Institution: University of Oxford		
Unit of Assessment: 1 – Clinical Medicine		
Title of case study: Biomarker-enabled targeted use of steroids and biologics in asthma and COPD		
Period when the underpinning research was undertaken: Sept 2013 – Dec 2018		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Ian Pavord	Professor of Respiratory Medicine	Sept 2013 - present
Mona Bafadhel	Associate Professor of Respiratory Medicine	Jan 2014 - present
Period when the claimed impact occurred: Jan 2015 - Nov 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Asthma and chronic obstructive pulmonary disease (COPD) are the most common respiratory diseases. Work led by University of Oxford researchers showed that simple biomarkers – particularly blood eosinophil count – are highly effective in identifying the groups of patients with severe asthma or COPD most likely to benefit from specific treatments. In COPD, this biomarker-directed approach led to changes in international guidelines to target inhaled corticosteroids to patients where benefits are most likely to outweigh serious potential side-effects, such as pneumonia. In severe asthma, the University of Oxford-led analysis guided the NICE decision to recommend a biologic treatment, anti-interleukin-5 antibodies, based on biomarkers to target these highly effective but expensive drugs to the patients most likely to benefit, opening the market for pharmaceutical companies, giving treatment access to NHS patients, and ensuring cost-effectiveness for the NHS. This is the only biomarker-directed recommendation of biologics for a non-malignant condition. As a result of the predictive biomarker, treatment failure rates are less than 20%, approximately half of those seen in other inflammatory conditions. Access to biologics has brought transformative improvements in quality of life to sufferers of severe asthma for whom conventional treatments were failing.

2. Underpinning research

Background (research prior to 2014)

Previous research led by Pavord and Bafadhel whilst at the University of Leicester (before 2014) showed that it was clinically important to consider the pattern of lower airway inflammation when diagnosing and treating asthma and COPD. They showed that asthma and COPD differ in the pattern of lower airway inflammation and suggested that it was clinically important to distinguish them; eosinophilic asthma and COPD are associated with a better response to corticosteroids than non-eosinophilic disease. Bafadhel identified that the peripheral blood eosinophil count is a relevant marker of eosinophilic airway inflammation in COPD, and Pavord showed that exhaled nitric oxide is a simple, clinically accessible biomarker of eosinophilic airway inflammation in asthma. Whilst at the University of Leicester, Pavord also led clinical trials of a monoclonal antibody targeting the major cytokine that is required for proliferation of eosinophils, interleukin-5 (IL5; mepolizumab), in severe eosinophilic asthma.

Biomarkers for inhaled corticosteroids

Research at the University of Oxford, by Pavord and Bafadhel independently, showed that the peripheral blood eosinophil count can be used to identify patients with COPD who are at high risk of exacerbations and are likely to respond well to inhaled corticosteroids (ICS) [1,2]. Specifically, collaborating with industrial partners, Pavord and Bafadhel led post-hoc analyses of previous randomised controlled trials: two trials of fluticasone furoate (analysis led by Pavord, data provided by GSK) [1]; and three trials of budesonide–formoterol (analysis led by Bafadhel, data provided by AstraZeneca) [2]. These analyses showed that blood eosinophil count predicts clinical

response to ICS and thus could be used to stratify patients. In particular, ICS had a significantly greater benefit for patients with higher eosinophil counts. The analysis by Bafadhel [2] was the first to investigate blood eosinophil counts as a continuous variable, which enables thresholds (for reducing exacerbations, improving lung function and so forth) to be determined. A potential increased risk of pneumonia is one of most important adverse effects of ICS. Pavord led a study (collaborating with GSK) showing that this risk could be mitigated by targeting use of ICS to patients with COPD with higher blood eosinophil counts [3]; in contrast, for patients with lower blood eosinophil counts, the risk of pneumonia outweighed the benefit of ICS [3].

