PRE-ACT: Prediction of Radiotherapy side Effects using explainable AI for patient Communication and Treatment modification

Collaborators: Adam Webb, Nicky Aston, Tim Rattay, Christopher Talbot and the PRE-ACT Consortium

Institutes: NIHR Leicester Biomedical Research Centre Cancer Theme

Abstract Rationale: The multi-centre European study PRE-ACT will use Artificial Intelligence (AI) to predict side-effects from radiotherapy in breast cancer patients (including skin ulceration, breast atrophy, arm lymphedema, and heart damage). Current approaches use low-dimensional statistical approaches and not all available complex imaging and genomics data. AI is already used in some aspects of radiotherapy delivery, but PRE-ACT will leverage its potential towards prediction of side-effects and provide an easily understood explanation to support shared decision-making between the patient and physician regarding radiation treatment.

PRE-ACT runs 2022-2027 and includes partners with expertise in computing, AI, radiation oncology, medical physics, genetics, psychology and health economics. Datasets from three breast cancer cohorts (REQUITE, CANTO and HypoG-01, total N=8,924) will be used to create an AI tool with built-in explainability for side-effects of breast cancer radiotherapy after regional nodal irradiation (RNI), notably, long-term arm lymphedema. Models will be incorporated into Therapanacea's ART-Plan™ radiotherapy platform to create a CE-certified world-leading product.

RNI's role in breast cancer remains debatable. An interventional randomized-controlled trial will run to test the effectiveness of our models. Some patients deemed to be high-risk for arm lymphodema will be advised of their high-risk status and provided with an arm compression sleeve. Remaining patients, and those deemed low risk, will form the control groups and will not be advised. A communication package emerging from systematic co-design methodology will ensure predictions are communicated to stakeholders effectively. The outcomes of the project will advance the field of personalised radiotherapy and bring it closer to clinical implementation.

Intrinsic expression of the cytokine receptor STX3 predicts response to α-PD-1 immune checkpoint inhibition in Non-Small Cell Lung Cancer

Collaborators: Aimee Vaughan, Gareth J Miles, Giuditta Viticchie, Ian R Powley, Tamihiro Kamata, Howard Pringle, Marion MacFarlane, Catrin Pritchard.

Institutes: Leicester Cancer Research Centre, MRC Toxicology Unit

Abstract Rationale: Lung cancer is the leading cause of cancer incidence. Non-Small Cell Lung Cancer (NSCLC) accounts for ~85% of cases; the main sub-classifications being lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC). NSCLC outcomes have significantly improved through the development of inhibitors targeting the PD-1/PD-L1 checkpoint axis. As not all patients respond there is an interest in understanding mechanisms of resistance to allow patient stratification and develop novel combinations to improve efficacy.

Objectives: This study aimed to identify cytokines highly expressed in NSCLC and investigate their role in α-PD-1 therapy response.

Methods: The Cancer Genome Atlas (TCGA) was used to determine highly expressed cytokines in NSCLC. To assess the expression and localisation of the cytokines and to monitor changes in expression in response to α-PD-1 therapy, a patient-derived-explant (PDE) model was used.

Results:

The cytokine TXLNA was found to be highly expressed in NSCLC. The cognate receptor STX3 was chosen for further study. TCGA data showed high STX3 expression linked to better survival in LUAD, while high STX3 expression linked to worse survival in LUSC. NSCLC PDEs found a response rate of 47% for pembrolizumab and 44% for nivolumab, both are within clinical trial range of response. STX3 expression in neutrophils, tumour cells and unidentified STX3 positive cells were found to have a significant positive correlation with apoptotic fold cell death in α-PD-1 treated PDEs.

Conclusion: Our findings propose the TXLNA/STX3 axis as potential predictive biomarkers and/or combination therapy targets in the treatment of NSCLC with α-PD-1 therapies.

Building a 3D Co-culture Model of Intestinal Mucosa to Investigate the Molecular Mechanisms of Inflammatory Bowel Disease

Collaborators: Aurora Vilardi, Dr Sam Khan, Dr Cristina Tufarelli

Institutes: Cancer Research Centre, Institutes University of Leicester, Leicester, UK

Abstract Rationale: Over the last decades, in-vitro systems have attempted to recapitulate the intestinal microenvironment, aiming to reduce the use of animals and the variability across and within species. 3D co-culture models rely on the stratification of different cell types lying on a biosynthetic membrane. This approach allows handling with standard culturing conditions at a moderate cost, as well as flexibility in introducing and investigating individual variables.

Objectives: The aim of this project is to build a 3D co-culture model of intestinal mucosa that mimics healthy and diseased conditions, particularly in the context of Inflammatory Bowel Disease (IBD). Methods: The co-culture of colon epithelial cells and dermal fibroblasts onto Alvetex® Scaffold, a novel membrane proven to recapitulate structural and functional features of the human intestine, would facilitate mucosal development. Robustness and integrity of these models are tested by means of fluorescein isothiocyanate dextran 20 kDa, a known marker of paracellular transport across the epithelium. In mimicking IBD, dextran sulfate sodium is applied to disrupt the intestinal mucosa and increase epithelial permeability, an established pathophysiological hallmark of IBD.

Results: Our findings suggest that 3D co-culture models supported by Alvetex® membranes can be implemented to recapitulate the intestinal mucosa. Additionally, these systems could offer a valid alternative to develop epithelial leakiness in-vitro, hence mimicking IBD. Conclusion: Overall, we developed intestinal 3D co-culture models that allow the detailed investigation of molecular and biological features by taking a reductionist approach. The reproducibility of these models further provides evidence of their potential use as preclinical and preventive tools.

Successful generation of tumour-infiltrating lymphocytes (TIL) for adoptive cell therapy from mesothelioma

Collaborators: Dean A Fennell,1 Charlotte Poile,1 Aleksandra Bzura,1 Joanna Dzialo,1 Apostolos Nakas,2 Kudzayi Kutywayo,2 Arvind Natarajan,3 Courtney Herman,3 Ryan Kovatch,3 Brittany Bunch,3 and Anand Veerapathran3

Institutes: 1 University of Leicester, Leicester, UK , 2 University Hospitals of Leicester NHS Trust, Leicester, UK, 3 Iovance Biotherapeutics, Inc., San Carlos, CA, USA

Abstract Rationale:

Objectives:

- Patients diagnosed with mesothelioma have a poor prognosis with a median overall survival of ~18 months

- First-line standard of care for patients diagnosed with mesothelioma is immune checkpoint inhibitor (ICI) therapy using ipilimumab and nivolumab followed by a second-line of care using systemic platinum-based chemotherapy
- Often, patients progress within 7 months of receiving these treatments
- Adoptive cell therapy (ACT) with autologous tumour-infiltrating lymphocytes (TIL) allows for expansion of T-cells from tumour tissue, leading to a polyclonal T-cell product with a diverse T-cell receptor (TCR) repertoire capable of recognizing an array of patient-specific tumour neoantigens
- Here, we describe the successful generation of TIL product from mesotheliomas and subsequent phenotypic and functional characterization of the TIL

Methods:

- A small-scale 22-day manufacturing process was used, including pre-rapid expansion protocol (pre-REP) and rapid expansion protocol (REP) for the generation of TIL from mesotheliomas

Results:

- 5 of 6 final TIL products (83%) manufactured from mesotheliomas showed acceptable TIL product attributes

- Median yield of TIL from the 5 tumours on Day 11 was 41×10^6 and on Day 22 was 53×10^9 viable cells

Conclusion:

- These feasibility data suggest that viable TIL can be successfully expanded from mesothelioma tumour tissue
- This manufacturing process can be used to support potential clinical investigation of TIL cell therapy in patients with mesothelioma

Bemcentinib and pembrolizumab in patients with relapsed mesothelioma: MIST3, a phase IIa trial with cellular and molecular correlates of efficacy

Collaborators: Matthew G Krebs,1 Amy Branson,1 Shaun Barber,2 Charlotte Poile,2 Amy King,3 Alastair Greystoke4, Sam Moody4, Luke Nolan5, Molly Scotland2, Liz Darlison2, Amrita Bajaj3, Bruno Morgan3, Cassandra Brookes2, Peter Wells-Jordan2, Catherine Jane Richards3, Anne L. Thomas2,3, Dean Anthony Fennell2,3

Institutes:[1] The Christie NHS FT and The University of Manchester, Manchester, UK [2]The University of Leicester, UK [3]University Hospitals of Leicester NHS Trust, UK, [4]Northern Cancer Centre, Newcastle, UK

[5]University of Southampton NHS Trust

Abstract Rationale:

Objectives:

- Targeting PD1 axis is a standard approach for treating mesothelioma, and is effective in the relapsed setting, however, responses are only observed in a fraction of patients.

