Diagnosing asthma:

A 21st century challenge

Contents

Foreword

For too long, asthma has been diagnosed as a single condition

This simplistic clinical labelling is not shared by those affected by the condition. Get a group of people with asthma together and any one of them will be aware that the pattern of their symptoms, triggers and responses to medication are likely to be quite different to the other person badged with the same condition sitting next to them. For example, for decades steroids have been viewed as a one-size-fits-all treatment to control symptoms, and yet we are now understanding that perhaps as much as half of people with asthma do not respond to them.

The current clinical pathway is hampered by a lack of definitive diagnostics. However, it is also held back by a pathway reliant on generalist rather than specialist skills and randomly managed trials of treatment. It is no wonder this has resulted in a high rate of misdiagnosis, with people unnecessarily spending years on the wrong treatment, resulting in a loss of qualify of life.

For someone already struggling with new symptoms of coughing, breathlessness and the fear of being unable to breathe in the event of an asthma attack, the lack of a definitive diagnosis adds insult to injury. It is particularly galling when the difficulty of diagnosis means that people with asthma aren't taken seriously. Examples of people who've contacted us for help include a woman who, in the midst of an asthma attack, was told by a paramedic that she probably 'didn't really have asthma'; and a mother who still has to say her son only has 'suspected asthma' despite four years of terrifying emergency hospital visits coupled with coughing, wheezing and sleepless nights.

As the global asthma population increases by millions each year to reach a predicted 400 million in 2025 we want to stop this happening for many more families. To achieve this it is critical that we develop new ways to answer three fundamental, but currently difficult questions:

- Do I have asthma?
- Will I/my child have asthma?
- What type of asthma do/will I have?

Changing the status quo is not without challenges but with significant investment in research and innovation it could be possible within the next five years to make big steps forward. This will require leadership, speeding up trials and, most importantly, a collaborative approach to share data that can build a more complete picture of a complex condition with an array of mechanistic causes.

Asthma UK exists to stop asthma attacks. We believe accurate diagnosis of specific asthma types will end the frustration faced by healthcare professionals as well as the confusion felt by people with asthma. Most critically we must ensure people receive the right diagnosis in order to target treatments that can prevent asthma attacks and save lives. This paper sets out how we can achieve that. To show our determination to achieve progress in diagnostics, Asthma UK is also launching a themed funding call in diagnostics. Together we hope to stimulate the innovative science needed to solve this pernicious problem.

Kay Boycott
Chief Executive

Redefining a diagnosis of asthma

What is asthma?

Asthma is a long-term, heterogeneous condition affecting the airways that causes symptoms of wheezing, shortness of breath and coughing and can lead to life-threatening asthma attacks. In the UK, there are over 5.4 million people with asthma[1], of which 1.1 million are children, making it the most common long-term condition for under 16-year-olds. Global asthma prevalence is growing; it is currently at 334 million[2] and predicted to rise to 400 million by 2025 across all ages[3].

A diagnosis of asthma is often life-long, but the condition is episodic and severity can vary from day to day, month to month and across a lifetime. Despite its prevalence and impact, progress on improving outcomes has stalled for the past ten years. Hospital admissions have plateaued while asthma deaths have reached their highest level in a decade[4].

Asthma: one name for many distinct airways diseases

Failure to improve outcomes for people with asthma could be attributed to an over-simplification of a complex condition about which our scientific understanding is still incomplete. The current approach to diagnosis illustrates this simplification, requiring recognition and recording of variable

