

20661-D05 WP11 Market entry barriers, summary

20661 Airway Disease Analysis and Prevention

EIT Health

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1 Executive Summary

Scope of the ADAPT project: To validate a new, minimally invasive diagnostic device for local sampling in chronic airway disease patients in combination with new biomarker assays. **Aim:** To allow early detection of allergic rhinitis and asthma and enable endotyping of such patients to support decision on treatment. **Added value:** The ADAPT concept is a less invasive, more sensitive, and reliable assessment of local airway inflammation compared to current clinical practice. The concept is particularly attractive to assessment in children below 5 years of age, for which lung function tests are not readily available. **Who:** Children, adolescents and adults. **Where:** Primary care and specialists, with the vision to develop it further into home sampling, send-in for analysis.

Scope of this WP: A market research field study was conducted through in-depth interviews with pediatricians in Germany, Italy, and France on the diagnostic process for wheezing children, including treatment and follow-up, and the value of the ADAPT concept of nasal sampling for measurement of airway biomarkers in wheezing and asthma.

This WP report summarizes: Results from the market research study, including conclusions and recommendations extracted from 30 one-hour in-depth interviews with experienced European pediatricians.

Results from this WP: The study described herein has identified challenges and opportunities in diagnosing wheezing and asthmatic children and outlined the potential role of biomarkers in monitoring treatment and recovery. Addressing challenges and opportunities identified herein will be critical to achieving commercial success with the ADAPT concept and this study is an important part of our commercialization strategy towards this goal.

2 Introduction

Approximately one third of the European population will develop asthma. Onset can happen throughout life but is most common in early childhood, making asthma the most common chronic childhood disease. Importantly, diagnosis is complicated by the existence of a variety of different asthma phenotypes (1) and lack of a clear definition of the asthma condition. In children, asthma is defined as a chronic inflammatory disorder of the airways, associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing. Below 5 years of

age, clinical symptoms of asthma vary and are nonspecific, which is why a symptoms-only approach, to define diverse **wheezing phenotypes**, represent current practice (2).

Wheezing and asthma thus represent a continuum of chronic airway diseases with shared clinical and functional features. Wheezing is diagnosed by auscultation with a stethoscope and is typically a high-pitched sound heard during the expiratory phase, resulting from narrowing of the smaller airways. Approximately 50% of all children will experience at least one wheezing episode before the age of 6 years (3) with evidence of viral infection in 80-90% of these episodes (4,5).

Currently, there are no diagnostic tools to support phenotyping of wheezing, nor any tools to predict which wheezing children will develop asthma. The diagnosis of asthma in children is based solely on history of symptoms (wheezing, cough, chest tightness, shortness of breath). In adolescents and adults, diagnosis includes assessment of expiratory airflow limitation, sometimes with the support of biomarkers, such as blood eosinophil counts (B-Eos) and measurement of fractional concentration of exhaled nitric oxide (FeNO), neither of which are used for infants and small children. If asthma is misdiagnosed, children with untreated asthma are at risk of potentially life-threatening asthma attacks while those that do not have asthma receive unnecessary medication.

In 2019, we identified wheezing children as one important group of patients that could benefit from improved diagnosis (6). We also identified wheezing children as a commercially attractive application for the ADAPT concept. Thus, herein (WP11), we wanted to investigate this further, to map:

- What is the current process of diagnosis of wheezing children? What is used to support the diagnosis, and what is the current treatment for wheezing children? How confident and satisfied are physicians with current diagnostic tools?
- What drives current behavior in diagnosis? Where are the unmet needs regarding diagnostic tools used for diagnosing wheezing children, as well as the treatment guidance?
- Finally, and most importantly, what are pediatricians' perceptions of the ADAPT product concept, and how does it compare to other diagnostic tests?

We therefore initiated and performed a market research field study in which we collected feedback from pediatricians across Europe to understand the current diagnostic tools used for diagnosing and phenotyping wheeze and asthma, and the clinical unmet needs associated with this.

3 Market Research Study

To better understand the market for respiratory diagnostics, Thermo Fisher Scientific has conducted a market research field study together with an external agency, the SKIM group, in 2020.

30 pediatricians in Germany, Italy and France (10 per country) were recruited to the study and interviewed anonymously on their experience of diagnosis wheezing children.

3.1 Research objective and methodology

The market research study focused on qualitative research to identify **opinions** and **feelings** from pediatrician routinely engaged in diagnosis of wheezing children. Results and conclusions from this study should not be considered statistically valid or projectable; rather the intention was to gather insight, provide direction and clarify issues.

3.1.1 Screening pediatricians for inclusion into study

A number of pediatricians were screened by SKIM and 30 were selected to match the inclusion criteria in 3.1.2. To get a broad representation, both office-based and hospital-based physicians were selected, including pediatricians working in the emergency room (ER).

3.1.2 Inclusion criteria

- Work as a pediatrician or general practitioner specialized in pediatrics.
- Treat at least 15 wheezing children of 5 years old and younger per month.
- Are personally involved in diagnosing, treating, and monitoring of wheezing children of 5 years old and younger.
- Spend at least 65% of their time in direct patient care.
- The respondent is knowledgeable in treating wheezing children and is interested in contributing his/her opinions on this topic.
- Have 3 -35 years of experience.
- Are not affiliated with a pharmaceutical company, advertising, marketing, or market research.

Table 1. The target group comprising a total of 30 pediatricians from Germany, Italy, and France. Physicians were selected to represent general practitioners (GP) and specialists working at hospitals, including ER, as well as office-based physicians.

	DE		IT		FR	
	Office based	Hospital based	Office based	Hospital based	Office based	Hospital based

Pediatrician/GP specialized in pediatrics	n=3	n=5	n=5	n=3	n=5	n=3
ER pediatrician		n=2		n=2		n=2
Total	n=10		n=10		n=10	

3.1.3 Discussion guide

To structure the interviews and make sure all essential aspects were captured, Thermo Fisher Scientific together with the SKIM group developed an extensive discussion guide (full discussion guide is found in Appendix 1) to serve as a manuscript for all interviews, regardless of country. The discussion guide was translated to Italian, German and French and used by each moderator when conducting the 10 interviews in each country.

Briefly, the discussion guide was designed to capture the following:

3.1.4 *Current diagnostic process*

- What is the current process for diagnosis of wheezing children?
- What are the current treatments for wheezing children?

3.1.5 *Current diagnostic tools*

- What tools are used to support the diagnosis?
- How confident and satisfied are physicians with current tools?

3.1.6 *Drivers of current behavior in diagnosis*

- Unmet needs in diagnosis of wheezing children.
- What are the current treatments for wheezing children?
- How confident and satisfied are physicians with current diagnostic tools.
- Evaluation of Product Concept.

3.1.7 *Presentation of the (ADAPT) nasal sampling and testing product concept and soliciting feedback from pediatricians on:*

- The nasal testing concept.
- How the (ADAPT) concept compares to other diagnostic tests.
- How physicians would expect to use it.

3.2 Performing the study

The study was originally planned as a focus group study. However, the COVID-19 pandemic forced us to rethink the study approach and we therefore decided to instead do in-depth telephone interviews. Doing in-depth interviews offers several advantages—it allowed us to go deeper into the questions and allowed the pediatrician to really think about our questions without being interrupted or affected by a group setting. A focus group study, on the other hand, would offer more feedback because of group discussions. Having considered both options, we decided that since the ADAPT product concept is mature with respect to the sampling device, in-depth interviews would serve our purpose of evaluating it better than focus groups, since each individual opinion is captured in detail.

The pediatricians were interviewed anonymously through one-hour in-depth telephone interviews in their native language, one by one, one country at a time starting with Italy. For each country, a native speaking moderator conducted the interviews. The SKIM group together with Thermo Fisher Scientific held one-hour moderator briefings, with the moderator in each country, prior to starting the series of interviews—to communicate the expectations with the discussion guide. Simultaneous translations were done in parallel with the interviews and available for listening in real time. At least one representative each from Thermo Fisher Scientific and SKIM listened to every one of the 30 interviews in real time to make sure interviews were conducted as agreed. There was no mentioning of Thermo Fisher Scientific to the pediatricians. Interviews were conducted during April to May 2020. Recordings of the interviews were then kept for 90 days.

The study was designed for qualitative market research focusing on identifying opinions and feelings from pediatrician routinely engaged in diagnosis of wheezing children, rather than the percentage of people who have them. Nonetheless, some quantitative data were collected and are summarized in the final report (Appendix 2). The qualitative data is briefly summarized below, in 3.3.2. More details are found in the report.

3.3 Findings

A comprehensive summary of all findings extracted from the interviews, along with conclusions and recommendations based on these findings are found in the final report. An excerpt from the final report is summarized below, including some informative quotes from pediatricians. Additional quotes are found in the final report (Appendix 2).

3.3.1 Some quotes from interviews

“It is really, really interesting what you have showed me” (Ped, university hospital, DE)

“It is better for the general public if experience counts less and you have more tools available” (Ped, office-based, DE)

“There is a grey area between infectious diseases and inflammatory diseases. If you have something that could help with this that would be interesting...I could initiate treatment with greater peace of mind” (Ped, hospital, FR)

“Problem for us is waiting time until patient gets to meet specialist. Would be good to know as much as possible until then” (Ped, ER, IT)

3.3.2 Identified unmet needs

3.3.3 *Unmet need 1: Physicians need a more reliable diagnostic test for young children.*

Feedback from pediatricians

- Physicians do not see the clinical relevance of the test yet, as they do not see that this test generates results that can predict asthma development.
- A diagnostic test will only be valuable if it gives a definite diagnosis and leads to a therapy decision.
- Physicians stressed the importance of high specificity and sensitivity of the test, especially in children younger than 5 years of age.
- An objective test will help physicians make diagnosis less dependent on their own experience.

What is needed?

- Studies and scientific publications are needed to prove the predictive and diagnostic capability of this test, especially in children younger than 5 years old.
- Reference range needs to be clearly defined and supported by solid data.
- Clear guide on interpretation of the results which leads to a clear diagnosis or treatment implication.
- Peer review and recommendation by guideline are important to further drive adoption.

Goal

- Reassure physicians about sensitivity of the test and that results link to a specific clinical implication.

3.3.4 *Unmet need 2: Physicians need a diagnostic test that provides an indication of the long-term condition.*

Feedback from pediatricians

- A diagnostic test that can confirm asthma diagnosis is considered valuable.
- Biomarker is not a key measurement that physicians use in their diagnostic process of wheezing children.
- B-Eos is known, but most physicians find the measurement unreliable.
- While measuring biomarker in nasal mucosal fluid is found to be innovative and credible, physicians need more data to show that it is more accurate and superior to measuring biomarkers in blood.

What is needed?

- More education and information regarding biomarker measurement in diagnosing asthma should be shared with physicians to generate more awareness and confidence.
- Studies and data that show correlation between EDN value and asthma diagnosis.

- Evidence is needed to show that measuring EDN in nasal mucosal fluid is possible and has a better indication and accuracy in identifying respiratory diseases compared to blood test.

Goal

Raise awareness and credibility of biomarker measurement in asthma diagnosis among physicians.

3.3.5 *Unmet need 3: Physicians need a non-invasive and suitable diagnostic test for young children.*

Feedback from pediatricians

- Most physicians are positive about the sampling method as it is less invasive than blood test.
- However, physicians need more clarifications and instructions on the correct sampling procedure and need indication to show that enough material is collected for testing.
- Also, a few physicians question the sampling device, as it seems quite stiff and long for young children.

What is needed?

- It is important to provide clear instructions on how to collect the sample properly, including preparations before the test and sample storage conditions.
- Provide indication on the device to indicate ample material is collected for testing.
- Give information on the material of the sampling device and give physicians the actual prototypes to reassure them and to gain experience.

Goal

- Educate physicians on the correct sampling procedure and reassure physicians that the sampling device is comfortable for use with young children.

3.3.6 *Unmet need 4: Physicians need a diagnostic test that gives input for treatment decision and management.*

Feedback from pediatricians

- Currently, a place for this concept is seen in long-term disease and therapy management for patients who have recurring wheezing episodes or have already diagnosed with asthma.
- It can be used as a pre-screening test before running other more invasive tests for allergy or asthma diagnosis.
- It will give input for physicians to initiate, monitor and adapt the use of steroids.
- More suitable for office-based pulmonologists and physicians in asthma outpatient clinic in the hospital.

