Driving investment in asthma research and innovation:

a strategy for personalised medicine in asthma

5.4

million people in the UK have asthma

Asthma is a major national and global health challenge. It affects more than 5.4 million people in the UK and 334 million globally. Between 200,000 and 250,000 people in the UK have a severe form of the condition which destroys daily lives, severely limits activities and causes long periods of time away from school and work. Despite significant, though fragmented, effort we have seen very few new treatments emerging, leading to an over-reliance on oral corticosteroids which have significant toxic side-effects when taken long-term[1, 2, 3].

Asthma UK and its international and cross-sector partners have set out 15 key research priorities that must be addressed to reduce asthma attacks, hospitalisations and deaths. Acting on these priorities would transform outcomes for people with asthma and

create opportunities for the technology and life sciences sector through the development of much-needed diagnostics, treatments and digital health technologies to support asthma management.

This short report outlines the extent of the unmet need in asthma before explaining the 15 research priorities, how they were developed and agreed, and the wider scientific and economic opportunities associated with them. The argument is that asthma's high global prevalence and the wider scientific and economic potential associated with addressing the priorities means that a relatively small investment would have a huge impact on people with asthma, researchers and the UK economy.

Unmet need

The low level of funding available for asthma research restricts innovation and limits efforts to address the unmet need in the UK and the rest of the world. Unlike conditions such as cancer and heart disease, which have long been the focus of significant funding and focused, coordinated efforts, asthma research remains chronically underfunded and underexposed[4]. Consequently, asthma remains poorly understood and, more importantly, ineffectively treated.

Researchers still do not understand what causes asthma or why people seem to get different types of asthma[5]. Very little progress has been made in categorising these subtypes[6]. As a result, existing asthma treatments are a one-size-fits-all approach to a complex and varied condition. The ineffectiveness of current treatments is exemplified by the fact that 200,000-250,000 people in the UK have asthma that is so severe that the usual treatments don't work or have significant side-effects[7]. In addition, many patients who could manage their asthma on their own struggle to do so because of complex treatment regimens, inhaler devices that are difficult to use and poor adherence.

The last few decades have seen huge developments in our understanding of asthma but the limited research funding available means that it could take many more decades to transform these findings into new treatments if a new approach to prioritisation and funding is not adopted. This would be a disaster for people with asthma, especially people with severe asthma. However, the European Asthma Research and Innovation Partnership (EARIP), led by Asthma UK, has shown that there is wide-ranging international agreement on how to answer the questions surrounding asthma. What is now required is coordinated research activity with the clear objectives of reducing asthma attacks, hospitalisations and deaths.

The methodology

EARIP was a European Commission FP7-funded initiative designed to inform research and innovation priorities for asthma over the next decade. The over-arching objective was to develop and agree the most important asthma research priorities that, if prioritised and funded, would significantly reduce mortality from asthma in Europe[8].

The three-year project brought together experts and leaders from across academia, patient groups, health professionals and pharmaceutical companies. Following a detailed and rigorous research gap analysis, these stakeholders reached consensus on the priorities for asthma research through the widely-respected James Lind Alliance process[9]. This process involved working groups using the Delphi and e-Delphi process to gather and prioritise the uncertainties that surround current asthma treatments[10]. These uncertainties were all checked to ensure they cannot be answered by existing knowledge or research. Then, they were prioritised and ranked in order of importance (1=high). Each priority area provided the basis for a state-of-the-art publication, three of which (on asthma mechanisms, optimising healthcare systems and a 'roadmap' of research priorities) will be published imminently (May 2017). In February 2017, the priorities were officially adopted by Europe's leading respiratory scientists[11].

The resulting research priorities represent an internationally agreed agenda for asthma research and development. It identifies 15 priorities, each accompanied by a set of research questions, that if tackled will lead to new treatments, diagnostics and technology-enabled self-management tools. Key research questions are included alongside each priority. The sum total represents a blueprint for the development of new treatments, health technologies and an eventual cure for asthma[12].

