FORUM
Academy of Medical Sciences

Exemplar clinical pathways for a stratified approach to severe asthma

Summary report of a meeting held on 20 March 2017 at the Academy of Medical Sciences, supported by NHS England

The Academy of Medical Sciences

The Academy of Medical Sciences

The Academy of Medical Sciences is the independent body in the UK representing the diversity of medical science. Our mission is to promote medical science and its translation into benefits for society. The Academy's elected Fellows are the United Kingdom's leading medical scientists from hospitals, academia, industry and the public service. We work with them to promote excellence, influence policy to improve health and wealth, nurture the next generation of medical researchers, link academia, industry and the NHS, seize international opportunities and encourage dialogue about the medical sciences.

The Academy of Medical Sciences' FORUM

The Academy's FORUM was established in 2003 to recognise the role of industry in medical research, and to catalyse connections across industry, academia and the NHS. Since then, a range of FORUM activities and events have brought together researchers, research funders and research users from across academia, industry, government, and the charity, healthcare and regulatory sectors. The FORUM network helps address our strategic challenge 'To harness our expertise and convening power to tackle the biggest scientific and health challenges and opportunities facing our society' as set in our Strategy 2017–21. We are grateful for the support provided by the members and are keen to encourage more organisations to take part. If you would like further information on the FORUM or becoming a member, please contact forum@acmedsci.ac.uk.

Opinions expressed in this report do not necessarily represent the views of all participants at the event, the Academy of Medical Sciences, or its Fellows.

All web references were accessed in March 2017

Exemplar clinical pathways for a stratified approach to severe asthma

Summary report of a meeting held on 20 March 2017 at the Academy of Medical Sciences and supported by NHS England

Contents

Executive Summary

The Academy of Medical Sciences' FORUM, supported by NHS England, convened a roundtable on 20 March 2017 to discuss 'Exemplar clinical pathways for a stratified approach to severe asthma'.[1] This was held as part of a series of meetings between the Academy and NHS England exploring the adoption of stratified medicine across the NHS using diabetes, cardiovascular disease and severe asthma as exemplars, and will inform NHS England's future approach to embedding personalised medicine in the NHS.[2,3]

The meeting brought together participants from across the healthcare sector with an interest in respiratory disease, to discuss a stratified patient pathway for the management of severe asthma, and the opportunities and barriers to implementing such an approach in the NHS. In particular, participants explored stratification of asthma patients based on medicines adherence to enable more effective targeting of adherence interventions and identification of those severe asthma patients who are genuinely unresponsive to standard asthma drugs. Discussions then focused on the use of different biomarkers to identify and subtype severe asthma patients and direct treatment strategies.

Participants identified a number of key steps that need to be taken to address current challenges and drive adoption of a stratified approach to the management of severe asthma in the NHS. These included:

- **Improved adoption of already available patient adherence technologies and diagnostic tools** to facilitate stratification (based on a scientific approach using biomarkers coupled with decision-making algorithms), which are currently underutilised, despite robust scientific evidence supporting their use.
- **Establishing a robust evidence base for stratified pathways** and continuously strengthening this base, as well as considering different methods of evidence generation. A **widespread, systematic approach to data collection** including disease registries and integration of genetic, physiological, diagnostic and other data sources will enable stratification and evaluation of stratified pathways and interventions to direct commissioning and reimbursement decisions.
- **Patient and clinician engagement** to facilitate behavioural change and understanding of adherence and stratified treatment interventions, and support shared decision-making so that stratified pathways are also considered in the context of individual patient needs.
- Better streamlining and **integration of NHS care pathways and referral routes** for severe asthma across primary, secondary and social care, ensuring that there are adequate entry points for early identification in primary care through the use of biomarkers, and clear routes for specialist referral and treatment escalation.
- Ensuring **scalability of stratified pathways** across the country, depending on both the nature and design of technologies and interventions, but also **capacity and capability in the healthcare system** to ensure a systematic approach and equity of access, such as capabilities for adoption of technologies such as biomarker testing in primary care.
- Recognising the complexities of managing 'unknowns', for example, areas where patient stratification or subtypes are less well-characterised. **Stratification is an iterative process** relying on ongoing evidence generation, new treatment and diagnostic development, and trialling of different approaches in clinical practice.
- **Continued horizon scanning** for new scientific developments and clinical approaches is essential to ensure preparedness of the healthcare system for such stratified approaches.

---

[1] Severe asthma is defined by the European Respiratory Society and American Thoracic Society as 'asthma which requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy'. In essence, it is asthma which is poorly controlled and symptomatic, with a heightened risk of severe exacerbations that could require hospitalisation. Chung KF, *et al.* (2014). International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. European Respiratory Journal **43,** 343-373.

[2] Academy of Medical Sciences (2015). *Exemplar clinical pathways for a stratified approach to diabetes.* https://acmedsci.ac.uk/file-download/41569-57cfd3c90098c.pdf

[3] Academy of Medical Sciences (2016). *Exemplar clinical pathways for a stratified approach to cardiovascular disease.* https://acmedsci.ac.uk/file-download/41570-57cfd5170e1de.pdf

Background

Stratified medicine offers a wealth of opportunities for the healthcare sector, potentially enabling patients to benefit from more targeted treatments while delivering efficiencies across the healthcare system.[4] It represents a move away from a 'one size fits all' approach to one which better manages patient health on a more personalised level using emergent approaches in areas such as diagnostic tests, 'omics' technologies, molecular pathways and data analytics. This presents a powerful opportunity to better target therapies to achieve the best outcomes in the management and prevention of disease.[5,6]

In recent years, the Academy of Medical Sciences has played an active role in supporting the implementation of stratified approaches in the NHS. Most recently, it has held a series of roundtables in partnership with NHS England exploring adoption of a stratified approach in the NHS, using diabetes, cardiovascular disease and at this meeting, severe asthma, as exemplars.[7,8] These roundtables built on the Academy's previous work in this area including its report on 'Realising the potential of stratified medicine' and a 2015 meeting on 'Stratified, personalised or P4 medicine', and moved towards looking at how scientific developments in stratified medicine can be translated and integrated into clinical practice.[9] To date, NHS England's main focus in this area has been on the NHS contribution to the 100,000 Genomes Project and embedding genomic technologies in clinical care pathways. It recognises the need to locate this initiative within a broader strategy for personalised medicine and is therefore in the process of developing its approach to personalised medicine.[10]

Asthma is a chronic inflammatory disease of the airways affecting ~5.4 million people in the UK. Patients with asthma can be further subtyped into those with severe asthma – that is, asthma that is poorly controlled using regular asthma interventions – and this is currently estimated to affect ~250,000 people in the UK.[11,12] Asthma is usually controlled with bronchodilators or inhaled corticosteroids, however, some patients do not respond to these treatments while others do not adhere to their treatment regimens. More recently, alternative treatment options have emerged, such as highly selective biologics – however, these drugs, which have different molecular targets, are costly, so it is important that the right drug is selected to ensure effective, efficient use of interventions. Therefore, there is an opportunity for stratification of patients to identify those who do not respond to traditional interventions and direct treatment selection, and those who are non-adherent and may benefit from adherence intervention, to potentially drive better patient outcomes and efficiencies for the healthcare system.

