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Acceptability and feasibility of biomarkers of airway eosinophilic inflammation for the management of preschool wheeze: a qualitative study

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ABSTRACT

Objective: This study aimed to examine whether biomarker tests: finger-prick, skin-prick, and offline fractional exhaled nitric oxide (FeNO), are acceptable and feasible as a guide to treatment decisions, uniquely combining the perspectives of parents of preschool children with wheeze and healthcare professionals (HCPs) working in NHS primary care.

Design: Qualitative interview study. Criterion sampling was used to recruit 16 parents from 16 families, and convenience sampling to recruit 16 HCPs (doctors and nurses) from 14 primary care NHS practices. Qualitative data were collected via online one-to-one interviews and focus groups (FG), conducted on Microsoft Teams, transcribed and thematically analysed within the NVivo software package.

Results: Parents described the biomarker tests as acceptable when they were supported by evidence of effectiveness and empathetic communication from HCPs. Skin-prick testing was the most preferred test by parents as it helped them minimise allergen exposures. HCPs favoured finger-prick and FeNO tidal breathing test due to greater familiarity and feasibility in primary care. Time constraints, cost of devices, and training to perform the biomarker tests were reported as barriers to implementation. Both groups agreed that testing frequency should depend on wheeze severity. Finally, a proposed future randomised controlled trial examining whether a biomarker-based approach is superior to the current symptom-based approach was regarded as acceptable and feasible.

Conclusion: Finger-prick, skin-prick, and FeNO testing are conditionally acceptable and feasible in clinical practice for preschool wheeze. However, there should be evidence of their effectiveness, empathetic communication between parents and HCPs and tests' cost-effectiveness to support NHS funding.

KEY MESSAGES

What is already known in this topic: Preschool wheeze is common, yet its management is usually based on symptoms rather than biomarkers. While abnormal blood eosinophil count, atopic sensitization, and FeNO tidal breathing may be associated with future wheeze attacks and act as a guide to ICS treatment in preschool children, their use in primary care lacks evidence on feasibility and acceptability.

What this study adds: This study found that parents and healthcare professionals consider these biomarker tests acceptable and feasible if supported by evidence of effectiveness, and clear communication between parents and healthcare professionals.

How this study might affect research, practice, or policy: Findings indicate that biomarker-guided management could be implemented in a randomised controlled trial of preschool wheeze care, but challenges like time, cost, and training must be addressed.

Competing Interests statement

L. Fleming reports receiving institutional payments for consulting fees from AstraZeneca, Sanofi, GSK, and Regeneron, and for lectures or educational events from AstraZeneca and Sanofi. All payments have been made to her institution. She also serves as a chief investigator on an NIHR HTA grant and co-investigator on and NIHR EME grant. These activities are unrelated to the submitted work. I. Pavord reports other from Sanofi, other from Regeneron Pharmaceuticals, Inc., non-financial support from Excerpta Medica, during the conduct of the study; other from Aerocrine AB, other from Almirall, other from AstraZeneca, other from Boehringer Ingelheim, grants and other from Chiesi, other from GSK, other from Novartis, other from Regeneron Pharmaceuticals, Inc, other from Sanofi, other from Teva , other from Circassia, other from Dey Pharma, other from Genentech, other from Knopp Biosciences, other from Merck, other from MSD, other from Napp Pharmaceuticals, other from RespiVert, other from Schering-Plough, outside the submitted work. C. Griffiths is an investigator in the Genes and Health Programme. Genes & Health is/has recently been core-funded by Wellcome (WT102627, WT210561), the Medical Research Council (UK) (M009017, MR/X009777/1, MR/X009920/1), Higher Education Funding Council for England Catalyst, Barts Charity (845/1796), Health Data Research UK (for London substantive site), and research delivery support from the NHS National Institute for Health Research Clinical Research Network (North Thames). Genes & Health is/has recently been funded by Alnylam Pharmaceuticals, Genomics PLC; and a Life Sciences Industry Consortium of Astra Zeneca PLC, Bristol-Myers Squibb Company, GlaxoSmithKline Research and Development Limited, Maze Therapeutics Inc, Merck Sharp & Dohme LLC, Novo Nordisk A/S, Pfizer Inc, Takeda Development Centre Americas Inc. A. Perikleous, G. Lewis, SJ. Bowen and A. Bush have no conflicts to disclose.

MAIN TEXT

Introduction

Wheeze in preschool children is common and distressing, leading to impaired quality of life, repeated hospital admissions, and family stress [1, 2]. In the UK, its prevalence in 2017 was 7.7%. Although overall prevalence declined between 2008 and 2018, wheeze attack rates increased significantly, with preschoolers experiencing the highest attack rates compared to older children [3, 4].

Currently, there are no clinical tests to guide treatment decisions in preschool wheeze; management relies on medical history and symptom reporting. Some children have underlying eosinophilic airway inflammation and respond well to inhaled corticosteroids (ICS), whereas others do not [5]. Understanding the underlying airway pathology could enable better-targeted therapies and improve outcomes [5]. The 2024 European Respiratory Society (ERS) Task Force suggested biomarkers like blood eosinophil count (BEC) and allergic sensitisation could help identify children more likely to respond to ICS [6]. However, before biomarker-based strategies can be implemented, their acceptability to parents and feasibility in clinical practice must be assessed.

Sekhon *et al*. outlined that acceptability depends on perceived effectiveness, burden, ethics, understanding, and practicality [7]. Few studies have explored the acceptability and feasibility of finger-prick blood sampling, skin-prick testing (SPT), and fractional exhaled nitric oxide (FeNO) tidal breathing (offline) testing in preschool children with wheeze.