Biomarkers for biologics that reduce airway inflammation

At the University of Oxford, Pavord led a post-hoc analysis of two randomised controlled trials (DREAM and MENSA) of mepolizumab in severe eosinophilic asthma (analysis by Pavord, data from GSK) [4]. His analysis showed a close relationship between pre-treatment blood eosinophil count and the clinical efficacy of mepolizumab, in patients with a history of exacerbations. Clinically-relevant reductions in exacerbation frequency occurred in patients with a baseline blood eosinophil count of ≥ 150 cells/μL, with most significant benefit in patients with ≥ 300 cells/μL and a history of exacerbations. This provided a pre-treatment biomarker to select patients likely to maximally benefit from this biologic.

Pavord contributed to the design and analysis of a randomised controlled trial, with Sanofi and international collaborators, for another biologic, dupilumab (an anti-IL4/13 biologic), in moderate-to-severe uncontrolled asthma [5]. Notably, following the successful identification of biomarkers for other biologics (including [4]), this trial was specifically designed to assess biomarker-directed patient stratification. For example, prespecified subgroup analyses were included according to baseline blood eosinophil count and exhaled nitric oxide. The trial showed that the maximal reduction of severe asthma exacerbation, improvement of lung function and asthma control occurred in patients with higher baseline levels of eosinophils and exhaled nitric oxide. Collectively, use of these simple reliable predictive treatment response biomarkers is an example of precision medicine, targeting use of costly biological agents. Such predictive biomarkers had not previously been identified for any treatment pathway in respiratory medicine.

3. References to the research

*University of Oxford employees at time of research in bold; industrial partners indicated with *; citations from Google Scholar, 10/2020.*

1. Pascoe S*, Locantore N*, Dransfield MT, Barnes NC*, **Pavord ID**. Blood eosinophil counts, exacerbations and response to the addition of inhaled fluticasone furoate to vilanterol in patients with COPD: a secondary analysis of data from two parallel randomised controlled trials. *Lancet Resp Med* (2015) 3:435-42 DOI: 10.1016/S2213-2600(15)00106-X (Citations: 581)
2. **Bafadhel M**, Peterson S*, De Blas MA*, Calverley PM, Rennard SI*, Richter K*, Fagerås M* Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. *Lancet Resp Med* (2018); 6:117-126 DOI:10.1016/S2213-2600(18)30006-7 (Citations: 167)
3. **Pavord ID,** Lettis S*, Anzueto A, Barnes N*. Blood eosinophil count and pneumonia risk in patients with chronic obstructive pulmonary disease: a patient-level meta-analysis. *Lancet Respir Med* (2016) 4:731-41 DOI: 10.1016/S2213-2600(16)30148-5 (Citations: 105)
4. Ortega HG*, Yancey SW*, Mayer B*, Gunsoy NB*, Keene ON*, Bleecker ER, Brightling CE, **Pavord ID**. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. *Lancet Respir Med* (2016)4:549-56 DOI:10.1016/S2213-2600(16)30031-5 (Citations: 304)
5. Castro M, Corren J, **Pavord ID**, Maspero J, Wenzel S, Rabe KF, Busse WW, Ford L, Sher L, FitzGerald JM, Katelaris C, Tohda Y, Zhang B*, Staudinger H*, Pirozzi G*, Amin N*, Ruddy M*, Akinlade B*, Khan A*, Chao J*, Martincova R, Graham NMH*, Hamilton JD*, Swanson BN*, Stahl N*, Yancopoulos GD*, Teper A*. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. *N Engl J Med* (2018) 378:2486-2496. DOI: 10.1056/NEJMoa1804092 (Citations: 517)

Funding to the University of Oxford includes: **NIHR Postdoctoral Fellowship** to Bafadhel, £480,363 (PDF-2013-06-052, 2014-18); **NIHR Senior Investigator election** and grant to Pavord, £75,000 (NF-SI-0513-10041, 2014-19); **Sanofi-Aventis Group**, An exploratory, randomized, double-blind, placebo-controlled study of the effects of dupilumab on airway inflammation of adults with persistent asthma, £31,839 (2016-19).