The research priorities explained

Understanding asthma

Research priorities:

- Identify, understand and better classify the different forms of asthma, their progression, and effect on airway inflammation and the immune system. (*EARIP priority 1*)
- Identify biomarkers for exacerbations and understand the interactions between biomarkers, risk and comorbidities. (*EARIP priority 9*)
- Understand the increase in asthma (both childhood asthma and different types of asthma, such as allergic and hyper-responsive asthma) to help develop primary and secondary prevention strategies. (*EARIP priority 10*)
- Explore the interaction between asthma, socio-economic and psychological factors, and comorbidities to reduce the risk of severe exacerbations. (*EARIP priority 13*)
- Understand the impact of exposure to substances known to trigger asthma, and the impact of strategies that regulate and control this exposure. (*EARIP priority 15*)

Detailed description

Asthma is complex; severity and responses to treatment vary widely for reasons that researchers do not fully understand. Researchers do agree that asthma is not a single condition but several conditions with broadly similar symptoms. The difficulty in understanding and developing new therapies comes from a lack of understanding of the different subtypes.

The foremost priority for asthma research is the classification of asthma phenotypes[13]. A phenotype is a characteristic of an organism that reflects the interaction between the organism's genotype and its environment. Phenotypes can increasingly be identified using markers found in blood, urine and breath; these are known as biomarkers. Classifying asthma phenotypes using biomarkers will allow researchers to identify the asthma subtype in individual patients. This will allow them to personalise treatments and care plans, and prevent asthma attacks and hospital visits[14]. Attacks are universally accepted as the major cause of asthma mortality and also contribute hugely to the healthcare costs associated with asthma[15].

The potential for new treatments based on different asthma phenotypes represents an important opportunity for the UK life sciences sector. Asthma is one of the most promising avenues to pursue the development of state-of-the-art techniques that combine new technologies and research methods, such as "'omics research". These techniques quickly measure thousands of compounds in the body such as proteins and DNA (eg genomics, transcriptomics, proteomics and metabolomics)[16]. Previous approaches allowed for the measurement of only a few substances at a time. What used to take months, if not years, to measure can now be done in hours.

The Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) project (2009-2015) used 'omics techniques on hundreds of people with asthma[17]. It has significantly enhanced our understanding of asthma and has had a significant impact on decision-making within the pharmaceutical industry, which is actively using U-BIOPRED data to inform its pipeline of new treatments. The next step is to widen the scope of such studies and use the data to expand our understanding of the mechanisms of asthma in order to drive the development of new treatments. U-BIOPRED showed that asthma phenotypes and new biomarkers can be identified and studied if resources are made available.

In summary, the EARIP project has identified the key questions to be answered and U-BIOPRED has shown that the research methods are available. These projects have clarified the landscape and set out what needs to be done to move forward.

What is needed now are resources. Substantial investment into large-team science is needed where patients, academia and industry can work together to validate the biomarkers, check their stability over time and use the findings to develop new diagnostics and new treatments, especially for the types of asthma for which current treatments are severely limited. Longitudinal studies, standardised outcome measures, biobanks and systems biology approaches to integrate data are key factors which could lead to the development of simple biomarkers that can be used at the point-of-care.

The return on this investment would be an improved understanding of asthma that can be used to rapidly develop diagnostic tools, new treatments and technologies, for which there is a huge global market. The asthma therapeutics market is predicted to reach $25.6bn per annum by 2024[18]. The medicines and technologies would transform the lives of millions of people with asthma, position the UK at the cutting edge of 'omics research and help ensure the UK maintains its world-leading position in the field of asthma research.

Diagnosing asthma

Research priorities:

- Develop tools for quick, accurate and low-cost diagnosis to distinguish asthma from other causes of breathlessness, cough and wheeze. (*EARIP priority 6*)
- Evaluate the role of lung function testing and new ways of measuring airway inflammation in monitoring asthma. (*EARIP priority 8*)

Detailed description

Asthma can severely impair quality of life and is in some cases fatal, yet there is no simple way of diagnosing it. Instead, a diagnosis is made using patient history and a set of breathing tests that compare results to age group benchmarks[19]. This approach is inaccurate. It makes it impossible to differentiate between asthma and other causes of breathlessness, cough and wheeze, or between different subtypes of asthma. As a result, asthma often goes unrecognised, putting people's lives at risk, while others may be taking treatments they do not need because they do not have asthma at all. In addition, there is no diagnostic test for children under the age of five. This situation is not acceptable.

