Institution: University College London

Unit of Assessment: 1 – Clinical Medicine

Title of case study: Elucidating the early determinants of chronic lung disease: development of tools to enhance measurement and interpretation of lung function

1. Summary of the impact

We have made substantial contributions to the diagnosis of lung disease by providing tools to assess and interpret lung function accurately across the entire lifespan. These contributions include: effects of lung disease being more clearly distinguished from those of normal growth, development and aging; increased understanding of the early determinants of adult respiratory disease and improved diagnosis of chronic obstructive lung disease. **Commercially available equipment** for assessing lung function in infants and preschool children has been developed based on our work and our recently developed **multi-ethnic, all-age lung growth charts** have been endorsed internationally and are now in widespread use.

2. Underpinning research

Respiratory diseases cause around 50% of acute illness in children. Over 20 years, the Portex Respiratory Unit at the UCL Institute of Child Health (ICH) has developed methods and equipment, enabling studies of lung growth and development during early life. We have created sophisticated all-age, multi-ethnic 'lung growth charts' (reference equations) which have allowed effects of disease to be identified more clearly. These tools have been incorporated into commercially available equipment. Prior to the 1990s, assessment of infant lung function was limited to a few specialised physiology laboratories. Professor Janet Stocks co-founded the European Respiratory Society/American Thoracic Society (ERS/ATS) Task Force on infant lung function testing to facilitate more widespread and standardised applications. During the 1990s, an increasing number of infant lung function tests were developed and validated by this group, resulting in the first textbook in the area **[1]** which is now used in infant laboratories world-wide. Stocks has subsequently updated this textbook via a series of published reports and chapters to establish standards both for users and manufacturers **[2, 3]**.

Having successfully established standardised methods for assessing lung function in sleeping infants **[1-3]**, there remained the challenge of undertaking measurements in awake preschool children, in whom respiratory problems are common, but complex to diagnose. Children below 5 years were hitherto considered 'untestable', but the ICH team achieved a high success rate in 3-5 year-olds, and participated in international efforts to standardise their application **[3]**. Hence, for the first time, continuous assessments of lung function became feasible from birth to old age. Development of the multiple breath washout technique (collaboration with P. Gustafsson, Sweden), has revolutionised the way in which early lung disease can be detected in young children with Cystic Fibrosis (CF) **[3, 4]**. Measurements during the preschool years are predictive of lung function at school age, providing a window for earlier therapeutic interventions **[4]**.

These developments allowed increasing application in clinical management and facilitated research into the early determinants of lung disease: e.g. effects of low birth weight and maternal smoking in pregnancy on subsequent lung health, and evolution of lung disease following extremely preterm birth (MRC EPICure study) and in those diagnosed with CF. In 1998, JS established the London CF collaboration (LCFC) **[4]**, which has demonstrated that children diagnosed through newborn screening have significantly better growth and lung function when compared with their clinically diagnosed counterparts, and that undertaking routine chest CTs is not diagnostically helpful during the first year of life.

Use of lung function tests to guide clinical management of lung disease requires appropriate reference equations with which to detect abnormalities. These were, however, poorly developed for infants and preschool children and for those not of white European ancestry. Commencing in 1995

with publication of prediction equations for lung volumes from birth to adulthood, the ICH team led numerous initiatives to rectify this situation (in collaboration with Professor Philip Quanjer, Netherlands), culminating in the recent publication of 'All-age' multi-ethnic equations for spirometry **[5, 6]**. These have improved our interpretation of lung disease in children with CF and sickle cell disease, especially during the transition to adult care, and also in elderly patients with COPD.

3. References to the research

[1] Stocks J, Sly P, Tepper RS, Morgan WJ (eds). Infant Respiratory Function Testing: a practical guide. New York: Wiley-Liss, John Wiley & Sons, Inc. Publication, 1996. ISBN:0471076821. Available on request.

