaldo, A., Cimbalo, C., Castaldo, R. J., D'Antonio, M., Scorza, M., Salvadori, L., et al. (2020). Cystic fibrosis-screening positive inconclusive diagnosis: Newborn screening and long-term follow-up permits to early identify patients with CFTR-related disorders. *Diagnostics, 10*. Basel, Switzerland.
Castellanos, M. E. P., Barros, N. F., & Coelho, S. S. (2018). Biographical ruptures and flows in the family experience and trajectory of children with cystic fibrosis. *Ciência & Saúde Coletiva, 23*, 357–368.
Charmaz, K. (2014). *Constructing grounded theory*. Los Angeles: Sage.
Chudleigh, J., Barben, J., Ren, C. L., & Southern, K. W. S. (2022). International approaches to management of CFTR-related met-abolic syndrome/cystic fibrosis screen positive, inconclusive diagnosis. *Int J Neonatal Screen, 8*.
Chudleigh, J., Ren, C. L., Barben, J., & Southern, K. W. (2019). International approaches for delivery of positive newborn bloodspot screening results for CF. *Journal of Cystic Fibrosis, 18*, 614–621.
Cystic Fibrosis Trust. (2020). *UK cystic fibrosis registry annual data report 2019*. London: Cystic Fibrosis Trust.
Driscoll, S. J., Heinz, K., Goddard, P., Desai, M., & Gilchrist, F. J. (2024). Outcome data from 15 years of cystic fibrosis newborn screening in a large UK region. *Archives of Disease in Childhood, 109*, 292.
Etchegary, H., Green, J., Parfrey, P., Street, C., & Pullman, D. (2015). Community engagement with genetics: Public perceptions and expectations about genetics research. *Health Expectations, 18*, 1413–1425.
Etchegary, H., Pullman, D., Simmonds, C., Rabie, Z., & Rahman, P. (2021). Identifying aspects of public attitudes toward whole genome sequencing to inform the integration of genomics into care. *Public Health Genomics, 24*, 229–240.
Fereday, J., & Muir-Cochrane, E. (2006). Demonstrating rigor using thematic analysis: A hybrid approach of inductive and deductive coding and theme development. *International Journal of Qualitative Methods, 5*, 80–92.
Freeman, L., Delatycki, M. B., Leach Scully, J., & Kirk, E. P. (2022). Views of reproductive genetic carrier screening participants regarding screening for genes associated with non-syndromic hearing loss. *Prenatal Diagnosis, 42*, 1658–1666.
Ginsburg, D. K., Salinas, D. B., Cosanella, T. M., Wee, C. P., Saeed, M. M., Keens, T. G., et al. (2023). High rates of anxiety detected in mothers of children with inconclusive cystic fibrosis screening results. *Journal of Cystic Fibrosis, 22*, 420–426.
Groves, T., Robinson, P., Wiley, V., & Fitzgerald, D. A. (2015). Long-term outcomes of children with intermediate sweat chloride values in infancy. *Jornal de Pediatria, 166*, 1469–1474. e1461-1463.
Gunnett, M. A., Baker, E., Mims, C., Self, S. T., Gutierrez, H. H., & Guimbellot, J. S. (2023). Outcomes of children with cystic fibrosis screen positive, inconclusive diagnosis/CFTR related metabolic syndrome. *Frontiers in pediatrics, 11*, Article 1127659.
Hassan, L., Dalton, A., Hammond, C., & Tully, M. P. (2020). A deliberative study of public attitudes towards sharing genomic data within NHS genomic medicine services in England. *Public Understanding of Science, 29*, 702–717.
Jones, J. E., Jones, L. L., Calvert, M. J., Damery, S. L., & Mathers, J. M. (2022). A literature review of studies that have compared the use of face-to-face and online focus groups. *International Journal of Qualitative Methods, 21*, 1–12.
