Institution: University of Brighton	
Unit of Assessment: A3 Allied Health Professions, Dentistry, Nursing and Pharmacy	
Title of case study: Personalising asthma care for children	ICS [3]

1. Summary of the impact

Improved approaches to the management of asthma treatment in children, new NHS and BUPA healthcare guidance and changes in UK media attitudes have arisen from fundamental and clinical research at Brighton into the effects of genotype variation on responses to asthma medicines in children. Direct clinical benefits in quality of life resulted from the first-ever randomised clinical trial on genotype specific treatments for asthma. The subsequent worldwide media debate led to wider professional and public understanding of genetically-directed treatment choices and personalised medicines, with particular impact on parents of children with asthma.

2. Underpinning research

Research over the last two decades has identified that asthma in childhood is representative of several disease strands within a broad clinical entity. The research that underpins this case study focuses on improving understanding of the mechanisms underlying asthma in children and adolescents, with a particular focus on pharmacogenetics and potential therapeutic implications. The overall research programme explored a number of lines of investigation to progress towards the definition of, more 'personalised' sub-types of asthma disease in childhood.

Through systematic investigation led by MUKHOPADHYAY at Brighton and Sussex Medical School, and in partnership with the University of Dundee, new insights have arisen on the aetiology and management of children's asthma. Two common asthma medicines act via a single body molecule in the airway, the beta2-receptor. These medicines appear to be effective in only a proportion of children with asthma. Other children continue to have asthma attacks (exacerbations) despite the use of these medicines. In 2009, the team demonstrated that the at-risk (Arg16) genotype is associated with exacerbations in asthmatic children and young adults exposed daily to beta2-agonists, regardless of whether the exposure is to short-acting salbutamol or long-acting agonists, such as salmeterol [reference 3.1]. Asthma patients using their inhaler on a daily basis, who carry the gene variant, were shown to have a 30% greater risk of asthma attacks than those who do not carry the variant. The first-ever randomised controlled trial into the role of intervention by genotype demonstrated the benefit of selecting treatment based on patient genotype [3.2]. The use of Montelukast as an alternative to salmeterol as a tailored second-line asthma controller therapy for those children with the at-risk (Arg16) genotype led to improvements in both symptom and quality of life scores for these patients. This highlighted the potential benefit of moving towards a personalised approach to the management of this condition.

Other studies of gene variation for the protein filaggrin has produced insights into the unified role of filaggrin-related skin barrier defects on early allergy-related problems [3.3, 3.4] and later asthma severity, including a greater risk of asthma attacks in children [3.5]. Filaggrin is a protein that helps maintain normal skin barrier function; common loss-of-function as a result of mutations in the gene encoding filaggrin increase skin permeability and allergen entry across the skin. The associated increase in allergen exposure quickly worsens symptoms, such as skin rashes and asthma attacks, in some children with allergies. The research determined the natural history and burden of atopic disease conferred by the two most common filaggrin mutations and led to the discovery of other genetic variants driving faster airway remodelling, a key pathological event in childhood asthma, and predisposing some patients to more severe clinical disease in some individuals [3.6]. This additional line of investigation may lead to a diagnostic test that helps select individuals for new treatment strategies. This has led to a US patent application from the Universities of Brighton and Sussex in 2013.

Key Researcher: Somnath Mukhopadhyay: Chair in Paediatrics (Oct 2007–to date)

3. References to the research

[3.1] BASU, K., PALMER, C.N., TAVENDALE, R., LIPWORTH, B.J. and MUKHOPADHYAY, S. (2009) Adrenergic beta(2)-receptor genotype predisposes to exacerbations in steroid-treated

asthmatic patients taking frequent albuterol or salmeterol. *Journal of Allergy and Clinical Immunology*. 124(6): 1188–1194. [Quality validation: leading peer-reviewed journal]