- AXL receptor tyrosine kinase is a key facilitator of immune escape and drug resistance conferring a more aggressive phenotype.
- Preclinical studies suggest a more than additive effect of dual PD-1 and AXL inhibition.

Methods:

- We developed a multi-centre, phase IIa trial to evaluate the efficacy of AXL/PD-1 inhibition with bemcentinib (Bem)/pembrolizumab (Pem) in patients with mesothelioma as arm 3 of the Mesothelioma Stratified Therapy umbrella trial (NCT03654833, MiST3)

Conclusion:

- MiST3 met its primary endpoint for disease control rate and warrants further evaluation in patients who are refractory or who have relapsed following prior standard immunotherapy.

LCT13b, a transcript driven by an aberrantly active LINE1, has functional roles in colon cancer

Collaborators: Cristina Tufarelli[1,2], Chris Neophytou[2], Natasha Vafadar-Isfahani[2], Inna Guterman[1], Maria Mintseva[1], Paulina Rzasa[1], Sanya Aggarwal[1], Emma Parrot[1], Andy Lee[2], John Williams[2], David Guttery[1], Alessandro Rufini[1], Richard M Badge[3], Karen Brown[1], Jonathan N Lund[2]

Institutes: [1]Centre for Cancer Research, University of Leicester, Leicester Royal Infirmary, Leicester, UK; [2]Division of Medical Sciences and Graduate Entry Medicine, School of Medicine, University of Nottingham, Derby, UK; [3]Department of Genetics and Genome Biology, University of Leicester, Leicester, UK.

Abstract Rationale: LINE1 are repetitive DNA elements of viral origin best known for their ability to move to new locations in the DNA. A less studied aspect is the effects caused by the mobilisation independent consequences of the aberrant activation of LINE1 promoters that can, for example, produce transcripts coding novel oncogenes or drive epigenetic silencing of tumour suppressor genes.

Objectives: To determine if expression of LCT13b, a transcript driven by the aberrantly active promoter of a LINE1 that is unable to move, plays causal roles in colon cancer.

Methods: Quantitative RT-PCR in colorectal tissues; analysis of publicly available tumour (TCGA) and adenoma RNAseq datasets; ELISA on sera and protein extracts from primary tissues; stable transformation of cancer and non-neoplastic cell lines using CRISPR/Cas9 mediated HDR.

Results: LCT13b carries the intact open reading frame of GNGT1, a retina specific gene coding the gamma subunit of transducing, a heterotrimeric G-protein. LCT13b/GNGT1 is expressed in about 52% of tumours, with higher levels associated with worse survival. Patients' tumours and sera have higher levels of GNGT1 than, respectively, matched normal tissues or healthy volunteers' sera. In normal tissues, LCT13b increases with age and ~ 50% of premalignant adenomas express LCT13b. Expression of LCT13b in non-neoplastic colon epithelial cells drives their transformation.

Conclusion: Activation of the LIN1 promoter driving LCT13b increases the risk of colon cancer development in part by driving ectopic expression of GNGT1. Future work will investigate the potential of LCTs as targets for preventative therapies.

lyTesting Curcumin and Resveratrol as Novel Therapies for Endometrial Cancer in Patient Derived Explants

Collaborators: Gareth Miles, Catrin Pritchard, Esther Moss

Institutes: University of Leicester

Abstract Rationale: The patient-derived-explant (PDE) preclinical model has been shown to mirror clinical responses to chemotherapy and can be used to research potential novel therapies. An exploratory investigation was performed to investigate the effect of the drugs curcumin and resveratrol on endometrial cancer (EC).

Objectives: To determine if curcumin or resveratrol had any efficacy as a therapeutic agent in EC PDEs.

Methods: ECs from patients undergoing surgery were processed into PDEs, cultured and separately treated with standard-of-care chemotherapy (carboplatin and paclitaxel doublet), and low and high doses of curcumin and resveratrol. Multiplex immunofluorescence staining was used to analyse the viability markers c PARP (apoptosis) and Ki67 (proliferation), with CAM5.2 used as a tumour mask. Inform was used to quantify data from multiplex images. Drug response was compared to the vehicle control (DMSO).

Results: Both curcumin and resveratrol were shown to induce apoptotic and necrotic cell death responses in EC PDEs that were higher than responses observed in standard of care chemotherapy. Resveratrol was also shown to have a dose dependent impact on tumour proliferation.

Conclusion: Curcumin and resveratrol appear to induce a cell death response in EC and warrant further investigation as a potential therapeutic option.

Exceptional responses to Bruton's Tyrosine Kinase inhibitors in patients with relapsed/refractory Mantle Cell Lymphoma (MCL)

Collaborators: Dr Caroline Cowley, Dr Susann Lehman, Prof Jacqui Shaw – Leicester Molecular Diagnostics

Dr Dan Hodson – University of Cambridge

Institutes: University of Leicester, University Hospitals of Leicester, University of Cambridge.

Abstract:

Rationale: Inhibitors of Bruton's tyrosine kinase (BTKi) are a mainstay of treatment of chronic lymphocytic leukemia, where durable responses are seen in nearly all patients. In contrast, in MCL, only 75% of patients respond and responses are mostly of brief duration. Nevertheless, a small subset (~20%) of patients enter durable complete responses (CRs). We have studied a cohort of 10 exceptional responders (ER's) who entered CRs of >3 years duration (range 3-9 years) in order to: (i) understand mechanisms underlying ER and; (ii) determine whether sensitive methods of detection of residual disease might presage relapse.

Objectives:

1) Is there an underlying molecular signature associated with ER?
2) Can digital droplet PCR (ddPCR) using cellular and plasma ctDNA provide presage of relapse?
3)

Methods: Clinical and molecular features of the MCL cohort treated with BTKi were collected. Molecular features included whole exome mutational profiling, *IGHV* analysis, copy number variation and t(11;14)(q13;q32) translocation. Depth of response was assessed using patient-specific ddPCR or Lymphotrack assays.

Results: Other than t(11;14)(q13;q32), but there were no common mutations, nor mutations in genes of the B cell receptor signalling pathway. In serial cellular and plasma DNA samples, three cases initially showed clearance of ctDNA. In two patients who subsequently relapsed, it was possible to detect recurrent tumour DNA in plasma ctDNA 18 months prior to radiological and clinical relapse.

Conclusion: A subgroup of patients with R/R MCL may enter durable CR with single agent BTKi. Serial monitoring of plasma ctDNA samples demonstrated early detection of progressive disease.

Implementation of the Patient-Derived Explant (PDE) model for predicting the efficacy of immune checkpoint inhibitors (ICIs)

Collaborators: Naila Abid[1], Gareth J Miles[1], Giuditta Viticchie, Tamihiro Kamata, Howard Pringle[1], Anne Thomas[1], Marion MacFarlane, Catrin Pritchard[1]

Institutes: [1]Leicester Cancer Research Centre, University of Leicester, Robert Kilpatrick Clinical Sciences Building, Leicester Royal Infirmary, Leicester, LE2 7LG

Abstract Rationale: Melanoma accounts for the highest number of deaths from skin cancer. Despite existing therapies for metastatic melanoma, new treatments are sought due to the number of patients developing progressive disease and unresponsive to the current therapies

Objectives: To establish a metastatic melanoma (MM) PDE model, which represents the "live" culture of MM tumour fragments and retains tumour architecture intact.