The causes and triggers of asthma

Viruses

Allergens

Bacteria

Hormones

Stress

Diet

Pollution
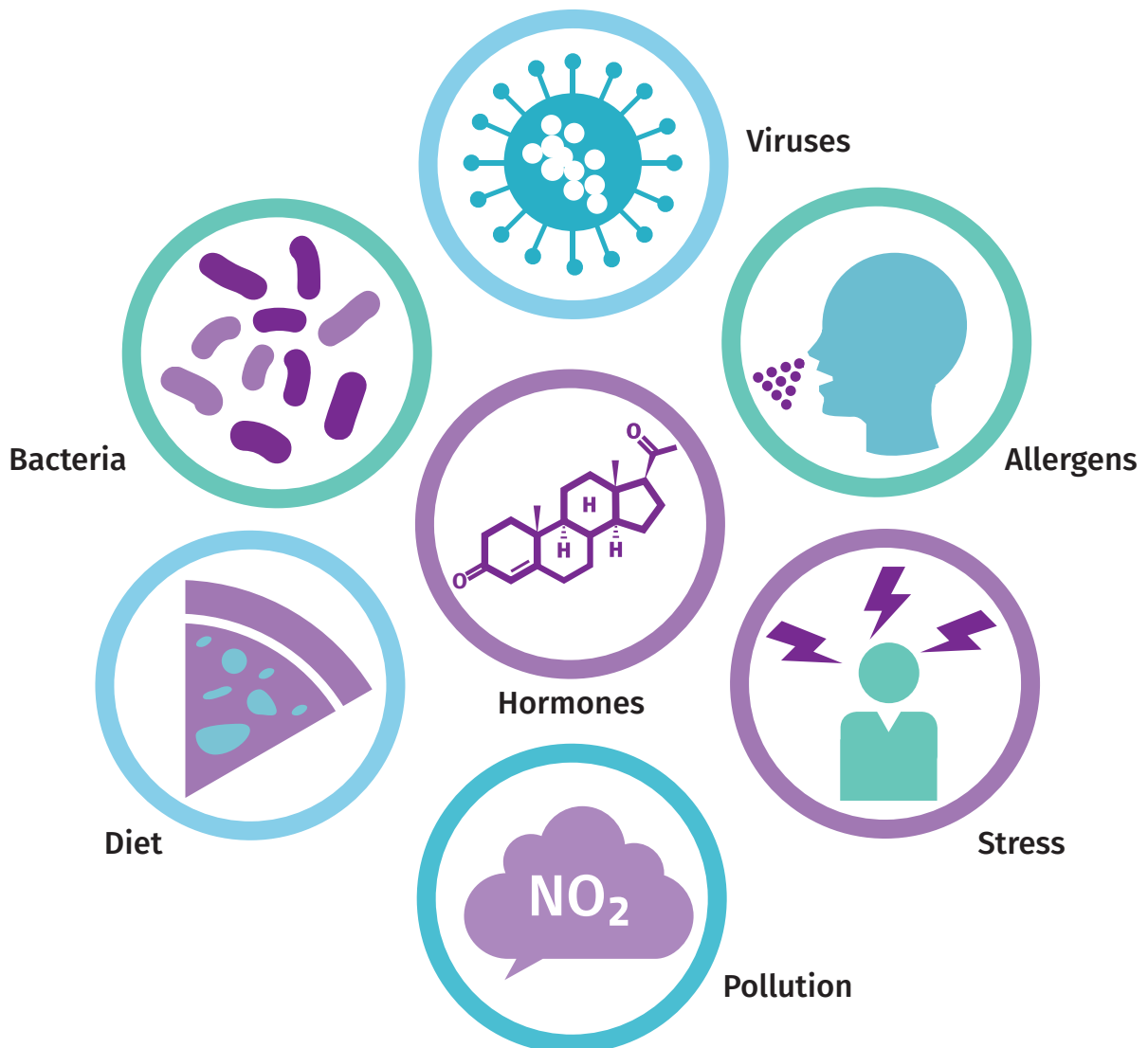
symptoms such as wheezing, coughing and tightness of the chest, and use of a range of imperfect tests to confirm a diagnosis. So far, we know that there are many different things – such as viruses, allergens and pollution – that cause asthma or trigger attacks but not why or how they do it. This needs much more research.

Asthma therefore is best thought of as an umbrella term for a 'heterogeneous mix of pathobiologically distinct mechanisms'[5]. In other words, there are different mechanistic causes for what appear to be similar symptoms, all of which are termed 'asthma'. The authors of a recent ground-breaking report commissioned by *The Lancet*[6] recommend deconstructing airway diseases into component parts before planning treatment with a focus on traits that are identifiable and treatable, and in turn measured and ideally modifiable[7].

Towards a future of personalised medicine

In order to get the right treatment, people who appear to have asthma symptoms need a diagnosis for their specific 'type' of asthma, and data from objective tests should be the basis for selecting that treatment. This is true even if, as is becoming clear, there are some types of asthma for which there are no effective treatments that don't have damaging side effects. In the absence of specific treatments, a clearer understanding of what is triggering someone's symptoms could help them manage them more effectively; for example, an early diagnosis of a type of asthma that is triggered by dust or air pollution might help a person to avoid these triggers.

"By using new technologies such as artificial intelligence to build on the existing knowledge base, and developing new studies, we can make such leaps that within five years we can have profiles of different types of asthma that can help to personalise treatment."

Professor Sven-Erik Dahlén, Director of the Centre for Asthma and Allergy Research at the Karolinska Institutet, Stockholm, Sweden

Diagnosing asthma today

At present we do not have the tools to accurately diagnose asthma or its sub-types. Diagnosis has historically been reached by seeing if symptoms respond to treatment ('trial by treatment'). This is both inefficient and wasteful when we consider that at least 50% of people with asthma may respond poorly to inhaled corticosteroids[8].