[3.2] LIPWORTH, B.J., BASU, K., DONALD, H.P., TAVENDALE, R., MACGREGOR, D.F., OGSTON, S.A., PALMER, C.N., and MUKHOPADHYAY, S. (2013) Tailored second-line therapy in asthmatic children with the Arg(16) genotype. Clinical Science; 124(8):521–528. doi:10.1042/CS20120528. [Quality validation: this paper is the 'most read' paper over the past 3 years for this journal (maximum downloads for any paper in this journal between September 2010 and August 2013)]

[3.3] BISGAARD, H., SIMPSON, A., PALMER, C.N.A., BØNNELYKKE, K., MCLEAN, I., MUKHOPADHYAY, S., PIPPER, C.B., HALKJAER, L.B., LIPWORTH, B., HANKINSON, J., WOODCOCK A., and CUSTOVIC A. (2008) Gene-Environment Interaction in the Penetrance of Eczema in Infancy Replicated in Two Birth-Cohort Studies: Filaggrin Loss-of-Function Mutations Triggered by Cat Exposure. PLOS Medicine 24;5(6):e131. [Quality validation: 105 cites]

[3.4] HENDERSON, J., NORTHSTONE, K., LEE, S., LIAO, H., ZHAO, Y., PEMBREY, M., MUKHOPADHYAY, S., DAVEY SMITH, G., PALMER C.N.A., IRWIN MCLEAN, W.H. and IRVINE, A.D. (2008) The burden of disease associated with filaggrin mutations: a population based, longitudinal birth cohort study. *Journal of Allergy and Clinical Immunology;* 121(4):872–877. [Quality validation: 106 cites]

[3.5] BASU, K., PALMER, C.N.A., LIPWORTH, B.J., MCLEAN, W.H.I., TERRON-KWIATKOWSKI, A., ZHAO, Y., LIAO, H., SMITH, F.D.J., MITRA, A., and MUKHOPADHYAY, S. (2008) Filaggrin Null Mutations Are Associated With Increased Asthma Exacerbations In Children And Young Adults. Allergy; 63(9):1211–1217. [Quality validation: leading peer-reviewed journal]

[3.6] MUKHOPADHYAY, S., SYPEK, J., TAVENDALE, R., GARTNER, U., WINTER, J., LI, W., PAGE, K., FLEMING, M., BRADY, J., O'TOOLE, M., MACGREGOR, D.F., GOLDMAN, S., TAM, S., ABRAHAM, W., WILLIAMS, C., MILLER, D.K. AND PALMER, C.N.A. (2010) Matrix metalloproteinase-12 is a therapeutic target for asthma in children and young adults Journal of Allergy and Clinical Immunology. 126:70–76. [Quality validation: leading peer-reviewed journal]

Peer-reviewed research grants:

SPARKS (charity) Do filaggrin gene defects cause atopic sensitisation and atopic disease in young children? (2008–2011), total funding: £196,185

4. Details of the impact

New insights into the aetiology and management of children's asthma have arisen from the development of an understanding of differences in patient responses to medicines arising from genotype variation. This has led to opportunities for more 'personalised' treatment. The impact resulting from this research occurred as a consequence of a targeted dissemination plan that has infiltrated the media and been picked up by health organisations, health professionals and the wider public.

Impact on media: Following University of Brighton press releases in 2009 and 2013 the different areas of asthma-related genotype research have received immediate and widespread public attention both within the UK and worldwide with over 160 reports covered in local, national and international newspapers, radio and television shows including BBC Radio 4, www.bbc.co.uk, ITV/Channel 4, *The Times*, *The Daily Telegraph*, *The Guardian*, *The Daily Mail*, *The Daily Express*, and other leading newspapers in the UK, US, Canada, Australia and India. The Science Media Centre, an organisation with a mission to help scientists proactively set the agenda by bringing new science or evidence to journalists, presented the first phase of research at a press conference in London on 5th October 2009. The mediation of this research through this organisation, which positions itself between scientists and journalists, has informed the direction of the debate. The media debate now centres on the possibility of personalised healthcare and questions on the cost effectiveness of the current strategy of uniform prescribing where all patients follow a stepwise escalation of treatment over the course of their disease. As a result of this attention the Department of Health contacted the university expressing interest in the findings. Subsequently, research outcomes were disseminated to the public and health care professionals through a Reuters worldwide press release that emphasised the international

relevance of the findings as, although the research focused on children of Northern European origin, the 'at-risk' gene change is more common in South Asia and Africa, where beta2-agonists are widely used in children with asthma (source 5.1).