What is needed?

- Get insights from the pulmonologists and physicians in asthma outpatient clinics in their current ways of diagnosis confirmation and treatment monitoring, and their perceptions on using this test in diagnosis.
- Provide evidence to show how this test can help them decide, monitor, and refine their treatment approach in asthma patients.

Goal

- Explore and emphasize the potential benefits of this test in long-term disease diagnosis and therapy management.

3.3.7 *Unmet need 5: Physicians need a diagnostic test that supports quick diagnosis of multiple diseases.*

Feedback from pediatricians

- However, the concept is not seen as valuable in an acute setting due to non-predictive results and the turnaround time.
- Physicians are hesitant to put young children through invasive diagnostic tests unless there is a valid reason.
- Physicians do express the need to have asthma diagnosed early and recognize that they need a reliable tool that help give quick diagnosis to very young children.
- It's also important to be able to communicate the test results and a definite diagnosis to calm parents.

What is needed?

- To really support differential diagnosis in acute situation, consider including multiple biomarkers (infection marker, allergy marker) into the test as these measurements are considered relevant in distinguishing different conditions in acute setting.
- If turnaround time can be shortened or eventually bring it to the level of a quick test, this would increase its clinical relevance.

Goal

- Enhance the ability of the test in supporting differential diagnosis in acute setting to further drive the clinical relevance.

3.3.8 *Unmet need 6: Physicians need to be reassured that the sample is collected correctly and see the advantages of home sampling.*

Feedback from pediatricians

- Physicians do not yet see the advantage of home sampling test in providing a more comfortable way to perform diagnostic test on young children, which could make physicians' job easier as they can focus on the discussion during consultation.

- Physicians do not trust that the parents can perform it correctly as they still have many questions about the sampling procedure in a clinical setting. It is a need for physicians to eliminate any human errors.
- Physicians cannot see, logistically, how the home sampling test can timely help them in diagnosis of wheezing children.

What is needed?

- Additional safety measures and instructions need to be provided to the parents to ensure that the test is performed correctly.
- Facilitate gaining experience to help them get used to it and feel at ease.
- Advantages associated with home sampling for young patients needs to be communicated explicitly to the physicians.

Goal

- Improve diagnostic confidence and assist physicians in assessing and balancing the risks and benefits of home sampling.

4 Conclusions

When assessing wheezing children, many clinicians use *age* as the primary diagnostic parameter followed by family history, if parents have allergy or asthma. However, several pediatricians mentioned the need for an objective test, both to make diagnosis less dependent of experience but also for communicating the diagnosis to parents, which was mentioned by several as a very important and challenging task for the clinician. Several physicians also said that the ideal respiratory test should measure multiple aspects including inflammation, infection, and allergy because airway disease diagnostics, especially in children, is considered a “grey area” in which diagnosis is difficult and tests are scarce.

Many of the pediatricians also requested studies that show the benefit of the concept i.e., scientific publications, along with recommendations on how to *use the test result* for e.g., therapy selection and changes in treatment. Furthermore, we should have a clear instruction for sampling—how to handle children with clogged nosed or a lot of mucus and describe when and if the nose needs to be washed. We were also told to clarify *who* should *take* the sample, how to get the sample to the lab, and if all labs can handle the sample.

Results and conclusions from this study represent an important part of the commercialization strategy for ADAPT and will provide the future direction for commercialization of a nasal diagnostic panel for airway diseases. Addressing the challenges and seizing the opportunities identified herein will be critical to achieve this goal.

5 References

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Appendix 1—Discussion guide

Discussion guide - TDIs

PROJECT: Wheezing Children Market understanding

REF: F3812

Date: 1 April 2020

This document serves as only a guide to the flow of discussion during the research session. Quality is key in all research, so moderators may digress from or re-order sections in this guide to ensure value & depth of insight to meet the research's objectives. All timings are approximate & some techniques may not be used if the moderator feels they are not appropriate.

Questions in bold

Probes in Italics

Introductions in normal text

Instructions for moderators in blue and Italics

Study objectives – not to be disclosed to respondents

The main objectives of the study are:

- I. To understand the current process (diagnosis and monitoring), diagnostic tools and treatment approach for wheezing children.*
- II. To get insight into HCPs' satisfaction with current diagnostic tools*
- III. To understand current driver for current diagnostic behaviour*
- IV. Identify unmet needs in diagnostic tools and diagnostic process for wheezing children*
- V. To gain insight into HCPs' perception of Thermo Fisher's product concept*

	60 minutes
Module A: Introduction and Warm-up	5 mins
Module B: Current diagnosis and management of wheezing children	30 mins
Module C: Evaluation of new diagnostic assay and sampling concept	15 mins
Module D: Impact and expectations	8 mins
Wrap up and closure	2 mins

Module A: Introduction and Warm-up (5 min)

Objectives:

- Warm-up and background information
- Capture background information

*Moderator: Try to keep this section short. Please have on hand the information the respondent has provided in the screener. First capture spontaneous reactions to the **bold** questions. Only then continue with follow up questions and probes.*

Moderator say: Thank you for your participation in this interview. My name is XXX and I work for XXX, an independent market research agency. I have no vested interest in the outcome of this study, so please feel free to give your opinions openly.

Today we would like to have a discussion with you on diagnosis and management of wheezing children, with a clear focus on the young children 5 years of age and younger. We will discuss how wheezing children are currently managed by you. Then, we will show you a new product concept of a diagnostic assay to gain your views and opinions on how this product can be used and further improved.

Before we start, I would first like to read some housekeeping instructions to you:

- This discussion will take approximately **60 minutes**.
- Our discussion will be audio recorded for analysis purposes so that I have a record of what we talked about and I don't have to write everything down.
- All the information and opinions you give are completely anonymous and confidential, your identity will not be revealed. This information will be used for research purposes only and will not be passed on to any third parties beyond the research company and the commissioning company.
- The purpose of this research is not to influence you or your behaviour in any way but just to have your honest feedback. You will not be targeted for any sales or promotional activity as a result of taking part in this research.
- You have the right to refuse to answer some of my questions or to withdraw from the market research at any time.
- This study is sponsored by a healthcare company and representatives of the sponsoring company as well as some of my colleagues are listening in this interview.

A1

To start our discussion of today, please tell me something about your background and current practice.

Please make sure you do not reveal your name or the place you work.

- What is your job title?*
- In what type of hospital/center/practice do you practice? (e.g. University/Teaching hospital, Community/District hospital, Private hospital, Private clinic etc.)*
- What is your role in diagnosing and treating wheezing children?*

A2

Let us start with a short exercise and I would like to encourage you to speak out the first thing or word that comes to mind, without much thinking, when I say:

- Wheezing children*

- b. *Diagnosis of wheezing children*
- c. *Diagnostic tools for wheezing children*

Moderator: Let participants associate freely, only probe when relevant diagnosis tools or biomarkers are mentioned.

A3

How do you define wheezing symptoms in children?

- a. *What are the phenotypes of wheezing children? Age? Family medical history? Medical history? [Only probe on this if not mentioned. Please keep this high level, do not need to go in-depth on phenotypes]*

A4

What are the key challenges in diagnosing wheezing children in general?

Moderator: First capture unprompted answers, only probe when relevant diagnosis tools or biomarkers are mentioned.

Probe:

- a. *Why? In which ways, if any, does this limit you in diagnosing wheezing children?*
- b. *How do you currently deal with it?*
- c. *What, if anything, could help you overcome this challenge?*

A5

To what extent do you use biomarkers to diagnose wheezing children?

If biomarkers are used, probe:

- a. *Which biomarkers? i.e. measurable indicators*
- b. *What information do the biomarkers provide you with?*
- c. *What are the advantages of these biomarkers? For you as a physician? For your young patients?*
- d. *What are the limitations you experience when specifically using these biomarkers to diagnose wheezing in young children (5 years old and younger)?*

Module B – Current diagnosis and management of wheezing children (30 min)

Objectives:

- To understand the current process of diagnosis of wheezing children.
- To gain knowledge about current diagnosis tools and treatment approach for wheezing children
- To get insight into HCPs' satisfaction with current diagnostic tools
- To understand current driver for current diagnostic behaviour
- Identify unmet needs in diagnostic tools and diagnostic process for wheezing children

Moderator say: As mentioned earlier, today we will be discussing diagnosis and management of wheezing children, specifically young children of 5 years of age and younger. First, we would like to understand more about the diagnostic process and management of wheezing children. As part of your pre-work, you have already given us some information by writing down the process step by step. Now I would like you to show us a complete view of the process.

You will be presented with a patient case (SHOWCARD 1a & SHOWCARD 1b). We are going to do a Differential Diagnostics Simulation exercise. I would like you to show me how you perform differential diagnosis if this patient came under your care. I would like you to show us the diagnosis and treatment approach that reflects your current practice. If it helps, please think of a certain patient you have treated based on the patient case descriptions.

[Show patient profiles, randomly select 1 out of the 2 to show first]

Take note of the clinical benefits and limitations associated with each diagnostic tool/ test. Please record this on MODERATOR SELF COMPLETION FORM. We will use this information in Module C (questions C5) and would like to refer to this discussion.

B1

First, based on the patient case descriptions, what is the ultimate goal or outcomes you would like to achieve for this patient?

- a. To what extent does this patient case represent the wheezing children you see? Majority? Or is this a rare case to you?
- b. What other clinical objectives do you want to achieve? Why?
- c. What are other factors that would prompt you to set different clinical objectives?
- d. *[For physician working in hospital setting]* Probe for differences in the ER setting vs. polyclinic setting.

Now, I would like you to tell me the approach, step by step, on how you would achieve this goal through differential diagnosis. I would like you to think of the first condition you would like to rule out or investigate as a start.

Moderator note: For each condition to rule out, repeat question 2 – 6 until the whole process is complete. Please only focus on capturing the steps.

B2

What is the condition you would like to first rule out or diagnose?

B3

What, if any, diagnostic tools or tests will you use to rule out or diagnose this condition?

- One or more tools/tests needed?

B4

What is the next step if the result of this test (or other tests-recall from above) is positive?

- If treatment is being prescribed, what treatment do you prescribe?
- What are the main criteria you consider when deciding on treatment?
- Will you monitor the response to treatment?
- What will you do to monitor it?
- What will you monitor at this point? E.g. treatment effect, symptoms progress, etc.

B5

What is the next step if the result of this test is negative?

- Rule out another condition? (Start from question 1 again for the next condition)

B6

Will you give interim treatment while waiting for the result?

- What interim treatment will you give?
- Why? What is rationale behind prescribing this treatment?
- What is the main clinical objective you want to achieve with this interim treatment?

B7[Ask at the end of the process]

Would you continue to monitor this patient?

- What exactly do you do to monitor this patient?
- In what frequency?
- Is it different for age groups?

Moderator say: Thanks a lot for walking me through the process. Now, I have a few more questions to ask you about your approach for this patient.

Moderator note: Ask B8-B14 to help us understand the main clinical objective leading to the approach, the steps in the approach and rationale, which and how patient characteristics influence choices, which tests they use to support differential diagnosis, as well as the unmet needs throughout the approach.

More thorough discussion and probing of B8-B14 after the first patient case. For the 2nd patient case, go through the questions and focus on identifying the differences between the 2 approaches for the 2 patient cases.

Moderator note: For the following question, please distinguish what they currently do in their practices and what they wish they can do. Also, please get insight into the most common and general approach used in general practice beyond the patient cases.

B8.

To what extent does this approach represent what you do in your practice?

Probe:

- a. *What could be done differently? Why?*
- b. *What are other factors or circumstances that would prompt you to deviate from this approach? Why?*
- c. *[For hospital setting] Probe for differences in the ER setting vs. polyclinic setting.*

B9.

Now, let's look at the order of condition you would diagnose or address first. Please help me understand the reasons behind the order or prioritization of condition diagnosis.

Moderator note: To anticipate the potential impact of Covid-19 pandemic on their answers, please make sure they first answer these questions based on a non-outbreak situation. Then, quickly capture what the potential impact of Covid-19 on the reasons and protocols in a long run would be, especially on probe b regarding viral infection.