This study uniquely combined parent and HCP perspectives on the acceptability and feasibility of finger-prick, SPT, and FeNO tidal breathing (offline) testing in NHS primary care settings, thereby supporting future personalised treatment approaches for preschool

wheeze, and informing the design of a planned randomised controlled trial of preschool wheeze biomarker-based treatment.

METHODS

Study Design

The TAILOR study was a pragmatic, observational study on preschool wheeze (November 2021-December 2023). We examined whether BEC, allergic sensitisation and FeNO alone or in any combination were associated with future wheeze attacks and ICS treatment. Families were approached in NHS primary and secondary care settings and given seven days to decide on participation after receiving study information. Informed consent was obtained before baseline testing, which included finger-prick BEC test, SPT for allergic sensitisation, and FeNO offline testing. A second optional biomarker testing occurred three-to-four months following baseline. Children were followed for one year to record wheeze attack occurrence. At the end of follow-up, a focus group (FG) or one-to-one interviews with one parent per family and HCPs was conducted to collect their views on the acceptability and feasibility of biomarker-guided ICS treatment. Ethical approval was granted by Queen's Square Research Ethics Committee (REC reference: 21/PR/1195), and the study was registered at clinicaltrials.gov (NCT04942483).

Sampling and Recruitment

Criterion sampling was utilised to recruit parents who had taken part in biomarker sampling within the TAILOR study. All parents were invited by AP via telephone to participate in FG or interviews. Convenience sampling was used to recruit HCPs [general practitioners (GPs) and nurses] working in NHS via email. Practices involved in identification and approach of eligible families in the main study were contacted by AP, while the Thames Valley and South Midlands National Institute for Health and Care Research (NIHR) network and the East

Midlands Research Delivery Network (RDN) approached all practices in their network. Written informed consent was obtained from all participants.

Data Collection

Topic guides for FG and interviews were developed based on a literature review [7-12]; they were reviewed by the study team before use, but not formally piloted. Open-ended questions encouraged participants to share views freely. Topic guides' core structure remained consistent, but discussions were iteratively adapted using earlier FG insights to explore broader relevance with later participants. Interviews and FG were conducted online via MS Teams by AP (male pharmacist, PhD candidate), with a second researcher present for notetaking. Sessions were audio-recorded, transcribed, and pseudonymised by AP. Transcripts were not returned to participants for comments/corrections. No renumeration/voucher was provided for their participation.

Qualitative Data Analysis

Thematic analysis was performed within the NVivo 14 software. Coding was conducted by AP and GL (female postdoctoral researcher, qualitative experience) to explore differences or similarities and ensure preconceptions did not unduly affect analyses. Analysis followed Braun and Clarke's iterative process [13], actively seeking contrasting views to ensure a balanced interpretation. Themes were derived from the data. Pragmatism was used as the philosophical paradigm, while an inductive approach was used to develop inferences [14]. Parent themes were derived from FG discussions, whereas HCP themes were drawn from one-to-one interviews and two FGs; individual interviews were often conducted to maximise participation given conflicting schedules.

RESULTS

Participants

Parents

Of the 95 families enrolled in the TAILOR study, 30 (31.6%) responded to telephone invitations to participate in qualitative interviews or FG discussions. Sixteen families (53.3%) attended FG, and five families (16.7%) would only accept participating in one-to-one interviews, but these were not invited as data saturation had already been reached from the focus groups. Nine families (30%) did not attend scheduled FG (Figure 1). There were no differences in the clinical characteristics of children whose families did and did not participate in the FG discussions (Table 1). Parents attending FG were all White, of whom 15/16 (93.8%) were female, aged 32-53 years (children's age range: 20-63 months). There were three FG with three parents and two with five and two parents, respectively, based on their availability.

HCPs

Sixteen HCPs (8 male) participated only in the qualitative component of the TAILOR study (Table 2). The majority were GPs (N=14), while the remaining two participants were practice nurses. The sample included a broad range of professional experience (3-24 years) (Table 2). HCPs were drawn from practices with varying number of patients registered, enabling capturing insights into the feasibility of biomarker testing across practices of differing sizes.

FG and one-to-one interviews lasted approximately 60 and 35 minutes respectively, and there were no repeated interviews.

Thematic findings from parents' semi-structured interviews

Analysis generated five themes, with illustrative quotations given in Table 3.

Theme 1: Providing evidence for usefulness of the biomarker tests.

Parents expressed strong support for biomarker testing, conditional upon evidence demonstrating its efficacy in guiding ICS treatment decisions. Objective data-based therapies would reassure them compared to the current symptom-based approach. Preferences for testing frequency varied; parents of poorly controlled children favoured frequent monitoring, while parents of stable children preferred testing only when needed. However, some parents would accept any frequency if supported by evidence and clinical rationale.

Theme 2: Demonstrating regard for parent and child feelings; giving clear answers or reassurance.

Parents felt that doctors often failed to address their concerns and worries, thus would prefer more communicative HCPs who clearly explain their child's condition and any explanation regarding their treatment decisions. This would provide reassurance and reduce their anxiety. Objective biomarker measurements would strengthen parents' trust to doctors' decisions, rather than the latter relying solely on children's symptoms and medical history.

Theme 3: Parents preferences across the available tests.

Parents were eager to improve their child's health and quality of life. In this study, 9/14 parents (64.3%) preferred SPT due to familiarity from prior experiences and the belief it can help identify a potential cause of wheeze, thus offering relief and a sense of action. While most parents preferred SPT, some favoured finger-prick and FeNO tests, though they did not describe why they preferred the finger-prick test.

