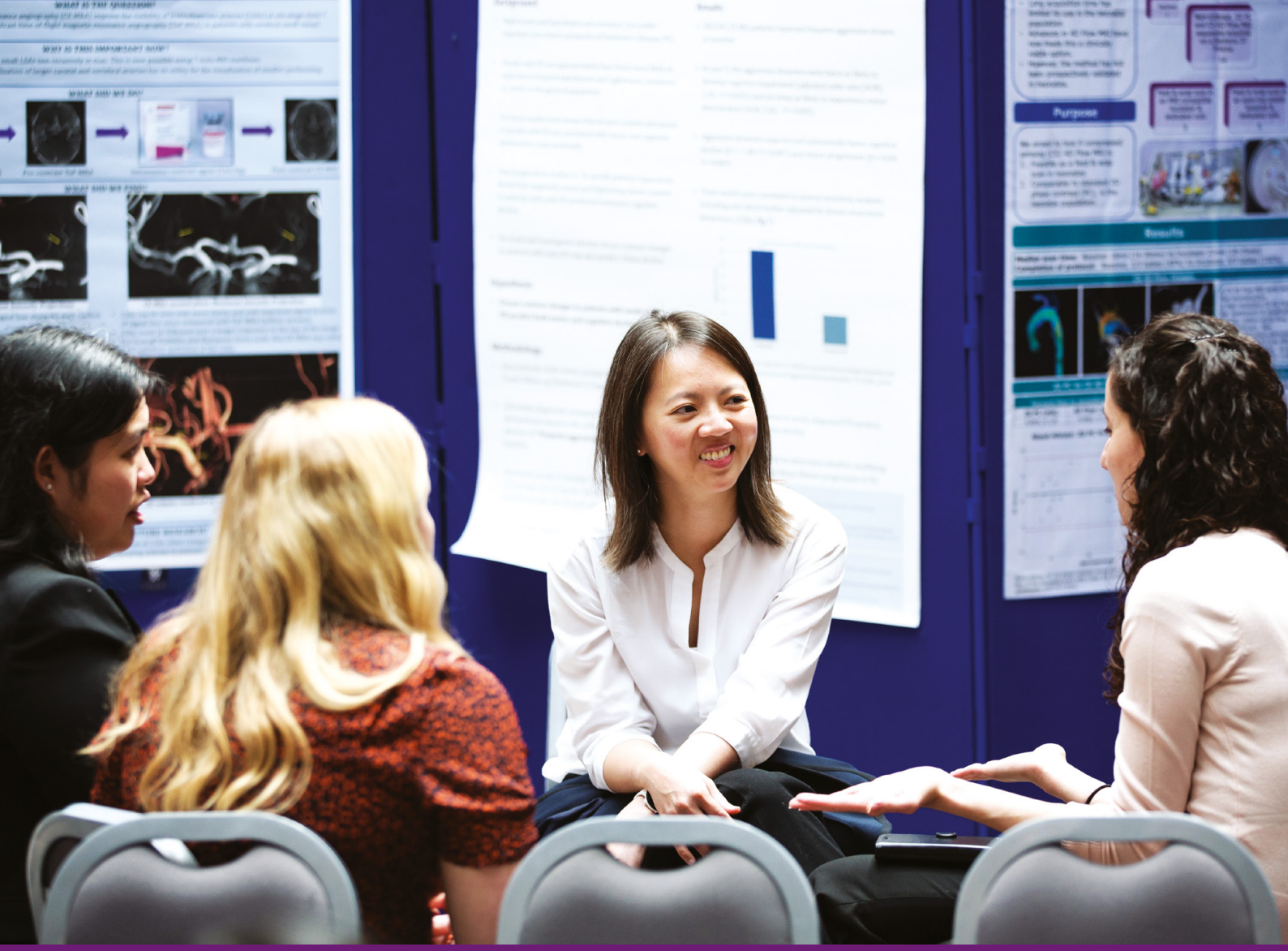

Clinical Academics in Training Annual Conference 2023

Abstract booklet

Wednesday 7 June 2023

The Academy of Medical Sciences

wellcome

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The Academy of Medical Sciences