- a. *Why certain conditions need to be addressed first or later? Please especially get a good understanding the rationale behind the priority of Asthma diagnosis.*
- b. *Is it because the urgency (e.g. symptoms severity) or impact of the condition? What other factors affect the priority of condition diagnosis? E.g. limitation on diagnostic tools, time to get test results, hospital guideline, etc.?*
 - *If not mentioned yet, probe: To what extent would you consider testing for viral infection? At what point in this process? What exactly should lead to testing for viral infection? E.g. comorbidities?*
- c. *What patient characteristics play a role in the prioritization in this approach?*
 - *Age*
 - *Medical history*
 - *Type of wheezing*
 - *New (first time) vs recurrent wheezing episodes*

B10.

[If this is not covered in B9] **If anything, what would you like to do differently with regards to the order or prioritization of condition diagnosis?**

- a. *If not, what would be ideal?*
- b. *What is preventing you to rule out conditions in your preferred order? E.g. availability of certain diagnostic tools, availability of diagnostic markers, protocols, guidelines, no suitable diagnostic tools for young children?*
- c. *[If Asthma is not the first condition to rule out] Specific probes for Asthma:*
 - *Would you say that potential Asthma is diagnosed timely enough for this patient? If it is up to you, how early would you like to diagnose Asthma for this patient?*
 - *How important is it to diagnose Asthma (even) earlier for this patient?*
 - *What, if any, is the impact of earlier Asthma diagnosis on achieving the treatment goal?*
 - *What are the factors that have prevented you from diagnosing Asthma (even) earlier?*

B11.

Let's look at the diagnostic tests / tools for each step. Why do you select these diagnostic tools?

- a. *What clinical information does each of these tests provide you?*
 - *How relevant is this in setting the diagnosis?*
 - *In which way does this information help you decide on the treatment approach?*
- b. *Are these diagnostic tools the most ideal diagnostic tools to use at each step?*

- *If not, why not? What would be ideal?*
- c. *What are preventing you from using the tools you desire? E.g. availability of certain diagnostic tool, protocol/not recommended in guidelines, no suitable diagnostic tool for children?*

B12.

How about the treatments selected here?

- a. *What is the treatment goal for each treatment?*
- b. *How do the diagnosis results impact the treatment you select and prescribe?*

B13.

What are some treatments you would like to prescribe, but not able to? Why?

- a. *What is limiting you? E.g. cannot prescribe certain treatment without a positive confirmation from diagnostic test, not available, etc.*
- b. *What would be the potential impact?*

B14.

Now, let's look at how you would monitor this patient. What outcomes do you want to achieve for this patient with this monitoring plan?

- a. *What can be improved in terms of how this patient is monitored?*
- b. *How would this improvement impact the way patient is monitored?*
- c. *What is limiting you? What will be the potential impact?*
- d. *How do diagnostic results affect the way this patient is monitored?*

Moderator note: After the discussion of the 1st patient case, please go through B1-B7 for the 2nd patient case. For the 2nd patient case, please go through B8-B14, but focus on identifying the differences between the 2 approaches for the 2 patient cases.

[For question B15 – B17, only ask if answers are not captured from previous questions.]

B15.

To what extent do you think this is the ideal approach to achieve the goal and outcomes of these patients?

[Please check for both patient cases.]

- a. *What are the things you would wish to change or improve to make it an ideal approach?*
- b. *How would these changes impact the diagnosis and management of wheezing children?*

B16. If mentioned in B15 or earlier

You mentioned that you would wish to make these changes. What are the barriers that prevent you from doing that now?

- a. *E.g. hospital policy or guideline, availability of diagnostic tools?*

B17.

In general, how satisfied are you with the currently available diagnostic tools in supporting the diagnosis and management of wheezing children?

- a. *What is missing?*
- b. *What can be improved? E.g. time to get results, availability of tools in hospital, accuracy, specificity of diagnostic test, etc.*

Module C – Evaluation of new diagnostic assay concept (15 min)

Objectives:

- Understand initial reactions to the concept of new Product X
- General evaluation of the Product X
- Detailed evaluation of the Product X on several KPIs

Moderator say: I am now going to show you a product description of a potential diagnostic assay, Product X that can be used for diagnosing wheezing children (SHOWCARD 3a & SHOWCARD 3b). Please take a few minutes to look at the concept individually and read the information carefully.

Moderator: Put up Product X on the screen. Allow +/- 2 minutes for the respondent to read the description. Throughout the discussion, please ensure the respondents understand that the key feature of the product is measuring EDN through nasal mucosal lining fluid.

C1.

What is your overall reaction to the product?

- a. With regards to possible benefits of this product, what comes to mind first?

C2.

Is there anything new or surprising to you about the product or its description?

C3.

Is there anything unclear?

- a. Is there any information missing that you want to see? Why?
- b. What other information?

C4.

On a 1 to 7 scale, where 1 indicates “very negative” and 7 “very positive,” how would you rate your first impression of this product? Why?

Moderator say: Let’s go over the product profile in detail.

C5.

How similar is this product to other products on the market? Which products?

- a. On what attributes are they similar?
- b. On what attributes are they different?
- c. Which attributes of what products do you prefer? Why?
- d. How does this product compare to what you currently use for diagnosis?

C6.

Now, I would like to focus on the sampling method. What do you think about the sampling method by measuring biomarkers using nasal mucosal fluid in diagnosis of wheezing children?

- a. *What do you think about the sampling device? What are the advantages? What can be improved? Suitable for children?*
- b. *What are your experiences with nasal mucosal lining fluid sampling in general, even from other indications? e.g. Cerebrospinal fluid (CSF) Leak Diagnosis. What is your perception on this sampling method?*
- c. *What are the advantages of this sampling method for biomarker testing? How would it compare to a blood test?*
- d. *What are the drawbacks or concerns you have regarding this sampling method?*
- e. *If there is a potential to use this sampling device as a home sampling device, what do you think about this?*
 - *For what purpose would you use it (e.g. monitoring)*
 - *For what patients would this be relevant?*
 - *Does it address a current unmet need? Why?*

Moderator note: throughout the discussion in C7, please refer to the benefits and limitations/ drawbacks as recorded on the MODERATOR SELF COMPLETION FORM to challenge physician to provide tangible feedback when comparing the different tests.

C7.

Now, keep in mind that this diagnostic assay is measuring different biomarkers using nasal mucosal fluid. How does it compare to the following tests:

- 1. Measurement of blood eosinophilis (B-Eos)**
- 2. Fractional concentration of exhaled nitric oxide (FeNO)**
- 3. Sputum analysis**

Probe per biomarker:

- a. *[Specifically, for measurement of blood eosinophilis (B-Eos)] Assuming the nasal sampling and blood sampling will yield the same accuracy, which method would you prefer for biomarker measuring for wheezing children?*
- b. *What are the advantages and disadvantages to you as a physician and to the patients?*
- c. *What kind of information do you expect to get from Product X, but not from other method?*
- d. *What do you expect Product X would enable you to achieve in the diagnostic process that other methods cannot offer?*
- e. *What specifically in the presentation of Product X makes you think this way / have these expectations?*

Moderator: Please put up the worksheet on the screen and go through the attributes with the physicians and capture the rating for each attribute. Capture this in the grid provided.

Moderator say: I now would like you to rate this product on several attributes. Please use a scale from 1 to 7 with 1 being “not at all” and 7 “very”.

C8.

How appealing do you find this diagnostic assay?

- a. *What exactly makes it appealing? Why?*

C9.

How useful do you expect this diagnostic assay to be?

- a. *In which ways do you expect this diagnostic assay to be useful?*

C10.

To what extent does this diagnostic assay address any unmet needs in diagnosis of wheezing children?

- a. *Which unmet need? How relevant is this for you as a physician/ your patient?*

C11.

When using this diagnostic assay in your diagnostic process, how confident would you be that it supports differential diagnosis in wheezing children?

- a. *What makes you feel confident/ less confident?*
- b. *What would be the consequences/impact on next steps and treatment?*
- c. *[If physician shows low confidence] What kind of evidence/ information would you need to see in order for your confidence in this diagnostic tool to grow?*
- d. *[If physician shows low confidence] Who should provide you with this: share of voice (KOLs), the company developing this?*

C12.

How credible do you find that this diagnostic assay can measure a small airway inflammation biomarker in nasal mucosal lining fluid?

- a. *Why credible/ less credible?*
 - *[If physician indicates that it's less credible] What kind of evidence/ information would you need to see for your confidence in this diagnostic tool to grow?*
 - *[If physician indicates that it's less credible] Who should provide you with this: share of voice (KOLs), the company developing this?*
- b. *Would your expectation differ if it would be measured in blood or urine?*
 - *What would be the expected differences in terms of sensitivity and specificity when comparing nasal fluid, blood and urine sampling for measuring EDN?*
 - *What impact would this have?*

C13.

Thinking of the two patients we have discussed earlier and knowing this diagnostic assay has a treatment consequence, how do you envisage using this diagnostic assay in the diagnostic process?

- a. *When in the diagnostic process? Why at this stage?*
- b. *How would it improve the current diagnostic process?*
- c. *To what extent would this diagnostic assay (measuring EDN biomarker using nasal mucosal fluid) ensure timely diagnosis of Asthma?*
- d. *Moderator if at a later stage please probe: why wouldn't you use this earlier? What are the barriers or concerns that prevent you from using this diagnostic assay earlier in the diagnostic process?*
- e. *To what extent would you use this in monitoring of the disease and effect of the treatment?*
- f. *[ER]: How likely would this become part of the routine test? When in the pathway? For what type of patients?*

Module D – Impact and expectations (8 min)

Objectives:

- Evaluate advantages and disadvantages of Product X
- Evaluate likeliness to adopt Product X and assess impact on current practice
- Evaluate willingness to pay

D1

Now, I would like to do a little exercise. I would like you to imagine that you met your colleague, also a *[pediatrician, GP, ER physician, depending on respondent's specialty]* in the elevator. You have only about 60 seconds to communicate what you have seen and been told about the benefits of this new diagnostic assay Product X (measuring EDN in nasal fluid) . What would you tell your colleague?

D2

Based on what you have just told your colleague, do you think your colleague would be convinced to consider using this diagnostic assay? Why?

- *What would your colleague debate about?*
- *What kind of questions might he or she ask?*
- *What concerns might he or she have?*
- *What potential barriers that would prevent your colleague to use Product X?*
- *What should be improved or added in order for your colleague to be convinced?*

D3

We have just talked about the benefits and potential barriers for using Product X, how likely is it that you would adopt this concept (measuring EDN in nasal fluid) if it were launched and reimbursed? Please rate your likeliness to adopt on a scale of 1 to 7, where 1 = highly unlikely and 7 = highly likely.

- a. *How quickly would you adopt this product? (e.g. off label, need to adopt in guidelines, experience from colleagues needed)*
- b. *Would you use it to support diagnosis in wheezing children of 5 years old and younger?*
 - *Would you use it for specific wheezing phenotypes and which ones?*
 - *Would you use it in every case of this phenotype?*
 - *If not, what is the reason?*
- c. *How about for patients who are already having a blood test to measure other parameters, how likely are you going to use this diagnostic assay to measure EDN by nasal fluid, assuming the nasal mucosal lining fluid test is as accurate as the blood test?*
 - *In case you already have a blood test for testing the biomarkers, how likely would you use this nasal sampling? Would you use it to replace blood tests or complementary to blood tests?*
 - *To what proportion of patients would you use blood test vs. this concept (using nasal fluid test) to measure EDN. Please give me your best estimate.*
- d. *What other patient groups would you use Product X for diagnosis?*
- e. *If not likely to use, what are reasons not to use the product?*
- f. *If home sampling is possible for this diagnostic test, what is the likeliness to adopt this product for home sampling? Please rate your likeliness to adopt on a scale of 1 to 7, where 1 = highly unlikely and 7 = highly likely.*

D4.

To what extent would you personally consider checking if your practice, direct colleagues and/or lab are willing to adopt this concept?

- a. *What would you need in order to do so? Material, support?*
- b. *How far would you be willing to go to have your practice acquire/use these tests? Who are the people you would reach out to? Who are the people you would share this material with to pursue the switch?*

D5.

In terms of encouraging your use of this product, what would be the most important information you would need to see?

- a. *What points about this product do you think the manufacturer should be emphasizing to physicians?*
- b. *What are the things that you would like the manufacturer to know or consider when developing instructions, service or programs around this product?*
- c. *Are there any improvements you would suggest optimizing this profile?*

D6. NPS

When you think of the product concept as it is, how likely would you recommend it to a colleague? Please indicate your answer on a scale of 0 to 10, where 0 = highly unlikely and 10 = highly likely.