Tests that measure lung function (peak flow rate and spirometry) and tests for airway inflammation (for example, fractional exhaled nitric oxid (FeNO)) can aid clinical diagnosis but no single test can objectively confirm asthma or identify all the different types of asthma, and some are particularly invasive or expensive. The invasive nature of these tests usually precludes diagnosis in preschool children.

The result is that asthma is commonly misdiagnosed. There are several studies of over-[9] and under-[10]diagnosis of asthma that highlight the problems that result from an over-reliance on clinical evaluation[11]. One study found that a third of adult individuals with physician-diagnosed asthma did not have asthma when objectively assessed[12]. This is important because the fact that asthma has been thought of as a single condition has led to the assumption that a single class of treatments – inhaled corticosteroids – will work for everyone. However, as mentioned previously, while steroids are undoubtedly effective for many people with asthma, for many they will not be the most effective treatment[13]. This may be associated with considerable cost to the NHS given that medication accounts for about 60% of the £1.1 billion spent on asthma annually[14].

Up to 50% of people with asthma respond poorly to steroids

To give people with asthma the best chance of successfully controlling their symptoms and preventing life-threatening asthma attacks we urgently need a better mechanistic understanding of asthma, more effective ways of identifying those mechanisms through improved diagnostics and a range of treatments that can be tailored to precise mechanisms.

Annual spend on asthma in the UK

Prescription items			GP & nurse consultations	Disability Living Allowance			
£666m			£160m	£147m			

Prescription items	**59.9%**		Ambulance	**3.0%**
GP and nurse consultations	**14.4%**		Accident and Emergency	**1.2%**
Disability Living Allowance	**13.2%**		Intensive care	**0.4%**
Hospital admissions	**7.7%**		Out of hours calls	**0.2%**

Where research and innovation are needed to progress asthma diagnosis

Following a comprehensive gap analysis and a series of consensus-gathering exercises across Europe, the Asthma UK-led European Asthma Research and Innovation Partnership (EARIP) – a three-year, EU-funded project that brought together leaders from industry, academia and people with asthma via patient groups – recently published a roadmap for investment in asthma research and development[15]. Fifteen priorities were agreed, the top one being the need to identify and classify different types of asthma.

Compellingly, many of the other priorities related to the need for better diagnostic tests, building on a soon-to-be published review of the priorities for future research into diagnostics[16]. This opportunity ties in with the acknowledged need for investment to develop effective diagnostics to position the UK as a global leader in life sciences[17].

In July 2017, to build on the work of EARIP and to identify opportunities for UK research and development and investment in asthma diagnostics, Asthma UK and Innovate UK's Knowledge Transfer Network brought together over 80 experts from a wide range of backgrounds for a day of presentations, discussions and debates. Attendees included world-class academics, leading small and medium-sized enterprises (SMEs), major pharmaceutical organisations and representatives from UK-wide funding organisations.

Discussions focused on the three key areas of opportunity for asthma diagnosis. The following sections provide an overview of the discussions.

1. Development of a low-cost, accurate diagnostic test that improves diagnosis of asthma in primary care

The challenge here is to try to improve the accuracy and ease of use of existing tests and bring the costs down to enable widespread adoption.

a. Improving the accuracy and reproducibility of spirometry testing by reducing the burden on patients and healthcare professionals to increase use in primary care

The accuracy and reproducibility of spirometry testing depends on significant effort by the patient[18].

> "We need more systematic use of biomarkers in asthma, for stratification and/or adherence monitoring and for targeting treatments. We should adopt them at scale and pace and align them with an evidence-generating facility such as the National Institute for Health Research."

Professor Sue Hill, Chief Scientific Officer for NHS England

Healthcare professionals need to coach the patient and recognise unacceptable results[19], and an individual must be symptomatic at the time of visit for a positive test[20][21].

Standards for the high-performance use of spirometry already exist[22]. However, training is expensive, and the long intensive courses required to ensure competence are hard for healthcare staff to attend or afford. To improve accuracy and reproducibility, experts thought that the following solutions should be implemented:

- Enable the transfer of data from spirometers to GP software to avoid transcription errors
- Integrate spirometry data with other patient data and enable the data to be shared across platforms to develop diagnostic algorithms
- Consider establishing community-based diagnostic hubs
- Redesign spirometers to make them more user-friendly
- Foster collaboration between spirometer manufacturers, education providers and people with asthma to optimise training, including online courses and robotic simulations

b. Developing low-cost devices that combine existing tests to speed up asthma diagnosis without sacrificing accuracy

To improve the diagnostic pathway, a target of £5 per patient per test was proposed. To account for the pressures in primary care, the test should take no longer than two to three minutes. This compares with the current diagnostic pathway which can take 43 to 62 minutes, with a total cost of £57.93 to £71.80[23].

