Respiratory Research Review™

Making Education Easy

Issue 152 – 2018

In this issue:

Abbreviations used in this issue

CT = computed tomography
D_{LCO} = diffusing capacity of the lungs for carbon monoxide
FEV = forced expiratory volume
FVC = forced vital capacity
HR = hazard ratio
ILD = interstitial lung disease
IPF = idiopathic pulmonary fibrosis
LAM = lymphangioleiomyomatosis
NSIP/UIP = nonspecific/usual interstitial pneumonia
QOL = quality of life
VEGF = vascular endothelial growth factor

Welcome

to the September issue of Respiratory Research Review, with the topic of ILD (interstitial lung disease). The field of ILD is buzzing with activity, and it is a pleasure to see how clarity of thinking is translating into better clinical care.

Our colleagues Robert Kaner, Kevin Brown and Fernando Martinez published a synopsis of our progress over the last century for the centennial celebration of Am J Respir Crit Care Med. Possibly more germane is the review by Ganesh Raghu – 'Idiopathic pulmonary fibrosis: lessons from clinical trials over the past 25 years'. Ganish Raghu reviews the key lessons from clinical trials, one of the most important of which may have been the negative PANTHER trial, confirming that anti-inflammatory therapy with steroids has no role in the treatment of IPF (idiopathic pulmonary fibrosis).

'Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper' is set to become a landmark paper and our reference standard for the radiological diagnosis of IPF. Based on the 2011 ATS/ERS/JRS/ALAT guidelines, the authors defined diagnostic criteria further and importantly upgraded the former 'possible IPF' category to 'probable IPF', with the effect that honeycombing is not a prerequisite anymore. There is now a new indeterminate category in addition to a 'most consistent with a different diagnosis' category. The guidelines give guidance about specific clinical information, indications for tissue biopsies, and guidance for multidisciplinary teams. In a discussion paper, some of our clinical leaders in this field give suggestions on rethinking our classifications – 'Time for a change: is idiopathic pulmonary fibrosis still idiopathic and only fibrotic?'. They are discussing that the principle classification may include: i) pulmonary fibrosis driven by epithelial dysfunction; ii) pulmonary fibrosis driven by inflammatory dysfunction; iii) occupational or drug-induced pulmonary fibrosis; and iv) pulmonary fibrosis due to smoking.

We hope you enjoy the twelve papers we selected. The interested reader may enjoy exploring the following topics further: 'Lymphangioleiomyomatosis diagnosis and management: high-resolution chest computed tomography, transbronchial lung biopsy, and pleural disease management. An official American Thoracic Society/Japanese Respiratory Society Clinical Practice Guideline', a practical guideline focussing on four main clinical questions: i) the diagnosis cannot be complete based on CT features; ii) some patients may need a transbronchial lung biopsy; iii) a pleurodesis should be offered after the first pneumothorax; and iv) a pleurodesis should not be considered a contraindication to lung transplantation.

'Pulmonary alveolar proteinosis in adults: pathophysiology and clinical approach' is a very pragmatic review convincingly defining pulmonary alveolar proteinosis as an autoimmune disease with antibodies against GM-CSF (granulocyte-macrophage colony-stimulating factor) and suggesting that therapy be structured according to the concept of treating an autoimmune disease.

'Current understanding and management of pulmonary Langerhans cell histiocytosis' is a state of the art review encompassing both a review of the pathophysiology and practical treatment suggestions. 'Primary Sjögren's syndrome' is a practical review of diagnostic criteria, management options and clinical guidance in adverse events. European authors also report on the 'International management platform for children's interstitial lung disease (chILD-EU)'.

'Palliative care in interstitial lung disease: living well' (Lancet Respir Med) has a life-assuring focus highlighting patients' and caregivers' needs including: i) access to specialist care; ii) backing with support groups, rehabilitation and self-management; iii) treatment of comorbidities like sleep apnoea, reflux disease, lung cancer and cardiovascular complications; iv) treatment with disease-modifying mediations like pirfenidone or lung transplantation; and v) end-of-life care, including the discussion of advanced care planning.

We hope you enjoy reading the synopsis as much as we did creating it; this really is a rather dynamic area of respiratory illness. We are looking forward to your questions and comments.