D7a.

Are you aware of the prices of current diagnostic tests?

1=no

2=yes

D7b. <skip if D7a = 1>

What do you expect to be a reasonable price for the product concept you've evaluated?

- a. *Price per test?*

D8.

If this diagnostic assay can support the measurement of other biomarkers using nasal fluid, what biomarkers would be relevant and important to measure in supporting the diagnosis and management of wheezing children?

- a. *How would this development help or improve the diagnosis and management of wheezing children? Specifically asthma?*

D9.

What developments regarding differential diagnosis in wheezing children do you expect in the future?

- a. *How do you think these developments will impact your current practice?*
- b. *What about the sampling procedures? What other sampling procedure would be good development? Why?*

D10.

What other, if any, applications of the nasal measurements of inflammation do you see, in addition to the wheezing children?

Wrap up and closure (2 min)

Is there anything you would like to add to the discussion that we have not yet discussed but that you feel is relevant?

Thank you very much for your time and your valuable feedback.

MODERATOR SELF COMPLETION FORM

Moderator please use this form to record the benefits and limitations/ drawbacks associated with each of the diagnostic tool/ test physicians use in the diagnosis pathway (Module B)

DIAGNOSTIC TOOL 1: [SPECIFY WHICH] _____

BENEFITS	LIMITATIONS/ DRAWBACKS

Showcard 1a: Patient case group 1

Patient	2-year-old girl
Gender	Female
Age	2
Medical history	Nonatopic. Parents report several respiratory infections after child entered preschool at age 1. Diagnosed with bronchiolitis, based on symptoms, at a previous visit to ER. Otherwise healthy child.
Current wheezing symptoms	High pitched wheezing during the expiratory phase. Low oxygen level and difficulties breathing.
Previous wheezing events	One previous, clinically confirmed episode of wheezing. Parents report additional instances of wheeze.
Initial diagnosis	Bronchiolitis? Respiratory failure? At risk of developing asthma?
Diagnostics performed to achieve diagnosis	Auscultation.
Previous treatment in record	None.
Response to initial treatment given during visit	Improvement of symptoms and oxygen levels with β 2-agonist nebulization.

Showcard 1b: Patient case group 2

Patient	5-year-old boy
Gender	Male
Age	5
Medical history	Atopic by skin prick test. Recurrent symptoms including rhinitis and cough between colds. Otherwise healthy.
Current wheezing symptoms	High pitched wheezing during expiratory phase. Currently with respiratory infection.
Previous wheezing events	Episodic wheeze.
Initial diagnosis	Airway inflammation? Asthma?
Diagnostics performed to achieve diagnosis	Auscultation. Lung function (FEV1).
Previous treatment	As needed short acting β 2-agonist (SABA) plus inhaled corticosteroids (ICS).
Response to initial treatment	Slight improvement of symptoms with SABA and ICS.

Showcard 3a: Description of Product X

Insights

In children, asthma is defined as a chronic inflammatory disorder of the airways, associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing. In children below 5 years of age, the clinical symptoms of asthma vary and are nonspecific. Currently a symptoms-only approach that defines the diverse wheezing phenotypes has been recommended.¹

- Wheezing is a common symptom experienced by children, which is associated with multiple respiratory conditions, not only with asthma. Accurate differential diagnosis of wheezing in children based on type and degree of airway inflammation is hampered by the lack of support of reliable biomarkers: blood eosinophil counts may be too variable, and sputum eosinophils are difficult to measure.

Introducing a new diagnostic biomarker assay using nasal sampling

A minimally-invasive diagnostic assay measuring an inflammatory biomarker in nasal mucosal lining fluid to support differential diagnosis and treatment considerations in wheezing children.

- This diagnostic test measures activation of eosinophils in the nose, by measuring an eosinophil granule protein (EDN) which reveals fundamental insights in the mechanism of the disease and supports the diagnosis, treatment and monitoring over time.

Sampling Procedure

- This diagnostic test comes with a nasal sampling device enabling a minimally-invasive 1-minute sampling procedure.
- It will be available in two versions: one specially designed for children from 2 years of age, and one version for adults.

Clinical relevance

- First biomarker assay to support differential diagnosis of airway disease in children
- Guides treatment decision, e.g. to treat inflammation by inhaled corticosteroids (ICS)
- Minimally-invasive procedure
- CE- marked nasal sampling device which has been assessed to meet high safety, health, and environmental protection requirements

1. ERS Lung White Book (www.erswhitebook.org). 2013. ERS and European Lung Foundation

Showcard 3b: Picture of Product X

Minimally-invasive, CE-marked nasal sampling device



Size for children	
Width	4.5 mm
Length	27 mm

Size for adults	
Width	7 mm
Length	28 mm



Worksheet: KPI rating worksheet (C8 – C12)

Please use a scale from 1 to 7 with 1 being “not at all” and 7 “very”.

Attributes	Rating
How <u>appealing</u> do you find this diagnostic assay?	
How <u>useful</u> do you expect this diagnostic assay to be?	
To what extent does this diagnostic assay <u>address any unmet needs</u> in diagnosis of wheezing children?	
How <u>confident</u> would you be that Product X supports differential diagnosis in wheezing children?	
How <u>credible</u> do you find that this diagnostic assay can measure a small airway inflammation biomarker in nasal mucosal lining fluid?	

Appendix 2—Final report

Lead with

Purpose



EIT Health is supported by the EIT,
a body of the European Union

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SKIM senior manager

Ana Edelenbosch

SKIM senior manager

F3812 Wheezing Children study - Final report

Presentation at ADAPT meeting

[September 21, 2020]

Table of contents



Research Objective and methodology

- Sample composition and demographic



Detailed findings

- Current diagnostic process
- Detailed evaluation of product concept
- Impact and future expectations



Conclusion and Recommendations

Reporting notes

Qualitative research seeks to identify a range of **opinions** and **feelings** rather than the percentage of people who have them.

It should not be considered statistically valid or projectable; rather it should be used to gather insight, provide direction, and clarify issues.

Research Objective and methodology

Sample composition and demographic

Background and objectives of the research



This study is part of the ADAPT activity that has received funding from EIT Health. EIT Health is supported by the European Institute of Innovation and Technology (EIT). EIT is a body of the European Union that receives support from the European Union's Horizon 2020 Research and innovation program.

The objective is to further expand the diagnostic portfolio by gaining deep understanding of the current situation and unmet needs in diagnosis and management of wheezing children. In addition, Thermo Fisher Scientific can understand the potential adoption and interests of the product concept to further develop the new diagnostic assay to give accurate information to support earlier diagnosis and treatment for wheezing in children.

1

What are current processes of diagnosis of wheezing children? What is used to support the diagnosis? What are the current treatments for wheezing children?

2

How confident and satisfied are the physicians with the current diagnostic tools?

3

What drives current behavior in diagnosis? Where are the unmet needs regarding the diagnostic tools used in diagnosing wheezing children as well as the treatment guidance?

4

What are physicians' perceptions on Thermo Fisher's product concept? How is this product concept compared to other diagnostic tests? How do physicians expect to use this?

Research Methodology – 60 min telephone depth interviews



60 minutes Web assisted Telephone In-depth interviews



Web-assisted telephone in-depth interviews were conducted to provide appropriate setting to **elicit information, detail**, as well as **exploration**.



Each interview was audio-recorded, simultaneously translated and transcribed.

Web conferencing technology was used to present the description and visuals of the product concept via screensharing.



A discussion guide was developed in collaboration between SKIM and Thermo Fisher to give structure and keep consistency of all interviews across different countries.



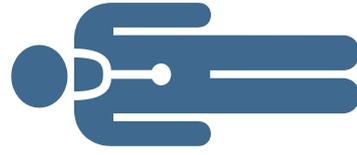
The discussion guide as well as the concept that was evaluated were unbranded. Respondents were not aware of which company was sponsoring the research.

To ensure consistency and alignment with the research objectives, all moderators were individually briefed by both SKIM and Thermo Fisher prior to the interviews.

Discussion guide outline:

Key modules and objectives:	Duration
Module A: Introduction and Warm-up <ul style="list-style-type: none"> Warm-up and background information Capture background information 	5 mins
Module B: Current diagnosis and management of wheezing children <ul style="list-style-type: none"> To understand the current process of diagnosis of wheezing children. To gain knowledge about current diagnosis tools and treatment approach for wheezing children To get insight into physicians' satisfaction with current diagnostic tools To understand current driver for current diagnostic behaviour Identify unmet needs in diagnostic tools and diagnostic process for wheezing children 	30 mins
Module C: Evaluation of diagnostic assay and sampling concept <ul style="list-style-type: none"> Understand initial reactions to the concept of new Product X General evaluation of the Product X Detailed evaluation of the Product X on several KPIs 	15 mins
Module D: Impact and expectations <ul style="list-style-type: none"> Evaluate advantages and disadvantages of Product X Evaluate likelihood to adopt Product X and assess impact on current practice Evaluate willingness to pay 	8 mins
Wrap up and closure	2 mins

The target group



Sample (n=30):

- Pediatricians
- General practitioners specialized in pediatrics
- Emergency Room pediatricians (ER)

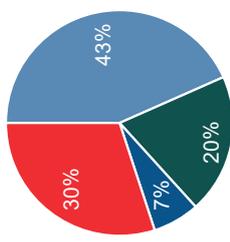
Screening criteria:

- Work as a pediatrician or general practitioner specialized in pediatrics
- Treat at least 15 wheezing children of 5 years old and younger per month
- Are personally involved in diagnosing, treating and monitoring of wheezing children of 5 years old and younger
- Spend at least 65% of their time in direct patient care
- The respondent is knowledgeable in treating wheezing children and is interested in contributing his/her opinions on this topic
- Have 3 -35 years of experience
- Are not affiliated with a pharmaceutical company, advertising, marketing or market research

	DE		IT		FR	
	Office based	Hospital based	Office based	Hospital based	Office based	Hospital based
Pediatrician/GP specialized in pediatrics	n=3	n=5	n=5	n=3	n=5	n=3
ER pediatrician		n=2		n=2		n=2
Total		n=10	n=10	n=10	n=10	n=10

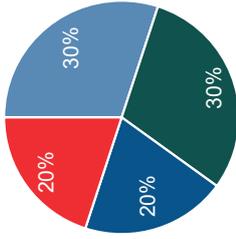
Sample specifics

Practice setting total (n=30)



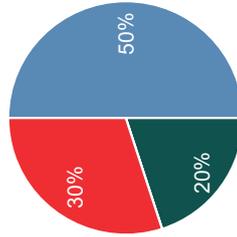
- Office based
- University/Teaching hospital
- Private clinic
- Community/public hospital

Practice setting DE (n=10)



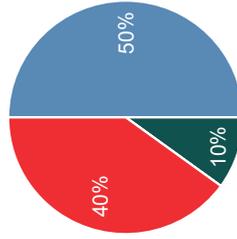
- Office based
- University/Teaching hospital
- Private clinic
- Community/public hospital

Practice setting IT (n=10)



- Office based
- University/Teaching hospital
- Private clinic
- Community/public hospital

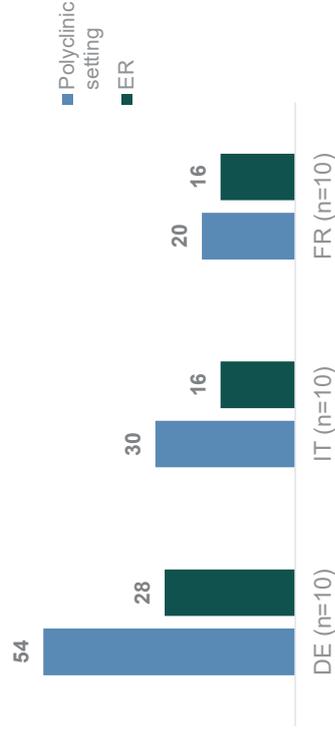
Practice setting FR (n=10)



- Office based
- University/Teaching hospital
- Private clinic
- Community/public hospital

	IT (n=10)	DE (n=10)	FR (n=10)
Average years of experience	18.5	21.0	20.6
Average % time direct patient care	87	88	89

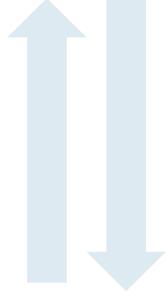
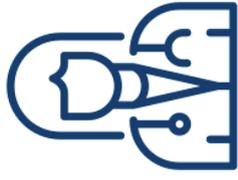
Average # of wheezing children managed in a typical month



Current diagnostic process

Process, diagnostic tools used and key unmet needs

Current diagnosis process is often uncertain as it relies on human subjective factors...