[2] Frey U, Stocks J, Coates A et al. Standards for infant respiratory function testing: Specifications for equipment used for infant pulmonary function testing. Eur Respir J 2000; 16:731-740. http://erj.ersjournals.com/content/16/4/731.full.pdf

[3] Stocks J, Lum S. Pulmonary function tests in infants and preschool children. In: Wilmott RW, Boat TF, Bush A, Chernick V, Deterding R, Ratjen F, eds. Kendig's disorders of the respiratory tract in children. Philadelphia, USA: Elsevier; 2012: 169-210. ISBN:978143719840. Available on request

[4] Aurora P, Stanojevic S, Wade A, et al. Lung Clearance Index at 4 years predicts subsequent lung function in children with Cystic Fibrosis. Am J Respir Crit Care Med 2011; 183: 752-8. http://dx.doi.org/10.1164/rccm.200911-1646OC

[5] Stanojevic S, Wade A, Stocks J et al. Reference Ranges for Spirometry Across All Ages: A New Approach. Am J Respir Crit Care Med 2008; 177:253-260. http://dx.doi.org/10.1164/rccm.200708-1248OC

[6] Quanjer PH, Stanojevic S, Cole TJ et al. Multi-ethnic reference values for spirometry for the 3-95 year age range: the global lung function 2012 equations. Eur Resp J 2012:40; 1324-43. http://dx.doi.org/10.1183/09031936.00080312

For all-age multi-ethnic equations, see also www.lungfunction.org.

Peer-reviewed funding:

Since 1993, the research programme has been supported by peer-reviewed grants totalling £6.8m, (JS PI: £4.7m), including £1.3m from the Wellcome Trust, £881,700 from the MRC, £700,626 from the CF Trust and £253,559 from Asthma UK.

4. Details of the impact

Over the past 15 years, the respiratory physiology team at ICH has played a major role, both nationally and internationally, in the development, validation and standardisation of methods of assessing respiratory function in infants and preschool children. As a result, standardised equipment, software and guidelines for infant and paediatric lung function tests are in widespread use around the world.

Impacts on development of equipment

In 2000 [ref 2], we published recommendations on equipment for assessing infant lung function. Accordingly, such equipment has been developed in line with our recommendations, and is now commercially available and in use world-wide. For example, we worked with CareFusion on their BabyBody device – they report on this collaboration as follows: "*The current 5th generation, Jaeger MasterScreen BabyBody, resulted from collaborative efforts of the Jaeger R&D and the Portex Respiratory Unit teams. This collaboration ensured that the MasterScreen BabyBody was cross-validated against existing, previously validated instruments, so that compliance could be achieved with the ATS/ERS guidelines* [ref 2] *which represent the current standards of paediatric health professionals in this field*". This device has been sold around the world **[a]**.

Similarly, since publication of our research showing that the lung clearance index is a far more sensitive measure of early lung disease than standard spirometry [refs 3 & 4], commercially available multiple gas washout devices such as the ndd EasyOne ProLAB have been developed, to enhance widespread international clinical usage **[b]**.

All-age reference equations for lung function

During the past five years, we have published all-age reference equations to improve accurate diagnosis of lung disease [refs 5 & 6], which have rapidly led to changes in practice (see below) and commercial equipment around the world. We made the GLI-2012 equations available through the resource website (www.lungfunction.org) which had 7,488 unique visitors in the first six months of 2013, with over 500 hits each from the USA, Canada, Japan, Germany and the Netherlands. The GLI-2012 equations have been endorsed by all major international respiratory societies including the European Respiratory Society, the American Thoracic Society, the Australian and New Zealand Society of Respiratory Science; the Asian Pacific Society for Respirology; the Thoracic Society of Australia and New Zealand; and the American College of Chest Physicians **[c]**. They have also been adopted by both national and international professional clinical and public health organisations such as the UK CF registry, the Health Survey for England **[d]** and the US NIHR Sickle Cell Anaemia Sleep and Asthma Cohort (SAC) study **[e]**.

These equations have also changed the way lung function is reported in commercial equipment, due to our identification of appropriate age-specific lower limits of normal for spirometric outcomes, rather than dependence on fixed thresholds. Morgan Scientific, a leading manufacturer of pulmonary function instrumentation and software, reports that: "*As soon as we heard about the GLI initiative we eagerly accommodated the equations, I believe we were the first manufacturer to do so. As our customer base is heavily centred in …pediatric hospitals in the USA, there has been keen interest in adopting the GLI set*" **[f]**. Other manufacturers who have confirmed their use of our equations include: CareFusion, Medical Graphics corporation, Cosmed, Ganshorn, Medikro, Medisoft, Medset, MIR, Morgan, ndd Medical and nSpire **[g]**.