Kind regards

Professor Lutz Beckert
lutzbeckert@researchreview.co.nz

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References: 1. Woodcock A et al. *Lancet.* 2017; 390 (10109):2247-2255. 2. Bleecker ER et al. *JACI In Practice.* 2014; 2(5): 553-561. 3. Breo Ellipta Data Sheet, GSK New Zealand. **Breo® Ellipta®** (fluticasone furoate/vilanterol trifenatate inhaler 100/25mcg per inhalation) is a **Prescription Medicine** for the regular treatment of asthma in adults and adolescents aged 12 years and older and for the regular treatment of COPD. Before prescribing please read the Data Sheet available from medsafe.govt.nz for contraindications, precautions and adverse events information. Breo Ellipta is not recommended for relief of acute symptoms or an acute exacerbation. **Adverse events involving GlaxoSmithKline products should be reported to GSK Medical Information** on 0800 808 500. Breo Ellipta was developed in collaboration with Innoviva Inc. TAPS DA1852JS/JUN18/FFT/0013 INSIGHT8780

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ERRATUM

In issue 151 of Respiratory Research Review there was a mistake in one of the comments. We should have stated that the only biologic agent funded for the treatment of asthma in NZ is omalizumab, a monoclonal antibody targeting IgE.

Diagnostic ability of a dynamic multidisciplinary discussion in interstitial lung diseases

Authors: De Sadeleer LJ et al.

Summary: These researchers retrospectively compared diagnoses made before and as the result of multidisciplinary discussions for 983 consecutive patients, among whom specific diagnoses were made for 80.5%. Among 183 patients with unclassifiable ILD, suggestions for further investigations to establish a definite diagnosis were made for 16.0%. The multidisciplinary discussions resulted in a change in diagnosis for 191 patients in those who had received a diagnosis before the discussion, while in those who had not been diagnosed prior to the multidisciplinary meetings, 79.5% received a diagnosis after the meeting. There was a trend toward better prognostic discrimination between IPF and other ILDs for diagnoses made as a result of the multidisciplinary meetings, compared with diagnoses made beforehand (p=0.08), particularly in patients who had discordant diagnoses before and after multidisciplinary discussions.

Comment: The current standard for classifying and diagnosing ILDs is via a multidisciplinary meeting because of the broad differential diagnosis, paucity of robust diagnostic criteria and significant interobserver variability. Researchers from Leuven report on almost 1000 ILD multidisciplinary meeting discussions held over 10 years. The multidisciplinary meeting diagnosis is set as the gold standard and changed from the pre-meeting diagnosis in 40% of cases; the next challenge may be to validate the multidisciplinary meeting diagnosis against objective outcomes a few months or years later. **Bottom line: an ILD multidisciplinary meeting was able to make a definite diagnosis in 80% of cases and gave recommendation for further investigations in the others.**

Reference: Chest 2018;153:1416–23
Abstract

Diagnostic utility of surgical lung biopsies in elderly patients with indeterminate interstitial lung disease

Authors: Vaszar LT et al.

Summary: The medical records of a cohort of 55 patients aged ≥75 years who had undergone surgical lung biopsy were reviewed to evaluate the benefit of this investigation for diagnosing idiopathic interstitial pneumonia. The patients' FVC was 70% and their D_{LCO} was 48% of predicted. IPF was identified in 67% of patients, including 61% of those who had high-resolution CT findings that were inconsistent with UIP (usual interstitial pneumonia). The respective 30-day and 90-day mortality rates were 10% and 15%.

Comment: These researchers report on surgical lung biopsy data on patients at least 75 years old at the Mayo Clinic. The 2011 ATS/ERS IPF guidelines suggested performing a biopsy in patients with either probable IPF or without a definite diagnosis. Seventy-seven percent of patients with possible IPF and 66% of patients with CT findings inconsistent with IPF eventually had a diagnosis of IPF from the biopsy, an endorsement of the Fleischner guidelines. However, the 30-day and 90- day mortality rates in the subgroup of patients who underwent biopsy with IPF were 15% and 21%, respectively. Lauren Troy from Melbourne articulated a sharp editorial. **Her bottom line: surgical lung biopsy and cryobiopsy should be abandoned in older patients with ILD.**

Reference: Respirology 2018;23:507–11
Abstract

An epithelial biomarker signature for idiopathic pulmonary fibrosis

Authors: Maher TM et al.