As patients are too young to express themselves, physicians are fully dependent on parents/ caregivers for information. However, gathering all necessary information from parents is challenging as they are not always reliable, might have a subjective interpretation of symptoms or simply cannot focus on the questions in stressful situation.

*"The child himself in particular when we interview him, since young children often have difficulty articulating the nature / type of distress, the timing / periodicity etc. It is often difficult for them to clearly describe their symptoms."
" (FR, GP, office based)*

*"Reliability of parents in description, i.e. giving us a more accurate anamnesis; in referring triggers, there are parents who are very careful and others who are more confusing even."
" (IT, GP)*

*"How accurate parents are at reporting symptoms vary and makes correct assessment difficult. Auscultation is also difficult. Some sounds are misleading."
" (Ped, ER, IT)*

It's also a challenge for physicians to calm down and deal with parents without a definite diagnosis. Parents are worried and they need to know the cause of the disease and the prognosis of their children.

*"You have to give proof to the parents. You cannot just say that it is bronchiolitis for the first two years and then say it is asthma without proof."
" (FR, Ped, office based)*

Implicitly, physicians expressed some underlying emotional needs:

- They need to feel confident about their diagnosis
- They feel the need to alleviate parents' stress by giving them an answer.



... which reveals the need for diagnostic tests to empower physicians to set a definite diagnosis and take clinical treatment decisions in a timely manner

‘Determining the cause and performing differential diagnosis quickly to make the right treatment decision timely in young children’ is a key challenge faced by most physicians in wheezing children



Need for non-invasive diagnostic tools suitable for young children

Tests are either too invasive or require cooperation of very young children. E.g. blood test, PFT*, chest X-ray

“In most cases a pulmonary function test cannot be executed at this age.” (DE, Ped Hospital)

“I don't like to radiate children just for a yes or no reason, but there is nothing else in fact, there are no other reliable tests that allow for a very fast diagnosis.” (FR, Ped, Office-based)



Need more reliable diagnostic test for quick diagnosis in young children

There are no quick tests available to perform the diagnosis of multiple diseases quickly. Also, results of the tests, e.g. allergy test, are not always reliable for young children.

“Lack of a rapid test... if we do a (blood) draw for a biomarker, we cannot be timely. Our handicap in asthma is the ability to do a certain diagnosis. We can treat symptoms, but also we need to go deeper to investigate the trigger.” (IT Ped Hospital based, ER)

“When these children are so small, very often, allergic tests don't show to be positive, and therefore you don't get to anything.” (IT, GP)



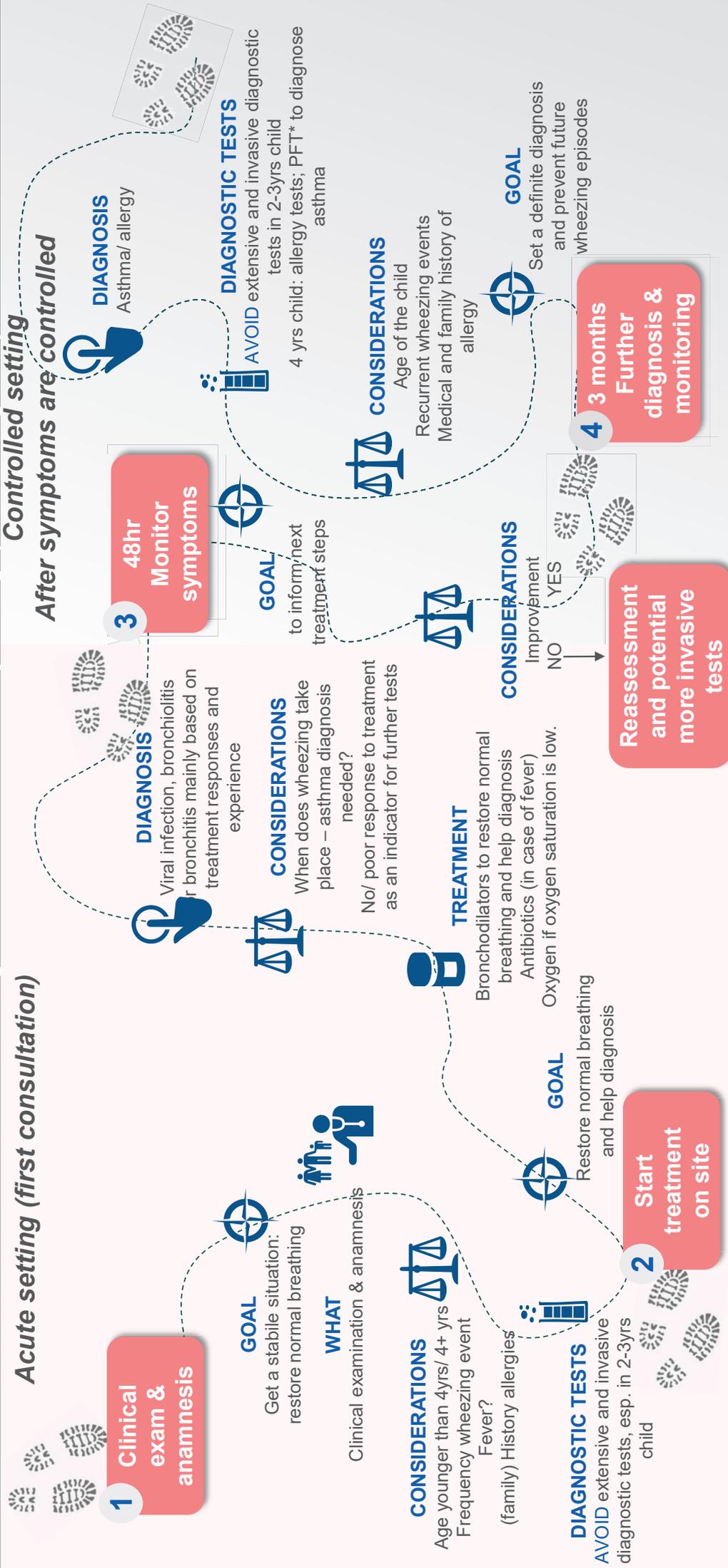
Need diagnostic tests that provide an indication of the disease severity

The evaluation of the disease severity is important to predict risk of recurrence and support treatment decision.

“Another problem is understanding when the situation is getting worse or changing, because children have an impairment and the situation can get worse from a moment to another.” (IT, Ped Hospital)

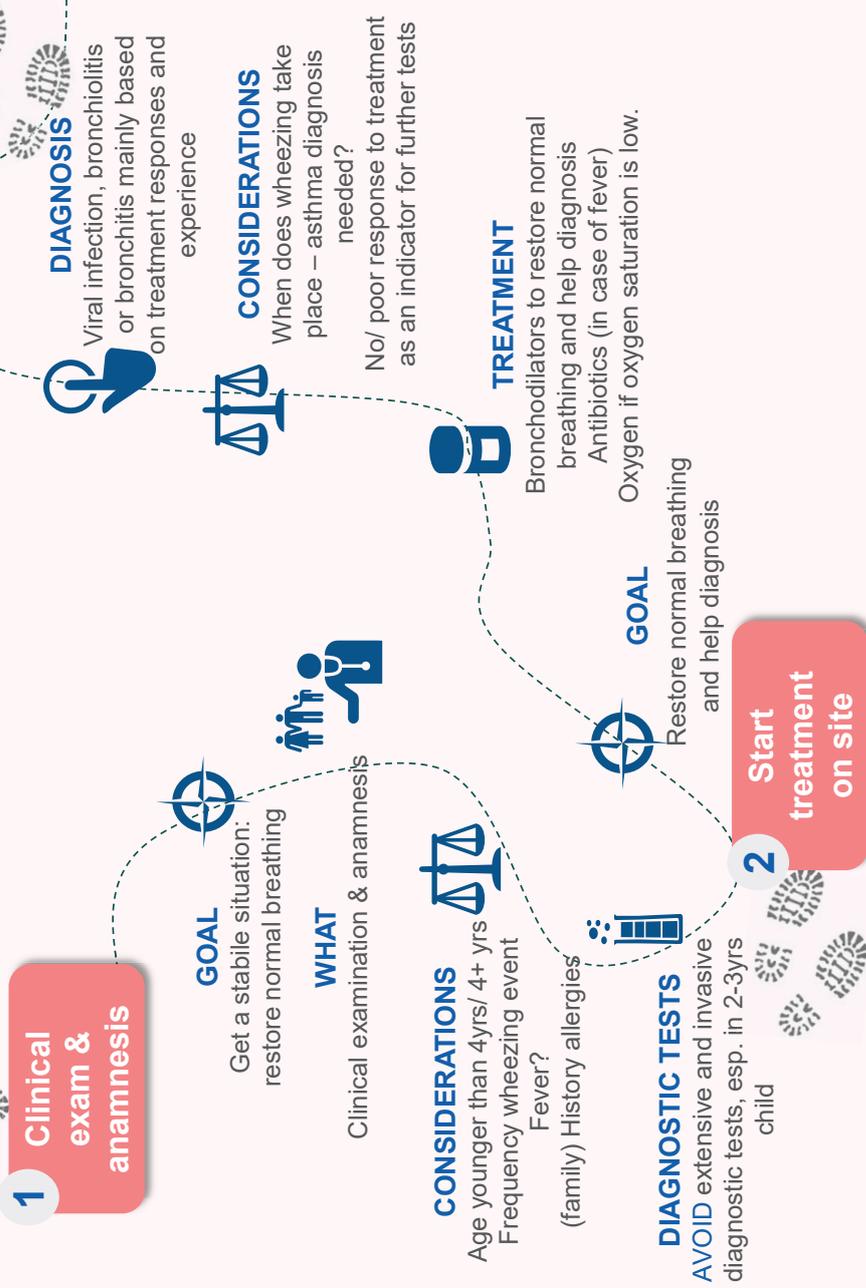
“Cause is not always clear. Main challenge is to find out what is going on. To quantify obstruction of respiratory tract, which is not easy. We cannot define severity. We cannot define root cause. How to overcome this? We treat them. We are pragmatic about this.” (GP, DE)

The pathway from acute to controlled setting features challenges posed by the missing of reliable and non-invasive diagnostic tools in a young patient group



In acute setting, physicians would benefit from quick, non-invasive tests to inform next steps irrelevant of the patient's age; current practice is *trial-error* based

Acute setting (first consultation)



CHALLENGES

- **FULL & RELIABLE INFORMATION** – physicians rely on info provided by parents and young patients
- **INVASIVE DIAGNOSTIC TESTS** – to help diagnosis physicians should put children through invasive diagnostic tests that require collaborations
- **REASSURE PARENTS** – calming and reassuring parents in the acute setting is challenging without objective measurements of the situation

NEEDS

- **OBJECTIVE TEST** to help them set an accurate diagnosis and eliminate human subjective factors
- **NON-INVASIVE TESTS** and non-invasive diagnostic tools that are more suitable for young children
- **QUICK TESTS** to help them set a definite diagnosis, decide on the right treatment needs and thus reassure parents

Opportunities

Empower physicians to perform quick differential diagnosis in acute setting and to diagnose asthma earlier by offering them a new diagnostic test that is suitable, noninvasive and accurate for young children. To do this, it's advisable to include multiple biomarkers in one diagnostic assay and further shorten the turn-around time.