As part of the EARIP project a working group of experts in asthma care identified the key research priorities in asthma diagnostics. The working group concluded that investment should be directed at improving tests to diagnose asthma in preschool-age children and integrating biomarkers in the diagnosis and monitoring of asthma.

In the UK, 1 in 10 children have asthma[20]. Lung function tests are not appropriate for children under five because they involve a series of instructions that toddlers struggle to carry out. Coughing, wheezing and a family history of asthma are indicators, but are not reliable given the number of other conditions characterised by these symptoms. As a result, children who experience serious asthma symptoms are often in and out of hospital for the first five years of their life before a diagnosis is made[21] and do not receive the most effective treatment. An effective diagnostic tool for children under the age of five would drastically improve the quality of life of parents and children across the country and globally.

Currently 4.3 million adults in the UK have asthma with many developing the condition later in life[22]. Although lung function tests are available, they are not particularly accurate because asthma varies day-by-day and month-by-month which means that a single measure of normal lung function one day does not mean that you will not have poor lung function the next. The tests do not differentiate between asthma subtypes. Identifying and classifying asthma biomarkers would allow the development of diagnostic tools that would enable clinicians to accurately diagnose asthma using biomarkers found in blood, breath or urine. We have already described how 'omics methods will give researchers the ability to identify and stratify asthma biomarkers. As a result, biomarker-based diagnostic tests that are able to distinguish between asthma subtypes are within reach if sufficient resources are made available.

The high global prevalence of asthma and the lack of effective diagnostic tests means that there is a global demand for new ones. Furthermore, the research pathway for achieving a workable diagnostic tool has been mapped out by the EARIP partnership. There are no unanswered questions on what needs to be done, only about where the required investment will come from.

Research into asthma biomarkers and new diagnostics represents a wide-ranging economic opportunity and a chance to improve the quality of life of millions of adults and children internationally. What is needed now are high-profile calls for more support for asthma research. The sheer number of people with asthma means that the support of decision-makers will be heard by the general public.

Treating asthma

Research priorities:

- Develop new treatments for the different types of asthma: treatment-resistant and steroid-resistant asthma, severe asthma, allergic asthma, hyper-responsive asthma. (*EARIP priority 5*)
- Assess the efficacy of existing and new drugs on different asthma phenotypes. (*EARIP priority 11*)

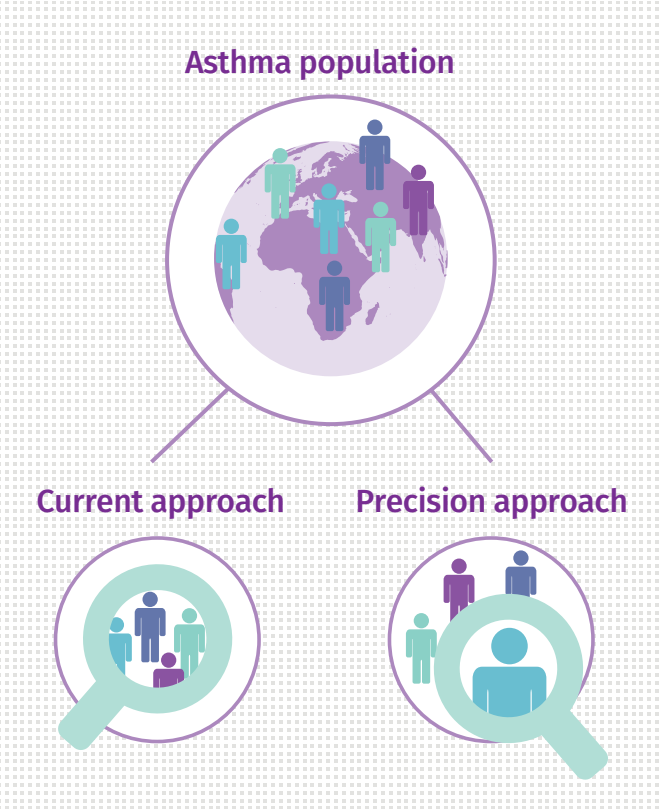
> The best example of precision medicine, in my opinion, does not come from cancer, it comes from asthma.
>
> Professor Sir John Bell, Royal Society of Medicine's 2015 Darwin lecture.