Further to this, recent studies propose further subtyping of severe asthma patients based on the physiological and biological nature of the disease.[13] While the sub-types have similar physiological symptoms such as constricted airways, difficulty breathing and acute asthma attacks, they have different biological characteristics. These differences have opened up opportunities for further stratification of treatment and new diagnostic and prognostic biomarkers are

---

[4] It should be noted that in this report, the terms 'stratified', 'personalised' and 'precision' medicine are used according to the speakers and delegates and confer the same meaning.
[5] Academy of Medical Sciences (2013). *Realising the potential of stratified medicine.* www.acmedsci.ac.uk/viewFile/51e915f9f09fb.pdf
[6] Association of the British Pharmaceutical Industry (2014). *Stratified medicine in the NHS.* www.abpi.org.uk/our-work/library/medical-disease/Documents/stratified_med_nhs.pdf
[7] Academy of Medical Sciences (2015). *Exemplar clinical pathways for a stratified approach to diabetes.* https://acmedsci.ac.uk/file-download/41569-57cfd3c90098c.pdf
[8] Academy of Medical Sciences (2016). *Exemplar clinical pathways for a stratified approach to cardiovascular disease.* https://acmedsci.ac.uk/file-download/41570-57cfd5170e1de.pdf
[9] Academy of Medical Sciences (2015). *Stratified, personalised or P4 medicine.* www.acmedsci.ac.uk/viewFile/564091e072d41.pdf
[10] NHS England Board paper (2015). *Personalised medicine strategy.* www.england.nhs.uk/wp-content/uploads/2015/09/item5-board-29-09-15.pdf
[11] www.asthma.org.uk/advice/severe-asthma/what-is-severe-asthma/
[12] Severe asthma is defined by the European Respiratory Society and American Thoracic Society as 'asthma which requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy'. Chung KF, *et al.* (2014). *International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma.* European Respiratory Journal **43,** 343-373.
[13] Stratification of a disease on both its physiological and biological nature is termed 'endotyping'.

emerging with the potential to better monitor response to, and guide selection of, treatment. In particular, two widely available biomarkers that may enable this were discussed at the meeting: fractional-exhaled nitric oxide (FeNO) and blood or sputum eosinophil count (EOS). FeNO and EOS could be used to identify incomplete response to standard care anti-inflammatory therapy (and also provide insights into patent adherence) and guide treatment selection for severe asthma sub-types.

Introduction to a stratified approach

Introducing NHS England's Personalised Medicine Strategy

Professor Sue Hill OBE, Chief Scientific Officer, NHS England, introduced NHS England's strategy on personalised medicine, which was published in September 2015.[14] She highlighted the importance of the previous meetings on cardiovascular disease and diabetes, held jointly with the Academy, which have contributed towards NHS England's work programme around embedding personalised medicine in the NHS.

Professor Hill underlined four principles underpinning the sustainable future of the NHS: care and quality; health and wellbeing; finances and efficiency; and step changes in prevention, with science and innovation playing a key role in ensuring sustainability of the NHS. To fulfil these principles, she emphasised that the scientific and healthcare community must work together by:

- Embracing and spreading disruptive technologies as they arise.
- Supporting patients to play an active role in their care.
- Harnessing the power of comprehensive digitisation of health information.
- Driving the focus from managing ill-health to preventative and prognostic strategies.

The shifting healthcare paradigm: moving towards personalisation

A paradigm shift is taking place in healthcare provision, moving from treatment of disease to managing population health with emphasis on prevention, early detection and personalisation of care. Such personalisation will drive medicines optimisation and better management of adverse drug reactions. This has the potential to improve health outcomes, enable identification and uptake of innovative approaches and provide efficiency savings in the healthcare system where, for example, adverse drug reactions account for 1 in 15 hospitalisations, costing the NHS £88m each year.[15]

Professor Hill emphasised that genomics is central to NHS England's Personalised Medicine Strategy, which will build upon the legacy of the 100,000 Genomes Project. The 100,000 Genomes Project has provided the catalyst to build the infrastructure, capacity and capabilities for embedding a genomic medicine service in the NHS to transform healthcare delivery and research. This will enable the NHS to better focus on preventative and predictive care, the importance of which is outlined in the NHS Five Year Forward View with the aim to implement such an approach to healthcare delivery by 2020.[16]

In addition to genomics, other data are available to drive personalisation. These include transcriptomics, metabolomics, proteomics and environmental data, which can be combined with information such as genetics and diagnostic data to better define phenotypes and create opportunities for the development of new interventions. Professor Hill noted that with 30-50% of prescriptions proving ineffective at treating disease, combining functional genomics and diagnostic data

[14] www.england.nhs.uk/wp-content/uploads/2015/09/item5-board-29-09-15.pdf
[15] Pirmohamed M, *et al.* (2004). *Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients.* BMJ **329**, 15
[16] NHS England (2014). *Five Year Forward View.* www.england.nhs.uk/wp-content/uploads/2014/10/5yfv-web.pdf

to create this *'panorome'* could help clinicians to select the most effective treatment. The unique patient data afforded by these new technologies can create a personalised care plan that maximises the opportunity for better health outcomes by bringing together the multiple layers of a patient's genetic, biological, clinical and environmental data.

A strategy for personalised medicine

In 'Improving Outcomes through Personalised Medicine', NHS England sets out a ten-year framework for the delivery of personalised or 'P4' medicine across the NHS – that is, predictive, preventative, personalised and participatory.[17]

Professor Hill observed that genomic strategies are already being successfully applied across many rare diseases and cancers to guide the most effective treatment. However, many opportunities still exist for routine use of genetic testing in other more common diseases. She explained that functional genomics incorporating whole genome sequencing complemented by simpler and cheaper genetic tests will be routinely exercised in the NHS by 2020, enabling the UK to continue to position itself as a world leader in genomics and stratified medicine. The commissioning system will need to prepare for these changes and the infrastructure required, including essential informatics capabilities, and regulators and commissioners need to work together to support rapid development and adoption of new techniques. A cross-sector approach involving the NHS, academia, industry and patients will help to drive these new innovations in line with the goals of the Government's Industrial Strategy.

Stratification of severe asthma

Asthma affects over 5 million people in the UK, causing significant morbidity and mortality and resulting in over 90,000 hospital admissions and 1,200 deaths annually.[18,19,20] Professor Hill emphasised that the healthcare costs of managing asthma in the UK is £1.1bn per year, and significantly, three of the ten most costly drugs prescribed in the NHS are asthma treatments.[16] She highlighted the opportunities for stratification to enable more effective use of these interventions and optimise patient treatment whilst minimising costs.[21]

Professor Liam Heaney, Professor of Respiratory Medicine, Queen's University Belfast, Professor Ian Pavord FMedSci, Professor of Respiratory Medicine, University of Oxford and Professor Salman Siddiqui, Professor of Airway Disease and Respiratory Medicine, University of Leicester, provided an overview of stratification in severe asthma with a focus on patient adherence and use of diagnostic biomarkers.

Patient adherence in asthma

Professor Heaney opened by explaining that patient adherence is particularly poor with inhaled corticosteroids (ICS), which are standard drugs used to treat asthma. This is a major challenge for the healthcare system with 35-40% of patients with difficult to control asthma collecting less than half of their ICS prescriptions.[22] He highlighted that outcomes for a large proportion of asthma patients would significantly improve with better adherence to therapy, resulting in fewer exacerbations, hospitalisations and deaths. In addition, a lack of adherence confounds diagnosis of treatment-resistant asthma and so can result in unnecessary treatment escalation and inappropriate use of costly interventions. These implications of poor adherence go beyond the patient's experience as the increase in avoidable exacerbations that poor adherence can cause pose notable economic and time burdens on the healthcare system.