Theme 4: Factors affecting children's willingness to undergo testing.

Parents highlighted several factors influencing children's acceptance of the three biomarker tests: (a) age (younger children struggle with the FeNO testing as they may not understand

instructions), (b) previous biomarker test experiences (positive experiences enhance cooperation), (c) empathetic interaction by HCPs, (d) use of diversionary techniques (i.e., toys, cartoons, stickers), (e) biomarker testing order (in this study, performing the FeNO test last, may have reduced its acceptability due to fatigue or stress from the previous tests) and (f) clear instructions before testing (using videos and information sheets to prepare children performing these tests).

Theme 5: Factors affecting willingness to take part in a future intervention study.

Parents reported that participation in a future intervention study, comparing a biomarker-based approach to current methods to guide ICS treatment decisions and whether it is associated with reduced wheeze attacks, depends on children's wheeze condition and concerns about health safety. They also emphasised the importance of receiving the biomarker test results and clear explanation of treatment decisions. Follow-up questionnaires should be brief, utilise lay language and focus on relevant periods.

Thematic findings from HCPs' semi-structured interviews

Analysis generated four themes, with illustrative quotations given in Table 4.

Theme 1: Feasibility requires parents' acceptance and children's cooperation.

Parents may express concern when their child becomes upset during testing and may ask HCPs to stop. This may affect feasibility, as they could stop testing and prevent HCPs from obtaining the necessary measurements. Additionally, children's cooperation is unpredictable and influenced by age. Respondents noted that younger children may better tolerate finger prick tests due to limited awareness but struggle with FeNO tests because they cannot follow instructions. Conversely, older children may perform FeNO tests more successfully but resist finger pricks due to greater awareness and negative past experiences.

Theme 2: Practical, evidence-based, financial, and clinical considerations for implementing biomarkers.

HCPs find finger-prick and FeNO testing more feasible as they are quick, simple, and provide objective results. However, younger children may struggle with FeNO testing. SPT was seen as less practical due to its invasiveness, time-consuming nature, training needs, perceived anaphylaxis risk and limited clinical value, as some respondents thought that allergen avoidance may be challenging for many families. HCPs would adopt biomarker tests only if supported by evidence predicting future wheeze attacks and ICS treatment response, and if endorsed by guidelines as with FeNO testing [15-17].

High device and their consumable costs currently limit implementation. Demonstrating that these biomarkers predict ICS treatment response is crucial to secure funding from healthcare bodies, ultimately enabling NHS implementation. Testing frequency should reflect wheeze severity, with poorly controlled children requiring frequent assessments. Consumable costs and time demands influence testing frequency since time-consuming or expensive tests can increase workload and healthcare costs for practices, respectively.

Theme 3: Maximising efficiency to incorporate testing into practice.

The short duration of GP appointments (10-15 minutes) makes it impractical to incorporate biomarker testing. Rather than proposing double appointments, HCPs suggested delegating healthcare assistants (HCA) or nurses before the GP consultation, ensuring time efficiency and cost-effectiveness due to their lower staffing costs.

Theme 4: Perceived barriers and facilitators for trial feasibility.

HCPs emphasize that realistic recruitment targets, child safety, and strong supporting evidence are essential for a future intervention study. Financial incentives would be crucial

for participation. Research-active practices may be better equipped to meet study demands. Clear communication will be necessary to prevent parental bias toward intervention groups, ensuring both study arms are seen as providing equally valid care without influencing decisions.

Similarities and differences between parents' and HCPs' semi-structured interviews. Both parents and HCPs agreed biomarker tests must be evidence-based to be accepted, with HCPs additionally seeking guideline support. Both groups mentioned testing frequency should reflect wheeze severity, though some parents would accept any frequency if evidence-based. Children's cooperation depends on age and prior experiences, affecting testing success. On the other hand, there were differences. Parents would like empathetic HCPs, detailed explanations of their child's condition and care for their worries and concerns. Thus, doctors could start expressing their thoughts and doubts regarding children's diagnosis, because parents appreciate having a clear, transparent and honest discussion. Finally, parents preferred SPT, whereas HCPs found them less feasible due to time, training needs, and rare anaphylaxis risks, making implementation dependent on HCPs' readiness.

DISCUSSION

To our knowledge this is the first study to explore both parent and HCP perspectives on the acceptability and feasibility of finger-prick, skin-prick, and FeNO tests. The findings showed these tests are acceptable and feasible under the following conditions: (a) there is evidence of their effectiveness, (b) empathetic interaction and clear communication between parents and HCPs is established and (c) there is evidence of their cost-effectiveness to support NHS funding.

Parents seek empathetic interactions, clear explanations and shared decision-making from HCPs, consistent with previous research highlighting the importance of reassurance and clearer communication [8, 18-22].

Our findings align with those of Wajid *et al*. [18], who found that parents were frustrated by diagnostic uncertainty and favoured investigative tests to guide treatment pathways. However, our study additionally included the views of HCPs, providing a broader, implementation-focused perspective.

Most parents preferred SPT because it gave them an active role in helping their child. This finding aligns with Clement *et al*., who reported that parents' interest in allergies is driven by their desire to improve their child's condition and exclude allergies as the causing factor for their symptoms [10]. However, SPT detects allergic sensitisation, not allergy, leading to misconception regarding causality. In contrast to parents, HCPs regarded SPT as less feasible due to the training required, time demands, and the risk of adverse reactions, despite the extremely low incidence of anaphylaxis (one in 55,000 patients) reported in large studies [23].