The majority of people with mild to moderate asthma control their symptoms effectively with inhaled corticosteroids, which are the mainstay of asthma treatment. Oral corticosteroids (OCS) are used if symptoms do not improve or get worse. Corticosteroids treat the inflammation that causes asthma symptoms such as breathlessness and wheeze but do not tackle the underlying asthma mechanism that causes the inflammation. Long-term oral corticosteroid use can cause serious side-effects such as osteoporosis, diabetes and Cushing's syndrome, which go on to cost health services across the world billions of pounds[24, 25].

The long-term goal of this priority is to develop new, more effective asthma treatments. A greater understanding of asthma phenotypes and their biomarkers should allow researchers to develop treatments that target specific asthma subtypes. These should ideally tackle the source of the inflammation as opposed to the inflammation itself, which is what the majority of current treatments do.

The fact that asthma has many phenotypes makes this a challenging task. However, this complexity provides opportunities to study the interactions between different phenotypes and the environmental factors which trigger the inflammation that makes asthma a highly personalised condition that varies widely between individuals.

Also known as 'precision' or 'stratified' medicine, personalised medicine involves tailoring treatment specifically to each individual based on their unique biological characteristics. It is being applied to many other conditions, including cancer, but is highly relevant in asthma. Personalised medicine is widely considered to be the most important upcoming trend in modern medical research[26].



Moving away from a one-size-fits-all approach to asthma treatment

Developing personalised treatments will depend on access to large patient cohorts and the collection of very large amounts of genetic and phenotypic data.

Investment across asthma subtypes should result in the classification of the majority of asthma phenotypes, further opening the door to new treatments. We are at the beginning of a fundamentally new approach for the diagnosis and treatment of asthma, which would transform the lives of millions of people.

However, there is work to be done. There remains a large drug development gap for those with non-eosinophilic severe asthma, who also respond poorly to existing corticosteroid treatments and make up an estimated 40% of the severe asthma population[27]. Currently the treatment pipeline is made up almost exclusively of treatments for eosinophilic asthma. The non-eosinophilic cohort urgently needs investment and attention. As has been made clear, the research tools exist but have yet to be applied to the right areas.

For more information on the need for new asthma treatments please see Asthma UK's Severe Asthma report.

Managing asthma

Research priorities:

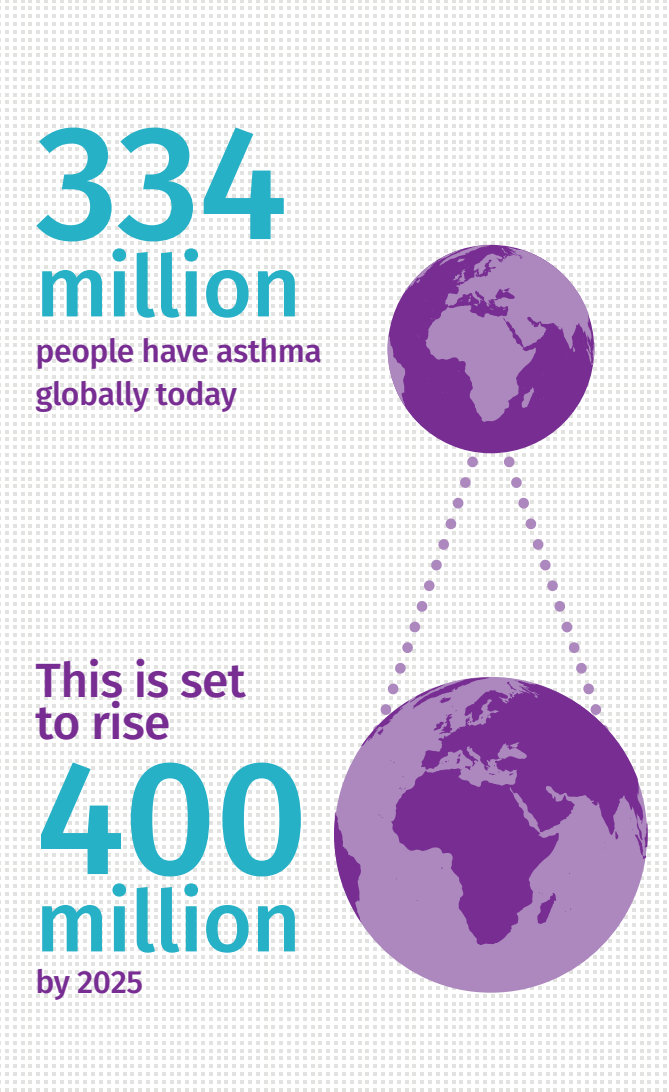
- Assess the effectiveness of patient-professional communication to develop patient-professional partnerships, for example to optimise self-management and adherence. (*EARIP priority 2*)
- Assess impact, adoption and transferability of best practice in regional, national and European asthma programmes, care pathways and asthma clinics. (*EARIP priority 4*)
- Evaluate the implementation of supported self-management, the educational needs of patients and caregivers, and the challenges faced and training needs of professionals. (*EARIP priority 7*)
- Develop tools to assess asthma self-management and asthma inhaler technique in primary care settings. (*EARIP priority 12*)