Following this widespread exposure of the various research outcomes there has been a perceptible change in attitude within the leading UK media. This is evidenced by the change between the 2009 reports that concentrated on describing the findings and the 2013 reports that recognise and acknowledge the implications of this for the future. Sarah Boseley's report in *The Guardian* carried the title 'Asthma inhaler may not work for some children, study shows' (6th October 2009), whilst in contrast, the 2013 report in *The Guardian*, written by the same journalist, was entitled 'Genetic tests could pave the way for personalised asthma drugs' (8 January 2013). This article also highlights the practical application through an expert testimonial that states that these results are 'a wonderful example of stratified or personalised medicine working its way into practice' (5.2). Similarly, in 2009, the BBC reported the findings under the heading 'Asthma inhaler failing children'. However, in 2013, the BBC published an analysis of the later research by leading science journalist Tom Feilden under the heading 'Is this the shape of medicine to come?'. In this analysis Feilden states that the study 'does help paint a picture of what this Brave New World of personalised medicine may actually look like' (5.3). The debate has changed from a descriptive account of the findings and the failure of regular medicines to a realisation of the implications due to the progression in this area of research. Although the future of personalised medicine is yet to be determined our research has provided the first real evidence and first tangible step towards such management, the possibility of which has been recognised throughout the media. Further evidence is provided the inclusion of our research in a televised programme describing the ten most important scientific breakthroughs of the past 50 years, written and presented by Lord Robert Winston as broadcast in 2010. Our research into genotype-directed personalised asthma care was highlighted as the first real evidence of the tangible effects of the human genome project being referred to by Lord Winston as a key example of how decoding the human genome can lead to widespread practical benefit in a common childhood disease (5.4).

The outcomes of the subsequent randomised controlled trial that showed benefit through asthma treatment personalised by genotype were presented at a further press conference in January 2013 at the Science Media Centre and MUKHOPADHYAY was interviewed on the Radio 4 Today programme while print editions of all major newspapers such as *The Guardian* and *The Daily Mail* carried the story in detail. The impact of the results was also picked up and presented on prime time television in a special edition of 'Bang Goes the Theory', a programme that considers the science behind the headlines and tackles the issues that affect lives. This programme highlighted the personal story of one patient involved in the trial and documented the resulting benefit to him as a patient that no longer has the fear of severe attacks as the symptoms are under much better control. This programme recognised this trial as a remarkable impact on the children involved.

Change in awareness and guidance from the NHS and BUPA: The widespread dissemination and debate in the media has led directly to a change in the awareness amongst professionals, patients and the public and has resulted in two key messages from the NHS, BUPA UK and BUPA International presented through reactive guidance on their websites (5.8, 5.10):

- All parents should visit a doctor if they feel their child's asthma symptoms are not being controlled or are being made worse by asthma medicines
- There are other medicines available if salbutamol or salmeterol do not work well in children with asthma

Specifically related to the 2009 publication, NHS Direct provided substantial guidance to health professionals and the public in the UK noting that this study is of value given the high prevalence of asthma and the universal use of bronchodilators in the management of asthma (5.6). A key point in this guidance is that if a young person has been prescribed a long-acting daily bronchodilator such as salmeterol and their asthma is worsening, they should consult their doctor as this medication may need to be removed. Other community information websites (e.g. pharmacy websites in England, Northern Ireland) present similar guidance to the public (5.9). This awareness has reached consultants in Scotland, Southeast England and India and has started to influence the day-to-day management of patients with asthma when considering the prescription of medicines (5.5, 5.6, 5.7).