Kharrazi, M., & Kharrazi, L. D. (2005). Delayed diagnosis of cystic fibrosis and the family perspective. *The Journal of Pediatrics, 147*, S21–S25.
Kharrazi, M., Yang, J., Bishop, T., Lessing, S., Young, S., Graham, S., et al. (2015). Newborn screening for cystic fibrosis in California. *Pediatrics, 136*, 1062–1072.
Kinsella, S., Hopkins, H., Cooper, L., & Bonham, J. R. (2022). A public dialogue to inform the use of wider genomic testing when used as part of newborn screening to identify cystic fibrosis. *Int J Neonatal Screen, 8*.
Lumertz, M. S., Rispoli, T., Rosa, K. M. D., & Pinto, L. A. (2019). False-negative newborn screening result for immunoreactive trypsinogen: A major problem in children with chronic lung disease. *Jornal Brasileiro de Pneumologia, 45*, Article e20180062.
Monaghan, T. F., Rahman, S. N., Agudelo, C. W., Wein, A. J., Lazar, J. M., Everaert, K., et al. (2021). Foundational statistical principles in medical research: Sensitivity, specificity, positive predictive value, and negative predictive value. *Medicina, 57*.
Morton, G., Thomas, S., Roberts, P., Clark, V., Imrie, J., & Morrison, A. (2022). The importance of early diagnosis and views on newborn screening in metachromatic leukodystrophy: Results of a caregiver survey in the UK and republic of Ireland. *Orphanet Journal of Rare Diseases, 17*, 403.
Munck, A., Bourmaud, A., Bellon, G., Picq, P., & Farrell, P. M. (2020). Phenotype of children with inconclusive cystic fibrosis diagnosis after newborn screening. *Pediatric Pulmonology, 55*, 918–928.
NHS England. (2022). *Cystic fibrosis screening laboratory handbook*. London: NHSE.
Nyström, M. E., Karltun, J., Keller, C., & Andersson Gäre, B. (2018). Collaborative and partnership research for improvement of health and social services: researcher's experiences from 20 projects. *Health Research Policy and Systems, 16*, 46.
Ooi, C. Y., Castellani, C., Keenan, K., Avolio, J., Volpi, S., Boland, M., et al. (2015). Inconclusive diagnosis of cystic fibrosis after newborn screening. *Pediatrics, 135*, e1377–e1385.
Ooi, C. Y., Sutherland, R., Castellani, C., Keenan, K., Boland, M., Reisman, J., et al. (2019). Immunoreactive trypsinogen levels in newborn screened infants with an inconclusive diagnosis of cystic fibrosis. *BMC Pediatrics, 19*, 369.
Paul, D. B. (2021). Imagining life with a genetic disorder: The challenge of evaluating health states that exist from birth. *OBM Genetics, 5*, 130.
Perobelli, S., Zanolla, L., Tamanini, A., Rizzotti, P., Maurice Assael, B., & Castellani, C. (2009). Inconclusive cystic fibrosis neonatal screening results: Long-term psychosocial effects on parents. *Acta Paediatrica, 98*, 1927–1934.
Prakash, S., Penn, J. D., Jackson, K. E., & Dean, L. W. (2022). Newborn screening for Pompe disease: Parental experiences and follow-up care for a late-onset diagnosis. *Journal of Genetic Counseling, 31*, 1404–1420.
Quinn, L. M., Narendran, P., Randell, M. J., Bhavra, K., Boardman, F., Greenfield, S. M., et al. (2023). General population screening for paediatric type 1 diabetes—a qualitative study of UK professional stakeholders. *Diabetic Medicine, 40*, Article e15131.
Rahimzadeh, V., Friedman, J. M., de Wert, G., & Knoppers, B. M. (2022). Exome/genome-wide testing in newborn screening: A proportionate path forward. *Frontiers in Genetics, 13*.
Redgrave, S., & McNeill, A. (2022). A qualitative interview study of the attitudes toward reproductive options of people with genetic visual loss. *Journal of Genetic Counseling, 31*, 1231–1234.