HCPs highlighted several practical considerations for implementation. Tight schedules and heavy workloads limit their ability to incorporate these tests into routine practice, making it essential to integrate testing into existing workflows without increasing burden. Successful implementation would require nurses or HCAs' training on both technical (i.e., biomarker tests) and communication skills [incorporating distraction-based techniques (i.e., toys and cartoons] to facilitate children's cooperation. The success of these tests also depends on HCP's skills [24]. Although not mentioned by HCPs, offering biomarker tests in community-based healthcare settings, such as community diagnostic centres (CDCs) or intermediate

care clinics, could provide flexible appointment structures, relieve pressure on GP appointments, and facilitate wider adoption [25].

Health economics also affect feasibility. The costs of biomarker devices and consumables are significant barriers unless centrally funded. Negotiations with clinical commissioning groups are therefore essential to make these tests available across GP practices. El-Osta *et al*. reported that the lack of NHS reimbursement for point-of-care (POC) tests deters primary care adoption due to high initial and ongoing costs [26]. Comparable challenges were reported for the introduction of HbA1c POC test in UK primary care, but funding routes were developed [27, 28]. Similar routes could support adoption of biomarker tests for preschool wheeze. Future cost-effectiveness analyses should consider device/consumables costs, staff training, workflow adjustments and long-term savings from reduced exacerbations and unscheduled healthcare visits. It should be noted that parents' out of pocket expenses (for example travel and subsistence), as well as willingness or ability to pay for biomarker tests outside NHS (e.g., private testing or co-payment) were not assessed as we focused on NHS primary care costs. Future work should explore this, as out-of-pocket costs may affect acceptability.

In this study, HCPs mentioned that biomarker test adoption depends on proven ability to predict outcomes and guide treatment decisions, aligning with Ciardiello *et al*. [29]. They prefer quick, time-efficient tests, supported by guidelines and acceptable to patients [29]. High costs and lack of evidence or guideline support for the biomarkers tests would prohibit clinical practice implementation [29].

Parents in this study emphasised on transparency and children's safety to consider participation in a future intervention study. They expressed concern about randomisation in

the control group, fearing it may deprive their child of potential benefits, as previously identified [30]. Building trust between parents and researchers, explaining randomisation, blinding and right to withdraw are critical to improve participation and prevent misconceptions and complaints during the study [31, 32]. Best practices, such as the use of multimedia consent tools, lay summaries and parent advisory groups could support informed decision-making and improve recruitment rates. Additionally, parents of children with poorly controlled wheeze are more likely to participate in studies, while those whose children's condition is stable are less inclined to do so [21]. Finally, HCPs highlighted the need for realistic recruitment targets and adequate funding for participating practices. These concerns should be explicitly addressed in trial design, by involving more practices with smaller recruitment targets and providing resources to offset additional workload.

Strengths and limitations

The key strength of this study is that it captured the perspectives of both parents and HCPs regarding the three biomarker tests, helping to identify important barriers to implementing them in NHS primary care. While this study offered valuable insights, several limitations should be acknowledged. Although data saturation [i.e., the collection of qualitative data until the addition of new data does not yield new themes [33]] was deemed achieved within parents' FG, not inviting families who agreed to one-to-one interviews may be a limitation. These parents might have felt uncomfortable sharing personal experiences in group settings. The inclusion of parents with prior experience with biomarker tests enabled informed, pragmatic reflections on acceptability. However, this limits transferability to test-naïve populations. Participants also lacked ethnic diversity. Factors such as culture, health literacy, and the presence or not of previous biomarker testing could influence perspectives but were not explored. Future qualitative studies should consider deeper enquiry into these aspects of behaviour and belief, as well as broader recruitment strategies, and purposive sampling

strategies to support inclusion of children from diverse ethnic and demographic backgrounds to strengthen findings' transferability. Purposive sampling was not used to enable all parents from this study to participate, while convenience sampling for HCPs was used due to the study's time constraints, potentially leading to a less diverse sample. Additionally, HCPs lacked firsthand experience with the biomarker tests, making their feedback theoretical rather than practical. Although the sample was relatively homogeneous in professional roles, it was diverse in terms of gender, clinical experience, and practice size, allowing collection of varied perspectives on biomarker testing implementation in primary care. Despite these limitations, the study provides important insights for future research and practice.

Conclusion

This study, by uniquely combining parents and HCPs perspectives, showed that finger-prick and FeNO tests were the most acceptable and feasible, while SPT was the least feasible due to training, time, and safety concerns. These tests may be best used in nurse- or HCA-led clinics or CDCs, where sufficient time and child-friendly preparation can be provided. Implementation should be supported by clear communication, evidence of HCP and patient/parent perspectives, efficacy, and cost-effectiveness data from future trials.

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FIGURES AND TABLES (MAX: 5)

Figure 1. Recruitment and baseline testing flowchart.