The immediate challenge is to increase the probability of a correct diagnosis from 50% to 70%-80% and reduce the burden on healthcare professionals and people with asthma. This may be achieved by the addition of existing tests for leukotrienes, eosinophils, carbon dioxide (capnometry), tidal breathing and genomic analysis.

New biomarkers – markers of biological activity that can be measured easily, accurately and inexpensively – will need validation, development and commercialisation so that they can be adopted by the NHS. A diagnosis of asthma provides no detail on the severity or cause of the symptoms, which additional tools may improve.

The variability of asthma means that it cannot be diagnosed within a fixed timeframe which is why measuring the fluctuating nature of asthma symptoms to inform the diagnosis is essential. Developing devices for home use could allow for monitoring over a longer period without requiring additional staff time.

SMEs, academics and clinicians must now work together to develop the tools to improve diagnosis, enabling a clearer consideration of the most cost effective adjunct(s) to the diagnostic pathway.

Tests currently recommended for use in primary care

Spirometry	10-15 minutes		£9.49 – £13.14
FeNO	5-10 minutes		£10.01 – £13.66
Peak Expiratory Flow	20 minutes		£21.08
Bronchodilator reversibility	8-17 minutes		£17.35 – £23.92

2. Predicting future asthma in preschool children

Currently it is not possible to diagnose children suspected of having asthma until at least the age of five. This is because we are not yet able to differentiate between asthma and other wheezing illnesses in this age group, and the tests that can help are time-consuming and invasive and so not suitable for young children.

A range of indices have attempted to develop a score that predicts persistence of wheeze or bronchial obstruction in later life, but while these tools are easy to use, their specificity and sensitivity are not yet good enough for routine clinical use.

An analysis of these indices suggests that the presence of allergy and a history of severe wheezing episodes in preschool children may predict future asthma. Emerging evidence suggests that combining an index with existing biological markers for certain types of asthma would be useful. Research protocols that evaluate these ideas need to be developed and tested.

Improving understanding of biomarkers to predict future asthma

Children who begin wheezing in their first years of life and carry on wheezing during the years three to six, then again at 11, are more likely to continue to have asthma[24]. Allergic (atopic) wheeze is more prevalent among six- to 11-year-olds.

The ability to diagnose asthma earlier would be a significant step forward and research should be aimed at doing this and increasing the accuracy of diagnosis. As new biomarkers are identified, a predictive index that could distinguish between the development of eosinophilic and non-eosinophilic asthma before age five would be very beneficial.

3. Identification of new biomarkers for asthma diagnosis and monitoring

It is possible that the combination of several different biomarkers could accurately identify different asthma sub-types and provide a complete picture of an individual's asthma and how it changes over time.

The ability to stratify the asthma population into different sub-types would be invaluable in helping to ensure that specific drugs are given to individuals with specific types of asthma. It is likely that sub-types of asthma will be identified for which there are no effective treatments; however, this evidence of unmet need should drive the development of new therapeutic targets for the pharmaceutical industry.

The challenge is to identify three or four biomarkers associated with the disease process that can then be used to more accurately diagnose individual types of asthma. Each biomarker should measure a specific biological mechanism and should be affected by treatment so that the response to treatment can be measured.

Biomarkers must also be measured regularly over a long period to understand individual and normal physiological variations. In addition, it needs to be assessed how biomarkers change in various patient states so that warning signs or risks (or periods of remission) can be detected.

Ideally, diagnostic tools should be simple enough to be used at home but underpinned by cutting-edge technologies that can measure and analyse biomarkers and generate data that can be sent to a smartphone and provide decision support to a

Case Study – Team science improving asthma diagnosis

In 1993, Asthma UK, the Wellcome Trust and the Royal Brompton Hospital-funded research discovered a new protein called eotaxin that draws disease-fighting white blood cells called eosinophils to sites of inflammation and plays a major role in asthma. This research became the foundation for measuring eosinophils. Twenty-five years later, the measurement of eosinophils and markers for eosinophilic inflammation (such as FeNO) are being used to help diagnose this specific type of asthma. This collaborative effort changed our understanding of asthma, but we now need to improve our understanding of and ability to diagnose non-eosinophilic asthma.

healthcare professional. Tools that stratify risk and/or indicate which treatments are likely to be useful for patients and practitioners would be transformational.

