Institution: University of Brighton

Unit of Assessment: A3 – Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: Changing the clinical management of childhood asthma and eczema

Period when the underpinning research was undertaken: 2008 **–** 2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	**Role(s) (eg job title):**	**Period(s) employed by submitting HEI:**
Somnath Mukhopadhyay	Professor in Paediatrics	2007 – to date
Christina Jones	Lecturer in Paediatrics	2007 – 2018
Katy Fidler	Senior Lecturer in Paediatrics	2008 – to date
Stephen Bremner	Professor of Medical Statistics	2015 – to date
Tom Ruffles	Senior Clinical Fellow in Paediatric Respiratory Medicine	2019 – to date

Period when the claimed impact occurred: 2014 – 2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Brighton and Sussex Medical School (BSMS) research on the role of skin barrier function and gene variation in allergy-related diseases has led to a change in the management of paediatric asthma and eczema. This has become life-changing for the most severely affected patients. Research evidence was used to establish a new person-centred clinical approach at the Royal Alexandra Children's Hospital (Brighton) changing the provision of care for children under 6 months of age. The research is central to the Royal College of General Practitioners' training on allergy, with 5,489 health professionals trained since 2016. The findings are also a key reference point on the selection of appropriate treatments in the published guidance for health professionals from the National Asthma Council in Australia.

2. Underpinning research

One in five children in the UK is affected by eczema and one in eleven by asthma. Every 18 minutes a child is admitted to hospital because of these conditions. The immense burden of poorly controlled childhood atopic disease, principally asthma and eczema, includes direct costs from urgent GP care or hospital admissions, and indirect costs from work-related losses for carers, impaired quality-of-life and limitations in physical activities. This indicates the urgent need to improve management strategies for these conditions. Through a better understanding of specific disease subtypes that guide the development of 'precision medicine' strategies, Professor Somnath Mukhopadhyay and colleagues have created and tested new person-centred approaches for the management of childhood asthma and eczema. The goal of this research is to improve the quality-of-life of children with these conditions and reduce the overall burden from these diseases. Between 2008 and 2020, two areas of this research have made progress towards translating research findings to clinical benefit: i) skin barrier function and ii) genotype-led improvements in efficacy of medical treatments.

A protein known as filaggrin plays a key role in maintaining skin barrier function. Common variations in the filaggrin gene result in poor skin barrier function and greater chances of childhood atopic disease. The research group has tracked the impact of this important genetic defect throughout childhood, demonstrating poorer disease control, such as increased prescribing of asthma and eczema medicines, and greater risk of asthma attacks [reference 3.1]. This led to calls from experts in the UK and Japan for trials of precision medicine and targeted management for filaggrin-related eczema and asthma to reduce the worldwide burden of eczema and asthma. Additionally, the finding that significant interaction of this gene defect with *cat dander* exposure can lead to increased risk of infant eczema [3.2], provided direct evidence in favour of the 'outside-inside' (skin allergen entry triggering eczema) as opposed to the 'inside-outside' (gut allergen entry triggering eczema) hypothesis as driver for infant eczema. This work

directs clinician attention towards the recognition of filaggrin-related eczema as a specific eczema subtype where the effects of exposure to skin allergen, as opposed to gut allergen, requires more proactive diagnosis and management.

A parallel programme of research uses genotypic information to improve care by finding the right medicine for the child. An evolving body of work on treatment efficacy was led by this research team, advancing knowledge alongside other related studies worldwide. Mukhopadhyay's team demonstrated how adverse changes to the beta2-adrenoceptor gene led to diminished long-acting beta2-adrenoceptor agonist (eg salmeterol) efficacy, thus increasing the risk of asthma attacks in children [3.3, 3.4]. The clinical insight that salmeterol may not work in children with asthma carrying this gene change (who are nevertheless widely prescribed this medicine) led to a proof-of-concept randomised controlled trial comparing asthma control with salmeterol versus a controller medicine working through a different receptor [3.5]. The trial demonstrated for the first time that a personalised medicine approach may be more effective in the management of children's asthma, in comparison to the current 'one-size-fits-all' approach. These results led to the first real-life randomised controlled trial of precision medicine in children's asthma, recruiting from 235 GP practices across England and Scotland. This study confirmed that prescribing according to beta2-adrenoceptor genotype results in greater long-term improvements in paediatric asthma-related quality of life in comparison to standard prescribing methods [3.6, 3.7].

3. References to the research

[3.1] Soares, P., Fidler, K., Felton, J., Tavendale, R., Hövels, A., Bremner, S. A., Palmer, C. N. A., & Mukhopadhyay, S. (2018). Increased medication costs for filaggrin-related eczema and asthma. *British Journal of Dermatology*, *179*(3), e136–e136. https://doi.org/10.1111/bjd.17042 [Quality Validation: Output published in leading peer reviewed journal].