Table 1. *Difference between those who did and did not participate in the focus group discussions.*

Factor	Participated (N=16)	Did not participate (N=79)	*P*-value
Age (m), median (range)	33 (20 – 63)	36 (13 – 71)	0.73
Male sex, n. (%)	13 (81.3)	45 (57)	0.07
Prescribed inhaled corticosteroid at baseline, n. (%)	8 (50)	33 (41.8)	0.55
Allergic sensitisation, n. (%)	5 (31.3)	40 (50.6)	0.16
Blood eosinophil count (cells/μL), median (range)	500 (0 – 900)	400 (0 – 1400)	0.34
Fractional exhaled nitric oxide (ppb), median (range)	12.5 (6.5 – 14.5), N=3	6 (0 – 18.5), N=34	0.25
Experienced a wheeze attack (consensus approach), n. (%)	13 (81.3)	56 (70.9)	0.4
Number of wheeze attacks in the year following baseline, median (range)	2 (0 – 9)	1 (0 – 8)	0.17

Table 2. *Semi-structured interview and focus group healthcare professionals' demographics*

HCP ID	Occupation	Gender	Experience (years)[1]	Patients registered in practice[2]	Data source
GP1	Doctor	Male	18	10,268 (0-9 years old: 1,021)	Focus group 1
GP2	Doctor	Female	7	10,268 (0-9 years old: 1,021)	Focus group 1
GP3	Doctor	Female	18	16,631 (0-9 years old: 1,521)	One-to-one interview
GP4	Doctor	Male	5	58,389 (0-9 years old: 4,719)	One-to-one interview
GP5	Doctor	Female	24	9,365 (0-9 years old: 758)	One-to-one interview
GP6	Doctor	Female	8	24,639 (0-9 years old: 2,098)	Focus group 2
N1	Nurse	Female	17	24,639 (0-9 years old: 2,098)	Focus group 2
GP7	Doctor	Male	8	11,729 (0-9 years old: 947)	One-to-one interview
GP8	Doctor	Female	18	5.317 (0-9 years old: 336)	One-to-one interview
GP9	Doctor	Male	18	11,317 (0-9 years old: 1,008)	One-to-one interview
GP10	Doctor	Female	18	8,596 (0-9 years old: 1,146)	One-to-one interview
GP11	Doctor	Male	3	12,521 (0-9 years old: 1,015)	One-to-one interview
GP12	Doctor	Female	18	11,836 (0-9 years old: 1,174)	One-to-one interview
GP13	Doctor	Male	18	10,350 (0-9 years old: 967)	One-to-one interview
GP14	Doctor	Male	13	23,816 (0-9 years old: 1,806)	One-to-one interview
N2	Nurse	Male	22	4,305 (0-9 years old: 475)	One-to-one interview

[1] Years after registration as GP, as per the General Medical Council register[34] and years after registration as per the Nursing and Midwifery Council register[35], [2] Obtained from the NHS digital general practice data hub[36]

Table 3. *Thematic analysis from parents' focus group discussions*

Providing evidence for usefulness of the biomarker tests.	There needs to be evidence that the thresholds used are predictive of ICS treatment response to make parents feel reassurance	"*We didn't know if the brown inhaler was just a precautionary or whether he would be receptive to it, so with the tests we would feel better knowing that there is something that can be done for this.*" – P1 "*I think medicine is quite generalised and not all treatments work for everybody. So, if there is a way of testing individuals' responses and saying, oh well, that shows us exactly what we need to do, then I think that's a good thing*" – P5
	There needs to be evidence for biomarker testing frequency	"*I think if the research showed that having it quarterly was beneficial and that things could change, I think as a parent you do what you can. And if they want to test them more regularly because it would be beneficial then that is fine*" – P1 "*I'd be amenable to coming back once more in the year or however many more times you thought appropriate based on your findings*" – P7
	Biomarker testing frequency is affected by the children's wheeze severity	"*I think it would depend on how ill the child was. If it was [child's name] when he was born until the age of two years old where he was going into hospital every couple of weeks, I'd be happy to have a testing every couple of weeks. But now he is a bit older and it's not so much than an infrequent review every three, six months, whenever they personally needed.*" – P5 "*I don't feel she needs testing that often now, because we are able to manage any wheeze she does experience.*" – P11
Demonstrating regard for parent and child feelings; giving clear answers or reassurance.	Parents want doctors to show that they care more of their concerns and worries	"*So, one time [child's name] was taken from home by ambulance because of struggling with breathing, which was the worst part for me, but later having no interest from our GP that was a very bad experience, because as a parent you feel that there is no one to support you*" – P6 "*The hospital just sorts of saw him and that was it. I feel like the information was quite minimal to the point I've had to chase up the respiratory team myself and just go directly to the consultant we saw to ask for more information*" – P7
	Parents appreciate getting an explanation of what is happening with their child	"*In the UK, they don't do tests on the child, so medication is just thrown out like wildfire, really, depending on the symptoms. But is that the right treatment for the child? That's currently what happens in a child because they don't know what's wrong with them. So, you've got no test, they don't do any tests. The doctor just prescribes it based on how they're breathing, how sick they get, how much time they have the wheeze etc. That is the current life with the NHS*" – P12 "*We've had a lot of people say to us "he/she should be fine", "he does not have any problems", "does not have any allergies". Many people keep repeating this "he'll grow out of it" or "oh, it's this and he is not growing out of it". I think the lack of knowledge that we get as parents when they're little is quite hard.*" – P16
Parents preferences across the available tests.	Parents are more familiar with the skin-prick testing and can understand it better, which increases its acceptability	"*I would place the allergy test as number one because I probably understood it the best*" – P3 "*I would say the favourite is probably the allergy testing because obviously that's something that we're aware of and can take forward*" – P9
	Skin-prick test results help parents take measures to help their child	"*Being referred for an allergy test as a kind of first point of call would give parents some satisfaction that they were doing something for their children*" – P1 "*It has definitely helped us in certain ways that we've, you know, we've changed our carpet in our house to wooden flooring, we've got air purifiers in the house now, we change bedding more often. These things kind of gave us, you know, more options for how to help him/her.*" – P15
Factors affecting children's willingness to undergo testing.	Younger children find it difficult to understand and perform the FeNO tidal breathing test	"*I would place the balloon test last, just because my child was not 100% sure what to do with that one. It was a bit harder for him to get his head in the mask*" – P3 "*He hadn't quite grasped the concept of being able to blow. So, we struggled, but he didn't…it didn't upset him, it didn't bother him, so I think it's more on the age of a child and their development and skills that they have*" – P3
	A previous positive or negative experience with biomarker tests increases and reduces their acceptability by children, respectively	*"I think partly he didn't understand what he had to do with the balloon test, and he's had experiences in the past with other things coming near his mouth that have been negative for him, so I think maybe there's a bit of correlation" – P3* *"They were trying to do some blood test in the hospital shortly before came to you to do the tests. So, that's why it was very difficult to convince him that it was not as painful as it was in the hospital" – P6* *"[Child's name] responds quite well in those situations, and you made him feel extremely relaxed. I don't know if it's because over the last few years he's been to the hospital many times, has been in ambulances, has been to the doctors" – P7*
	Distracting children with toys and cartoons when performing the tests increases their acceptability as children associate it with fun	*"When we came to the hospital, and you had the toy with the bubbles. During this, there was lots of bubbles. That was lots of fun, which probably wasn't relevant to you to what you were trying to get from the visit, but definitely the bubble gun was our highlight" – P5* *"[Child's name] seemed to enjoy it. It was a good plan having the kind of toys and they laptop with Paw Patrol on, it kind of distracted him because otherwise it could have been a bit problematic" – P10*