Challenges for SMEs who may be interested in developing new biomarkers include access to biological samples and patient data, while researchers require better access to biobanks and existing patient data sets. The community needs to work collaboratively to overcome these challenges.

"Diagnosis is really important from a pharmaceutical company's point of view. In other therapy areas pharmaceutical companies are working with diagnostics companies to produce treatments that are right for specific patients and it makes sense for this model to be developed more in asthma."

Dr Sheuli Porkess, Interim Executive Director, Research, Medical and Innovation, Association of the British Pharmaceutical Industry

Case Study – The East Midlands Breathomics Pathology Node (EMBER)

EMBER[25] is one of the six Medical Research Council and Engineering and Physical Science Research Council-supported molecular pathology nodes, hosted at the University of Leicester with partnerships with Loughborough University and industry.

EMBER's goal is to develop novel breath-based systems for molecular pathology. Exhaled breath contains volatile organic compounds (VOCs) that reflect biological processes occurring within the lung and, via the vena cava, more distant organs. Analysis of VOCs in breath provides rapid at-patient and in-clinic non-invasive approaches for diagnosis, phenotyping and stratifying patients. Importantly the range of clinical conditions is large and includes respiratory infections, cancers, respiratory diseases such as asthma and chronic obstructive pulmonary disease, and cardiovascular disorders such as heart failure.

Key findings: the future of asthma diagnosis

Step 1

Faster and easier diagnosis (Do I have asthma?)

The immediate aim should be to improve existing diagnostic tools and make them fit for purpose. Research and innovation must improve the accuracy and reproducibility of devices. Devices must be portable to allow people to take them home. Additional tests and intelligent joining up of data are needed to provide a more nuanced diagnosis, potentially through validated algorithms, that can provide diagnostic support to healthcare professionals and give people with asthma information on the severity of and triggers for their asthma to improve symptom control.

Step 2

Earlier diagnosis (Will I/my child have asthma?)

Gathering objective data will improve the specificity and sensitivity of clinical indices to predict future asthma in children under five. Gradually we should expect to be able to predict different types of future asthma using a combination of biomarkers with an index (or indices).

Step 3

More accurate diagnosis (What type of asthma do/will I have?)

Finally, we need biomarkers and/or combinations of biomarkers that can accurately, quickly and inexpensively identify specific sub-types of asthma to enable treatment to be targeted effectively.

Recommendations

1. Major funders should collaborate and create 'grand challenge' funding to bring asthma diagnosis into the 21st century. Such funding could follow a roadmap to deliver the above steps:

   a. innovation to improve existing diagnostic tools

   b. new stratified cohort studies to study asthma (and response to treatment) over time and predict future asthma

   c. identification of new biomarkers, in particular for non-eosinophilic asthma

2. To drive innovation and in line with the recent Life Sciences Industrial Strategy[26], consider the creation of a UK Centre of Excellence for asthma diagnosis research and development.

3. Leadership in the respiratory community to promote the understanding that 'asthma' is an umbrella term for airway diseases that have many different phenotypes.

4. By 2023, asthma guidelines should recommend testing for eosinophilic or non-eosinophilic asthma and treat accordingly. Objective testing should precede treatment.

5. Publish and disseminate the EARIP paper on asthma diagnostics[27].

6. Creation of diagnostic hubs that share tools, expertise and data to speed up access to and the accuracy of diagnostic tests. Hubs should adopt and test the latest technologies that can rapidly advance our understanding of a person's asthma.

7. A cross-sector, 'team science', collaborative approach whereby vast data sets of objective data are shared to enable faster progress on accurately diagnosing specific types of asthma earlier.

8. Greater use by SMEs and academics of the National Institute for Health Research Medtech and In Vitro Diagnostic Co-operatives to evidence the clinical utility, clinical validity, cost-effectiveness and care-pathway benefits of innovative diagnostic devices.

9. Involve people with asthma in the development of new diagnostic tools such that they are set up for successful real-world adoption.

Acknowledgements

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About Asthma UK

Every ten seconds someone in the UK has a potentially life-threatening asthma attack and three people die every day. Tragically two-thirds of these deaths could be prevented, whilst others still suffer with asthma so severe current treatments don't work.

This has to change. That's why Asthma UK exists. We work to stop asthma attacks and, ultimately, cure asthma by funding world-leading research and scientists, campaigning for change and supporting people with asthma to reduce their risk of a potentially life threatening asthma attack.

We fight asthma in three ways:

- We fund world-class asthma research.
- We campaign to improve the quality of care received by people with asthma.
- We help hundreds of thousands of people a year with our expert advice and support.

To find out more about Asthma UK's work:

Asthma UK Helpline:
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Email us:
info@asthma.org.uk

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