Methods: Tumours were sectioned into explants and cultured for 16-24 h and then transferred into fresh media containing ICIs. On day 3, PDEs were fixed and FFPE blocks generated. Proliferation marker and cell death in the tumour and stroma areas were assessed by multi-immunofluorescence (mIF) with digital pathology quantitation to assess cell viability in response to ICIs. Biomarkers of interest (CD4, CD8, FOXP3) were also used for mIF to monitor the density and location of key immune cells in response to the ICIs.

Results: mIF analyses showed differential levels of $CD4^{+}FOXP3^{+}$ T regulatory cells (Tregs) and $CD8^{+}$ Cytotoxic T Lymphocytes (CTLs) infiltration into stroma and tumour areas of the MM-PDEs. Approximately 50% of MM tumours are "hot" tumours i.e. high levels of infiltrating CTLs. We have also observed differential apoptotic responses to ICIs across the MM-PDEs. We are currently evaluating whether there is a correlation between CTL infiltration and apoptosis induction in response to the ICIs and its link with clinical outcomes.

Conclusion: PDEs contextually preserve the tumour microenvironment. Tumours that have differential levels of T cell infiltration and are differentially sensitive/resistant to anti-PD1/anti-CTLA4 therapies in *ex vivo* culture. Further analysis of these data with clinical comparisons, will allow us to understand the extent to which the MM-PDEs are predictive of patient outcomes in the preclinical testing of ICIs.

Evaluating PTK7 Expression and Therapeutic Response to a PTK7-ADC in Breast Cancer Patient-Derived Explants (BC-PDEs): A Computational Approach for Personalized Medicine

Collaborators: Hina Zamir[1], Larissa Lezina[1], Pavandeep Sandhu[1], Naila Abid[1], Constantinos Demetriou[1], Marion MacFarlane[1], Howard Pringle[1], Catrin Pritchard[1], Himanshu Kaul[2], Gareth Miles[1]

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Abstract Rationale: The recurrence of breast cancer (BC) emphasises the need for novel treatment approaches. PTK7 is an inactive RTK highly expressed and has a role in carcinogenesis. A PTK7-targeted Antibody Drug Conjugate (PTK7-ADC) has been developed by Pfizer as a possible therapeutic option and the present study leverages BC-PDEs to assess its therapeutic impact for BC. By correlating drug responses with clinicopathological data and PTK7 expression, the aim is to direct individualized treatments and aid the design of future clinical trials with the PTK7-ADC.

Objectives: To correlate ex-vivo viability response data following treatment with the PTK7-ADC with clinicopathological data and build models that can accurately predict patient responses in the clinic to the PTK7-ADC in order to design future clinical trials.

Methods: BC-PDEs were subjected to PTK7-ADC treatment. Subsequent viability data: intrinsic and PTK7-ADC-induced changes in proliferation, apoptosis, and necrosis, intrinsic PTK7 biomarker expression and clinicopathological data were integrated to generate metadata. Metadata was analysed using R programming followed by correlational studies.

Results: Tumour displayed higher intrinsic PTK7 expression than stromal areas, with particular elevation in higher-grade tumours and a decrease in advanced stages. The PTK7-ADC induced a range of viability changes in BC-PDEs with ~30% of tumours showing a strong cell death response. However, this did not correlate with tumour grade, stage, molecular or subtype. There was also no correlation with PTK7 intrinsic expression and viability response to the PTK7-ADC.

Conclusion: In BC, while PTK7 expression correlates with more advanced disease grade, PTK7 expression is not a predictive biomarker for PTK7-ADC response, at least in BC-PDEs. This may suggest that the ADC operates through bystander mechanisms which require further investigation. suggest

Involving people with learning disabilities and carers in the process of designing visualisations about AI-generated health information: a review of methods used in the DECODE project.

Collaborators: Alison Drewett, Navjot Kaur, Sarah Rabbitte, Amy Wilkins and Panos Balatsoukas

Institutes: Loughborough University, Design School.

Abstract Rationale: Individuals with learning disabilities are at a higher risk of having multiple health conditions, and a lower life expectancy. They have challenges with verbal expression and reception, written and numerical literacy, and sensory difficulties. It is critical to identify ways to give people with learning disabilities health information.

Objectives: This paper shares early findings from focus groups with this group and their carers. These groups facilitate the design of communication methods about health information. The objective is to understand the best ways to give information to increase interest, engagement, and awareness.

Methods: Facilitators support participants in person-centred ways embracing total communication methods. The focus groups use adapted approaches to enable active involvement. Feedback mechanisms are not reliant on verbal skills and different visual stimuli are appraised.

Results: Early findings support the creation of meaningful and personally relatable materials. Designers need to be mindful of cognitive load and recognise that people with LD are experts by experience and have considerable knowledge about personal health conditions.

Conclusion: Health information needs to be produced creatively and flexibly, and not only rely on a combination of written of pictorial methods. Storytelling is a key way to support understanding. Generic recommendations need to be balanced with person-centred approaches.

Assessing regional variation and time trends in incidence of major lower extremity amputation in England

Authors: Anna Meffen [a b], Mark J. Rutherford [a], Rob D. Sayers [a b], Laura J. Gray [a]

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Introduction: Previous studies found regional variation in incidence of major lower extremity amputation (MLEA) in England, however, changes in regional variation over time and influential factors are unknown. This study uses Clinical Practice Research Datalink (CPRD) data from general practice along with link Hospital Episode Statistics to assess time trends and influential factors in regional variation of MLEA.

Methods: Non-traumatic cases of MLEA in adults between 01/01/2010 and 31/12/2019 were ascertained in HES-linked data from CPRD and linked to general practice and Lower Layer Super Output Area data for patient demographic and clinical history, this comprised the numerator data. The denominator data comprised of the CPRD dataset population data for patients registered during the study period who had available HES linkage. As access to clinical data is not available for the entire CPRD dataset, to investigate factors influencing regional variation, a large random sample was upweighted to form a denominator that represents the entire CPRD population.

Results: 8,584 patients undergoing an MLEA within the time period were identified. Age-standardised incidence rate was highest in the North East and lowest in the East of England (North East 16.1 per 100,000 person years 2010, 95%CI (11.7-20.4); East of England 8.1 per 100,000 person years 2010, 95%CI (5.5-10.7)). All regions saw a decrease in age-standardised incidence rates from 2010 to 2019. The largest decrease of 56.25% was seen in the East Midlands and the smallest of 8.1% in the North East. A proportion of the variation in incidence between regions is explainable by demographic factors.

Conclusion: Incidence of MLEA is higher in the North East of England and lowest in the East of England. Incidence of MLEA in 2019 compared to 2010 decreased with the magnitude of change differing by region the largest change being a halving of incidence in the East Midlands.

Functional investigation of PKN2 as a potential target for idiopathic pulmonary fibrosis.

Collaborators: Catherine E McMullan[1, 2, 3, 4], Molly Whitfield[5], Gill Elliott[1], Em Marston[1], Richard J Allen[2, 3], Louise V Wain[2, 3] and Katy M Roach[1, 2]

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Abstract Rationale: Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease characterised by lung tissue scarring. Rs115982800 was identified in a genome-wide association study of decline in forced vital capacity in individuals with IPF. Rs115982800 is located in the antisense RNA gene of protein kinase N2 (PKN2-AS1). The closest gene is PKN2, a serine/threonine-protein kinase expressed in fibroblasts which has been implicated in fibrotic processes underlying atrial fibrillation but has not been explored in IPF research.

Objectives: Investigate the expression and pro-fibrotic role of PKN2 in human lung myofibroblasts (HLMFs) and human IPF lung tissue.