[3.2] 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., & Custovic, A. (2008). Gene-environment interaction in the onset of eczema in infancy: Filaggrin loss-of-function mutations enhanced by neonatal cat exposure. *PLoS Medicine*, *5*(6), e131. https://doi.org/10.1371/journal.pmed.0050131 [Quality Validation: Output published in leading peer reviewed journal].

[3.3] Basu, K., Palmer, C. N. A., Tavendale, R., Lipworth, B. J., & Mukhopadhyay, S. (2009). Adrenergic beta(2)-receptor genotype predisposes to exacerbations in steroid-treated asthmatic patients taking frequent albuterol or salmeterol. *The Journal of Allergy and Clinical Immunology*, *124*(6), 1188-1194.e3. https://doi.org/10.1016/j.jaci.2009.07.043 [Quality Validation: Output published in leading peer reviewed journal].

[3.4] Turner, S., Francis, B., Vijverberg, S., Pino-Yanes, M., Maitland-van der Zee, A. H., Basu, K., Bignell, L., Mukhopadhyay, S., Tavendale, R., Palmer, C., Hawcutt, D., Pirmohamed, M., Burchard, E. G., Lipworth, B., & Pharmacogenomics in Childhood Asthma Consortium. (2016). Childhood asthma exacerbations and the Arg16 β2-receptor polymorphism: A meta-analysis stratified by treatment. *The Journal of Allergy and Clinical Immunology*, *138*(1), 107-113.e5. https://doi.org/10.1016/j.jaci.2015.10.045 [Quality Validation: Output published in leading peer reviewed journal].

[3.5] Lipworth, B. J., Basu, K., Donald, H. P., Tavendale, R., Macgregor, D. F., Ogston, S. A., Palmer, C. N. A., & Mukhopadhyay, S. (2013). Tailored second-line therapy in asthmatic children with the Arg(16) genotype. *Clinical Science (London, England: 1979)*, *124*(8), 521–528. https://doi.org/10.1042/CS20120528 [Quality Validation: Output published in leading peer reviewed journal].

[3.6] Ruffles, T., Jones, C., Palmer, C., Turner, S., Grigg, J., Tavendale, R., Hogarth, F., Rauchhaus, P., Pilvinyte, K., Smith, H., Littleford, R., Lipworth, B., & Mukhopadhyay, S. (2020). Effect of controller prescribing according to rs1042713 genotype on asthma related quality of life in young people (PACT): A randomized controlled trial. *European Respiratory Journal*, *56*(suppl 64). https://doi.org/10.1183/13993003.congress-2020.4617 [Quality Validation: Output presented at the 2020 ERS International Congress, selected by the ERS from 4,500 other presentations for a press release and a press conference, with coverage from the New Scientist, and the American Academy of Sciences. The output has since been published in the leading peer-review

European Respiratory Journal. Accepted 1 January 2021. https://doi.org/10.1183/13993003.04107-2020].

Key research grants

[3.7] Somnath Mukhopadhyay, [PI], Action Medical Research. [GN2203], 2014 – 2019, 'Personalised Therapy for asthma - children's RCT', Total funding GBP277,375. BSMS allocation: GBP32,502.

4. Details of the impact

A more personalised approach to clinical management is part of the 'silent revolution' unfolding within the NHS and worldwide. The novelty of the research led by Mukhopadhyay is evidenced by Sir Stephen Holgate, an internationally respected expert in asthma, who stated that these results constitute '*one of the first demonstrations of the application of personalised medicine to the clinical management of asthma*' [Source 5.1]. The impact of the research on treatment response and genetic variation has affected diverse beneficiaries (patients and carers, clinicians, trainees and regulatory bodies) locally, nationally and internationally. The evidence provided through the body of research has been used to create a notable shift in awareness of alternative treatment options, which is now improving clinical practice, informing GP training (UK), and is formalised within international treatment guidelines (Australia). Life-changing care is now being provided for the patients and families undergoing alternative treatment.