4. Details of the impact

5% of adults have asthma and 10% of these have severe asthma. 50% of patients with severe asthma have a type of inflammation characterised by high levels of eosinophils, called severe eosinophilic asthma. In the UK, 200,000 people have life-threatening, debilitating severe asthma, which cannot be controlled with the usual medicines. The World Health Organisation estimates that asthma causes loss of 15,000,000 disability-adjusted life-years and 250,000 deaths every year. COPD is one of the commonest chronic conditions, affecting an estimated 384,000,000 people globally. In the UK, COPD is diagnosed in 4.5% of people over 40; an estimated 1,200,000 people live with this diagnosis, and it is estimated that a further 2,000,000 people remain undiagnosed. It causes high levels of mortality and morbidity, being a common cause of emergency admissions and the third leading cause of mortality in the world.

Improved COPD outcomes and reduced risks by targeting inhaled corticosteroids

In 2019, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Science Committee COPD guidelines [A] recommended that ICS are used only where directed by a blood eosinophil indication, citing the University of Oxford research [1,2,3] as evidence. The recommendations are based on the consistent effects of ICS seen at ≥100 eosinophils/μL, as found in the University of Oxford analyses investigating blood eosinophil counts as a continuous variable [2]. This was the first time in any airway disease that ICS were targeted to a biomarker-identified patient population. Similarly, Pavord and Bafadhel's research influenced the European Respiratory Society guidelines, published June 2020, recommending withdrawal of ICS in patients with COPD without frequent exacerbations, but not withdrawing ICS if blood eosinophil count is ≥300 eosinophils/μL [B]. The importance of their research on both sets of guidelines was confirmed in a letter from the chair of the GOLD Science Committee [C], stating "[Pavord's] *work had implications on the GOLD report…and an official European Respiratory Society (ERS) guideline*". These international guidelines have been adopted into local practice, influenced by Bafadhel's research, confirmed by the chair of the Respiratory Prescribing Group for an NHS Trust [D].

Approximately 75% of patients with COPD are treated with ICS [D], whereas only 20% have blood eosinophil counts of ≥ 300 eosinophils/μL. In England around 80,000 people are diagnosed with COPD each year. This suggests that implementation of these guidelines results in approximately 44,000 fewer patients receiving ICS in England alone. According to the chair of an NHS Respiratory Prescribing Group "*Implementation of the guideline supports cost effective prescribing … leading to a reduction in prescribing costs as well as the knowledge that the risk of adverse effects from ICS are being minimised*" [D]. Therefore, the revised guidelines enable ICS to be used more economically and effectively, both improving treatment for severe disease and reducing adverse effects of treatment for other patients.

Targeting biologics for effective treatment for severe asthma

The University of Oxford-led analysis showed simple biomarkers identify which patients benefit most from life-changing anti-IL-5 monoclonal antibody therapy [4]. This has enabled life-changing, but expensive, treatments to reach the appropriate patient population. Use of these drugs in severe asthma is the only biomarker-directed use of biologics in a non-malignant condition.

Changes to international guidelines: In 2019, the Global Initiative on Asthma (GINA) recommended that anti-IL5 treatment for severe eosinophilic asthma should be for patients with blood eosinophils above a specified level and more than a specified number of exacerbations in the last year, and that high blood eosinophils and higher number of severe exacerbations are "*strongly predictive*" of good asthma response (citing [4]) [E]. The Chair of GINA confirmed the impact of Pavord's work on eosinophils: "…[Pavord's] *investigation of prognostic and predictive factors relevant to clinical management of patients with asthma…have led to changes in clinical recommendations for treatment of asthma in national guidelines and in the strategy report of the Global Initiative for Asthma (GINA)*" [F].