Methods: The genotype-tissue expression (GTEx) project was used to investigate PKN2 expression in bulk tissue (lung, cultured fibroblasts) and at cellular level (15 cell-types, n=578). IPF cell atlas was used to investigate PKN2 expression in single cell RNA-sequencing data (six studies). Immunofluorescence and immunohistochemistry examined PKN2 expression in HLMFs and human lung tissue. PCR was used to investigate if PKN2 expression changes with varying concentrations of transforming growth factor beta-1.

Results: GTEx detected PKN2 in lung tissue, cultured fibroblasts and in many cell-types including IPF-associated cells (28.2% lung fibroblasts). IPF cell atlas showed increased PKN2 expression in myofibroblasts compared to alveolar macrophages and showed IPF myofibroblasts had higher expression than non-fibrotic control cells (3/4 studies). PKN2 was detected in HLMFs (immunofluorescence) and human lung tissue (immunohistochemistry), with staining in fibroblasts and epithelial cells. RT-PCR showed HLMFs express PKN2.

Conclusion: PKN2 was detected in HLMFs and IPF tissue. Further work is required to elucidate the role of PKN2 in IPF-progression.

BADDIE3 (BRICCS CT Automated Deidentification of DICOM Images and Extraction)

Collaborators: Daniel Lawday, Heath Hopewell, Dr. Lucy Beishon, Justyna Janus, Helen Estall, Joanne Wormleighton, Meghali Banerjee, BRICCS Study, Richard Bramley

Institutes: NIHR

Abstract Rationale:We would like to present a poster to highlight the BRC Health Informatics Platform service to download, process, pseudonymize, and redact DICOM images and semi structured text reports from UHL systems for Machine Learning and other studies.

Objectives: The BRC currently has many studies which require images extracted from the UHL systems. Each batch can take between 5 - 30 minutes to identify the correct patients and images, download and pseudonymize them. For a reasonably sized study this can equate to a considerable amount of time. We have created a process to automate this task programmatically which can process millions of images and text reports. This can run continuously, reduce human error and accelerates the process.

Methods: 1. extraction of PID from UHL data warehouse including patient names, NHS Numbers, Hospital System numbers, Date of Birth, address, telephone numbers, postcodes, Email address and staff names from data warehouse.
2. text mining from semi structured reports in SQL data warehouse.
3. Downloading of images using CRIS API
4. Redaction of report text and images from PID in step one

Results & Conclusion:It's now possible to automate the pseudonymization and redaction of millions of reports. This enables large scale Machine Learning studies with text and images reports that would not have been feasible with manual methods.

Association between road traffic noise and incident dementia in UK Biobank

Collaborators: Xiangpu Gong, Anna Hansell, Samuel Cai

Institutes: Centre for Environmental Health and Sustainability, University of Leicester, University of Oxford, Imperial college

Abstract Rationale: There is emerging evidence to show that road and railway noise may be associated with all-cause dementia and its subtype. The evidence is particularly limited in middle to older age people.

Objectives: To investigate the association between road traffic noise levels and incident dementia in UK Biobank

Methods: We used incident dementia and traffic noise exposure data from the UK Biobank. UK Biobank enrolled over half-million adults between the age of 37 and 73 years old, covering a variety of settings, in terms of sociodemographic setting and urban-rural mix. Cox regression was used to quantify the relationship between incident dementia and road traffic noise, while adjusting for potential confounders, this including cardiovascular risk factors and air pollution.

Results: Participant with dementia were more likely to be males, deprived, and to be previous smokers compared with the rest of UK Biobank cohort. There was a clear pattern of increased road noise level exposure and deprivation. 30% of those with dementia and who were from deprived areas had a higher day-evening-night noise (Lden) exposure above WHO recommended levels (>60 decibels, db). There was a non-significant association between road noise levels of 50 to 60 decibels and incident dementia. Further analyses are being conducted to assess if this direction of association varies based dementia subtype.

Conclusion: We observed a pattern of a higher road noise exposure based on deprivation status in people with dementia in UK Biobank. There is also a trend for adverse association between higher noise levels above 50 db and incident dementia, however this is not statistically significant.

The creation of an animation for patient and public involvement in statistical methodology research

Authors: Worboys H[1], Gray L[1], Tyrer F[2], Greenwood J[3] on behalf of the PPI-SMART and PPI-SMART public involvement group

Institutes:[1]Biostatistics Research Group, University of Leicester,[2]Leicester Real World Evidence Unit, University of Leicester,[3]PPI-SMART public contributor, University of Leicester

ABSTRACT

Background: Patient and Public Involvement (PPI) is important to all aspects of health research. However, there are very few examples of successful PPI in statistical methodology research. One of the reasons for this is that it can be challenging to find individuals who are interested in statistical methods, and statisticians may also question the importance of PPI for their studies.

Methods: This project was conducted between July 2022 and August 2023. We developed an accessible animation to describe statistical methodology and the importance of PPI input to methods-based projects. We combined storyboarding and scriptwriting with feedback from PPI members and researchers.

Results: After three stages that incorporated feedback from the relevant stakeholders, we produced a final animation about PPI in statistical methodology. The resulting animation used minimal text, simple animation techniques and was of short duration (<3 minutes) to optimise the communication of the key messages clearly and effectively.

Conclusions: The resulting animation provides a starting point for members of the public to learn about PPI in statistical methodology and for methodologists who wish to conduct PPI. We intend to do further work to explore ways in which members of the public can be more meaningfully involved in methodology research.

Exercise as an anti-inflammatory treatment in Axial Spondyloarthritis (axSpA): a proof-of-concept study.

Collaborators: Roberts MJ[1] Hamrouni M[1] Linsley V[1] Moorthy A[1,2] Bishop NC[1]

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Abstract Rationale: Axial Spondyloarthritis (axSpA) is a painful, debilitating inflammatory arthritis of the axial skeleton affecting ~1 in 200 people in the UK. The underlying inflammatory profile with AxSpA is associated with accelerated risk of developing cardiovascular disease (CVD). Regular aerobic exercise programmes can have anti-inflammatory effects and reduce risk factors for CVD development via alteration of inflammatory immune cell phenotypes, but this is unknown for axSpA.

Objectives: To investigate the effect of a 12-week walking programme vs. usual care (UC) on proportions of pro-inflammatory non-classical monocytes in people living with axSpA taking NSAID therapy.

Methods: 20 participants (were randomly assigned to usual care (UC, n=10, 7 males) or walking intervention (n=10, 5 males). Walkers completed 5x30-minute bouts of walking/week, at an RPE 12-14 (somewhat hard, heart rate 120-140 beats/min). At baseline and week 12 spinal pain (visual analogue scale), monocyte subsets (flow cytometry) and plasma IL-6 (ELISA) were assessed. Data were analysed using a two-way mixed analysis of variance (ANOVA) with time as the within factor. Statistical significance was accepted as $P<0.05$.

Results: After 12 weeks, proportions of highly inflammatory non-classical monocytes were lower and less inflammatory classical monocytes higher in the walkers compared with baseline, with the opposite occurring in UC ($P<0.001$ for interaction). Plasma IL-6 decreased by 0.73 pg/mL (95% CI, -1.07 to -0.39 pg/mL) in the walkers yet increased by 0.10 pg/mL (-0.44 to 0.24 pg/mL) in UC ($P<0.002$). Spinal pain decreased by 1.1 (-2.7 to 0.5) in the walkers and increased by 1.2 (-0.4 to 2.9) in UC.

Conclusion: Walking exercise has potential as an anti-inflammatory adjuvant therapy supplementing NSAID treatment in patients with axSpA.

Impact of Frailty on Diabetic Foot Ulceration using Clinical Practice Research Datalink (CPRD): Multistate modelling

Collaborators: Prof. Tom Yates, Paddy Dempsey, Matthew McCarthy, Sharmin Shabnam, Prof. Kamlesh Khunti, Francesco Zaccardi

Institutes: This study is funded by the NIHR Applied Research Collaboration East Midlands (ARC EM). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

The research was carried out at the National Institute for Health and Care Research (NIHR) Leicester Biomedical Research Centre (BRC).