Summary: Potential biomarkers for predicting IPF outcomes were investigated using data from the PROFILE cohort study, which included treatment-naïve patients with IPF. A two-stage discovery and validation design was used. The discovery analysis evaluated 123 biomarkers in 106 individuals and 50 age- and gender-matched healthy controls, with promising, novel biomarkers further evaluated by immunohistochemical assessment of IPF lung tissue. A validation analysis examined samples from 206 additional patients recruited to PROFILE. Of four serum biomarkers considered to be suitable for replication, histological analyses established CA19-9 and CA-125 to be markers of epithelial damage. Patients with progressive disease were found to have significantly higher baseline levels of surfactant protein D (46.6 vs. 34.6 ng/mL [p=0.002]) and CA19-9 (53.7 vs. 22.2 U/mL [p<0.001]), and those whose CA-125 levels increased over a 3-month period were at greater risk of dying (HR 2.542 [CI 1.493, 4.328]).

Comment: We are in urgent need of identifying biomarkers to diagnose IPF, predict the clinical course, and forecast response to therapeutic interventions. In this paper, Toby Maher and colleagues report on the outcome of an immunoassay search of 123 biomarkers. The results fall short of finding the ideal biomarker; however, some may work in combination. At diagnosis, CA19-9, CA-125 and surfactant protein D levels were associated with increased mortality. Levels of the epithelial cell injury markers CA19-9 and CA-125 were also elevated in patients with progressive disease, and the CA-125 level increased further in the progressive phenotype. **Bottom line: once validated, the CA-125 biomarker may predict severe and progressive IPF.**

Reference: Lancet Respir Med 2017;5:946–55
Abstract

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Nintedanib with add-on pirfenidone in idiopathic pulmonary fibrosis

Authors: Vancheri C et al. on behalf of the INJOURNEY Trial Investigators

Summary: Patients with IPF and FVC ≥50% received a 4- to 5-week run-in with nintedanib 150mg twice daily and were then randomised to continue nintedanib alone (n=51) or with pirfenidone titrated to 801mg three times daily added (n=53) for 12 weeks in the open-label INJOURNEY trial. The respective rates of gastrointestinal adverse events (primary endpoint) in the nintedanib plus pirfenidone and nintedanib alone arms were 69.8% and 52.9%, and the respective mean changes in FVC from baseline to week 12 were –13.3mL and –40.9mL. Predose plasma trough nintedanib concentrations were similar regardless of whether it was administered with or without pirfenidone.

Comment: Combination treatment is successfully employed to treat asthma, hypertension, diabetes and many other illnesses. Medications licensed to treat IPF have different mechanisms of action and are safe when taken in combination (Respiratory Research Review, issue 126). This cohort of international researchers reports a small trial of adding pirfenidone to patients on regular nintedanib. Between 13% and 36% of patients discontinued one treatment, and only about half of the participants tolerated the full dose of both. Toby Maher in his accompanying editorial gives us the **bottom line: combination treatment cannot be recommended in routine clinical practice; however, this trial may suggest a new approach in treating IPF.**

Reference: Am J Respir Crit Care Med 2018;197:356–63
Abstract

The effect of anti-acid therapy on survival in idiopathic pulmonary fibrosis

Authors: Tran T & Suissa S

Summary: These authors methodologically reviewed ten observational studies reporting the impact of anti-acid therapy on mortality in patients with IPF. Four of five studies reporting that anti-acid therapy had beneficial effects in terms of mortality (pooled HR 0.46 [95% CI 0.30, 0.69]) were affected by immortal time bias; it was not clear if the fifth study was similarly affected. Among the five studies that were not affected by immortal time bias, there was no benefit of anti-acid therapy on mortality (pooled HR 0.99 [95% CI 0.81, 1.22]).