National approvals based on blood eosinophil thresholds: The UK National Institute for Health Care and Clinical Excellence (NICE) had issued interim guidance in April 2016 not to recommend the anti-IL5 biologic mepolizumab for use in severe asthma as it did not meet NICE cost-effectiveness criteria [Gi]. However, after the drug company GSK provided new modelling based on the specific severe asthma patient population with a blood eosinophil threshold of ≥300 cells/μL and a high number of exacerbations, which showed maximal benefit in the meta-analysis led by Pavord [Gii], (subsequently published in [4])], and also revised the price for the NHS, NICE amended its initial guidance in Dec 2016 and recommended mepolizumab for this specific patient population [Giii, iv]. Feedback received in the appraisal process and committee response also confirmed the importance of Pavord's analysis in this recommendation: for example, both NHS England and a Consultant Respiratory Physician referenced this research [4] with respect to choosing the appropriate patient population [Giv]. After the mepolizumab decision, NICE recommended two further anti-IL5 biologics (reslizumab in Oct 2017; benralizumab in Mar 2019), with stratification for blood eosinophil count and number of exacerbations as the criteria for selecting eligible patients [Gv, vi]. Subsequently, in Jan 2020, the recommendation for mepolizumab was aligned to benralizumab [Gvii], opening anti-IL5 biologic treatment to approximately 35,900 patients in England.

Blood eosinophil thresholds have thus become standard for enabling the NHS to provide biologics for severe asthma. The NHS England National Clinical Director for Respiratory Services stated in 2020 that as a consequence of Pavord's research, "*measurement of peripheral blood eosinophil counts is now part of routine practice for severe asthma care and has proven integral to several NICE Health Technology Appraisals for biologics in severe asthma*" [H]. According to Asthma UK:

> "*Pavord's work to establish the use of eosinophil levels as a biomarker that predicts response to treatment has transformed our ability to match the right patient to the right drug and to create vital eligibility criteria for using the new biologic drugs*" [I].

This was confirmed by the Clinical Lead of the UK Severe Asthma Registry (UKSAR) who stated that Pavord's University of Oxford research "*has been crucial to the success of Mepolizumab and other biologics as it has allowed us to target treatment effectively and demonstrate to regulators that the drug can be used efficiently and economically*" [J].

Wider approval of biologics: The US Food and Drug Administration and European Medicines Agency each approved the anti-IL4/13 biologic dupilumab for patients with moderate-to-severe eosinophilic asthma in 2018 [Ki] and 2019 [Kii], respectively, based on the pivotal clinical trial programme which included the eosinophil and exhaled nitric oxide biomarker-directed analysis (6). A retrospective real-life cohort study in France (64 patients, published May 2020), showed that patients treated with dupilumab outside of the clinical trials also had significantly improved asthma control and lung function, reduced oral steroid use, and reduced exacerbations [Li].

Improvements in clinical care and quality of life: Suffering from severe asthma has severely debilitating effects on the daily lives of patients, with breathlessness, anxiety, frequent hospitalisations, and toxic side effects from long-term high-dose corticosteroids. Asthma UK estimated that in April 2019 more than 3,000 people in the UK were being treated with biologics, such as mepolizumab, and this number is increasing [I]. An Asthma UK survey in 2020 of more than 200 people receiving biologic treatment showed "*for 1 in 5 it has been completely life-changing and for two thirds it has reduced their asthma symptoms and frequency of asthma attacks*" [I]. Asthma UK's qualitative research in 2019 showed dramatic improvements in quality of life. For example, two participants stated:

> "*I just wish I had been put on this biologic a lot sooner. Because the period I was suffering…it was just so depressing that sometimes you think your life is just not worth living anymore*" and
>
> "*What* [the biologic] *has also done is give me a sense of confidence…that extra dimension of freedom…That's an invaluable thing*" [I].

The transformative effect of the reduction of exacerbations for patients on mepolizumab is also illustrated by the testimonial of a carer submitted to NICE, describing the benefit to her daughter whilst being treated: "*she didn't have one episode of exacerbation of her asthma and finally felt that there was hope for her to have some kind of near normal life*" [Hiv].

The Clinical Lead for UKSAR has stated that

> "*Mepolizumab and other biological drugs…have had a massive impact on the lives of patients with the most severe forms of asthma. For example, the use of regular*

oral corticosteroids to treat severe asthma has been substantially reduced, and which was the most common therapeutic intervention for severe asthma" [J].