Detailed description

There is a strong body of evidence indicating that good care and management stops asthma attacks[28]. Research into the fourth EARIP priority has found that well-implemented asthma care programmes reduce attacks and hospitalisations[29]. Many people are able to effectively manage their own asthma care and it is estimated that 80% of people with asthma could effectively self-manage through improved medication adherence[30]. However, self-management at scale has, so far, been difficult to achieve. For example, between 30 and 70% of people with asthma do not take their asthma medication as prescribed[31].

Digital technology could lead to personalised, tailored support to help self-manage more effectively. Asthma-specific self-management research is essential to better understand this, as generic non-condition-specific research risks overlooking the influence of aspects such as medicine regimes, inhaler technique and triggers for attacks. Innovations in mobile and electronic health platforms have the potential to revolutionise self-management by providing support and enabling professionals to assess/monitor their patient's self-management remotely.

Furthermore, technology-enabled asthma management represents a significant economic opportunity.[32] Global asthma prevalence is growing; it is currently at 334 million and predicted to rise to 400 million by 2025 across all ages, with particularly significant increases projected in China and India. This rise in prevalence will lead to a rise



in demand for self-management tools. The global market for digital health is expected to be £43bn by 2018 and digital self-management tools such as monitoring apps and smart inhalers will be a growing part of this market.[33] People with asthma will need to be consulted throughout the development of new technologies. They will be the ones using these technologies every day. The UK, with its network of universities, pharmaceutical companies and patient organisations is ideally placed to create world-leading digital asthma self-management tools.

The size of the problem, the potential for improvement, the wide implications and the fact that solutions have been tested and are primed for investment should establish asthma management as a priority to be resolved through innovation.

For more information on tech-enabled asthma management please see Asthma UK's Connected Asthma and Smart Asthma reports.

Preventing asthma attacks

Research priorities:

- Assess the effect of infections in early childhood, the long-term effects of anti-inflammatory treatments, and use of anti-viral drugs and vaccines. (*EARIP priority 3*)
- Identify biomarkers for exacerbations and understand the interactions between biomarkers, risk and comorbidities. (*EARIP priority 9*)
- Investigate the impact of environmental factors on asthma and exacerbations, such as air quality (indoor and outdoor), climate, allergens and microorganisms and UV radiation. (*EARIP priority 14*)
- Understand the impact of exposure to substances known to trigger asthma, and the impact of strategies that regulate and control this exposure. (*EARIP priority 15*)

Detailed description

An asthma attack is a sudden worsening of asthma symptoms caused by the tightening of muscles around the airways (bronchospasm). During the asthma attack, the lining of the airways also becomes swollen or inflamed and thicker mucus is produced. In 2015, 1,302 people died as a result of an asthma attack in the UK[34]. Asthma triggers (factors that cause worsening asthma symptoms and asthma attacks) vary from person to person but include environmental factors such as air pollution and pollen. Exposure to these triggers can hugely disrupt the daily lives of people with asthma, impacting on quality of life and productivity. Strategies to control or prevent exposure should be priority topics for researchers.