Abstract Rationale: Diabetic Foot Ulcers (DFU) are a major complication of diabetes associated high morbidity and mortality. There is limited evidence on how frailty impacts upon the risk of developing DFU.This study investigated the impact of frailty on DFU development whilst accounting for the competing risk of death.

Methods: Data on adults with diabetes was collected from 2000 to 2022 through Clinical Practice Research Datalink (CPRD) Gold. Frailty was recorded using the Electronic Frailty Index (eFI). A multistate model was used to investigate three possible transitions: Transition 1, 'Diabetes' to DFU; Transition 2 'Diabetes' to 'Mortality'; Transition 3 'DFU' to 'Mortality'. The model was adjusted for age, sex, ethnicity, BMI, deprivation, and smoking status.

Results: 191,173 participants with a median follow-up of 8.78 [IQR: 4.78, 12.55] years were included. At age 60 years, the proportion of men who progressed to living with DFU at ten years follow-up according to frailty status were: Fit 2.31% [95% CI: 2.07,2.58], Mild 2.35% [2.12, 2.62], Moderate 2.78% [2.42, 3.20], Severe 2.96% [2.36, 3.70] and for women were Fit 1.66% [1.48, 1.86], Mild 1.72% [1.54, 1.92], Moderate 2.10% [1.83, 2.41], Severe 2.32% [1.85, 2.89]. The proportion of men who progressed to mortality at ten years follow-up were: FIT 19.29% [18.80, 19.80], Mild 24.73% [24.11, 25.40], Moderate 33.14% [32.20, 34.10], severe 42.72% [41.13, 44.33] and for women were FIT 15.40% [14.97, 15.83], Mild 19.87% [19.34, 20.40], Moderate 26.94% [26.14, 27.76], Severe 35.23% [33.83, 36.65].

Conclusion: Frailty increased the probability of developing a DFU and mortality.

Exploring the impact of air pollution exposure on bacterial behaviour and epithelial cell interaction

Collaborators: Lillie Purser, Jo Purves, Leighton Blake-Greaney, Sean Brennan, Chris Brightling, Julian Ketley, Julie Morrissey

Institutes: University of Leicester

Abstract Rationale: Air pollution is the single largest environmental health risk worldwide. Exposure to the most harmful component of air pollution, particular matter (PM), has been linked with non-communicable diseases including chronic obstructive pulmonary disease (COPD). Exposure to PM is one of the biggest risk factors for COPD disease exacerbations, that are frequently linked with bacterial infection by *Haemophilus influenzae* and *Moraxella catarrhalis*. COPD patients are also known to have a distinct lung microbiome composition when compared to healthy patients, with the balance of commensals and pathogens influencing epithelial integrity. However, the direct effects of PM on bacterial behaviour, and therefore their interaction with the lung epithelium, are unknown,

Objectives: Elucidate the impact of air pollution exposure on bacterial behaviour and bacteria-host interaction.

Methods: RNA-sequencing, qRT-PCR, cell culture infection, confocal imaging, ICP-MS.

Results: *H. influenzae* that were exposed to PM showed a significant iron-uptake response, potentially linked with an observed increase in epithelial cell adhesion through the upregulation of protein F, that is known to facilitate binding to respiratory epithelium.

Conclusion: Exposure of *H. influenzae* to a key component of air pollution significantly increases its ability to adhere to epithelial cells, a behaviour that is fundamental to its ability to cause infection.

Self-Care in Women Living with HFpEF: a Narrative Synthesis

Collaborators: McAllister, J.; Lawson, C.; Harte, A.; Singh, S.; Howe, J.

Institutes: LHIIP, Wellcome Trust, UHL, UoL, BRC

Abstract Rationale: Little is known about self-care within the majority female sex/gender population living with heart failure with preserved ejection fraction (HFpEF).

Objectives: To summarise and synthesise existing evidence.

Methods:

Study Design:

- All published methods
- No date limits

Narrative data was extracted for thematic analysis and data synthesis. Screening and full-text were reviewed by two independent researchers.

Inclusion criteria:

- HFpEF: >40% of sample
- Women: >40% of HFpEF (or total sample if not disaggregated)
- Self-care must be the focus

The Role of KCa3.1 Channels in Aortic Valve Stenosis

Collaborators: Molly Whitfield124, Saadia Aslam1,Metesh Acharya3, Stephen MDuffy2,Giovanni Mariscalco3,Gerry McCann14,Peter Bradding2 4,KatyMRoach2 4, Anvesha Singh14

Institutes:1Department of Cardiovascular Sciences, University of Leicester, United Kingdom2Department of Respiratory Sciences, University of Leicester, United Kingdom3Department of Cardiac Surgery, Glenfield Hospital, Leicester, United Kingdom4National Institute for Health Research Leicester Biomedical Research Centre, Glenfield Hospital, Leicester, United Kingdom.Abstract
Rationale:Aortic stenosis (AS) is characterised by the accumulation of fibrotic extracellular matrix and calcific mineral within the aortic valve (AV) leadingto reduced leaflet mobility, left ventricular outflow obstruction, and subsequent myocardial fibrosis (MF). Myofibroblasts are the key cells implicated in fibrosis owing to their pronounced and persistent production of extracellular matrixand contractile activity. KCa3.1 channels are expressed by myofibroblasts and promote pro-fibrotic activity in rodent hearts and several human organs. However, there is no data on the role of KCa3.1 channels inAS.

Objectives: To examine the expression and function of the KCa3.1 ion channel expression in MF and AS.

Methods: AVs were collected from severe AS patients undergoing surgical AV replacement. AV fibroblasts were isolated from the AV tissue. qRT-PCR, immunohistochemistry, immunofluorescence and patch clamp electrophysiology were utilised. The function of KCa3.1was examined using the selective KCa3.1 channel blocker senicapoc.Results:IHC/IF staining confirmed KCa3.1 protein expression in both AV fibroblasts andtissue. Patch clamp electrophysiology revealed functional KCa3.1 ion channels. KCa3.1 currents elicited by the channel opener 1-EBIO were blocked by senicapoc, proving the drug is efficacious in AV fibroblasts. qRT-PCR also confirmedbasal expression of KCa3.1 mRNA(KCNN4)in AV fibroblasts that was increased by TGF□1. Furthemore, senicapoc significantly reduced TGF□1-induced α-smooth muscle actin mRNA expression in AVfibroblasts.

Conclusion: The KCa3.1 ion channel is expressed in cultured stenotic AV fibroblasts and tissue, and may therefore contribute to the development of AS. Moreover, TGF□1-dependent upregulation of the channel suggests the biological effects of TGF□1 may be linked with KCa3.1 channel activity. Blocking KCa3.1 may represent an unexploited therapeutic target in reducing pro-fibrotic myofibroblast activity in AS

Development and application of a novel ex vivo patient-derived explant microbiome (PDEM) co-culture model for therapeutic screening of anticancer agents

Collaborators: Panashe Kativu[1], Rushad Malhotra Mukhtyar[1] Giuditta Viticchie[1], Despoina Theofanous[1], Caleb Green[1], Paulina Rzasa[1] Karen Brown[1], Sam Khan[1]

Institutes: [1]Leicester Cancer Research Centre, Department of Genetics & Genome Biology, University of Leicester, Leicester LE2 7LX, UK

Abstract Rationale: The gut microbiome interacts with intestinal cells and can drive colorectal cancer development, modulate immune responses and response to anticancer therapies. Existing in vitro models to study host-microbiome interactions lack features critical for accurately evaluating therapeutic interventions in a pre-clinical setting such as the tumour microenvironment, interactions with intrinsic immune cells and the microbiota.

Objectives: This project aims to develop a colorectal tissue patient-derived explant (PDE)-microbiome coculture model that preserves the complex tumour environment and cell interactions ex vivo. This model will help elucidate the impact of the microbiome on the immune system and the efficacy of cancer treatment and preventive therapies.