---

[17] NHS England (2016). *Improving Outcomes Through Personalised Medicine.* www.england.nhs.uk/wp-content/uploads/2016/09/improving-outcomes-personalised-medicine.pdf
[18] Mukherjee M, *et al.* (2016). *The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases.* BMC Medicine **14**, 113.
[19] Asthma UK (2016). *Annual Asthma Survey Report 2016.* www.asthma.org.uk/globalassets/get-involved/external-affairs-campaigns/publications/annual-asthma-care-survey/annualasthmasurvey2016final.pdf
[20] Office for National Statistics (2016). *Death registrations in England and Wales, summary tables: 2015.*
[21] NHS Digital (2016). *Prescribing Costs in Hospitals and the Community England 2015/2016.* www.content.digital.nhs.uk/catalogue/PUB22302/hosp-pres-eng-201516-report.pdf
[22] Gamble J, *et al.* (2009). *The prevalence of non-adherence in Difficult Asthma.* Am J Resp Crit Care Med. **180(9)**, 817-822.

Measuring and improving adherence

Professor Heaney explored a range of ways to assess adherence and the different challenges of each, including:

- Subjective measurements: Patient self-reporting or clinician assessment, although these have been shown to overestimate adherence.[23]
- Objective measurements: Electronic monitoring of frequency and timing of inhaled medication through smart inhaler technologies, or measuring plasma drug levels e.g. prednisolone, theophylline.
- Surrogate measurements: Prescription or dispensing records, dose counting, and inhaler weighing. However, accessing primary care prescription records is often difficult in some parts of the UK and these are only surrogate rather than direct adherence measures.

He noted that poor adherence is largely unintentional for many asthma patients and caused by factors such as poor inhaler technique or forgetfulness. Therefore it has been proposed that reminders or alarms linked to various devices, and smart inhaler monitoring technologies, could be an effective way to increase adherence, monitoring and decision-making. For example, the recent STAAR randomised trial found a 20% improvement in adherence in UK children who had electronic adherence monitoring with daily reminder alarms together with feedback in the clinic.[24] It also found that although there was no difference in Asthma Control Questionnaire (ACQ), which is a measure of symptom control, children in the intervention group required fewer courses of oral steroids and had fewer hospital admissions. These results suggest that increased adherence reduces acute asthmatic events requiring oral corticosteroid rescue therapy and hospital admission. Professor Siddiqui later emphasised the importance of patient engagement with technology and its holistic integration into the care process.

Professor Heaney emphasised that FeNO is an excellent biomarker for defining response to ICS in most patients with asthma, and when combined with smart inhaler monitoring provides an opportunity to measure response and adherence in these vulnerable patients. Measuring the short-term response of FeNO with directly observed ICS therapy over a week has been shown to distinguish adherent from non-adherent subjects with difficult to control asthma (FeNO suppression test - outlined below).[25] Those patients who have persistently high FeNO and other inflammatory biomarkers despite adherence to monitored treatment can be identified for escalation to biologic therapy.

Biomarkers for stratification of severe asthma

Professor Pavord explained that historically, it was assumed that the same broad strategy used for application of bronchodilator treatments would also work for anti-inflammatories in asthma. However, he argued that these treatments need to better targeted to ensure effective management of patients with severe asthma. Traditional symptom descriptions and lung function tests do not convey important information on airway pathology and inflammation – which are key to selecting the most effective intervention – and there are already simple measurements of inflammation available in primary and secondary care. It was later noted by Professor Siddiqui that a third of patients in primary care lack objective physiological evidence of asthma, and so inflammatory biomarkers may help to identify these patients, and, following a confirmed diagnosis of asthma, biomarkers could be used to identify patients that have so-called Type 2 (T2) high and T2-low asthma sub-types. T2-high patients may have severe asthma that is driven by a variety of immune and structural cells (e.g. TH2 cells) and as a consequence demonstrate elevated levels of inflammatory cytokines such as IL-4, IL-5 and IL-13, which may promote increased eosinophil (EOS) count. In contrast the T2-low patients have none of these features and do not appear to respond to corticosteroids – although a major confounder is the definition of T2-low asthma in patients that are already taking corticosteroids (this may necessitate corticosteroid withdrawal to prove that T2 asthma does not emerge during/after treatment withdrawal).

---

[23] Bae YJ, *et al.* (2009). *Severe asthma patients in Korea overestimate their adherence to inhaled corticosteroids.* J Asthma. **46**, 591-5.
[24] Morton RW, *et al.* (2017). *STAAR: a randomised controlled trial of electronic adherence monitoring with reminder alarms and feedback to improve clinical outcomes for children with asthma.* Thorax **72**,347-354.
[25] McNicholl DM, *et al.* (2012). *The Utility of Fractional Exhaled Nitric Oxide Suppression in the Identification of Nonadherence in Difficult Asthma.* Am J Respir Crit Care Med. **186.**

Eosinophil (EOS) count as a biomarker

Sputum measurements of EOS provide a non-invasive method to measure airway inflammation, and so have been proposed as a biomarker to stratify patients with severe asthma.[26] EOS count can also be measured via blood samples. Some evidence suggests that the EOS count also correlates to ICS response and could be predictive of response.[27,28] Therefore, reduction of EOS count could be a measurable target outcome for severe asthma patients. It was noted that clinical benefits of a reduction in EOS count are normally a decrease in severity and frequency of exacerbations without necessarily leading to improved symptoms. Professor Pavord argued that reducing exacerbations is of significant benefit to both the patient and healthcare system. The paradigm for exacerbation prediction in asthma has changed to consider two key areas which should be assessed in clinical practice: abnormality of airway function and EOS inflammation.

High EOS counts are not unique to asthma and have also been observed in airway diseases such as COPD and in other conditions such as allergy and parasite infection. As such, Professor Pavord warned of the reliance on traditional disease diagnoses in the face of new evidence for stratification based on biological traits. As these models for stratification do not adhere to the conventional disease classifications, it may be of benefit to establish new terminology that more accurately describes the disease state. For example, he proposed that *'eosinophilic airway inflammation'* may be more appropriate for guiding treatment, rather than a label of 'severe asthma'.