Clinical benefits

One benefit of our all-age equations is that they overcome the serious potential errors which can occur when a child is switched from paediatric to adult equations at 18 years of age. Previously, this could result in a sudden apparent drop in lung function by as much as 25%, simply due to the equations selected (Kirkby et al, Eur Resp J 2011:39;1256-7). Our all-age equations remove this sudden change, and as a result, are being adopted in an increasing number of establishments to ensure a smooth transition between paediatric and adult care. In 2011, Janet Stocks was awarded a Lifetime Achievement Award by the European Respiratory Society in recognition that her work has "*helped give paediatric medicine the tools to better understand and treat the respiratory illnesses of childhood*" **[h]**. She has also recently been awarded the British Paediatric Respiratory Society 2013 lifetime achievement award in recognition of her '*commitment in advancing the care of children with respiratory disease in the UK'* **[i]**.

Change in clinical practice

Our work has been widely cited in Standard Operating Procedures for measuring lung function, demonstrating the impact our work has had on clinical practice **[j]**.

Great Ormond Street Hospital report that: *"the substantial clinical impact that the work by Professor Janet Stocks and her team has made …[has occurred] not only at Great Ormond Street Children's Hospital, but also in other respiratory units …nationally and internationally… During the past 5 years we have introduced routine lung function tests for all clinically diagnosed infants with CF throughout infancy and the preschool years to help guide management – whereas in the past objective tests of lung function only commenced from 5-6 y upwards. This has led to the description of early changes in CF hitherto unidentified and an upscaling of our management protocols… [With the] published findings of Prof Stocks' group on early structural and functional changes… patient directed escalation of therapy to halt early changes during these crucial early years is introduced – with protocols that have been adopted by other centres in the greater London region. We are now interpreting all clinical lung function results using the GLI 2012 equations,*

which has overcome problems previously faced when interpreting results from children from Black and ethnic minorities and when transitioning between paediatric and adult care. This seminal work finally makes sense of the longitudinal tracking of lung function in children through childhood, adolescence and into adulthood….we are also now routinely using MBW as a sensitive marker of early lung disease in clinical practice…. Of considerable clinical significance is Professor Stocks' detailed review of outcome measures for assessing lung function… in newborn screened CF infants. This important work led to our clinical decision to limit CT scanning (with its inherent radiation burden) to just those children who are showing unexplained clinical decline and remove it from our routine surveillance programme with cost benefits to the NHS and reduction in harm to patients **[k]**.

In addition, Yale University report that: *Our work would not have been possible without the landmark publications by the research team at the University College London (UCL)…. It is because of the outstanding work of the UCL team that I am better positioned to evaluate and manage respiratory symptoms in aging populations, both as a pulmonologist and geriatrician"* **[l]**.

Training

Fully funded research fellows from around the world regularly apply to undertake training in the specialised paediatric respiratory laboratories at ICH, such that we now have collaborative satellite sites established in Southampton, Munster, Lisbon, Barcelona, Montreal, Toronto and Australia (Melbourne, Victoria; Perth, WA and Newcastle, NSW.

5. Sources to corroborate the impact

[a] Letter of testimony from CareFusion. Copy available on request including map of international distribution.

[b] Letter of testimony from ndd. Copy available on request

[c] http://www.lungfunction.org/faq/87-faq/181-have-the-gli-2012-equations-been-recommended-for-international-use.html Endorsement by major international respiratory societies. Full list on p.1,339 of reference 6. Copy of correspondence confirmation endorsement from the American College of Chest Physicians, Asia Pacific Society of Respiratory and Australian & New Zealand Society of Respiratory Science available on request.

[d] www.ic.nhs.uk/pubs/hse10report;

[e] Confirmation provided by co-ordinator of this study at the Washington University School of Medicine. Copy available on request.

[f] Email from Morgan Scientific. Copy available on request.

[g] Results of our survey available here: http://www.lungfunction.org/manufacturers.html. Full correspondence available on request.

[h] ERS Citation available at: http://www.ersnet.org/ers-funding/awards/item/4441-2011-ers-awardees.html

[i] Copy of BPRS Award letter available on request.

[j] Standard operating protocols
i) Primary Care Commissioning "Guide to quality Assured Diagnostic Spirometry" 2013 http://www.pcc-cic.org.uk/sites/default/files/articles/attachments/spirometry_e-guide_1-5-13_0.pdf;
ii) Nursing times article "How to Interpret Spirometry" 2011, http://www.nursingtimes.net/nursing-practice/clinical-zones/respiratory/how-to-interpret-spirometry-results/5037130.article;

[k] Testimony from Consultant in respiratory paediatrics, Great Ormond Street Hospital. Copy available on request.

[l] Testimony from Yale University Medical School. Copy available on request.