Methods: Fresh tumour obtained from 3 patients was used to optimise culture conditions. PDEs were recovered overnight (16h) in DMEM media, then cultured for 24h in DMEM supplemented with 1-10% fetal calf serum (FCS) or autologous serum (AS) +/- Insulin and Selenium (I/S) before harvesting. Multiplexed immunofluorescence for apoptosis, proliferation and tumour-associated markers was performed, followed by image analysis and quantitation of biomarker expression using Inform software (Akoya Biosciences).

Results: PDEs across all conditions resulted in increased tumour and stromal apoptosis, with a mean range of 1-22% compared with 0.5-0.7% in uncultured controls (T0). Mean tumour and stromal proliferation ranged from 3-50% in culture versus 20-22% in T0. PDEs cultured in 10% FCS + I/S resulted in the lowest levels of tissue necrosis and were similar to T0, at 7% and 10% respectively.

Conclusion: Preliminary results suggest that PDE culture maintains tissue integrity for up to 40h and enables the assessment of phenotypic biomarkers allowing future evaluation of drug response.

Synchronising accelerometery and exercise testing to describe clinically meaningful evaluations of free-living physical activity following pulmonary rehabilitation.

Collaborators: Phoebe H.I. Lloyd-Evans[1,2,3], Alex V. Rowlands[3,4,5], Wincey Katagira[6], Bruce J Kirenga[6], Pauline Ndagire[6], Dominic Malcolm[7], Sally J. Singh[1,2], Mark W Orme[1,2,3].

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3) Assessment of Movement Behaviour Group (AMBer), Leicester Lifestyle and Health Research Group, Diabetes Research Centre, University of Leicester, Leicester, United Kingdom.
4) NIHR Leicester Biomedical Research Centre, Leicester, United Kingdom.
5) Alliance for Research in Exercise, Nutrition and Activity (ARENA), UniSA Allied Health and Human Performance, University of South Australia, Adelaide, Australia.
6) Makerere University Lung Institute, Kampala, Uganda
7) School of Sport, Exercise and Health Sciences, Loughborough University, Loughborough, United Kingdom.

Abstract Rationale: Pulmonary rehabilitation (PR) is recommended for patients with post-tuberculosis lung disease (PTLD) to increase physical activity (PA). Evaluation of PA intensity does not currently account for individual differences in exercise capacity (1). Consequently, it can be challenging to evaluate changes in PA following PR in an individualised and clinically meaningful manner (2).

Objectives: To describe changes in PA following PR.

Methods: Trial of PR for patients with PTLD in Uganda (3). Participants (n=16; aged 39.8±3.3 years) wore a waist-worn accelerometer during the incremental shuttle walk test (ISWT) to generate personalised intensity cut-points associated with each of the 12 levels of the ISWT (1.80- 9.54kmph) (Figure-1a). An additional cut-point (½ level-1) was defined to show a lower intensity (>0.9km/h). PA assessed using generic moderate-to-vigorous PA (MVPA), brisk walking and vigorous PA (VPA) cut-points (4) were compared to individualised ISWT cut-points. Time spent in free-living PA above these generic and personalised cut-points was compared for 7-days pre and post 6-weeks PR.

Results:

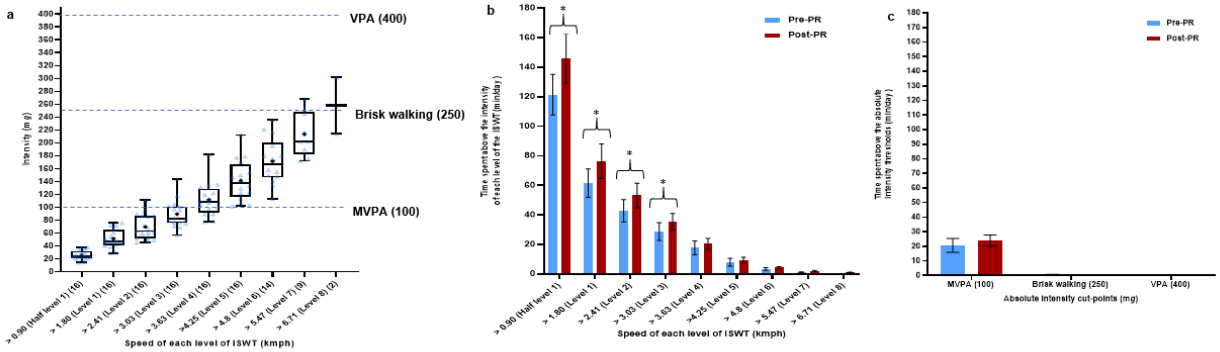

Figure 1a-b:
a) Box plot with scatter showing median, IQRs and range for intensity for each level of the incremental shuttle walk test (ISWT) before pulmonary rehabilitation. Moderate to vigorous physical activity (MVPA), brisk walking and vigorous physical activity (VPA) cut-points are shown (4).
b) Mean ± SE time spent per day for free-living physical activity above an intensity equivalent to each level of the incremental shuttle walk test (ISWT), before and after pulmonary rehabilitation.
c) Mean ± SE time spent per day for free-living physical activity above the defined generic intensity cut-points (MVPA, Brisk walking, VPA), before and after pulmonary rehabilitation.

Following PR, individualised cut-points showed participants were more physically active, spending +25 min/day moving equivalent to above ISWT ½ level- (>0.9kmph) (p=0.0006), of which +15 min/day were above ISWT level-1 (>1.80 kmph) (p=0.0110) and +6 min/day above ISWT level-3 (>3.03 kmph) (p=0.0443) (Figure-1b). There were no significant changes in PA determined using generic intensity cut-points (Figure-1c).

Conclusion: Individuals with PTLD were more physically active and at greater intensities following PR. Using individualised PA intensity cut-points may offer additional insights and be more sensitive to changes following PR.

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One year health-outcomes in adults hospitalised with COVID-19 who received systemic corticosteroid treatment: prospective cohort study

Collaborators: Richard J Russell[1], Olivia C Leavy[2], Steven Kerr[3], Ewen Harrison[3], Annemarie Docherty[3], Nazir Lone[3], Louise Wain[2], Aziz Sheikh[3], Chris Brightling[1], Rachael Evans[1]

Institutes:

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2. Department of Population Health Sciences, University of Leicester, UK
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Abstract Rationale: Prolonged health problems are common after COVID-19 and often persist beyond one year. Corticosteroids improve survival in patients with acute COVID-19 requiring oxygen therapy, but little is known about whether corticosteroids improve longer-term outcomes.

Objectives: To investigate whether systemic corticosteroids administered for acute COVID-19 affect health outcomes 1 year after hospital discharge.

Methods: Data from a UK multicentre cohort study of survivors post-hospital with COVID-19 (PHOSP-COVID) was used to compare health outcomes at 1 year between patients administered steroids for acute COVID-19 and those not. Included patients received at least supplemental oxygen during admission. Primary outcome was health-related quality of life (EQ5D-5L utility index). Secondary outcomes included patient reported outcome measures (e.g., FACIT fatigue score), measures of physical performance (e.g., incremental shuttle walk test) and measures of organ function (e.g., lung function). Propensity weighting was used to allow comparison between treatment groups.

Results: 1226 patients discharged between 1/2/20 and 31/3/21 were included: 64.4% male, mean age 58.6 years and 18.1% received invasive mechanical ventilation. 731 (59.6%) received corticosteroids. Balance between treatment groups was achieved (standardised mean difference <0.1) using weighting by the inverse of propensity for treatment. At 1 year median (IQR) EQ5D-5L utility index was 0.77 (0.60, 0.88) in patients who received steroids and 0.76 (0.62, 0.88) in those who did not (p=0.77). There were no differences in any secondary outcomes between patients receiving steroids or not.