Comment: Established treatments for IPF are pirfenidone and nintedanib. The role of antireflux treatment is less clear; however, it comes with the promise that the successful suppression of microaspirations via antireflux therapy, weight loss or surgical treatment may stabilise IPF and improve survival. This methodological review of ten observational studies is casting doubt on the survival effect of antireflux treatment, mainly because of immortal time bias. The authors and also Micheal Kreuter and Ganesh Raghu in their accompanying editorial come up with the same **bottom line: the evidence for anti-acid therapy on survival remains uncertain and, eventually, only a properly conducted randomised controlled trial will give some certainty.**

Reference: Eur Respir J 2018;51:1800376
Abstract

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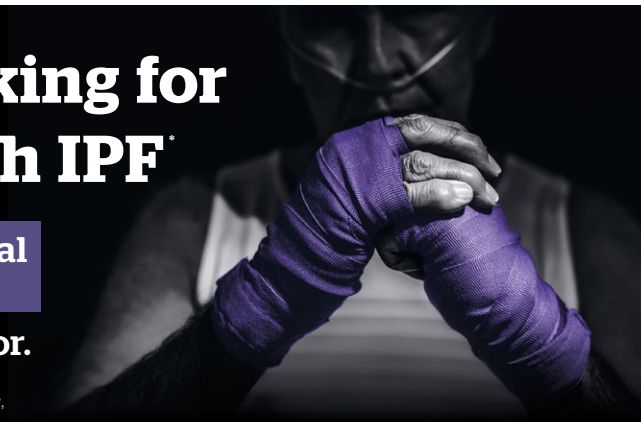

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Esbriet is a funded medicine for patients with IPF who meet pre-defined criteria. Prescription and doctors' fees may apply.

*Idiopathic Pulmonary Fibrosis

Reference: 1. Fisher M, et al. J Manag Care Spec Pharm 2017;23:(3-b):S17-S24

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Health-related quality of life in idiopathic pulmonary fibrosis

Authors: Glaspole IN et al.

Summary: Relationships between health-related QOL (according to St George's Respiratory Questionnaire) and demographic features, physiological features, comorbidities and symptoms were explored using data for 516 patients from the Australian IPF registry. While a univariate analysis showed significant associations between health-related QOL and demographic, clinical and physiological features, the only significant relationships that persisted in multivariate analyses were between St George's Respiratory Questionnaire score and dyspnoea (R^2=0.71 [p<0.0001]), cough severity (R^2=0.06 [p<0.0001]) and depression (R^2=0.04 [p<0.0001]); these associations were confirmed in a linear mixed-effects model of combined baseline and longitudinal data, along with an association with predicted FVC (p=0.005). There was no evidence of an association between health-related QOL and mortality risk.

Comment: Patient-reported outcomes focus less on lung function measures and survival, and more on health-related QOL and symptoms. Our colleagues from Australia report on the QOL of more than 500 patients using the Australian IPF registry. The three main components determining QOL are: i) dyspnoea, which is the strongest determinator of QOL; ii) unproductive, dry cough; and iii) mood disturbances in the form of depression. Managing these symptoms should become part of our focus. **Bottom line: shortness of breath, cough and depression are major contributors to QOL and should become targets for therapeutic interventions.**

Reference: Respirology 2017;22:950–6
Abstract

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A novel formulation of inhaled sodium cromoglicate (PA101) in idiopathic pulmonary fibrosis and chronic cough

Authors: Birring SS et al.

Summary: Twenty-four patients with IPF and chronic cough received inhaled sodium cromoglycate 40mg and placebo each three times a day for 2 weeks in a randomised crossover manner, separated by a 2-week washout period in this proof-of-concept phase 2 trial, and a parallel study with similar design enrolled 28 patients with chronic idiopathic cough (27 received treatment). In the IPF cohort, sodium cromoglycate use reduced the mean daytime cough frequency from 55 (baseline) to 39 per hour at day 14 compared with placebo (p=0.0241), but no significant benefit was seen in the chronic idiopathic cough cohort. Both cohorts tolerated sodium cromoglycate well, with similar incidences of adverse events between sodium cromoglycate and placebo treatments; there were no severe or serious adverse events reported.