Although asthma is currently not a top priority to diagnose in acute setting, physicians expressed limitations and wishes of having the right tools to diagnose early

"It would be interesting to find out how children develop asthma. You should detect them. If the child isn't atopic and the parents are fine as well, how high are chances the child will become an asthmatic? The anamnesis isn't complete." (GP, DE)

"Well, of course I would like to have a simple examination method telling me that the person has asthma. Just a small prick test telling me would be great. Asthma is usually a disease that can have several causes." (GP, DE)

"Pulmonary function tests aren't doable for small children. You can't make an asthma diagnosis for children under 5. Data for pulmonary function is missing. You're only treating the symptoms here." (GP, DE)

"Problem for us is waiting time until patient gets to meet specialist. Would be good to know as much as possible until then." (Ped, ER, IT)

"The issue in children < 5 is the fact we cannot perform PFT (pulm function test) or FEV1. If I could have a system that provided me with early stage compression volume data that would be very reliable, it would be good thing!" (Ped, ER, FR)

"Well, it would be nice to have something in future which allows me to predict to that mom: "she will be an asthmatic, or he will be not". But, again... it's pretty hard to be 100% confident in saying this. You can get an idea, thanks to the anamnesis, collecting symptoms, and everything... but I have no 100% confidence to say this." (Ped, office-based, IT)

"There is a grey area between infectious diseases and inflammatory diseases. If you have something that could help with this that would be interesting...I could initiate treatment with greater peace of mind". (Ped, hospital, FR)

Having diagnostic tools that inform treatment decisions seems to be a relevant opportunity in the **controlled** setting

CHALLENGES

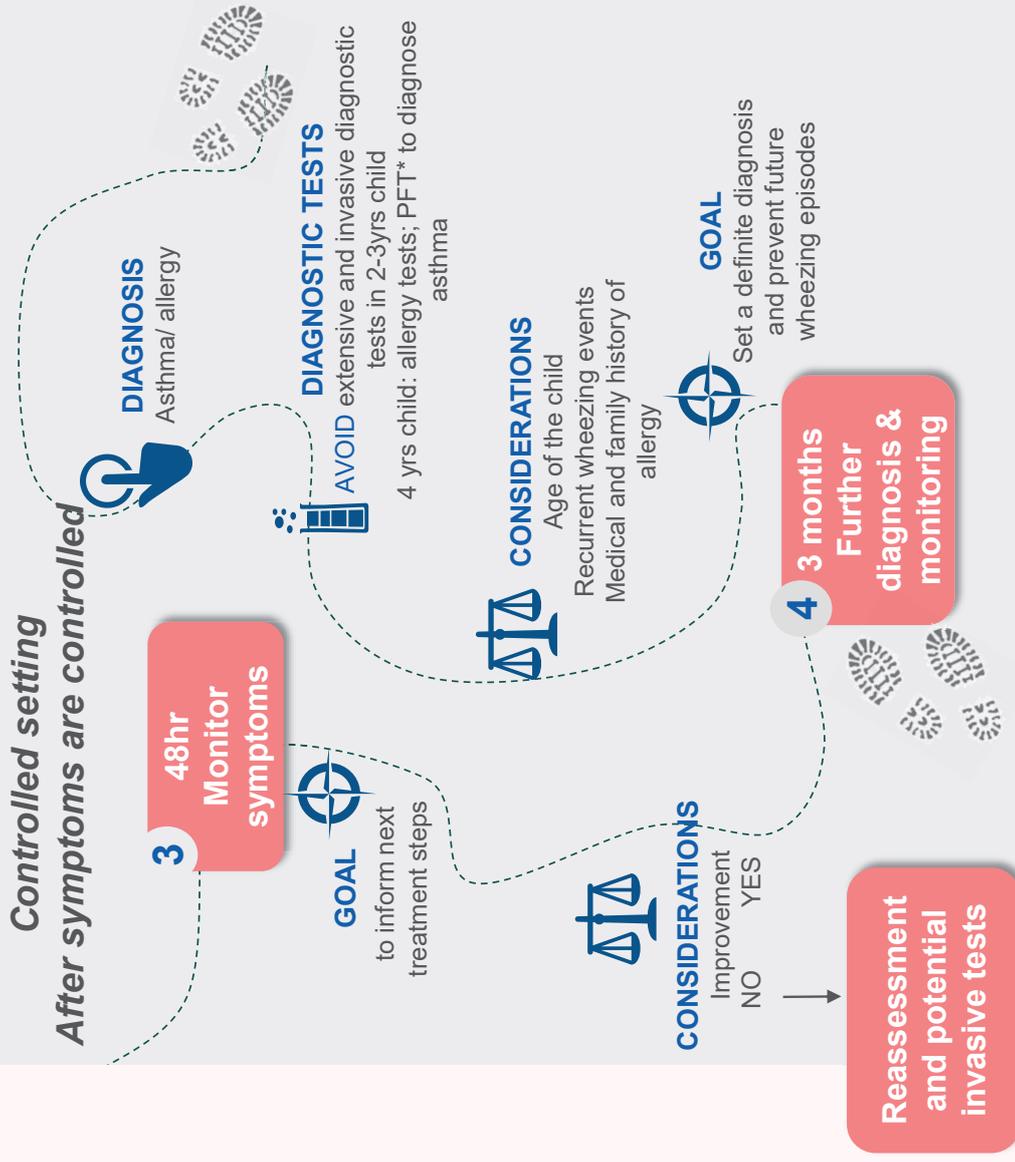
- ASSESS DISEASE SEVERITY
- Give long-term PROGNOSIS
- INVASIVE OR UNSUITABLE DIAGNOSTIC TESTS to distinguish between allergy and asthma in young children
- UNRELIABLE DIAGNOSTIC TEST RESULTS – asthma test results might be inaccurate for young children (younger than 4 yrs old)

NEEDS

- RELIABLE AND NON-INVASIVE DIAGNOSTIC TESTS –suitable for very young children
- DIAGNOSTIC TESTS THAT INFORM TREATMENT DECISIONS - provide an indication of the disease severity to aid treatment decisions

Opportunities

Physicians already see a place of this new diagnostic tool in supporting their treatment decisions in a controlled setting. It can be used as a screening test to distinguish asthma and allergy before putting the children through more invasive tests.



Two patient profiles with different characteristics were presented as stimuli to help physicians talk through the diagnostic processes

Younger child with more acute symptoms with less medical history

Patient	2-year-old girl
Gender	Female
Age	2
Medical history	Nonatopic. Parents report several respiratory infections after child entered preschool at age 1. Diagnosed with bronchiolitis, based on symptoms, at a previous visit to ER. Otherwise healthy child.
Current wheezing symptoms	High pitched wheezing during the expiratory phase. Low oxygen level and difficulties breathing.
Previous wheezing events	One previous, clinically confirmed episode of wheezing. Parents report additional instances of wheeze.
Initial diagnosis	Bronchiolitis? Respiratory failure? At risk of developing asthma?
Diagnostics performed to achieve diagnosis	Auscultation.
Previous treatment in record	None.
Response to initial treatment given during visit	Improvement of symptoms and oxygen levels with β 2-agonist nebulization.

Almost all physicians indicate that this patient profile is representative of their wheezing children population, except for 4 office-based physicians indicating that this is a rarer case for them

Older child with more extensive medical history and recurring episodes of wheezing

Patient	5-year-old boy
Gender	Male
Age	5
Medical history	Atopic by skin prick test. Recurrent symptoms including rhinitis and cough between colds. Otherwise healthy.
Current wheezing symptoms	High pitched wheezing during expiratory phase. Currently with respiratory infection.
Previous wheezing events	Episodic wheeze.
Initial diagnosis	Airway inflammation? Asthma?
Diagnostics performed to achieve diagnosis	Auscultation. Lung function (FEV1).
Previous treatment	As needed short acting β 2-agonist (SABA) plus inhaled corticosteroids (ICS).
Response to initial treatment	Slight improvement of symptoms with SABA and ICS.

This patient profile is considered a good representative of physicians' patient population. Only 1 physician working in hospital indicated that he see less of this type of patients.

The recurrent wheezing events and age drive the approach: to restore breathing until new episode versus investigate long-term treatment initiations



Younger child with more acute symptoms with less medical history



Treatment goal

Short-term:

- Restoring normal breathing
- Prevent conditions from worsening



Diagnosis priority

Rule out viral infections, bronchiolitis and bronchitis first

- **No specific diagnostic test** except for oximeter, **except a couple mentions about RSV* swab test in the ER.**
- X-ray, blood gas analysis or blood test will be performed, but only if there is a definite need for that e.g. not responsible to Beta-2 agonist or the need to further confirm infection .



Diagnostic tool



Reasons for the approach

- Allergy and asthma diagnosis would only be done if there are recurring episodes
- Viral infection most frequently occurs with very young kids that just started pre-school or daycare
- Too young to have accurate results from allergy or asthma testing



Older child with more extensive medical history and recurring episodes of wheezing

Long-term:

- Besides restoring breathing, focus is to prevent getting recurrent obstructions

Confirm diagnosis of asthma mainly due to the age of the boy and recurring episodes. Lung function test and prick test were already performed, hence strong indication for asthma.

- **PFT test** would be done to determine severity of asthma
- **Blood test** (IgE**, CRP***, Eos**** is already included in regular blood work up)
- **Prick test** to identify allergy and allergen

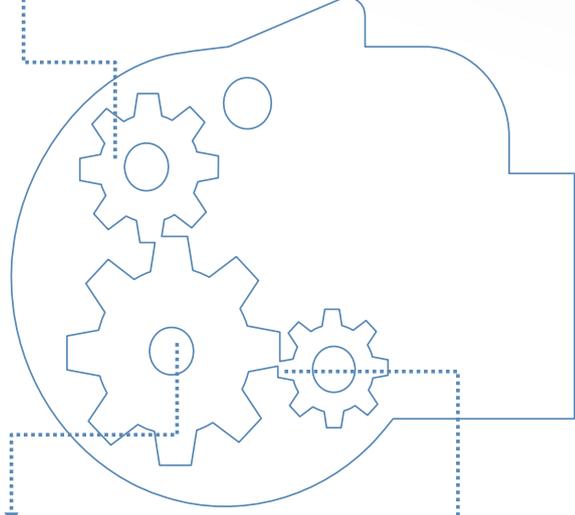
- Proper asthma diagnosis is needed due to age, medical and family history of allergy
- Parents need to know if this is going to be a chronic disease
- Physicians need to initiate or adjust long-term treatment to prevent evolving into a chronic disease

First treatment do not differ much between the 2 cases, but consideration and initiation of long-term treatment is a key focus for the 5-year-old.

Lack of access and insufficient understanding of clinical relevance leads to doubts of the reliability and low usage of biomarker measurements in diagnosis

General understanding of the clinical relevance of biomarker tests is insufficient. 25 out of 30 physicians mentioned that they do not use biomarker measurement, but in fact they do measure them. They just don't necessary classify or define them as biomarkers.

Some physicians simply have no access to biomarker tests as they are only available in certain hospitals, or they are not eligible to order biomarker tests (commonly ordered by pulmonologists and allergists).



Physicians know of eosinophils, yet they do not consider it to be a parameter to determine wheezing diagnosis and treatment decision. If it is considered, it is usually when asthma diagnosis is needed mostly at a later stage.

- Physicians have the perception that eosinophils measurement is not reliable, especially in children younger than 5, for different reasons:
- The current measurement of biomarker is mainly on cell counts.
 - They believe it only offers them an indication rather than a definite prediction of the disease.
 - Other conditions can also cause increase of eosinophils.

"I don't, I never do them as first step. I generally do them after the patient has gone through several steps, several episodes. When a child has a bronchiolitis, a first asthmatic bronchitis, I don't really care to know his/her eosinophils. But if he does relapses 5 other times, maybe at this point, I want to discover it." (GP, IT)

"When patient is too young, you don't get anything from the results." (Ped, office-based, DE)

"I think biomarkers are used but in university hospitals." (Ped, ER, FR)

"Recent biomarkers like ECP has not been a success" (GP, IT)

Evaluation of Product Concept

Perceived benefits, concerns and evaluation of product concept on key KPIs

Information and information needed

Product concept description

Showcard 3a: Description of Product X



Insights

In children, asthma is defined as a chronic inflammatory disorder of the airways, associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing. In children below 5 years of age, the clinical symptoms of asthma vary and are nonspecific. Currently, a symptoms-only approach that defines the diverse wheezing phenotypes has been recommended.¹

- Wheezing is a common symptom experienced by children, which is associated with multiple respiratory conditions, not only with asthma. Accurate differential diagnosis of wheezing in children based on type and degree of airway inflammation is hampered by the lack of support of reliable biomarkers: blood eosinophil counts may be too variable, and sputum eosinophils are difficult to measure.

Introducing a new diagnostic laboratory test using nasal sampling

A minimally-invasive diagnostic test measuring eosinophil granule protein (EDN), an inflammatory biomarker, in *nasal mucosal lining fluid* to support differential diagnosis and treatment considerations in wheezing children.