Fractional-exhaled nitric oxide (FeNO) as a biomarker

Fractional-exhaled nitric oxide (FeNO) is also a measure of active inflammation in the airways and has been shown to be predictive of responsiveness to ICS and for identification of T2 asthma.[29] FeNO measurements are useful along with clinical assessment to identify T2-high and T2-low patients and to assess ICS response and patient adherence to ICS treatment when aligned with smart inhaler technology.[30,31] FeNO response to monitored ICS treatment in patients with difficult to treat asthma is a helpful for clinical phenotyping as it can usefully identify those patients who are likely to respond well to high dose ICS/LABA (long-acting beta-adrenoceptor agonist) therapy (standard care) and those who, despite good adherence with inhaled treatment, are likely to require additional treatment. A FeNO measurement of >45-50 ppb has been proposed as the predictive threshold for a response to ICS (in ICS naïve patients), and in patients with severe asthma is predictive of high risk of severe exacerbations.[32] Thus a FeNO of 45 ppb could be used as an initial cut-off for 'biomarker high' patients with severe asthma. In this patient group, the key clinical question is whether high FeNO is due to poor adherence with ICS or persistent inflammation which is unresponsive to high dose ICS. The Refractory Asthma Stratification Program (RASP-UK) funded by the Medical Research Council is a collaborative effort across a number of NHS, academic and industry partners, looking into the use of FeNO measurements and FeNO suppression testing using remote monitoring technology as a means of stratification.[33]

The evidence base for stratification

Professor Siddiqui suggested that the priorities for new referrals should be to confirm diagnosis through tests, measure and optimise adherence and identify relevant co-morbidities. If a patient is confirmed to have severe asthma and there are no issues with adherence, biomarkers could then be used to guide treatment such as ICS, biologics or bronchial

---

[26] Eosinophils are a type of white blood cell that is found in the blood and sputum and elevated levels of eosinophils is indicative of inflammation.
[27] Green RH, *et al.* (2002). *Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial.* Lancet **360**, 1715-1721.
[28] Bafadhel M, *et al.* (2012). *Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial.* Am J Respir Crit Care Med. **186**, 48-55.
[29] Martin MJ, *et al.* (2016). *The utility of exhaled nitric oxide in patients with suspected asthma.* Thorax **71,** 562-564.
[30] The FeNO suppression test involves measuring FeNO prior to and directly after a course of ICS that is supervised by the clinician. If FeNO levels fall, or are 'suppressed' by the ICS, positive response to ICS is confirmed.
[31] Smith AD, *et al.* (2005). *Exhaled nitric oxide: predictor of steroid response.* Am J Resp Crit Care Med. **172(4),** 453-459.
[32] Dweik RA, *et al.* (2011). *An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications.* Am J Respir Crit Care Med. **184(5)**, 602-615.
[33] www.rasp.org.uk

thermoplasty, and to help identify patients for participation in clinical trials to further increase the evidence base.[34] Alongside this, patient adherence is key to maximising the strength of the diagnostic and prognostic evidence and, for some, this will require patient engagement with technologies and self-reporting.

Professor Siddiqui emphasised the importance of a robust evidence base for selecting biomarkers to direct treatment, and cautioned against fixing a *'biomarker-high'* threshold before it has been sufficiently tested. He also stressed that widespread implementation of new tests such as FeNO and EOS count into the NHS is a major challenge, particularly in primary care. However, the use of NHS specialised severe asthma centres as 'test beds' to further validate available T2 biomarkers provides an exciting opportunity to develop an empirical evidence base for these biomarkers for the purpose of stratification. He also noted that whilst there are known biomarkers that can already be used to stratify severe asthma patients, there is not yet sufficient evidence available for using genetics for stratification. Therefore there is an opportunity for further collection of genetic data and continued research into the role of genetics in severe asthma and its capacity to aid stratification. Ultimately, any biomarkers that are integrated into asthma care pathways need to be fit-for-purpose for use in both primary and secondary care.

Translation into the clinic

Professor Pavord emphasised the importance of focusing on *'treatable traits'* – that is, characteristics relevant to disease expression. Combinations of biomarkers such as FeNO and EOS count could allow greater stratification of patients and better understanding of the underlying pathology. Professor Pavord highlighted that he believed these biomarkers for airway inflammation to be ready for implementation in the clinic and could provide a better approach to managing severe asthma on a more personalised level than current clinical practice.

Biomarkers could also be used for selection of specific treatments for severe asthma patients. For example, amongst other inflammatory markers, high EOS count can be driven by IL-5, which has already been used effectively as a treatment response biomarker (to select anti-IL-5 biologics), or FeNO which is linked to IL-13 driven inflammation could be used as a measurement to potentially select anti-IL-13 biologics. Blood EOS count is already used in this way in some areas of clinical practice. Professor Pavord gave the example of mepolizumab, an anti-IL-5 biologic which was ineffective in non-stratified asthma patient groups but significantly effective in reducing severe exacerbations for patients with high EOS count, as now proposed in NICE guidance.[35]

However, Professor Heaney highlighted that when considering the patient pathway for 'biomarker-low' patients (i.e. patients whose current symptoms did not appear to be driven by persistent T2 inflammation), careful thought should be given to the precise mechanism of persistent symptoms including non-asthma causes and extra pulmonary factors such as obesity and physical deconditioning. Current national and international efforts to explore the mechanisms in biomarker-low patients and develop this evidence base are ongoing, however, there are challenges when using poorly characterised patient populations (also with a mix of adherent and non-adherent individuals). Professor Heaney also emphasised that while there is a significant opportunity to improve patient outcomes through better adherence, robust evidence for adherence interventions delivering patient-important clinical outcomes is currently lacking. This is primarily because of poor quality studies, and so improved trial design with feasible long-term interventions aligned with objective adherence measures is required. In addition, behavioural interventions targeting adherence may not be suitable for every patient and 'clinical stratification' is also required to identify the patient population most likely to respond. If new smart inhaler technologies become more widely available, equally important is the availability of decision aids and clear guidance for clinicians to make complex treatment decisions around using these technologies in partnership with patients.

---

[34] Bronchial thermoplasty is a procedure where the conducting airway walls are heated leading to reduced smooth muscle that is normally responsible for airway constriction during an asthma attack and other epithelial changes.
[35] Ortega HG, *et al.* (2014). *Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma.* N Engl J Med. **371,** 1198-1207.

Challenges to stratification

Professor Siddiqui outlined some of the key challenges to stratification of severe asthma including lack of standardised, integrated 'whole body' care pathways in asthma services. Identification and management of co-morbidities are often not fully integrated into treatment plans so that they are not necessarily effectively treated alongside persistent asthma symptoms. He also stressed that whilst there are opportunities for stratification, not all aspects of the care pathway are suitable for stratification. For example, there is currently little evidence for stratifying the use of bronchial thermoplasty and so incorporating this into a stratified patient pathway may be challenging until the evidence base is further developed.

In addition, although there are now reasonable biomarkers to identify T2 asthma (i.e. inflammatory markers such as high FeNO and EOS count), there are no clear clinical definitions for non-T2 asthma and this poses difficulties in validating potential diagnostic and theranostic biomarkers in this space.

Professor Siddiqui also outlined the confused referral system for asthma patients including lack of referral to specialist clinics for those with poorly controlled asthma symptoms and exacerbations, and difficulties discharging back to primary care for those whose asthma is controlled following referral. The disconnect between primary and secondary care is further exemplified by the difficulties that secondary care clinicians have when attempting to access prescription records, a valuable source of data. Other primary care data which may not be shared with the specialist clinic can be equally useful in helping to understand the disease and management. These issues could be resolved through better communication routes between GPs and specialist clinics. Additionally, these cross-sector clinical informatics integration issues could be addressed by existing national organisations such as NHS Digital.

Professor Siddiqui described his vision for the future where an integrated biomarker platform incorporating a range of 'omics data can sit alongside well defined molecular pathology networks and Genomics England Clinical Interpretation Partnerships (GeCIPs) to help develop a robust framework for asthma stratification and evaluation of new biomarker technologies.