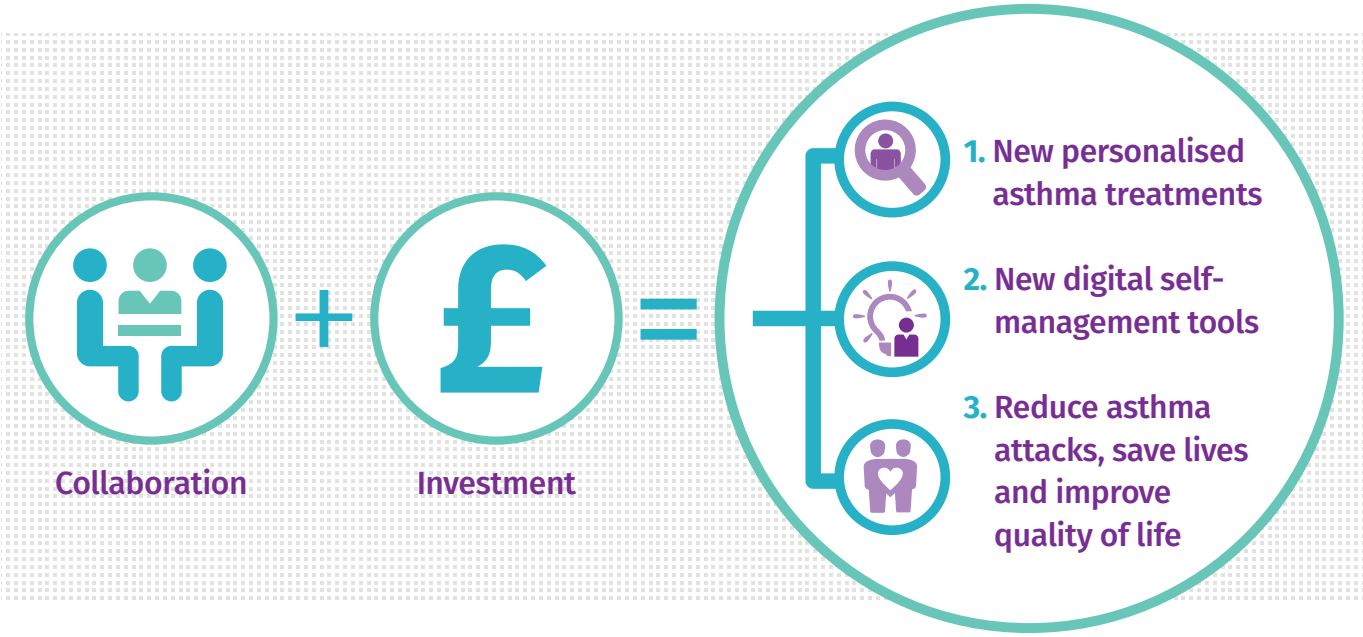
More broadly, further research is needed into the interactions between people's asthma and their environment, and the role of environmental factors in infections and long-term asthma management. For example, environmental factors such as the impact of smoking and pollution on childhood lung development.

In addition, there is a need for more research into how asthma changes over time. For example, very little is known about the relationship between lung infections and viruses, and the severity of asthma later in life. This relationship and the effect of anti-viral or anti-bacterial treatments and even vaccines must be explored as it is a promising avenue for new treatments[35].

Summary

These priorities are aimed at areas with high impact on people with asthma and high potential for commercial breakthroughs, such as diagnostics, mechanisms and e-health, where all stakeholders have a common goal. The high global prevalence of asthma, a multi-billion-pound global market and the demand for new treatments, diagnostics and self-management tools represent an enormous opportunity to drive substantial economic growth.

The focus is also on creating partnerships that include patient organisations, healthcare systems, researchers and the pharmaceutical industry. Partnerships between healthcare professionals and patients will also help create new approaches to self-management of asthma, reducing GP appointments and hospital visits. Wider partnerships involving multiple stakeholders will bring together a range of expertise and perspectives to make full use of a 'team science' approach spanning all fields of research[36].