Comment: As the Australian IPF registry data confirm, the dry unproductive cough in patients with IPF majorly influences QOL. It does not respond well to therapy for reflux disease or postnasal drip. In this study from the UK, the researchers trialled a new formulation of cromoglycate 40mg. They are not certain about the mechanism of action and don't believe the effect is due to mast cell stabilisation, but rather due to a direct activity on the C-fibre nerve activity. **Bottom line: high-dose inhaled sodium cromoglycate reduced the cough frequency by about a third in patients with IPF.**

Reference: Lancet Respir Med 2017;5:806–15
Abstract

Oxygen therapy for interstitial lung disease. A mismatch between patient expectations and experiences

Authors: Khor YH et al.

Summary: Semistructured interviews were undertaken in 12 adults with ILD who used domiciliary oxygen therapy and 12 who did not. Considerable variation in domiciliary oxygen therapy usage was reported by the patients who used this therapy. Patients who did not use oxygen therapy indicated that they would expect it to relieve dyspnoea, whereas those who did use it emphasised its benefits for other non-dyspnoea-related physical symptoms. Both groups raised practical and psychosocial challenges of using oxygen therapy.

Comment: This is another great clinical paper from our Australian colleagues, reporting on qualitative, semistructured interviews of patients with IPF just about to receive long-term oxygen therapy, and patients who had been on therapy for about a year. One recurring theme amongst all patients was that it was symbolic for the progression of their illness and a sign of the 'beginning of the end'. Patients who had been on oxygen for a while emphasised aspects like less tiredness, less heart pounding and the expectation of better survival. **Bottom line: many oxygen-naïve patients expected relief of dyspnoea with oxygen therapy.**

Reference: Ann Am Thorac Soc 2017;14:888–95
Abstract

Exposure to respirable crystalline silica in the construction industry – do we have a problem?

Authors: McLean D et al.

Summary: This pilot study measured personal exposure to respirable dust and crystalline silica in 39 samples obtained from construction workers in NZ operating at sites where exposure to respirable crystalline silica would be expected; nine static samples were obtained from adjacent locations. Around half the samples contained crystalline silica that exceeded the New Zealand Workplace Exposure Standard, and 56% exceeded the more stringent international recommendation. The highest respirable dust and crystalline silica levels were seen for the tasks of concrete grinding and cutting. Two of four static samples collected close to the cutting of silica-containing Linea board exceeded the international recommendation.

Comment: This is a local pilot study by NZ colleagues, with particular relevance to us in Christchurch. Increased silicosis exposure over a prolonged period of time can cause the progressive and irreversible ILD, silicosis. In the past, exposure was mainly through coal mining, and the NZ government has awarded more than 1500 pensions. The authors sampled respiratory dust using a portable pump set in workers driving Bobcats, jackhammering, polishing, grinding, drilling or crushing concrete or cutting Linea board. **Bottom line: concrete grinding, polishing and cutting frequently causes silica exposure exceeding agreed safety levels.**

Reference: N Z Med J 2017;130(1466):78–82
Abstract

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Pathologic findings and prognosis in a large prospective cohort of chronic hypersensitivity pneumonitis

Authors: Wang P et al.

Summary: These researchers prospectively examined the surgical lung biopsy slides of samples obtained from 119 patients with chronic hypersensitivity pneumonitis, diagnosed by surgical lung biopsy, to differentiate the major pathological patterns and score the presence of specific histopathological features. Transplant-free survival was significantly worse for patients whose slides showed a fibrotic NSIP (nonspecific interstitial pneumonia), bronchiolocentric fibrosis or UIP pattern than those whose slides showed a pattern of cellular NSIP or peribronchiolar inflammation with poorly formed granulomas. Survival did not differ among patients whose slides showed a fibrotic NSIP pattern, a bronchiolocentric fibrosis pattern and a UIP pattern. Subsets of biopsy samples from all pathological patterns included fibroblastic foci, and all slides with a UIP pattern included peribronchiolar fibrosis. The presence of fibroblast foci or dense collagen fibrosis was an independent predictor of time to death or transplantation.