Adopting a stratified approach in the NHS

Translation and implementation of scientific knowledge into the clinic, such as advances in biomarkers, genetics, diagnostic tests and personalised interventions, is a key challenge to stratification of patient pathways. Therefore participants discussed the need for continued evidence generation around stratification and ways to ensure a robust evidence base to support the integration of such advances, including economic evidence. In addition, participants explored the 'readiness' of both the science and healthcare system for clinical adoption of a stratified approach to severe asthma such as scalability, capacity, capability and engagement that need to accompany implementation. Finally, the importance of integrated care pathways and streamlined, effective referral systems was discussed.

The evidence base for stratification

Stratifying based on patient adherence

Delegates agreed that patient adherence presents a particular challenge with inhalers as many factors can reduce adherence including poor recall of instruction, low comprehension, forgetfulness or poor inhaler technique. There is an opportunity to improve adherence in non-adherent asthma patients to improve outcomes, and FeNO suppression tests could be used in the clinic to identify non-adherent patients using a 'positive suppression outcome' (ie. they become biomarker-low when adherence to treatment is improved). This can also be used to stratify severe asthma or 'non-responding' patients from those who may benefit from adherence interventions.

Potential methods for improving adherence include adherence technologies (such as device assistance, monitoring and reminders) and also strategies such as combined inhalers (Maintenance and Reliever Therapy, MART) that deliver both a regular maintenance treatment and immediate relief with additional doses of a rapid onset long-acting bronchodilator and ICS together, and potentially improve the amount of ICS delivered over time (although not improving patient adherence directly). However, although there is some evidence available to support MART, one delegate noted that a review of the evidence of MART suggested it did not improve outcomes.[36] It was agreed that there needs to be clear evidence on the benefits of each adherence technology or device and these interventions should be simple and not further complicate existing treatment regimens. An adherence rate of 80% is widely considered as a meaningful threshold for achieving positive health outcomes, and new technologies may allow more accurate measurement of adherence and allow clinicians to take action to improve adherence.

Stratifying severe asthma using biomarkers

Many participants argued that there is a sufficiently robust evidence base for implementing the use of FeNO and EOS count for stratification of severe asthma in routine care. It was felt that although development of further biomarkers is welcome, known inflammatory biomarkers and diagnostics can already enable widespread stratification of patients with uncontrolled asthma. FeNO and EOS count could also be used to predict response to ICS and therefore help guide treatment selection. This would build upon the ACQ and physical measurements such as FEV1/FVC which are a good indicator of symptom control and effectiveness of ongoing treatment but do not correlate well with the presence of airway inflammation.[37,38]

---

[36] Chapman KR, *et al.* (2010). *Single maintenance and reliever therapy (SMART) of asthma: a critical appraisal.* Thorax **65**, 747-752.
[37] Ratio of forced expiratory volume in one second (FEV1) to forced vital capacity (FVC): the determination of the vital capacity from a maximally forced expiratory effort.
[38] Marsden PA, *et al.* (2016). *Objective Cough Frequency, Airway Inflammation, and Disease Control in Asthma.* Chest **149**, 1460-1466.

Participants suggested that there is potential for effective use of triple therapy of LABA, long-acting muscarinic receptor antagonists (LAMA) and ICS to effectively control severe asthma symptoms. Triple therapies could potentially tackle the traditional 'switching' and escalation of interventions, as there is evidence to suggest that triple therapy is more effective than traditional interventions for patients with COPD who have a high level of inflammatory biomarkers such as FeNO and eosinophils.[39]

Improving the evidence base

Despite the current evidence available – such as that on the utility of FeNO and EOS count – there remains a need for further evidence on other aspects of stratification in severe asthma. For example, more evidence is needed on the best approach for patients who are consistently non-adherent with ICS and whether they should be escalated to a biologic therapy. Biologics may improve adherence as they are taken less frequently and administered by injection in hospital, however, they are costly and so it is challenging to justify use in patients where bronchodilators or ICS may be as effective. In addition, there remains an evidence gap around the targeting of specific biologic treatments based on biomarkers, and more research is needed on new biomarkers for non-T2 patients who may be non-responsive to other treatments, as most new treatments are currently targeted at inflammatory pathways that may only benefit T2 patients.

There are also challenges around evidence generation. For example, using surrogate markers reduces costs and timelines of randomised controlled trials (RCTs) and is key to driving development of new treatments and their pricing, alongside enabling innovation. There was concern that the quality of RCTs is vital to commissioning, but that high costs involved can lead to the use of non-specific patient populations that may compromise the robustness of trial results. The challenge of conducting RCTs in small, stratified patient groups was highlighted, and it was recognised that pharmaceutical companies need support from commissioners to ensure that these studies are carried out using methods that will produce results that are meaningful for commissioning decisions. Furthermore, the real world applicability of RCTs is complicated by higher adherence observed during trials due to increased monitoring, compared to real world medicine use. This is often not measured or mitigated both due to the complexities of doing so and lack of awareness of the impact on outcomes.

Data collection for stratification

The importance of capitalising on opportunities for data collection was emphasised. For example, participants highlighted the role of the 100,000 Genomes Project and it was noted that Asthma UK has applied for asthma to be included in the 100,000 Genomes Project to underpin genetic understanding. There may be further opportunities for collecting genetic information on large patient populations and it was agreed that there is not yet sufficient evidence around genetics to stratify patients at this level.

The need for large scale, accessible data sources in routine care was emphasised, such as the value of registries in collecting data for better stratification. In addition, registries enable identification of possible participants for clinical trials and it was noted that enrolment in asthma trials can be as low as 10% compared to 40% in some oncology trials. The UK severe asthma registry, coordinated by Queens University Belfast, was cited as a highly useful tool to aid data collection on severe asthma patients.[40] It includes DNA samples correlated with other data such as phenotypic and transcriptomic data, and is now being expanded across the UK to create a national registry. Efforts are underway to link the registry to international data sets. Participants noted that mandatory collection of blood samples from all patients entering asthma clinics would enable mapping of genetic and biomarker links to create new opportunities for innovation in asthma management. In addition, the importance of routinely collecting baseline data was described. This is already being done in some areas and enables stratification through opportunities for monitoring treatment outcomes and identifying patients who fall outside normal ranges for treatment selection. It was proposed that this could potentially include psycho-social data to allow further tailoring of disease management based on patient needs.

---

[39] Montuschi P, *et al.* (2016). *Triple inhaled therapy for chronic obstructive pulmonary disease.* Drug Discov Today **21**, 1820-1827.
[40] https://cl2.n3-dendrite.com/csp/asthmadev/frontpages/index.html

Finally, delegates reiterated the importance of trial data and the role of the NHS in enabling and commissioning multi-centre, large cohort trials on a national scale to accelerate development of new technologies.

Patient engagement

Engagement to drive behavioural change

Greater patient engagement has many potential benefits for stratification including engagement on adherence, self-management and involvement in decision-making. As such, delegates stressed that clinical pathways should consider patient engagement as a cornerstone of stratification, as, for example, it has been shown to improve adherence through empowering and educating patients.