	HCPs need to be patient with children, supportive and engaging.	"*Coming in with a 3-year-old can be quite chaotic, but you made it really simple and easy for us and you were very understanding*" – P4 *"We felt that when we first came to you, you were really interactive with [child's name] and he was really comfortable with the whole process and I think he had been in hospital quite a lot and was getting quite anxious about it, but actually the experience was great, and he loved the bubble machine" – P16*
	FeNO testing was performed last, and children may have not liked it because they were disturbed or tired from the previous two tests.	*"From our experience, it was the last test my child did, and I think he got quite stressed out from the previous tests. Potentially doing the FeNO test first just because my child had got a bit stressed out by this skin prick test and I think he wasn't in sort of the most compliant mindset for the last test" – P3* *"I think he struggled with the balloon test. I think he possibly got a bit bored by that point or something. I think the FeNO test was the least favourite" – P8*
	Younger children who struggled with FeNO test would benefit from having a preparation or an exercise prior to the meeting so that they know how to exhale in the gas collection bag.	*"Maybe some pre-information about what's coming, so that we could practise, or something could help. So, a video or a leaflet or an e-mail, saying we're going to have to practise blowing up a balloon" – P1* *"I know that in the preparation for the appointment, it said quite what was going to happen, but if there was a way to know in advance, a way that we could have to potentially practice at home, so it wasn't so alien and that could have been helpful before the appointment" – P3*
Factors affecting willingness to take part in a future intervention study.	Participation in a future intervention study may be affected by child's condition.	"*From the perspective of my own child, every time he gets a virus, he's got chest problems, which is why he's part of this study*" – P2 "*My child's condition would affect my judgment on whether or not to participate*" – P3
	Parents are concerned that participation in the intervention study may lead to wheeze attacks and hospitalisations.	"*Through the current approach, my child's condition is managed, I guess through the test approach it's an unknown. I don't know if it is a better way of managing it or not. I'm personally nervous of the changes to medication that would then result in more hospital admissions*" – P3 "*For him to be completely just based on results…I'm 50-50 about it. The steroid inhaler has been a game changer for him, and we haven't been in hospital…it's been a huge improvement. But it took us a couple of years to finally get what he needed.*" – P16
	Parent would like to have the tests results, explanation of the treatments suggested and justification why the treatment was given.	"*I think it's apparent just being given that information in advance like you've gone, you've put your children through this, and they don't particularly enjoy the prick test and the blood test, but being able to walk away knowing you did it and you've had those results and especially the allergy one, I think it's quite important that you are given that information*" – P1 "I would like to know the test results. I think there should be a meeting for parents to tell them more about different type of treatments which would be prescribed to our children, what kind of side effects they would have." – P6
	1. Parents like quick and simple questionnaires.	"*The monthly questionnaires coming through, I was able to answer them quite quickly. The questions weren't too long*" – P1 "*The questionnaires weren't a problem; they were quite short and easy to fill in*" – P8 "*The questionnaire had quite short simple questions which was not time consuming and were to the point*" – P9 "*The questionnaires haven't been an issue; they've been quick and convenient*" – P11

Table 4. *Thematic analysis from healthcare professionals' focus group and one-to-one discussions*