Comment: Hypersensitive pneumonitis is at the frontier of research attention within ILDs. It is related to antigen exposure; however, the antigens are not always identifiable. It was thought to be rare; however, it may be the correct diagnosis in about half of cases of IPF. The interobserver variability is high and as the accompanying editorial suggests, this illness may need two treatments, one for inflammation and one for fibrosis. This Chinese-American research co-operation reports on about 200 patients with biopsy proven hypersensitivity pneumonitis. **Bottom line: patients with inflammatory forms of hypersensitive pneumonitis had a much better survival than patients with fibrotic subforms.**

Reference: Chest 2017;152:502–9
Abstract

Long-term effect of sirolimus on serum vascular endothelial growth factor D levels in patients with lymphangioleiomyomatosis

Authors: Taveira-DaSilva AM et al.

Summary: These researchers measured VEGF-D levels, lung function and extent of lymphatic disease, before and during sirolimus therapy, in 25 patients with LAM (lymphangioleiomyomatosis). FEV_1 and D_{LCO} stabilised with sirolimus treatment over a period of 4.5 years, along with resolution of lymphatic disease, reduced angiomyolipoma size and a reduction in VEGF-D level from 3720 to 945 pg/mL [p<0.0001]). Yearly changes in predicted FEV_1 and predicted D_{LCO} were reductions from –7.4 to –0.3% and from –6.4% to –0.4%, respectively (p<0.001 for both). A significant correlation was seen between lower VEGF-D level and sirolimus therapy (p<0.001), but there was no significant relationship between reduction in VEGF-D level and FEV_1 or D_{LCO} during sirolimus therapy. The magnitude of decrease in VEGF-D level was not related to the effect on lung function. Compared with patients without lymphatic disease, those with lymphatic disease had higher serum VEGF-D levels, a greater reduction in VEGF-D levels and better long-term sustained improvement in lung function.

Comment: LAM truly is a rare lung disease, where lung tissue is slowly replaced by an innumerable number of thin-walled cysts with the complications of chylous pleural effusions, pneumothoraces and progressive respiratory failure. It has now been characterised as a low-grade metastasising neoplasm and the disease can be slowed down with sirolimus. CA-125 and serum VEGF-D are emerging biomarkers. Please see the ATS guidelines and editorial for more clinical background. In this case series of 25 patients with LAM the **bottom line is: sirolimus reduces VEGF-D levels, and stabilises lung function over many years.**

Reference: Chest 2018;153:124–32
Abstract

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Predictors of mortality in pulmonary sarcoidosis

Authors: Kirkil G et al.

Summary: This analysis included 452 patients with sarcoidosis who had complete pulmonary function testing and chest imaging data and ≥8 years of follow-up. The researchers sought to determine factors that predict respiratory death in sarcoidosis. Right heart catheterisation confirmed pulmonary hypertension in 29 patients. Forty-two patients died during the study, including 38 from sarcoidosis-associated respiratory failure and four from non-sarcoidosis causes. Patients who remained alive during follow-up were significantly younger than those who died from sarcoidosis. Higher mortality was seen for black patients, stage 4 chest radiographs, >20% fibrosis on high-resolution CT scanning and pulmonary hypertension. Cox proportional hazards regression revealed that age, extent of fibrosis and pulmonary hypertension were independent predictors of mortality.

Comment: This paper from Cincinnati is based on more than 1000 patients from a sarcoidosis clinic. About half had complete data with at least 8 years of follow-up and were included in this analysis. Overall, the prognosis of sarcoidosis is good with 5-year and 10-year mortality rates of 3.9% and 9%, respectively. Sarcoidosis is often a self-limiting systemic illness requiring no specific treatment. Most patients respond to simple anti-inflammatory therapy. However, this paper may assist in identifying patients who need more aggressive therapy or who may be considered for lung transplantation. **Bottom line: patients with advanced age, extensive fibrosis on CT scan and pulmonary hypertension had increased mortality.**

Reference: Chest 2018;153:105–13
Abstract

Independent commentary by Professor Lutz Beckert.

Professor Lutz Beckert is the Head of Department of Medicine of the University of Otago, Christchurch. He is also a Respiratory Physician at Canterbury District Health Board with particular clinical interests in interstitial lung disease, pulmonary vascular disease, respiratory physiology and COPD (chronic obstructive pulmonary disease). Lutz is happy to be contacted to discuss research ideas either as a sounding board or considering future collaborations.

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New Zealand Respiratory Conference 2018

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