Poor adherence may be non-intentional, for example through forgetfulness, poor understanding of why a treatment has been prescribed or poor inhaler technique, or intentional where patients actively choose not to take medication possibly due to lack of perceived benefit or 'need' or concerns about side-effects. For both patient groups there is an opportunity to drive behavioural change through better patient engagement but the intervention in these groups and in individual patients may need to be different. Improved communication between patient and clinician could improve patient understanding of the cause of asthma symptoms, disease biology and the importance of adherence (with little additional burden on the healthcare system). Therefore delegates agreed that support is needed for clinicians to feel confident in discussing adherence. In addition, it was agreed that adequate provision of information and educational tools are essential to improving adherence. An 80% threshold of adherence is typically used as a reasonable target to deliver a therapeutic dosing of medication.[41]

Participants discussed several ways to incentivise patients to better adhere to treatment regimens. For example, apps or smart inhalers seek to normalise treatments so that they become a routine part of daily life, and ways to simplify treatment regimens can also be effective.[42] In addition, participants noted that reimbursement for treatment in countries such as the USA is dependent on evidence of adherence, which promotes better engagement.

Overall, participants agreed that improving adherence requires a personalised approach. For some patients a technological intervention, such as a smart inhaler or alarm, may improve adherence. However, adherence may be more complex for other patients and so a better evidence base is needed on which adherence strategies work best for different patients. A stratified approach to adherence should also consider societal and personal factors and could incorporate shared decision-making to ensure treatment meets the patient's expectations.

Engagement in decision-making

Delegates felt that patient involvement in decision-making could have many benefits including patient empowerment and improved adherence. One way of engaging patients is in self-monitoring and reporting, for example through apps and wearables, and this also increases the volume and quality of data available for clinical decision-making. Empowering patients in this way may encourage them to increasingly discuss their treatment with their clinician, promoting shared decision-making and health management.

However, employing technologies for self-monitoring and reporting symptoms, and tracking progress or environmental data, is limited by ability to use such technology and devices. For example, there may be a 'generation gap' between

---

[41] Haynes RB. (1976) *A critical review of the "determinants" of patient compliance with therapeutic regimens.* In: Sackett DL, Haynes RB, eds. Compliance with therapeutic regimens. Johns Hopkins University Press, Baltimore.
[42] Asthma UK (2017). *Smart asthma: Real-world implementation of connected devices in the UK to reduce asthma attacks.* www.asthma.org.uk/globalassets/get-involved/external-affairs-campaigns/publications/smart-asthma/auk_smartasthma_feb2017.pdf

those who are comfortable using these technologies and sharing data, and those who are not. It is important that any innovation accounts for this and does not leave behind those who cannot or do not want to embrace these technologies.

Referral and integration of care pathways

Referral pathways

Management of severe asthma should involve the entirety of the healthcare system with coordination of services across primary, secondary care and social care, and involving a multidisciplinary healthcare team working with the patient. However, it was highlighted that a large latent pool of asthma patients with poorly controlled symptoms are not referred to specialist services. Although prescription records and acute exacerbations are recorded, this may be due to the absence of a system for automatic flagging or referral of patients based on this information. These patients can place a high burden on the healthcare system as uncontrolled asthma can lead to severe exacerbations that require hospitalisation. Therefore, this unmet need should be prioritised and could be better managed by linking up primary, secondary and social care to ensure that patients are appropriately escalated through the referral system.

In addition to effective referral processes, there is a need to ensure adequate entry routes into the system for patients who have little contact with primary care despite suffering asthma, and who only enter the system upon severe exacerbations. A clear feed in and referral pathway, and GP decision-support tools using informatics, could help to ensure identification of patients and routing into the correct patient pathway. It was cautioned that with these more effective feed-in and referral pathways, the patient population with both asthma and severe asthma may grow. Participants also emphasised the need to establish clearer guidance around pathways for de-escalating treatment, either by switching medication or being referred back to primary care from a specialist service.

New models of care

Participants also discussed the need for new terminology around severe asthma and separating the label of asthma from the disease pathology. If diagnosis and treatment is based around new biomarkers that are not specific, such as inflammatory markers that are found in several diseases, then a diagnosis of 'eosinophilic airway inflammation' may be more accurate. This also potentially provides greater understanding and reassurance for a patient who, if receiving a general asthma diagnosis, may wonder why they do not have the same management pathway as other asthma patients.

Economics of stratification

Delegates stressed that the stratification of severe asthma may require new funding and payment models that can incorporate outcomes-based reimbursement. In addition, the costs of poor adherence, and the burden placed on the healthcare system through uncontrolled asthma and exacerbations, are well characterised, but the health and economic benefits from adherence technologies and targeted treatments need to be quantifiable and significant to allow commissioners to make value-based decisions around the use of such tools. For example, it was agreed that there is not yet sufficient clarity around selection of the most appropriate biologic when other treatment options have failed. Although there are biologics developed that target different inflammatory markers, biologics continue to be developed that target the same inflammatory markers as pre-existing drugs. Therefore, not only is an economic/health rationale needed for using a diagnostic to guide biologic selection based on inflammatory markers, but an understanding of the cost-benefit ratios of different biologics and new treatments against standard of care is also essential.

Given the high cost of biologics, the clinical cut-off for their use was described as being primarily financially driven, rather than on evidence of improved health outcomes and effectiveness. The major benefit of successful biological treatment is a reduction in exacerbations, rather than symptoms. However, the responses to biological treatments are heterogeneous and unpredictable with dependence on a variety of adherence, genetic, physiological and environmental

factors. It is also difficult to estimate the impact on the frequency of exacerbations at the patient level unless there is a very dramatic reduction, as it is challenging to predict, for example, if there would be two or three episodes a year. Therefore decisions around risk reduction need to be made using clinical trial data and participants felt there was a strong research need to better define exacerbations and their economic or wider implications for the healthcare system, which is also particularly important for discussions around public health. In particular it was noted that exacerbation trials are expensive due to long study timelines and large patient populations required.

Therefore delegates agreed the importance of longitudinal monitoring of patients to build an economic argument and allow continual refinement of commissioning and treatment decisions.

Scalability, capability and capacity

Widespread adoption of a stratified approach to severe asthma in the NHS requires overcoming challenges of scalability, capability and capacity that are often seen with system-wide changes. In addition, stratified medicine, as it is intrinsically 'personalised', cannot be easily generalised in the same way as other new treatment guidelines and pathways. This is especially true for severe asthma where there is a focus on adherence and behavioural changes, and patient involvement in decision-making, which may not be easily standardised in the same way as the diagnostic tests and treatment selection.

The implementation of new pathways and technologies raises questions of standardisation and cross-compatibility to facilitate scalability. For example, if manufacturers are responsible for implementing new adherence tools then there is a risk that each individual drug, device or regimen could have a different technology, mirroring the confusion seen with the development of many different inhaler devices. This not only complicates treatment but could result in difficulties comparing data obtained with various devices and issues for patients trying to switch between technologies and devices. In addition, common discussions about consent and access to health data were raised and it was agreed that the use of data beyond direct care must be carefully considered. A set of uniform strategies for these technology and data barriers may be beneficial to support scalability and implementation.

Similarly, the evaluation and adoption of new care pathways could be piloted or trialled on a regional level, but ultimately adoption must be uniform nationally to ensure equity of care across the health system. The necessary system changes, as well as ensuring capacity and capability, need to be supported to ensure not only regional equity but also equity of access across patient demographics. The system wide changes should include implementation within both GP surgeries and specialist care and better integration between these to allow the translation of stratified measures, including adherence technologies, throughout the patient care pathway.