Impact on parents of children with asthma: The reports in the media led to considerable discussion on the Internet regarding the findings (5.11), with contributions on special interest sites, e.g. on parent/lay-person websites and Asthma Magazine (the magazine published by the charity Asthma UK for the public). In 2011 a Sussex-based charity (Haydn's Wish) was founded by a mother who lost her 9-year old child to acute allergic asthma. The charity utilised the underpinning research into filaggrin mutations, linking allergy and asthma attacks in children, to increase public awareness regarding the need for an integrated management of these conditions providing a resource for patients, by patients and healthcare professionals working in partnership (5.12). An example is a collaborative project with industry (Thermofisher plc) led to widespread dissemination of this message to primary care (over 15,000 emails to GPs and primary care nurses across the UK, 2013). The key messages from the research have been disseminated through this charity and used within educational materials to promote awareness. In the two years that this charity has been operating the founder of the charity has noted a perceptible change in awareness amongst school groups and parents (5.12). This research has therefore informed a debate not just about the role of asthma treatment, but personalised care across the range of human health conditions that has begun to be realised through an incremental change in practice and a marked change in public awareness.

5. Sources to corroborate the impact

5.1 'Inhalers may raise risk of asthma in some children', Oct 6 2009. Available at: . http://www.reuters.com/article/2009/10/06/us-asthma-gene-idUSTRE5952JQ20091006 [Accessed: 12 November 2013]. Press release that shows the international relevance.

5.2 Guardian articles, 'asthma inhaler may not work for many children', Oct 6 2009. Available at: http://www.theguardian.com/society/2009/oct/06/asthma-inhaler-ventolin-children-arg16 'Genetic tests could pave way to 'personalised' asthma drugs', 8 January 2013'. Available at: http://www.theguardian.com/society/2013/jan/08/genetic-tests-personalised-asthma-drugs [Accessed: 10 November 2013]. These articles highlight the change in debate.

5.3 'Asthma inhaler failing children', 6 October 2009, and 'Is this the shape of medicine to come?' 8 January 2013. Available at: http://news.bbc.co.uk/1/hi/health/8292915.stm, http://www.bbc.co.uk/news/health-20944960 [Accessed: 12 November 2013]. BBC coverage covering the changing debate.

5.4 'How Science Changed Our world.' Available at: http://topdocumentaryfilms.com/howscience-changed-our-world/ [Accessed: 12 November 2013] Lord Robert Winston documentary that highlights the contribution of this research to one of the top 10 scientific breakthroughs

5.5 Testimonial from Site Director, Postgraduate Institute of Medical Education and Research. India. This confirms that the research has affected practice when prescribing medicines.

5.6 Testimonial available from Consultant Respiratory Physician, Ninewells Hospital and Medical School. This confirms that the day-to-day management of prescribing medicines has changed as a result of the research.

5.7 Testimonial available from Consultant Paediatrician, BSUH Trust that confirms that the management of medicines has changed as a result of the research.

5.8 'Child asthma pumps questioned', October 7 2009. Available at: http://www.nhs.uk/news/2009/10October/Pages/asthma-pump-may-increase-attack-claim.aspx [Accessed: 8 November 2013]. Guidance based on research by NHS direct.

5.9 'Child asthma pumps questioned', October 7 2009, available at: http://www.andersonspharmacy.co.uk/news/45 [Accessed: 12 November 2013] Guidance provided by pharmacy websites.

5.10 Guidance provided by BUPA. Available at: http://www.bupa.co.uk/individuals/health-information/health-news-index/2009/hi-081009 asthma-medicines [Accessed: 12 November 2013]

5.11 Evidence of the discussion on special interest sites. Available at: http://www.nursingtimes.net/nursing-practice/clinical-specialisms/asthma/child-asthma-pumps-questioned/5007101.article, http://www.allmothers.net/asthma-inhaler-may-not-halt-attacks-among-gene-mutation-infants.html [Accessed: 12 November 2013].

5.12 Haydn's Wish, Charity website. Available at: http://www.haydns-wish.co.uk/. [Accessed: 12 November 2013]. Testimonial available from the founder confirming how the research has influenced their work and the research is disseminated to parents to raise awareness.