Feasibility requires parents' acceptance and children's cooperation.	Doctors care of parents' opinions or reactions	"*I think parents worry about their wheezing children. I imagine, they would be happy to have the testing done, but they may not be able to do the full testing because if they see their child stressed, they may not be willing to then let them have the other tests*" – GP1 "*In terms of the skin prick testing, I'm not sure how acceptable it would be to the parents if the child had finger prick testing first and they are already crying, then to go on further and have three skin prick tests, I think that would be quite distressing*" – GP2
	Children's cooperation is unpredictable during biomarker testing	"*I think it's just the unpredictability with that age group and it's like when giving childhood immunisation. Some children of that age are completely compliant and others, it takes you kind of four times as long as you hope*" – GP6 "*In my experience they're not necessarily the easiest ages to come on board. You know they've got minds of their own*" – GP8
	Successful performance of tests in practice may depend on children's age	"*Probably one to be finger-prick, second to be FeNO and skin-prick last in terms of tolerability I would say. The older the child then probably the FeNO first, finger prick second and skin prick testing last*" – GP3 *"I'd probably say FeNO, for maybe the four-and-five-year-old, finger-prick probably for the one-to-three, purely because you're not sure if they're going to reliably understand instructions to blow into the FeNO machine and I think that's possibly also part of the reason why we don't really tend to diagnose asthma in very young children, because if you give them a peak flow, they simply wouldn't follow the instructions very well. I think it would be a challenge for a 5-year-old to be re-pricked, especially if they had a bad experience in the past*" – GP11
Practical, evidence-based, financial, and clinical considerations for implementing biomarkers.	Finger prick test can be implemented in primary care because HCPs are competent in performing it, it is quick and easy to be performed and gives objective measurements	"*I think the finger prick testing because it needs just one needle, probably seems like the easiest to do*" – GP2 "*The finger prick is something we do for a random blood glucose measurement or something like that and the nurses obviously give injections to kids all the time*" – GP5
	FeNO test will be easy to be performed by the existing personnel and can be used in a wide age range of asthmatic patients	"*I think the FeNO would be very straightforward because we use FeNO already for adults and I think we are using it for teenagers but not small children yet*" – GP10 "*The FeNO test would be the easiest one to do. I can't see that being a problem at all because we already use that as kind of part of standard care*" – GP14
	It may be difficult to successfully perform the FeNO test in preschool children	"*FeNO testing using the NIOX machine it is actually very difficult for people to use. They take multiple times. I'd like to see how it is used on a child because I think that could be difficult for them to breathe out enough air*" – GP1 "*I suppose it could potentially be quite time consuming to engage children of that age and get the technique right. Probably getting reliable results in children of that age with FeNO testing is quite challenging*" – GP4
	GP practices do not perform SPT, and its implementation in primary care will require training	"*I mean from a clinician's perspective I suppose it's my unfamiliarity. Obviously, we have secondary care for that and the idea of me doing that, or one of our clinicians doing that, seems a little bit foreign*" – GP10 "*We've got no experience with using the skin prick. I don't think anybody does any skin prick test*" – GP13
	Skin prick testing may cause anaphylaxis, and treatment is a time-consuming procedure	"*There's risk of anaphylaxis and none of us would want to have anaphylaxis because number one, it's of course live threatening and secondly, it's incredibly time consuming*" – GP1 "*The other hesitation I can imagine that nurses could have if they were delivering the skin allergy test is worrying about anaphylaxis*" – GP5
	HCPs think that SPT may not be a useful test as it cannot provide objective measures of helping children	"*What is the benefit of knowing it? So, if your child is allergic to dust mite. What you're going to do? I mean it's good to know, but it's impossible to erase your house from dust mite. And then, if the family's got a beloved animal, a beloved dog, are you going to get rid of your dog? It's quite a difficult decision, isn't it? I think the skin-prick test results can be quite difficult to manage because a lot of people just want to do it for curiosity, but they're not willing to change their lifestyle*" – GP2 "*I wouldn't do the patch testing, because for example looking at tree pollen, there's nothing you can do about it. It's the same with people with hay fever. They want testing, but the only thing you can do is avoid the allergen, which is completely impossible. And so, you're treating the symptoms. And if you discover someone's allergic to pollen, then what? They're not going to live in a bubble at home. They're still going to go out, and you're just aware that they've got this allergy*" – GP1
	Doctors want evidence that the tests can predict response to treatment	"*It has to be justified. There has to be evidence that it works, so that we don't go into unnecessary cost when there is no evidence that it works*" – GP10 "*Everything is evidence-based medicine and if there's not good evidence to support its use then there is not really a point using it, because you're going to get unreliable results*" – GP11