Building capacity in clinical care

It was recognised that the role of GPs, asthma nurses and secondary care clinicians in aiding patient adherence, supporting shared decision-making, and understanding the patient role in innovation must be accompanied by training for clinicians to understand the issues and opportunities. Although there have been trials on a small scale, roll-out on a national scale will require further support.[43] Therefore it may be helpful to build a national, systematic strategy to support clinicians in these more 'behavioural' and 'personal' aspects of a stratified approach.

When considering implementation of the stratified pathways, it was noted that the FeNO biomarker is already used by some clinicians across the UK. Although its current use in primary care is relatively low, likely because of the cost of the FeNO measuring instrument, delegates noted that this biomarker is not technically difficult to use, and there have not

[43] The King's Fund (2011). *Making shared decision-making a reality*. www.kingsfund.org.uk/sites/files/kf/Making-shared-decision-making-a-reality-paper-Angela-Coulter-Alf-Collins-July-2011_0.pdf

been any significant challenges encountered with its use to date. Therefore it was felt that clinicians were already well equipped to use the biomarkers, and with relatively little support needed this could be easily implemented in the healthcare system. As described earlier, support will be required for clinicians to understand the various patient pathways and the ways in which these are presented to, and discussed with, patients.

Commissioning models for severe asthma

Participants noted the disconnect between the centralised commissioning process for asthma and specialised commissioning for biologics, particularly as the patient group with uncontrolled asthma is too large to fall within specialised commissioning and so would fall within local commissioning budgets. It is important that the system is able to recognise and address these factors to facilitate the necessary flow of funding into management of severe asthma patients. Registries which can collect essential data on patients who receive a biologic and interact with relevant parts of the service, could give a better understanding of the patient community that this involves and where this service should be placed within the NHS commissioning system.

Annex I: Agenda

12.30-13.00	**Lunch**
13.00-13.10	**Welcome** Professor Stephen Holgate CBE FMedSci (Chair), MRC Clinical Professor of Immunopharmacology, University of Southampton
13.10-13.30	**NHS England's approach to personalised medicine and commissioning in respiratory disease** Professor Sue Hill OBE, Chief Scientific Officer, NHS England
13.30-13.50	**Using patient adherence for stratification** Professor Liam Heaney, Professor of Respiratory Medicine, Queen's University Belfast
13.50-14.30	**Discussion 1: How can we better stratify patients with severe asthma based on patient adherence to treatment?** *The discussion will focus on initial stratification of patients with severe asthma based on adherence. Participants can refer to the pre-circulated straw man.*
14.30-14.50	**Stratification of severe asthma using diagnostic biomarkers and genetics** Professor Ian Pavord FMedSci, Professor of Respiratory Medicine, University of Oxford
14.50-15.10	**Translation into the clinic: linking biomarkers to treatment** Professor Salman Siddiqui, Professor of Airway Disease and Respiratory Medicine, University of Leicester
15.10-15.30	**Tea and coffee**
15.30-16.55	**Discussion 2: How can we better translate emergent technologies and diagnostics to optimise therapy in patients with severe asthma?** *This discussion will explore the evidence base behind stratification of patients with severe asthma, any barriers to stratification and potential ways forward. Participants may wish to refer to the pre-circulated straw man.* It is expected that the discussion will cover: • The evidence base for stepwise stratification of patients along the entire pathway, including adherence and genetic and biological markers, and where these can direct treatment. • Commissioning infrastructure and the role of different parts of the healthcare system in the patient pathway (e.g. primary/secondary care, Genomic Medicine Centres). • Economics of stratification. • Capacity and capability, and integration of expertise. • Ways to align sectors with an interest in this area across academia, NHS, industry and policy-makers, amongst others.
16.55-17.00	**Key conclusions and next steps** Professor Stephen Holgate CBE FMedSci (Chair), MRC Clinical Professor of Immunopharmacology, University of Southampton
17.00	**Close**

Annex II: Participants list

Chair

Professor Stephen Holgate CBE FMedSci, MRC Clinical Professor of Immunopharmacology, University of Southampton

Speakers

Professor Liam Heaney, Professor of Respiratory Medicine, Queen's University Belfast
Professor Sue Hill OBE, Chief Scientific Officer, NHS England
Professor Ian Pavord FMedSci, Professor of Respiratory Medicine, University of Oxford
Professor Salman Siddiqui, Professor of Airway Disease and Respiratory Medicine, University of Leicester

Participants

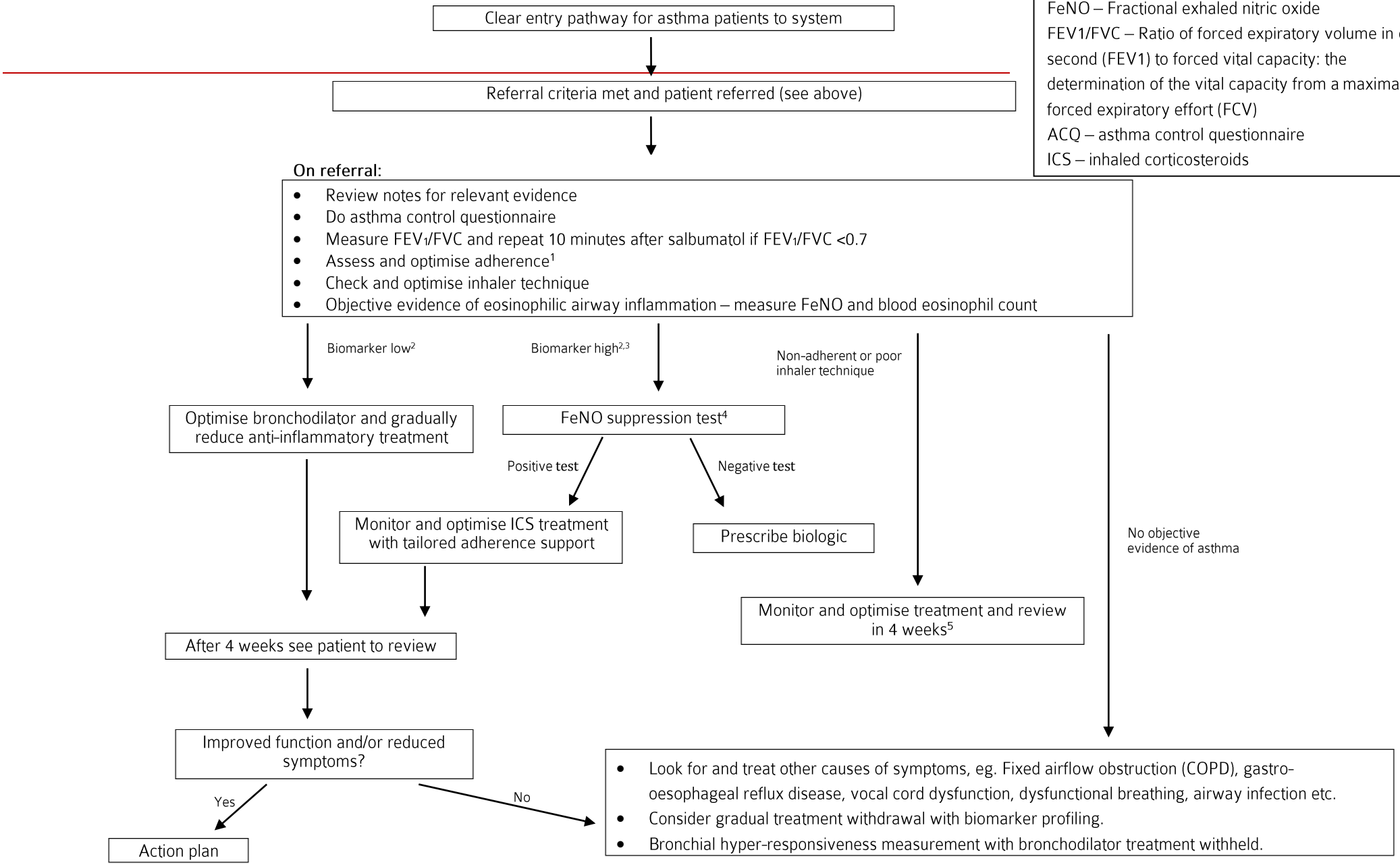
Professor Gary Anderson, Director, Lung Health Research Centre AstraZeneca and University of Melbourne
Professor Neil Barnes, Global Franchise Medical Head, GlaxoSmithKline
Ms Kathy Blacker, Regional Programme of Care Manager, NHS England
Ms Grainne D'Ancona, Principal Pharmacist, Respiratory and Sleep Medicine, Guy's and St Thomas' NHS Foundation Trust
Dr Melinda Goodall, Associate Director, National Institute for Health and Care Excellence
Dr Steve Holmes, GP and Clinical Respiratory Lead and Chair of Respiratory Programme Board (CCG), NHS Somerset
Mr John Holmes, Head of Medical Affairs, Teva UK
Professor Rob Horne, Professor of Behavioural Medicine, University College London
Dr David Jackson, Consultant Respiratory Physician, Guy's and St Thomas' NHS Trust
Mr Hasanin Khachi, Brand Manager – Respiratory & Inflammation Franchise, Novartis
Ms Jas Khambh, National Pharmacy Adviser to NHS RightCare, NHS England
Dr Andrew Menzies-Gow, Consultant in Respiratory Medicine, Royal Brompton Hospital
Professor Mike Morgan, National Clinical Director for Respiratory Services, NHS England
Dr John Pritchard, Chief Technology Officer, Respiratory Drug Delivery, Phillips
Professor Angela Simpson, Professor of Respiratory Medicine, University of Manchester
Professor Mike Thomas, Professor of Primary Care Research, University of Southampton
Dr Omar Usmani, Reader in Respiratory Medicine and Consultant Physician, Imperial College London
Dr Samantha Walker, Executive Director, Research & Policy and Deputy Chief Executive, Asthma UK
Dr Desmond Walsh, Head of Populations & Systems Medicine, Medical Research Council
Dr Bruce Warner, Deputy Chief Pharmaceutical Officer, NHS England