Remec, Z. I., Trebusak Podkrajsek, K., Repic Lampret, B., Kovac, J., Groselj, U., Tesovnik, T., et al. (2021). Next-generation sequencing in newborn screening: A review of current state. *Frontiers in Genetics, 12*.

Ren, C. L., Desai, H., Platt, M., & Dixon, M. (2011). Clinical outcomes in infants with cystic fibrosis transmembrane conductance regulator (CFTR) related metabolic syndrome. *Pediatric Pulmonology, 46*, 1079–1084.

Rueegg, C. S., Barben, J., Hafen, G. M., Moeller, A., Jurca, M., Fingerhut, R., et al. (2016). Newborn screening for cystic fibrosis - the parent perspective. *Journal of Cystic Fibrosis, 15*, 443–451.

Schlüter, D. K., Southern, K. W., Dryden, C., Diggle, P., & Taylor-Robinson, D. (2020). Impact of newborn screening on outcomes and social inequalities in cystic fibrosis: A UK CF registry-based study. *Thorax, 75*, 123–131.

Scotet, V., Gutierrez, H., & Farrell, P. M. (2020). Newborn screening for CF across the globe-where is it worthwhile? *Int J Neonatal Screen, 6*, 18.

Spiekerkoetter, U., Bick, D., Scott, R., Hopkins, H., Krones, T., Gross, E. S., et al. (2023). Genomic newborn screening: Are we entering a new era of screening? *Journal of Inherited Metabolic Disease, 46*, 778–795.

Terlizzi, V., Claut, L., Colombo, C., Tosco, A., Castaldo, A., Fabrizzi, B., et al. (2021a). Outcomes of early repeat sweat testing in infants with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome/CF screen-positive, inconclusive diagnosis. *Pediatric Pulmonology, 56*, 3785–3791.

Terlizzi, V., Claut, L., Tosco, A., Colombo, C., Raia, V., Fabrizzi, B., et al. (2021b). A survey of the prevalence, management and outcome of infants with an inconclusive diagnosis following newborn bloodspot screening for cystic fibrosis (CRMS/CFSPID) in six Italian centres. *Journal of Cystic Fibrosis, 20*, 828–834.

Terlizzi, V., Padoan, R., Claut, L., Colombo, C., Fabrizzi, B., Lucarelli, M., et al. (2020). CRMS/CFSPID subjects carrying D1152H CFTR variant: Can the second variant Be a predictor of disease development? *Diagnostics, 10*. Basel, Switzerland.

Tluczek, A., Ersig, A. L., & Lee, S. (2022). Psychosocial issues related to newborn screening: A systematic review and synthesis. *Int J Neonatal Screen, 8*.

Ulph, F., Cullinan, T., Qureshi, N., & Kai, J. (2014). Informing children of their newborn screening carrier result for sickle cell or cystic fibrosis: Qualitative study of parents' intentions, views and support needs. *Journal of Genetic Counseling, 23*, 409–420.

Ulph, F., Cullinan, T., Qureshi, N., & Kai, J. (2015). Parents' responses to receiving sickle cell or cystic fibrosis carrier results for their child following newborn screening. *European Journal of Human Genetics, 23*, 459–465.

Vears, D. F., Savulescu, J., Christodoulou, J., Wall, M., & Newson, A. J. (2023). Are we ready for whole population genomic sequencing of asymptomatic newborns? *Pharmacogenomics and Personalized Medicine, 16*, 681–691.

Vockley, J., Aartsma-Rus, A., Cohen, J. L., Cowsert, L. M., Howell, R. R., Yu, T. W., et al. (2023). Whole-genome sequencing holds the key to the success of gene-targeted therapies. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics, 193*, 19–29.

Wilson, J. M. G., & Jungner, G. (1968). *Principles and practice of screening for disease*. Geneva: World Health Organisation.