The benefits to patients of reducing long-term oral corticosteroid use include reductions in risk of osteoporosis, diabetes, glaucoma, stomach ulcers and susceptibility to infection. In 2020, a global, prospective, observational cohort study also confirmed that benefits of mepolizumab to patients in real-world settings are consistent with those seen in the clinical trials, with significant reductions in exacerbations and doses of corticosteroids [Lii]. This study also showed a discontinuation rate of less than 20%, (with only 4% of patients reporting lack of efficacy as the reason) [Lii]; approximately half the discontinuation rate seen for biologics in other inflammatory conditions without biomarker-guided treatment.

Commercial success for pharmaceutical industry: Total respiratory sales of mepolizumab (Nucala) for GSK exceeded GBP174,000,000,000 from 2016-2019, increasing year-on-year including GBP768,000,000 in 2019, GBP206,000,000 of which was from Europe [M]. Approvals for mepolizumab have continued to increase, including for paediatric use in the EU, and for self-administration in 2019. Overall, biologic therapies are driving growth in the asthma therapeutics market, much of this benefiting the UK pharmaceutical industry.

5. Sources to corroborate the impact

A. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: The GOLD Science Committee Report 2019, recommending blood eosinophil levels to determine use of ICS, citing [1] [2], and [3] as references 11, 31 and 38, respectively. DOI: 10.1183/13993003.00164-2019

B. Withdrawal of inhaled corticosteroids in COPD: a European Respiratory Society guideline. *Eur Respir J* (2020), citing research [2] and [3] as references 14 and 10, respectively. DOI: 10.1183/13993003.00351-2020

C. Letter from Chair of GOLD Science Committee (Sep 2020), stating that Pavord's research on blood eosinophil count influenced [A] and [B].

D. Letter from chair of Leicester, Leicestershire and Rutland Respiratory Prescribing Group, describing implementation of blood eosinophil-directed prescribing of ICS for COPD.

E. Global Initiative for Asthma (GINA), Global Strategy for Asthma Management and Prevention (2019 Update), p97, citing [4] with respect to treatment for severe eosinophilic asthma.

F. Letter from Chair of GINA (Oct 2020), confirming the contribution of Pavord's research to changes in guidelines and regulatory approvals.

G. NICE appraisals and decisions for biologics: i) First appraisal for mepolizumab April 2016; ii) Second appraisal for mepolizumab June 2016; iii) Final appraisal determination for mepolizumab Dec 2016; iv) Committee Papers from Final Appraisal for mepolizumab Dec 2016; v) Recommendation for reslizumab Oct 2017; vi) Recommendation for benralizumab Mar 2019; vii) Update to mepolizumab recommendation Jan 2020.

H. Letter from National Clinical Director for Respiratory Services, NHS England, (Oct 2020), describing influence of Pavord's biomarker research on UK respiratory medicine.

I. Letter from Direct of Research and Innovation, Asthma UK (Nov 2020), describing the benefits of mepolizumab to patients.

J. Letter from Clinical Lead of the UK Severe Asthma Registry (UKSAR) (Nov 2020), describing changes in clinical care and benefits to patients from mepolizumab.

K. Press releases on approvals of dupilumab: i) Sanofi press release on US Food and Drug administration approval, Dec 2018; ii) European Medicines Agency press release, Mar 2019

L. Journal articles on efficacy of biologics for asthma in real-world practice:
i) Dupin C et al., Effectiveness and safety of dupilumab for the treatment of severe asthma in a real-life French multi-centre adult cohort. *Clin Exp Allergy* (2020) doi: 10.1111/cea.13614;
ii) Harrison T, et al., Real-world mepolizumab in the prospective severe asthma REALITI-A study: initial analysis. *Eur Respir J* (2020) DOI:1 10.1183/13993003.00151-2020

M. GSK Annual Reports 2016, 2017, 2018, and 2019, including annual sales for mepolizumab (Nucala) for respiratory indications.