- This diagnostic laboratory test measures activation of eosinophils in the nose, by measuring EDN to reveal fundamental insights in the mechanism of the disease and support the diagnosis, treatment and monitoring over time.

Sampling Procedure

- This diagnostic test comes with a nasal sampling device enabling a minimally-invasive 1-minute sampling procedure.
- The sampling device is available in two versions: one designed for children from 2 years of age, and one for adults.
- The nasal sample is then sent to a laboratory for analysis.

Clinical relevance

- First biomarker-based laboratory test to support differential diagnosis of airway disease in children
- Guides treatment decision, e.g. to treat inflammation by inhaled corticosteroids (ICS)
- Minimally-invasive procedure
- CE-marked nasal sampling device, which has been assessed to meet high safety, health, and environmental protection requirements.

1. ERS Lung White Book (<https://www.erswhitebook.com/>), 2013. ERS and European Lung Foundation

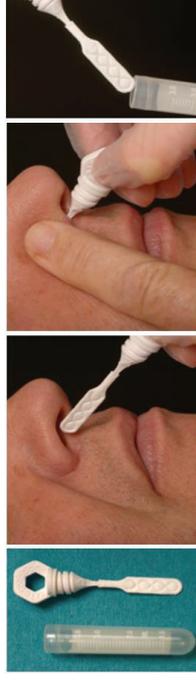
SKIMgroup.com

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The product concept was shown as Product X, an unbranded and unnamed sampling device. Brand and name were not shown to respondents to prevent potential bias.

Showcard 3b: Picture of Product X

Minimally-invasive, CE-marked nasal sampling device



Size for children	
Width	4.5 mm
Length	27 mm

Size for adults	
Width	7 mm
Length	28 mm

SKIMgroup.com

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Respondents took a couple of minutes to review Product X, after which a detailed qualitative evaluation took place. To quantify their impression, respondents were asked to rate Product X on several KPIs

Physicians' first positive reactions triggered by the new diagnostic test that supports diagnosis fade away quickly as they question the clinical relevance & evidence

On a 1 to 7 scale, where 1 indicates 'very negative' and 7 'very positive', how would you rate your first impression of this product?



Average rating: 6

Majority of respondents are positive about the concept on first impression. Ratings of the concepts from all physicians are between 5-7.

"5...as first impression because the product is good, but there are some info needing clarification." (GP, IT)

"6...This test is helpful in the diagnostic pathway. An increased number of eosinophils addresses me towards allergy-induced asthma." (Ped, ER, IT)

Italian physicians are more open to accept the benefit of the concept. In DE and FR, physicians cannot see how they can use it which affects their perceptions.



Average rating: 3.6

Nearly all respondents have a negative first impression of the concept. Only 3 office-based physicians rated the overall concept higher than 4)

"2. What do I do when this test is negative? I still have the symptoms. I'm not sure whether this will be very helpful for me." (Ped, office-based, DE)

"6...Every diagnostic is a good thing. It's very easy to handle, a very easy diagnostic measure, but need to see the value it has for Tx decision." (Ped, office-based, DE)



Average rating: 3.5

The highest rating received is 5, from 3 physicians. The rest of the physicians give rating lower than 5.

"5. Because if it can help us put things into perspective when diagnosing these patients, it could be interesting! I'm not sure it would change much anything in our therapeutic strategy." (Ped, hospital, FR)

"2... The type of infection can impact the rates of EOS. And here with this test we'll have much specificity but very low sensitivity... I don't want to be pessimistic but "meh"! And I'm not even considering the issues associated with the sampling method!" (Ped, hospital, FR)

Overview of the perceived benefits and barriers: prompted discussion

EXCITEMENT

Perceived benefits by physicians

-  **Support diagnosis**
A good supporting test that can offer additional information to complete the full diagnostic process
-  **Give indication for long-term condition**
Offer important information for parents and treatment decision.
-  **Non-invasive sampling method**
Less invasive and more manageable than blood test or PFT test in young children.
-  **Indication for the appropriate treatment approach**
(only mentioned by 3 GPs in IT)
-  **A potential new diagnostic tool**
A few physicians are simply excited more diagnostic tools for young children, as this is a key unmet need they face nowadays
-  **A new and innovative idea.**
'Measuring biomarkers through nasal mucosal fluid' is perceived as unique and new by a couple physicians.

HESITATION

Perceived barriers and concerns by physicians

-  **Stress the importance the sensitivity of the test**
Biomarker measurement is not seen as reliable.
-  **Lack of clinical relevance**
Does not give new information that changes or aids treatment decision.
-  **Does not support differential diagnosis**
Does not give definite differentiation between asthma and other diseases.
-  **Sampling method is still considered invasive**
Some physicians find the sampling method not easy to performed in young children.
-  **Turnaround time too long**
Needs at least a day, which does not support diagnosis in acute situations
-  **Not applicable for certain practice setting or specialties**
 - In ER setting, nasal testing cannot be provided (IT ER)
 - A few GPs mentioned that they cannot order this type of diagnostic tests for patients. Confirmation of allergy or asthma diagnosis is specialists' role.
-  **Cost and insurance coverage of the test**
Need to know if patients need to pay out of pocket and costs implication for their practice (Office-based)

✓ EXCITEMENT quotes

"Now the fact we can have a measurable and reproducible test for one of the parameters involved in asthma will allow us to validate diagnosis." (FR GP)

"To be able to provide a response to the mom, in the future, it could be an interesting point." (IT GP)

"Cytology is another test we use but it is more invasive, while as far as I read this one is more a swab." (IT, ped hospital)

"It is quite interesting: as I told you we are limited in diagnostic tools and tests especially in very young children." (FR GP)

"Simplicity, rapidity and important differential diagnosis. It is important for the therapeutic choice and to refer to specialist more selected patients." (IT GP)

"Seeing an eosinophil granular protein in the nose itself. I didn't know that; it is interesting and exciting." (Ped, hospital, DE)

"Nasal inflammation is present in all respiratory disorders. I would use it for the 2 YO girl to direct my treatment." (Ped, office-based, FR)

! HESITATION quotes

"But is it specific enough? I question its specificity, its sensitivity..." (FR GP)

"With biomarkers you can get more detailed measurements compared to blood work, but in the end you can't really use it, you acknowledge it but you don't really use it." (DE GP)

"I would like to see a 2-year old child leave this thing in their nose for a whole minute...that's really long...it's easier to draw blood, to be honest." (Ped, hospital, DE)

"We cannot offer any of other diagnostic tests, would have no use in offering only this testing procedure." (GP, IT)

"I think I would like to know what it costs for me, as a treating physician." (GP, DE)

Prompted mentions

To be convinced, physicians need evidence on sensitivity and specificity of the test and study data to prove that the test results will link to a clinical implication

EVIDENCE NEEDED

Proof and evidence needed to be convinced



Proof of sensitivity and specificity of the test

→ No false positives or negatives



Show correlation between EDN value and asthma

→ The value of the test links to a clinical end-point



Show that measuring EDN in nasal mucosal fluid is possible and can offer more accurate indication of respiratory disease than measuring biomarkers in blood



Clear definition and validation of the reference values that lead to clinical implication

→ Studies that show how the reference values are defined
→ Reference values should give input for treatment decision e.g. a certain value indicating an improvement or worsening of the condition, hence based on this, medications can be reduced or increased

“Data about test sensitivity, related to the number of eosinophils in the nasal mucosa. I would need to know if this test is accountable, the level of sensitivity, that should be >95% and specificity. Moreover, it has to be manageable to perform and to interpret.” (Ped, ER, IT)

“A correlation between the number of, and the activation of eosinophils with a phenotype, for instance with asthma. So you would need to do long-term observation to find out what happens to children with wheezing, how correlates the value with the development of asthma?” (Ped, hospital, DE)

“The idea is to see whether there is a true correlation between the nasal Eos levels and the fact the etiology is bronchial. So far this is something we don't know!” (Ped, hospital, FR)

“Will there be a cut-off value to say, ‘there are so many eosinophil granulates in the nose; he needs inhalation steroids?’” (Ped, hospital, DE)

Prompted mentions

While the novelty and the nasal sampling drive appeal, physicians doubt the benefits of biomarker testing in their practices

Average score on key KPIs
(7-point scale)

IT	DE	FR
6.4	3.7	4

Innovativeness and non-invasiveness drives appeal, however the low applicability affects the score.

“5...Well it's like the Mont Blanc: you are in front of it and you find it magnificent, but it doesn't mean that you are going to climb to its top!” (Ped, ER, FR)

“7...it allows a screening to understand if it is either allergy or infection.” (Ped, Hospital, IT)

IT	DE	FR
5.9	2.4	3.4

Some physicians can see the potential use of this test in a non-acute setting. Some doubts if it helps because the tests only give an indication that will have no impact on their treatment approach.

“1...1 for the acute treatment and 7 if validated for predictive significance.” (Ped, hospital, DE)

“4...it could be useful in a non urgent situation in which we don't have enough clinical elements nor any details on family / medical history that could help us determine an allergic etiology.” (Ped, hospital, FR)

IT	DE	FR
5.9	2.9	3.6

The concept did address the need of diagnostic test for very young children; however some physicians need to be convinced about the benefits and reliability of biomarker testing as well as the potential clinical consequences.

“3...I think it isn't trash, so I won't give it a 1, but I am just not really convinced. I don't know enough about the eosinophil granule proteins in the nasal mucosa... so, I can't imagine.” (Ped, hospital, DE)

“7...Assessing the differential diagnosis of infection vs atopy. If eosinophils number is high, it addresses towards an allergic disease diagnosis.” (Ped, ER, IT)



Appeal



Usefulness



Addresses Unmet needs

Physicians' knowledge on biomarkers is low that contributes to doubts around the biomarkers. This indicates a need for education on the types of biomarkers and their advantages and relevance in clinical practice.

Unprompted mentions

The concept addresses an important clinical need: it enables physicians perform differential diagnosis, but not yet in their current practice



Support differential diagnosis

Average score on key KPIs (7-point scale)

	IT	DE	FR
	6.1	3.8	3.3

Not all physicians see that it can help them in differential diagnosis in current practice, it can potentially be a supporting test to give a concrete diagnosis later in the diagnostic process.

"4...A differential diagnosis, will be difficult, because will it tell me whether there is an infection or not, or the cause of the inflammation." (Ped, office-based, FR)

"1...It doesn't support it in the clinical setting and in the outpatient setting I believe the cascade looks different. In case of frequent episode a specific allergen diagnosis would be made." (Ped, hospital, IT)

"5...It is a supporting test following a clinical visit. It could make more concrete a suspected diagnosis of allergic asthma." (Ped, office-based," (Ped, hospital, IT)



Credibility of 'EDN measurement in nasal mucosal fluid'

Even though more data and evidence is still needed, physicians think that it is possible to measure EDN in nasal mucosal fluid.

	IT	DE	FR
	6.1	5.6	4

"7...I don't have information or results on this, I would have to see that and compare it, but I can very well imagine this is credible." (Ped, office-based, DE)

"4...Well it is credible provided the trial is well designed." (GP, FR)

This concept is considered useful in long-term therapy management; inclusion of other inflammatory biomarkers can further enhance relevance in acute setting

Without sufficient evidence, physicians do not see the clinical application of this test in acute situation yet, but they do see potential usage of this test in the following aspects:

Long term therapy management

It can be used in monitoring long term therapy management mainly for patients who are diagnosed with asthma

Screening test

Before performing other more invasive tests for asthma and allergy in patients who have experienced recurring episodes of wheezing Turn-around time of a week is not an issue here, as a proper allergy tests might take even longer

Asthma outpatient clinic

It is found to be more suitable for office-based pulmonologists and physicians in asthma outpatient clinic in the hospital

Besides measuring EDN, measuring other biomarkers for inflammation and infection (e.g. CRP), allergens (e.g. IgE) and virus (RSV) with the test would be relevant in helping them diagnosing wheezing children. Also, measuring multiple biomarkers in one test would also be a plus.