Secretariat

Ms Liberty Dixon, FORUM Policy Manager, Academy of Medical Sciences
Dr Alexandra Milsom, Personalised Medicine Scientific Lead, NHS England
Ms Alexandra Pickard, Policy Manager, Medicines, Diagnostics and Personalised Medicines Policy Unit, NHS England
Mr James Squires, Policy Officer, Academy of Medical Sciences

Annex III: Draft clinical pathway for the stratification of severe asthma

Abbreviations
FeNO – Fractional exhaled nitric oxide
FEV1/FVC – Ratio of forced expiratory volume in one second (FEV1) to forced vital capacity: the determination of the vital capacity from a maximally forced expiratory effort (FCV)
ACQ – asthma control questionnaire
ICS – inhaled corticosteroids



[1] Non-adherence can be supported by by patient questionnaire or clinician assessment, but may be assessed more accurately, and in routine care, by prescription records suggesting <70% prescription filling and undetectable theophylline and/or undetectable prednisolone and/or normal cortisol levels

[2] Biomarker high is defined as >45 ppb FeNO and/or blood eosinophils (EOS) count of >0.3 x 10^9/L. Biomarker low is anything below this range, but it must be recognised that patients with an "intermediate" range of FeNO (25 – 45 ppb) or blood EOS count (> 0.15 x 10^9/L) may still merit an FeNO suppression test or treatment with ICS. Biomarker levels are a continuous range and the appropriate cut-offs for biomarker high and low are a continued area of research and may change in the future.

[3] In cases where a patient has biomarker high EOS but biomarker low FENO, a FENO suppression test would not be undertaken.

[4] A FeNO suppression test is performed by monitoring reduction in FeNO over a 5 to 7-day period with directly observed high dose inhaled steroid therapy – in the original description of the test using budesonide, >42% reduction in FeNO from the Day 0/Day 1 mean to Day 4/Day 5 mean was associated with poor adherence defined by poor prescription filling (McNicholl DM, *et al.* (2012). *The Utility of Fractional Exhaled Nitric Oxide Suppression in the Identification of Nonadherence in Difficult Asthma.* Am J Respir Crit Care Med. **186(11)**, 1102-1108.)

[5] For patients who are consistently non-adherent, more evidence is required on the best management pathways. Please see the main text for discussion on this topic.

Severe asthma clinical management pathway

A suggested stratified patient pathway based on the roundtable discussions can be found above.

Pre-referral

The European Respiratory Society and American Thoracic Society have guidelines on referral of asthma patients.[44] However, there was concern among the delegates that these guidelines are not always followed and requirements for referral may differ between primary care clinics. Therefore, a pathway for stratification of severe asthma stratification must also include robust guidance for the diagnosis of severe asthma and referral to a specialist service **or from secondary to tertiary care.**

Although the existing guidelines are a good starting point, shorter summary guidelines for when to refer to a specialist service could include the following referral criteria:

- Criteria of severe asthma as laid out in the European Respiratory Society and American Thoracic Society guidelines.[45]
- Asthma that requires high dose ICS and LABA or leukotriene modifiers/theophylline for at least the previous year (as per the steps 4 and 5 in the Global Initiative for Asthma 2015 Guidelines.[46]
- Asthma that has required systemic corticosteroids for at least half of the previous year to control symptoms.
- Asthma which remains uncontrolled despite this therapy, defined as:
    - Poor symptom control: ACQ consistently 1.5, ACT consistently 20 (or "not well controlled" by NAEPP/GINA guidelines).[47]
    - Frequent severe exacerbations requiring two or more bursts of system corticosteroids in the previous year.
    - Any serious exacerbations resulting in hospitalisation, intensive care unit stay or mechanical ventilation in the previous year.
    - Airflow limitation after appropriate bronchodilator withhold FEV_1 80% of predicted score.
    - Controlled asthma that worsens on the tapering of high doses of ICS or systemic CS, or biologics.

[44] Chung KF, *et al.* (2014). *International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma.* European Respiratory Journal **43,** 343-373.
[45] *Ibid.*
[46] Global Initiative for Asthma (2015). *Pocket guide for asthma management and prevention.* http://ginasthma.org/wp-content/uploads/2016/01/GINA_Pocket_2015.pdf
[47] *Ibid.*

The Academy of Medical Sciences

Academy of Medical Sciences
41 Portland Place
London, W1B 1QH
+44(0)20 3141 3200

info@acmedsci.ac.uk
www.acmedsci.ac.uk

@acmedsci

Registered Charity No. 1070618
Registered Company No. 3520281