	Practices are keener to use the biomarker tests if they are supported by asthma guidelines	"*It would need a bit like the BTS/SIGN and the NICE guidelines to have some trials saying that using these three tests will help to diagnose in this under five group with this degree of reliability*" – GP9 "*If there was evidence and it was incorporated into NICE guidelines, if all the national guidance was saying that this was best practise to check these things before making a diagnosis or changing treatments, then yeah, that would definitely make it more attractive.*" – GP13
	The inclusion of FeNO in guidelines facilitates its incorporation into daily routine practice	"*Obviously the FeNO evidence is there, certainly in the older children and actually we are looking at BIONA FeNO machine currently within our practise…Realistically, we should be spirometry and FeNO*" – GP12 "*The guidelines basically could have an effect on doctor's decisions on taking the equipment because since the guidelines mentioned FeNO that made it more acceptable, buying the FeNO device*" – GP13 "*I mean FeNO is turning into sort of gold standard, it's what you must have, every surgery should consider having it. And it's something we've had for a couple of years now, so that would appear to be a push from the world of asthma that this is good practise and therefore you should kind of have it alongside spirometry*" – GP14
	The cost of the devices and their consumables is an issue for implementation in primary care	"*For a practise to spend £4000 on the machine and then for the tests, it's not going to happen, and I think there's no way a practice is going to spend £4000 on the HemoCue device*" – GP1 "*That not something general practitioners are going to buy. I think it's quite unlikely that people will pay that kind of money per test*" – GP3
	GP practices cannot afford buying the devices on their own	"*If it was coming out of your wage how much would it make an impact, then? So, if I said I want you to do it in the hospital, but it's coming out of your monthly payment, would it make a difference?*" – GP9 "*Obviously the cost is a significant factor for the practise, especially at the moment when our expenses are shooting up and the money coming in is not*" – GP12
	Funding is essential for the tests to be implemented in primary care	"*If it works, the next day we would have to negotiate with the CCG or the ICB to make these available to all GP practices that they can each have one test or one offline kit which they can use*" – GP1 "*The key thing that we've got to be thinking about here is, how can we fund this to make it happen? Don't worry about the staff; that will occur if the healthcare provider, be that a hospital, a practice has appropriate funding to do it, they'll get it done*" – GP9 "*If there's no central funding to pay for the particular equipment it would be off putting*" – GP13
	If child's condition is poor, then biomarker testing should occur more frequently	"*I imagine that the well-controlled ones, we'd probably be doing it annually, but for those who are struggling we would probably be doing it six monthly or quarterly*" – GP10 "*I don't know how frequently would be looking at testing them, it probably depends on their symptoms and how well controlled they are… If they're well controlled, you're not going to bring them back for repeated tests multiple times per year, it might be an annual asthma review*" – GP13
	The frequency of tests per child, depends on the cost of the consumables and the time needed to perform the tests per child	"*I think it depends how costly it is really and if you rolled it out into practice, how costly it would be well both financially and time wise*" – GP12 "*I think it's about ongoing cost. You can always make a case for a piece of equipment, but the fact is how much is going to cost per child*" – GP3
Maximising efficiency to incorporate testing into practice.	Doctor appointments last 10 minutes and it may be difficult to do the tests in that meeting	"*I get the feeling that probably a 10-to-15-minute appointment to do these three tests are not enough*" – GP2 "*General practice appointments tend to be 10 to 15 minutes and there's no way we could fit any of that in*" – GP3 "*I think, as [nurse's name] said, without having that time pressure of the GP time, I think I would definitely be having it as a separate appointment*" – GP6
	The unpredictive nature of children during testing makes HCPs think that a separate appointment may be needed	"*Say you have a 20 minute or half hour appointment, we are going to find we frequently waste appointments trying to engage children with those tests and if they can't engage properly, I presume it would affect the reliability of the results*" – GP4 "*If I'm going to collect the breath again and explaining that depending on the age of the child, that can be probably another 20 minutes. So, you're asking for a one-hour appointment when I've got 10 minutes*" – GP9
	Tests are more feasible to be done by nurses or healthcare assistants	"*A test could be done on a different day a few days prior to the consultation with the nurse or perhaps by a technician, a suitably trained technician*" – GP3 "*Perhaps it should be a healthcare assistant if we can train them to do that and leave them*" – GP9
	Testing performed by nurses may be a cost-effective route in GP practices	"*I think ultimately if you could have a one of your respiratory nurses doing the tests prior to seeing a clinician ultimately that would be the most effective and probably cost-effective route*" – GP4 "*It feels like something that would sit better with a practise nurse activity and equally, if we had to look at it in terms of cost benefit type equation, having practice nurses is probably the right level of cost, in terms of staff costs*" – N2

Perceived barriers and facilitators for trial feasibility.	Practices must be given a realistic and feasible number of participants to recruit and in a feasible time period	"*The two big things that we found are a realistic number of recruits, so being realistic about the uptake of research within a population. You would probably get an uptake of somewhere between 10 and 15%. We might be able to find 40, but we're not going to find 400. And that puts us off going in, because we think we're not realistically going to be able to hit that number and if all of those children were half an hour appointment, 400 times, half an hour is a lot of days and weeks of nurses' kind of time to do that*" – GP14 "*I would make it a longitudinal study. It's good to have a roll out over several months because trying to recruit 60 in two months is sometimes logistically difficult. But if you have a target of how many per month that's a little easier*" – GP3
	Practices want evidence prior to participating in a future RCT	"*We want the evidence to give good care because there's a whole evidence-based medicine culture. We don't want to do things that are not safe, with no evidence. We want to do things that will improve care*" – GP1 "*It would have to be good quality, NIHR type level descriptors behind it, using a test that we don't quite know its accuracy yet*" – GP9
	Practices would like a financial incentive to participate in the future intervention study, either to be paid for the time they provide to the study (based on their hourly payment) or keeping a device at the end of the study	"*Remuneration that suitably covers nurse and doctor time for patients can make the randomised trial more acceptable to GP practices*" – GP3 "*I suppose the sort of first thing that everybody thinks of with these sorts of studies is free equipment. If you get to keep the FeNO equipment or the HemoCue, then that's something that you might keep using after the end of the study*" – GP13
	A future intervention study is more feasible in research-active practices as they have the capacity and capability to handle a RCT	"*I think randomised control trials would be something that research active practises would be eager to take on*" – GP4 "*I think it would probably need practices that very much had a culture of research and had experience of research to be able to carry this out efficiently*" – GP6 "*Some research surgeries have a lot more resources and have dedicated nurses, they've got allocated nurses that do full time research. So, they definitely would have capacity for something like this*" – GP11
	Parents seeing different treatment being given in the practice may make them intervene with treatment decisions	"*If I'm told that my four-year-old kid might have a risk of wheezing because of the biomarker tests, but I'm told I'm in the control group, I'm going to be very worried as a parent as to whether I should be having the inhaler. And then the parents are going to come and see their GP and say I'm in the other group and I'd really like him to have an inhaler. Because parents, you know, if your kid is sick, you'll do anything for your kid*" – GP1 "*Similarly with all the all the studies we run that that people would think that the intervention is going to be beneficial, but you know that's what the trial's there for isn't it?*" – GP4 "*You have to be very clear to the parents that actually this is being done as part of a research study. We don't know whether using biomarkers is more superior to not using biomarkers*" – GP6