Conclusion: Systemic corticosteroids administered during acute COVID-19 do not affect rates of persistent health problems 1 year after hospital discharge.

Personal air pollution exposure during morning commute car and active transport journeys

Collaborators: Marios Panagi [a], Hannah R. May [b], Jolanta A. Obszynska [b], Megan S. Evans [b,c], Anna L. Hansell [c], John Gulliver [c], Joshua D. Vande Hey [a,c]

Institutes:

a School of Physics and Astronomy, University of Leicester, b Leicester City Council, c Centre for Environmental Health and Sustainability, University of Leicester

Abstract Rationale: This study was undertaken to determine concentrations of pollutants by commute (active mode and driving mode), to gain an understanding of the differences between using real-life routes that were meaningful in a local context.

Objectives: We investigated the differences in pollutant concentrations in real world journeys in a typical medium-sized city in the UK. The results of which will be used to guide Leicester City Council policy and public messaging.

Methods:NO_2, O_3 and $PM_{2.5}$ concentrations were monitored on weekday morning commutes into Leicester city centre on four routes. A driving commute was made on all four routes and were paired with measurements made via an active commute (either driving or cycling). The average commute exposure to pollutants was determined and the inhaled dosage was estimated.

Results: Average in-car NO_2 and O_3 concentrations were higher than that measured in the cycling and walking. Average in car $PM_{2.5}$ were lower than average concentrations measured during cycling and whilst walking. We calculated higher cumulative doses of pollutants in the active commute compared to the driving commute. However, the health benefits of exercise, through improved physical and mental health as outlined in the literature are expected to outweigh any adverse impacts of the inhaled dosage of pollutants monitored.

Conclusion: Concentrations of air pollutants in cars can be considerably higher than concentrations faced by active travellers. Commuters sitting in cars can both miss the benefits of physical activity and be exposed to higher levels of NO_2 than in active transport, which is particularly important in countries like the UK with NOx exceedances.

Exploring whether lean body mass and cardiorespiratory fitness predict the acute drop in glucose levels following the initialisation of a low-calorie meal replacement diet in young adults with type 2 diabetes mellitus

Collaborators: Rishi Jobanputra, Professor Thomas Yates, Dr Matthew McCarthy

Institutes: 1. Diabetes Research Centre, University of Leicester, Leicester, UK 2. National Institute for Health Research (NIHR) Leicester Biomedical Research Centre, University Hospitals of Leicester NHS Trust and the University of Leicester, Leicester, UK

Abstract Rationale: Low-calorie meal replacement (LCMR) can lead to diabetes remission, however the trajectory of the acute glucose response and how measures of whole-body health, such as lean body mass (LBM) and cardiorespiratory fitness (CRF) affect this remain unknown.

Objectives: Understanding the trajectory of glucose levels during a 13-day period, when a LCMR intervention is delivered. To explore whether LBM and CRF influence this.

Methods: Twelve young adults with T2DM (BMI = 32.6 kg/m^2) were randomised to LCMR therapy. Continuous glucose monitoring (CGM) was conducted over the first 13-days. Exposure variables included LBM and CRF. Statistical analysis investigated the repeated day-by-day response.

Results: There was a significant effect for day (p<0.001), glucose levels reduced by ~2mmol/L from 9.30mmol/L [95% CI: 7.86 to 10.73] to 7.36mmol/L [95% CI: 6.27 to 8.46] from baseline to day-7 of the intervention, with minimal further reduction to day-13. The shape of this response was influenced by LBM and CRF (p<0.05) for interaction. Individuals with a low % LBM had increased glucose at baseline but displayed a greater drop in glucose during the start of the intervention. For example, between baseline and day-7, there was a 2.43 [95% CI: 1.67 to 3.20] mmol/l drop in those with a low LBM, compared to a drop of 1.43 [95% CI: 0.72 to 2.14] mmol/l in those with high LBM. Results for CRF found that those with a low fitness also displayed a greater drop in glucose during the start of the intervention, dropping by 2.14 [95% CI: 1.58 to 2.70] mmol/l after day-7, compared to 1.72 [95% CI: 0.70 to 2.74] mmol/l in those with high fitness.

Conclusion: Initialisation of a LCMR reduces glucose levels within the first 7-days. Reductions are further pronounced in individuals with a low LBM and low CRF, which requires further exploration.

Assessing Post-COVID Fatigue: A FACIT-Fatigue Study in Patients with and without Diabetes One Year After Hospitalisation

Collaborators: Safoora Gharibzadeh[1], Clare Gillies[1], Ash Routen[2], Claire Lawson[3,4], Cameron Razieh[1,5], Francesco Zaccardi[1], Louise Wain[6], Rachael Evans[7,8], Christopher Brightling[7], Simon Heller[9], Melanie Davies[4,10], John Petrie[11,12], Naveed Sattar[13], Jonathan Valabhji[14,15], Tom Yates[2,16], Kamlesh Khunti[1]

On behalf of the PHOSP-COVID Study Collaborative Group

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7. The Institute for Lung Health, NIHR Leicester Biomedical Research Centre, University of Leicester, Leicester, UK
8. University Hospitals of Leicester NHS Trust, Leicester, UK
9. Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK
10. NIHR Leicester Biomedical Research Centre and Diabetes Research Centre, College of Life Sciences, University of Leicester, Leicester, UK
11. School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Northern Ireland, United Kingdom
12. School of Cardiovascular and Metabolic Health, College of Medical and Veterinary Sciences, University of Glasgow, Glasgow G12 8TA, UK
13. Division of Metabolism, Digestion & Reproduction, Faculty of Medicine, Imperial College London, London, UK
14. Division of Metabolism, Digestion & Reproduction, Faculty of Medicine, Imperial College London, London, UK
15. Department of Diabetes and Endocrinology, St Marys Hospital, Imperial College Healthcare NHS Trust, London, UK
16. Department of Cardiovascular Sciences, University of Leicester, Leicester, United Kingdom

Objectives: Long-COVID refers to a condition where individuals do not recover for an extended period following the onset of COVID-19 symptoms, regardless of whether they were tested or not. Common symptoms include fatigue, myalgias, cough, sleepiness, and headache, with fatigue being predominant

among both hospitalised and non-hospitalised patients. In this study, we aimed to investigate the relationship between Long-COVID and diabetes, specifically focusing on fatigue, in individuals with and without diabetes one year after hospitalisation for COVID-19.

Methods: Our research, part of the PHOSP-COVID study, involved a multicentre, long-term follow-up of adults discharged from UK hospitals after COVID-19. We conducted detailed assessments at 12 months post-discharge. We utilised the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) scale to measure fatigue levels.

Results: The analysis encompassed 2,545 patients discharged between March 7, 2020, and March 31, 2021. Among them, 538(21%) had diabetes. PWD tended to be older, had higher rates of obesity, and had more comorbidities. One year after COVID-19 hospital discharge, fatigue scores were significantly higher in patients with diabetes, with scores of 40.0 (28.0-47.0) compared to 37.0 (26.0-45.0) in individuals without diabetes ($p<0.01$). Factors such as age, gender, ethnicity, socioeconomic status, and comorbidities also played a significant role in fatigue levels.

Conclusion: In conclusion, this study highlights the significant impact of diabetes on Long-COVID outcomes, with a particular emphasis on persistent fatigue. These results underscore the importance of addressing the long-term physical and mental health effects of Long-COVID, especially in individuals with diabetes, and the need to reduce disparities in healthcare outcomes for this population.

Public attitudes to data sharing and an opt-out approach to research participation: insights from the PHAST trial's national survey

Collaborators: Dr Sian Baldock, the PHAST PPI group, and Prof Matt Bown

Institutes: University of Leicester BHF Cardiovascular Research Centre, University of Leicester Department of Cardiovascular Sciences

Abstract Rationale: NHS Digital routinely process healthcare data to facilitate NHS services. Millions are spent on time-consuming data collection in trials when electronic data could also provide outcomes at a fraction of the cost.