“Maybe the markers of inflammation. CRP, procalcitonin (PCT), interleukin, and other proteins that are much more specific. Maybe the total IgE or the IgA as well. And specific IgE.” (Ped, ER, FR)

“I do see it as a test for specialists...on all patients with Asthmatic bronchitis who don't answer to inhaled corticosteroids.” (GP, IT)

“It looks like a first screening test” (to tell whether it is viral infection or allergy.)” (Ped, hospital, IT)

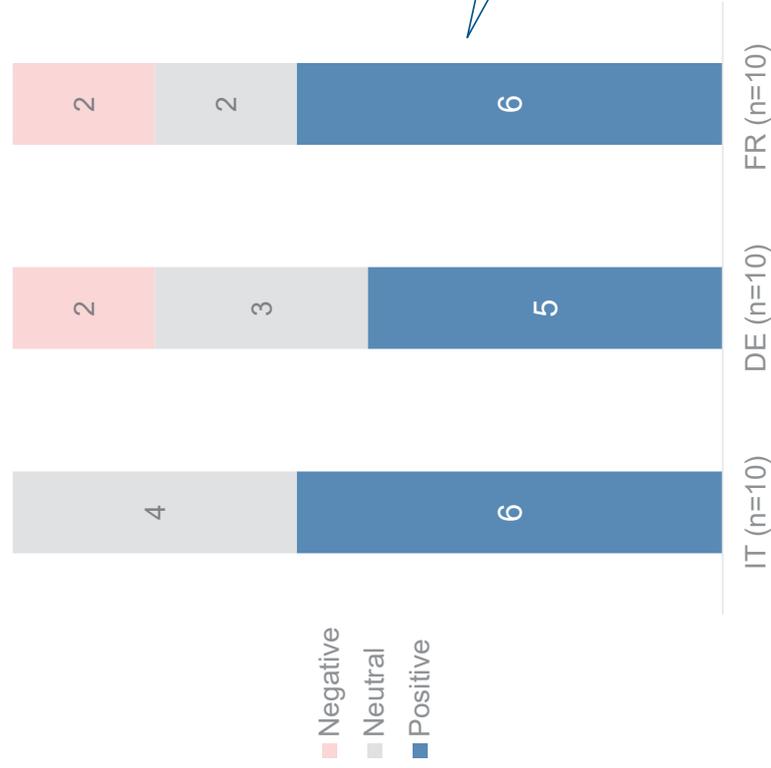
“Asthma is dynamic. You cannot just do one (snapshot) test for a long-term dynamic disease.. It has to be reproducible over time!” (ER, FR)

“It is useful. It does actually support me. Is there something allergic or is it infection?” (GP, DE)

“The only thing I liked is further down, clinical relevance, the part with corticosteroids, it would not be a decision aid but I could imagine this could be used for monitoring to make sure the steroid therapy is a success or if we can reduce the therapy and taper off the medication slowly.” (DE, GP)

Physicians are generally positive about the nasal sampling technique, but some still have doubts about its invasiveness on young children and its applications

Perceptions on nasal sampling techniques



“Well, imagine a 3 years old child: you’ll have to hold him tight and be brutal! It will not be the same from one child to the other! I think it will be very complicated! It’s got nothing to do with softness! It’s the fact you are approaching the child to introduce something in his nose!” (Ped, FR)

“If this allows the sampling tool to be completed with a reagent vial, and this prevents me from having to pass liquids and pads from here to there, I would be very positively impressed.... O.. I need to take it somewhere for processing?...it is not so useful and helpful anymore.” (GP, IT)

“It is easy to get, as easy as stool and urine. To be honest, not a lot (of benefit), because my treatment wouldn’t change as a result of it.” (Ped, Office-based, DE)

“That it is minimally invasive, that it is relatively quick: insert the swab, press the nose, take the swab out, close, send... it is elegant.” (Ped, hospital, DE)

“It can be something we can do in the office of a family paediatrician. Surely this has advantages over a blood test, because nasal eosinophils are one of the parameters. We do not remind because no one does the test.” (GP, IT)

“The test itself seems easy to do, practical, and will not be aggressive in the nasal cavity, so, the test in itself is receivable.” (Ped, FR)

Information on correct sample collection and the material of the device will generate confidence; offering clinical info comparable to a blood test is expected before adoption



Physicians indicate that nasal sampling technique is **less invasive** than blood test and X-ray and is **easier to perform** when compared to PFT test in young children.



Physicians **need information regarding the procedures and techniques required** to ensure the collection of sufficient materials for testing:

- *What if the nose is very dry?*
- *Will it then still be able to capture enough mucus?*
- *How will the sample be taken to the lab?*
- *Does it require much extra work for physicians?*
- *How to properly store the sample? Refrigerator needed?*
- *What if the child has a cold, would that affect the sampling?*

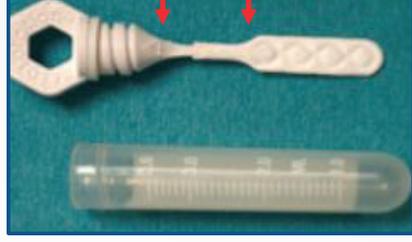


However, as physicians' positioning of the concept is in the long-term disease and therapy management, the concept is **expected to provide similar or improved clinical information** versus blood test in order to be considered. So, nasal sampling is preferred over blood test, **only if the test can provide the same information as a blood test (covering more than 1 parameter)**



If a blood test is already ordered, majority of physicians indicated that they are not likely to order this test on top of it.

Physicians need to be reassured about the **size and materials of the sampling device** would cause least discomfort on young children.



The length of the device still look quite long for children

“What is the material used for collecting sample? Is it soft?”

“When the blood test is done, it includes B-eos. Thus, the nasal sample won't be very useful to me.” (Ped, office-based, FR)

“ I will use this test instead [of a blood test] if it gives me more than just eosinophil” (Ped, office-based, DE)

Physicians need to be reassured that the sample collection is foolproof in a clinical setting before recognizing the benefits and potential of using it for home sampling

More than half of the physicians do not see the potential of using this test for home sampling as they do not trust that patients can perform it correctly and simply do not see the need of home sampling.

I would not have a parent do it. I would prefer to have it done by a professional, maybe a nurse at home that knows or some other HCP, but not the parents. (Ped, Office-based, FR)

"If this is all done at home, why does the child need it at all, then it's not really sick..'' (Ped, hospital, DE)

"I do not think it is relevant. We need diagnostic support. I do not like do-it-yourself stuff, those things need HCPs trained to do this. What will happen if sampling is not well done?" (Ped, ER, IT)

Only 5 physicians (in IT and FR) saw the potential benefits of home sampling in helping them monitor and manage patients

"I adopt telemedicine for any consultation. So, if a manufacturer can support me in this sense and provide such a test, I could ask to patients to come to me one time every year. In the future, it would be better to reduce the number of visits. (Ped, IT)

To help physicians believe in home sampling it is important to first alleviate several concerns:

- 1. Improved diagnostic confidence:** physicians need to trust that the sample is collected correctly to limit human factor in setting a correct diagnosis
 - Provide a thorough description of how the sample should be collected to inspire trust in parents' ability to collect it
 - Facilitate gaining experience to help them get used to it and feel at ease
- 2. Assess and balance the risks and benefits of home sampling:** there is unclarity on the time-advantages of the home sampling test as long as the test still needs to be sent to the lab for analysis. If not performed well, it negatively impacts time for diagnosis.
 - Communicate the benefits of this method to help them consider it quicker.

Example: It can be stressful for HCPs and young children to have any diagnostic tests performed on them. Home sampling test can offer a more comfortable experience for young children as it can be done by the people they trust (parents) and in a comfortable place (home). This can alleviate the stress of everyone during a consultation, physicians can focus on the discussion rather than trying to get the cooperation of young children.

Conclusions and recommendations

Overview of the key insights: Data and evidence to show clinical relevance



Physicians need more reliable diagnostic test for young children

- Physicians do not see the clinical relevance of the test yet, as they do not see that this test generates results that can predict asthma development.
- A diagnostic test will only be valuable if it gives a definite diagnosis and leads to a therapy decision.
- Physicians stressed the importance of high specificity and sensitivity of the test, especially in children younger than 5 years of age.
- An objective test will help physicians make diagnosis less dependent on their own experience.

Physicians need a diagnostic test that provides an indication of the long-term condition

- A diagnostic test that can confirm asthma diagnosis is considered valuable.
- Biomarker is not a key measurement physicians use in the diagnostic process of wheezing children
- B-Eos is known, but most physicians find the measurement unreliable.
- While measuring biomarker in nasal mucosal fluid is found to be innovative and credible, physicians need more data to show that it is more accurate and superior to measuring biomarkers in blood.

Physicians need a non-invasive and suitable diagnostic test for young children

- Most physicians are positive about the sampling method as it is less invasive than blood test
- However, physicians need more clarifications and instructions on the correct sampling procedure and need indication to show that enough material is collected for testing.
- Also, a few physicians question the sampling device, as it seems quite stiff and long for young children.



- Studies and scientific publications are needed to prove the predictive capability of this test, especially in children younger than 5 years old.
- Reference range needs to be clearly defined and supported by solid data.
- Clear interpretation of the results which leads to a clear diagnosis or treatment implication.
- Peer review and recommendation by guideline are important to further drive adoption.

Reassure physicians about sensitivity of the test and that results link to a specific clinical implication

- More education and information regarding biomarker measurement in diagnosing asthma should be shared with physicians to generate more awareness and confidence.
- Studies and data that show correlation between EDN value and asthma diagnosis.
- Evidence is needed to show that measuring EDN in nasal mucosal fluid is possible and has a better indication and accuracy in identifying respiratory diseases compared to blood test.

Raise awareness and credibility of biomarker measurement in asthma diagnosis among physicians

- It is important to provide clear instructions on how to collect the sample properly, including preparations before the test and sample storage conditions.
- Provide indication on the device to indicate ample material is collected for testing.
- Give information on the material of the sampling device and give physicians the actual prototypes to reassure them and to gain experience.

Educate physicians on the correct sampling procedure and reassure physicians that the sampling device is comfortable for use with young children



Overview of the key insights: Extend application from long-term to acute situations



Physicians need a diagnostic test that gives input for treatment decision and management

- At the moment, a place for this concept is seen in long-term disease and therapy management for patients who have recurring wheezing episodes or have already diagnosed with asthma.
- It can be used as a pre-screening test before running other more invasive tests for allergy or asthma diagnosis.
- It will give input for physicians to initiate, monitor and adapt the use of steroids.
- More suitable for office-based pulmonologists and physicians in asthma outpatient clinic in the hospital.

Physicians need a diagnostic test that supports quick diagnosis of multiple diseases

- However, the concept is not seen as valuable in an acute setting due to non-predictive results and the turnaround time.
- Physicians are hesitant to put young children through invasive diagnostic tests unless there's a valid reason.
- Physicians *do express* the need to have asthma diagnosed early and recognize that they need a reliable tool that help give quick diagnosis to very young children.
- It's also important to be able to communicate the test results and a definite diagnosis to calm parents

Physicians need to be reassured that the sample is collected correctly and see the advantages of home sampling

- Physicians do not yet see the advantage of home sampling test in providing a more comfortable way to perform diagnostic test on young children, which can make physicians' job easier as they can focus on the discussion during consultation.
- They do not trust that the parents can perform it correctly as they still have many questions about the sampling procedure in a clinical setting. It is a need for physicians to eliminate any human errors.
- They cannot see, logistically, how the home sampling test can timely help them in diagnosis of wheezing children.



- Get insights from the pulmonologists and physicians in asthma outpatient clinics in their current ways of diagnosis confirmation and treatment monitoring, and their perceptions on using this test in diagnosis.
- Provide evidence to show how this test can help them decide, monitor and refine their treatment approach in asthma patients.

Explore and emphasize the potential benefits of this test in long-term disease diagnosis and therapy management

- To really support differential diagnosis in acute situation, consider including multiple biomarkers (infection marker, allergy marker) into the test as these measurements are considered relevant in distinguishing different conditions in acute setting.
- If turnaround time can be shortened or eventually bring it to the level of a quick test, this would increase its clinical relevance.

Enhance the ability of the test in supporting differential diagnosis in acute setting to further drive the clinical relevance

- Additional safety measures and instructions need to be provided to the parents to ensure that the test is performed correctly.
- Facilitate gaining experience to help them get used to it and feel at ease.
- Advantages associated with home sampling for young patients needs to be communicated explicitly to the physicians.

Improve diagnostic confidence and assist physicians in assessing and balancing the risks and benefits of home sampling