4.1 Developing new personalised clinics for allergy-related disease care management

New paediatric personalised medicine clinics, in operation from 2016, and supported by the NHS and Rockinghorse, a Sussex-based charity, constitute a unique development at the Royal Alexandra Children's Hospital in Brighton (Royal Alex). These clinics have treated over 60 children with severe, often multi-system disease through repeat visits. The clinics draw on the deeper scientific understanding of the uniqueness of each child with regard to allergy-related diseases, and clinical problems that affect children according to their individual genetic traits and environmental exposures. This is in stark contrast to the way dermatology clinics were run previously, ie on the basis that allergy and eczema were separate entities. Leading paediatric dermatologist, Dr Jess Felton, attributes the shift in clinical practice at the Royal Alex to the research undertaken by Mukhopadhyay's team [5.2]. This shift directly influences practice by placing greater emphasis on allergy testing and the use of emollients from a very early age in children with eczema and related conditions. As a result, children under the age of 6 months, presenting with eczema are treated more proactively as the research showed that infants with these skin barrier defects develop more severe atopic disease. These clinics focus more on understanding the role of external allergens, performing skin prick testing for allergies in the dermatology outpatient clinic to help with diagnosis of selected type 1 allergies that may be adding to the severity of eczema. This joint clinic where dieticians, dermatologists and asthma specialists devise a care plan in collaboration with the child's parents has dramatically improved patient experience. NHS consultants and trainees report benefit from this innovative approach [5.2]. The carers interviewed in a 2019 survey (n=30) reported 100% satisfaction following treatment due to their changed care plan, their involvement in treatment decisions and the united approach of their clinicians [5.3]. [text removed for publication] [5.4].

4.2 Increasing awareness of the benefits of a patient-centred approach to the treatment of allergy-related diseases (healthcare professionals and the public)

To extend the clinical impact the research team disseminated their key research findings across a series of events in 2015-2016. This included study days for 43 trainee GPs in Sussex [5.5a], 44 attendees of the National Medical Students Paediatric Conference [5.5b] and presentations to 48 child health professionals in India through links with the Indian Academy of Paediatrics [5.5c]. Feedback from these events indicates that at least 124/135 (92%) of the professional audience had better awareness of how a poor response to asthma medicine could result from genetic variation in patients. All GPs in attendance confirmed they were now more likely to check whether asthma medicines were working in individual patients [5.5a-c]. The team tailored their findings to a health professional audience and disseminated them via presentations and commentary pieces in key UK health channels: Royal College of General Practitioners (RCGP), websites for the journals *Pulse* and *Nursing in Practice*. To build on this impact, the RCGP has

made this material available through its website and the research into genetic predisposition and its implications for patient care has been incorporated into the RCGP's online and in person CPD. The research underpins key guidance in the RCGP's e-learning module on allergy, developed in partnership with Thermo Fisher Scientific [5.6]. This course is designed to educate GPs about the various presentations of allergic disease, how to assess an atopic patient and when to investigate in primary care or refer to secondary care. This course has been completed by 5,489 healthcare practitioners across the UK since its launch [5.6].

In collaboration with the arts group Same Sky, the team organised and presented their work at a public participation event (May 2016) as part of the Brighton Fringe Festival (approximately 250 attendees). The views of the public, captured on video, indicate an increased understanding of a personalised approach to treatment and an interest in participating in the debate around this subject [5.7a]. Similar results were seen at the *New Scientist* Science Festival, London (2018) where 331 members of the public found the 'Personalised Medicine' stand to be important and educational, with 280 reporting a substantial increase in their understanding of how genes affect the way we respond to medicines and how genes affect diseases [5.7b]. The research findings were also presented to two primary schools in rural Portugal (52 children) and three schools in rural and urban West Bengal, India (239 children). As a result of this engagement a change in awareness of the potential of personalised medicine was recorded [5.7c].

4.3 Improving asthma management through genotype-based prescribing

New treatments for severely affected children have proved to be life changing for individual patients. One patient, Ewan Mackintosh, has declared that having faced multiple ineffective courses of treatment, the research-led decision to prescribe montelukast based on his individual genotype, caused his severe breathlessness to disappear virtually overnight [5.8]. Similarly, this has caused other children undergoing the new treatment regime to eradicate problems faced with every day activities including climbing stairs and playing sports [5.8]. The research findings led directly to the first large-scale comparison of genotype-based personalised care with standard care in asthma anywhere in the world. This was the first time that grant funding of this scale (Action Medical Research (AMR), grant GN2203, GBP277,375) was awarded to a precision medicine randomised controlled trial in the field of children's asthma (2015). Within the trial Mukhopadhyay and colleagues demonstrated the significant benefit of prescribing according to a patient's genotype. Of the 241 patients recruited from across England and Scotland, the 121 patients randomised to the 'personalised care' group, experienced a significant improvement in their quality of life as assessed on a wide range of activities, including physical activities, school work and sleep quality in comparison to the 120 patients randomised to the 'standard NHS care' group [reference 3.6]. Completed in 2019, the AMR have noted that the successful findings of this trial, the first of its kind in children and teenagers, are helping '*the charity to make a difference*' with children affected by disabling conditions. The AMR selected the project as an Action 'Steps Forward' for 2020 and included it in their 2020 Research Review for supporters and trustees due to positive results and its potential to provide a model for other diseases. These publications are used by the charity to demonstrate the value of donors' giving, and to inspire, motivate and help with communications and fundraising to encourage potential future supporters of the charity [5.9].