Objectives: To determine public acceptability towards an opt-out approach for trial participation and data sharing.

Methods: For PHAST (**P**eripheral arterial disease, **H**igh blood pressure, and **A**neurysm **S**creening **T**rial), a survey was developed with Patient and Public Involvement (PPI) input. The survey adopted a layered information approach and was distributed via social media.

Results: Of 210 respondents, 86.9% thought opt-out was reasonable. The acceptability improved following provision of additional information with more males finding the proposed trial approach reasonable (93.4% vs 87.6% females). 93.8% thought sharing pseudonymised data with researchers was acceptable.

Conclusion: This research identifies, in the context of a large, pragmatic, low-risk clinical trial, the majority consider an opt-out approach to trial participation and data sharing to be acceptable. There remains a small, but important proportion of the public who consider this approach to be unacceptable however, suggesting more must be done nationally to demonstrate the value of data sharing for research. A focus is needed on transparency, trust, and careful control, whilst avoiding specialist information overload.

Creation of a protocol to investigate the impact of the indoor environment on asthma patients

Collaborators: Thiphanie P. Riveron[a,b,c,d], Rebecca L. Cordell[b,c,d], Chris E. Brightling[d] and Anna L. Hansell[a,c,d]

Institutes:

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[c] Leicester NIHR Health Protection Research Unit in Environmental Exposures and Health, University of Leicester, Leicester, United Kingdom

[d] Leicester NIHR Biomedical Research Centre (Respiratory theme), Glenfield Hospital, Leicester, United Kingdom

Abstract Rationale: Nowadays, people spend 90% of their time indoors, which can lead to long-term exposure to indoor air pollutants with potential to trigger respiratory symptoms.

Objectives: To investigate personal exposure to volatile organic compounds (VOCs), particulate matter ($PM_{2.5}$) and fungi, and the contributions of these pollutants to disease symptoms/severity, in severe asthmatics

Methods: Protocols for a pilot study were developed and tested. Lung function and symptoms were monitored for 4 weeks via peak flow and asthma quality of life questionnaires. Air pollutant sensors measuring VOCs, $PM_{2.5}$, fungi were installed inside the participants' dwelling for one week.

Results:14 asthma patients were recruited and the existing protocol successfully collected complete data in 8/14 homes and partial data in the remaining 6 homes. The clinical protocol was well tolerated and adhered by the participants, but the environmental sampling protocol was less well tolerated. One patient withdrew from the study as family members were unhappy with the equipment in the living room and six patients did not follow the instructions correctly, leading to incomplete data collection. An optimisation of the sampling protocol was made to reduce the number and size of monitors, and to simplify the required patient input. The new protocol has been tested with a patient focus group and was well received.

Conclusion: The newly developed protocol requires testing within patient homes, but initial trials indicate it to be more suitable for application to larger scale studies.

Establishing a core outcome set for the BRC lifestyle theme

Collaborators: Thomas Wilkinson on behalf of BRC COS working group (Joe Henson, David Stensel, Rachael Evans, Neil Greening, James King, Luke Bryant, Thomas Yates)

Institutes: Leicester Biomedical Research Centre (BRC)

Abstract Rationale: Core outcome sets (COS) describe the minimum outcomes (and/or outcome measures) that should be measured in clinical studies. A COS is critical in the standardisation of outcomes across different trials and, as well as reducing research waste, aids in the synthesis and interpretation of data across studies.

Objectives: To develop a core outcome set for the BRC lifestyle theme.

Methods: Outcome domains and outcome measures were selected through a combination of expert knowledge from a core working group (and collaborators) and a scoping review of similar COS work. Outcome measures were chosen based on ease of use, psychometric properties, and appositeness to the BRC objectives.

Results: Whilst final development and consensus of measures is ongoing, we have established 17 core domains that will assessed: 1) Consent; 2) Demographics/EDI monitoring; 3) Health conditions; 4) Medication; 5) Biomarkers; 6) Cardiac health; 7) Anthropometric and body composition; 8) Smoking status; 9) Mental health; 10) Cognitive function; 11) Respiratory and lung functioning; 12) Symptoms; 13) Physical activity; 14) Physical function and fitness; 15) Diet and alcohol; 16) Sleep; 17) Health-related quality of life. Each domain has recommended outcome measures (e.g., GPPAQ for physical activity) and study-specific optional measures that are not mandatory but could be used in addition (e.g., RPAQ for physical activity). The COS will be operational for use by January 2024.

Conclusion: The establishment of a COS for the BRC lifestyle theme ensures that outcomes are collected using a standardised methodology and are consistent across different research studies.

A systematic review and meta-analysis of total ghrelin changes after weight loss induced by calorie restriction, exercise or a combination of both, in people with overweight or obesity.

Collaborators: Zhuoxiu Jin[1], Jiajin Li[1], Tonghui Shen[1], Alice Thackray[1,2], James King[1,2], Kevin Deighton[3], David Stensel[1,2,4,5]

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Abstract Rationale:

Objectives:

Altered gut hormone concentrations may reflect a physiological adaptation facilitating weight regain after weight loss. This study investigated changes in the orexigenic appetite hormone, total ghrelin, after weight loss achieved through calorie restriction, exercise intervention, or a combination of both.

Methods: A systematic search of PubMed (MEDLINE), EMBASE, SPORTDiscus, Cochrane Library, Web of Science, and ClinicalTrials.gov was conducted to identify randomized controlled trials (RCTs) reporting either pre- and post-intervention total ghrelin levels or the changes therein.

Results: 10 RCTs were included in the meta-analysis, representing a cohort of 1125 participants. The meta-analysis revealed a pooled standard mean difference (SMD) of 0.54 (95% CI: 0.12 to 0.96) indicating increases in ghrelin after weight loss induced by calorie restriction/exercise. There was significant between-study heterogeneity (I^2 =81.51%, Q = 49.31, df = 15, p < 0.0001). Subgroup analysis demonstrated that exercise had an SMD of 0.675 less than caloric restriction (95% CI: -1.18, -0.17; p = 0.009). Meta-regression showed a positive association between weight loss magnitude and ghrelin concentration increases (slope: 0.09; 95% CI: 0.01 to 0.16; p = 0.029).

Conclusion: Weight loss was associated with a notable increase in total ghrelin concentrations. Weight loss induced by exercise showed a more modest rise in ghrelin levels than weight loss induced by calorie restriction. Greater weight loss was linked to larger increases in ghrelin concentration.

Challenges and opportunities in resuming spirometry services in England post-pandemic with potential to adopt Artificial Intelligence decision support software: a qualitative study.

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Abstract Rationale: Spirometry services to diagnose lung disease in primary care are slowly restarting in England post-pandemic; evidence regarding best practice is limited.

Objectives: To explore perspectives on spirometry provision and potential for Artificial Intelligence (AI) decision support software to aid quality and interpretation in future pathways.

Methods: Semi-structured interviews were conducted with key stakeholders in spirometry services across England, recruited by snowball sampling. Interviews explored the pre-pandemic delivery of spirometry, restarting of services and perceptions of the role of AI. Transcripts were analysed using thematic analysis.

Results: 28 participants (mean [SD], 21.6 [9.4] years' clinical experience) were interviewed April-June 2022. Participants included 25 clinicians and 3 commissioners; 8 held regional and/or national respiratory network roles.

Four themes were identified: 1) Historical challenges in spirometry provision; 2) Inequity in post-pandemic spirometry provision and challenges to restarting spirometry in primary care; 3) Future

delivery closer to patients' homes by appropriately trained staff; 4) The potential for AI to have supportive roles in spirometry.

Conclusion: Stakeholders highlighted historic challenges and the damaging effects of the pandemic contributing to inequity in provision of spirometry nationally. Overall, stakeholders were positive about the potential of AI. General practitioners in particular were keen to explore its role in supporting clinicians in quality assessment and interpretation of spirometry. It was evident that validation of the software and trust in the process would be key for future implementation.