The UK is ideally placed to take advantage of these opportunities. Despite a global lack of investment, the UK is a world leader in respiratory research and is historically strong in this area[37]. This is largely the result of our existing infrastructure, including leading pharmaceutical companies such as GSK and AstraZeneca, alongside internationally renowned academics. Together with world-class research into digital technologies and bio-informatics, institutions across the UK contribute to this unique infrastructure which has recently seen £80m of investment from GSK in the Salford Lung Study.

The UK has the skills and the expertise to forge the required inter-disciplinary research partnerships and tackle the 15 priorities. With the right investment, truly transformative health technologies and new treatments become a very real possibility. EARIP has demonstrated a clear opportunity to transform health outcomes over the coming decade that is also associated with opportunities for strong international research partnerships and significant economic growth.

This investment must happen soon. Other European countries, notably Germany, are directing more funding towards respiratory research[38]. In addition, the UK's exit from the EU means that there is uncertainty surrounding funding and partnership schemes such as Horizon 2020. At the moment the UK is best placed to take advantage of the opportunities highlighted by the EARIP project. However, there is a risk that this competitive advantage will disappear if investment in asthma research remains at its current level and we do not take the initiative and form new domestic and international research partnerships.

Conclusion

The European Asthma Research and Innovation Partnership articulates international, cross-sector consensus on the research and development needed to improve asthma outcomes including reducing emergency asthma care and asthma deaths. If all 15 of the EARIP priorities were funded, the research questions addressed and the findings disseminated, global asthma outcomes would be transformed and the UK would be at the cutting edge of new approaches to health research such as genomics or personalised medicine. Furthermore, new markets for treatments, diagnostics and digital health tools would be opened up while avoidable use of NHS services would be reduced. In summary, investing in targeted asthma R&D is an opportunity to transform health and productivity outcomes and encourage economic growth.

The asthma challenges

EARIP

Understanding	Diagnosing	Treating	Managing	Preventing
• Identify, understand and better classify the different forms of asthma, their progression, and effect on airway inflammation and the immune system. (EARIP priority 1) • Identify biomarkers for exacerbations and understand the interactions between biomarkers, risk and comorbidities. (EARIP priority 9) • Understand the increase in asthma (both childhood asthma and different types of asthma, such as allergic and hyper-responsive asthma) to help develop primary and secondary prevention strategies. (EARIP priority 10) • Explore the interaction between asthma, socio-economic and psychological factors, and comorbidities to reduce the risk of severe exacerbations. (EARIP priority 13) • Understand the impact of exposure to substances known to trigger asthma, and the impact of strategies that regulate and control this exposure. (EARIP priority 15)	• Develop tools for quick, accurate and low cost diagnosis to distinguish asthma from other causes of breathlessness, cough and wheeze. (EARIP priority 6) • Evaluate the role of lung function testing and new ways of measuring airway inflammation in monitoring asthma. (EARIP priority 8)	• Develop new treatments for the different types of asthma: treatment-resistant and steroid-resistant asthma, severe asthma, allergic asthma, hyper-responsive asthma. (EARIP priority 5) • Assess the efficacy of existing and new drugs on different asthma phenotypes. (EARIP priority 11)	• Assess the effectiveness of patient-professional communication to develop patient-professional partnerships, for example to optimise self-management and adherence. (EARIP priority 2) • Assess impact, adoption and transferability of best practice in regional, national and European asthma programmes, care pathways and asthma clinics. (EARIP priority 4) • Evaluate the implementation of supported self-management, the educational needs of patients and caregivers, and the challenges faced and training needs of professionals. (EARIP priority 7) • Develop tools to assess asthma self-management and asthma inhaler technique in primary care settings. (EARIP priority 12)	• Assess the effect of infections in early childhood, the long-term effects of anti-inflammatory treatments, and use of anti-viral drugs and vaccines. (EARIP priority 3) • Identify biomarkers for exacerbations and understand the interactions between biomarkers, risk and comorbidities. (EARIP priority 9) • Investigate the impact of environmental factors on asthma and exacerbations, such as air quality (indoor and outdoor), climate, allergens and microorganisms and UV radiation. (EARIP priority 14). • Understand the impact of exposure to substances known to trigger asthma, and the impact of strategies that regulate and control this exposure. (EARIP priority 15)

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