4.4 Changes to Australian healthcare guidelines on asthma

In a 2015 review of childhood mortality, doctors in Australia were cautioned that the adverse gene-medicine interaction described in Mukhopadhyay and colleagues' research may have contributed to multiple asthma-related deaths in children in New South Wales between 2004 and 2013. The review revealed that a large number of children had been prescribed inhaled corticosteroids in combination with regular long-acting beta2 agonist (LABA; eg salmeterol). Citing the team's findings on the link between β receptor gene polymorphism and LABA adverse effects, the review drew the hypothesis that '*LABA use in the children who died from asthma may have, theoretically, put these children at risk of severe exacerbation and […] it might, therefore, explain the increase in asthma deaths seen in recent years*' [5.10].

In the 2015 version of the *Asthma Australia Handbook*, the national asthma guideline for health professionals in Australia, Mukhopadhyay's research is one of the key pieces of research evidence cited as part of the recommended stepwise approach to asthma management in

children, warning clinicians about the adverse gene-LABA medication interaction [5.11a-b]. As part of this approach, the guideline specifically states that response to treatment partly depends on genetics, referencing the team's finding that due to the child's genotype, only a proportion of children will respond to individual asthma treatments [5.11c]. This is to our knowledge the first example of genotype-based advice in any national guideline for asthma.

5. Sources to corroborate the impact

[5.1] Holgate, S. T. (2013). Immune circuits in asthma. *Current Opinion in Pharmacology*, *13*(3), 345–350. https://doi.org/10.1016/j.coph.2013.03.008. This confirms that the research is the first demonstration of the application of personalised medicine in clinical management.

[5.2] Testimonial from Dr Jess Felton, Lead Paediatric Dermatologist at the Royal Alexandra Children's Hospital, Brighton. This reports on the changed practice within the clinics and the improved results of treatments on children.

[5.3] Quantitative/qualitative assessments of patient/carer surveys at the Royal Alexandra's joint allergy clinics, alongside raw data. Feedback confirms improved experience for carers.

[5.4] [text removed for publication]

[5.5a-c] Quantitative and qualitative assessments of Mukhopadhyay's findings presentations to health practitioners in UK and India.

[5.6] PDF of RCGP e-learning module on allergy, with a statement from the RCGP confirming numbers trained and use within online and face-to-face CPD.

[5.7a] Brighton Fringe Festival 2016. 'BSMS Every Child is Different' video presentation https://www.youtube.com/watch?v=iL8IMGGKtNU&t=3s&ab_channel=BrightonandSussexMedicalSchool [Accessed 18 February 2021]

[5.7b] Quantitative and qualitative assessments of the New Scientist Live 2018 public engagement survey.

[5.7c] Patricia Soares PhD Thesis (July 2018) and internal analysis of the public engagement activities in West Bengal.

[5.8] Crichton, E. (n.d.). 'My symptoms virtually disappeared overnight': Tayport man hails asthma treatment as life-changing study goes global. *The Courier:* https://www.thecourier.co.uk/fp/news/local/dundee/1665157/my-symptoms-virtually-disappeared-overnight-tayport-man-hails-asthma-treatment-as-life-changing-study-goes-global/ [Accessed 18 February 2021].

[5.9] Testimonial from the Research Evaluation Manager at Action Medical Research, confirming the positive effects of the trial results and identification of this within the Action Steps Forward.

[5.10] Van Asperen, P. (2015). Deaths from childhood asthma, 2004–2013: What lessons can we learn? *The Medical Journal of Australia*, *202*(3), 125–126. https://doi.org/10.5694/mja14.01645 [Accessed 18 February 2021]. This highlights the new knowledge that genetic variation may have led to childhood mortality rates.

[5.11a] https://www.asthmahandbook.org.au/resources/medicines-guide/preventers/inhaled-corticosteroids#evref_step-up-options-in-children-with-asthma-that-is-not-controlled-by-low-dose-inhaled-corticosteroids_e-reddel-h-k-asthma. PDF available. Reference 3.5 cited p21 of 25

[5.11b] http://www.asthmahandbook.org.au/resources/medicines-guide/preventers/combinations. [Accessed 18 February 2021]. PDF available. Reference 3.5 cited p6 of 19

[5.11c] https://www.asthmahandbook.org.au/resources/medicines-guide/preventers/montelukast. [Accessed 18 February 2021]. PDF available. Reference 3.5 cited p9 of 15