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Contents

Welcome to CATAC 2023

'I am delighted to welcome you to our Clinical Academics in Training Annual Conference 2023, taking place in Cambridge this year. Supporting the next generation of researchers to reach their full potential is a key priority in our new vision and strategy, 'Making medical science work for everyone'. In this, our 25th year as an Academy, when we are focusing on the needs of emerging research leaders, we are thrilled to be opening up the conference and competitions this year to researchers in medicine and health across all clinical disciplines. We hope that you will find the conference a supportive environment in which to share and learn from others, as well as advance the Academy's team science approach in which the contributions of everyone are recognised.

Please join me in thanking Professor Rebecca Fitzgerald OBE FMedSci and Professor Charlotte Summers for hosting today's meeting and Professor Mary Dixon-Woods FMedSci for delivering the Keynote Speech. The Academy is aiming to give more voice to emerging research leaders in the Academy's work and I look forward to meeting you all in person at the conference.'

Simon Denegri OBE, Executive Director, Academy of Medical Sciences

'Each year, CATAC brings together researchers across disciplines to share and celebrate their work. It is a wonderful opportunity for researchers to network, spark new ideas, and build partnerships that can continue to develop well past the event itself. I hope that this conference proves both useful and inspiring, especially for those at the beginning of their academic careers, and I look forward to meeting everyone in Cambridge.'

Professor Rebecca Fitzgerald OBE FMedSci, co-host of CATAC 2023

'We have had an incredible standard of abstracts submitted this year, and I look forward to hearing more from researchers in person about the brilliant work they are doing. This conference is a fantastic opportunity to meet and build new relationships with clinical academics at all stages of their career, share experiences, and support one another. I would encourage you all to take full advantage of this chance to access the latest, cutting-edge research within academic medicine, and to share your own work with attendees.'

Professor Charlotte Summers, co-host of CATAC 2023

Keynote speaker

Professor Mary Dixon-Woods FMedSci

Mary Dixon-Woods is Director of THIS (The Healthcare Improvement Studies) Institute and The Health Foundation Professor of Healthcare Improvement Studies at the University of Cambridge.

She is a Fellow of the Academy of Social Sciences and the Academy of Medical Sciences, and an honorary Fellow of the Royal College of Physicians, the Royal College of General Practitioners, and the Royal College of Obstetricians and Gynaecologists. Mary is also a Professorial Fellow at Homerton College, Cambridge and an NIHR Senior Investigator.

Mary's programme of research is concerned with generating a high-quality evidence-base to support improvement in the organisation, quality, and safety of healthcare. Characteristically using mixed methods approaches, her work focuses on evaluation of quality and safety improvement interventions and programmes, culture and behaviour in health systems, and regulation and governance of health research and care. She has a special interest in methodological innovation in the study of healthcare improvement.

Programme

Lord Ashford Building, Anglia Ruskin University, Broad Street, Cambridge, CB1 1PT

09:00 **Registration and poster set-up**

09:30 **Welcome**
Professor Rebecca Fitzgerald OBE FMedSci

09:45 **Post-doctoral plenary competition**
Each competitor will have 10 minutes to present their research, followed by five minutes of questions from the judges and audience

'Implementation and outcomes of dolutegravir-based first-line antiretroviral therapy for people with HIV in South Africa: a cohort study'
Dr Jienchi Dorward, University of Oxford and Jubilee Street Practice

'Preterm Prelabour Rupture Of Membranes (PPROM) before 23 weeks' gestation: A prospective observational study'
Dr Laura Goodfellow, University of Liverpool and Liverpool Women's Hospital

'A randomised controlled trial of intensive compared to less intensive blood pressure control to prevent adverse cardiac remodelling in children with chronic kidney disease'
Dr Haotian Gu, King's College London and Guy's and St Thomas' NHS Foundation Trust

'Blood transcriptomic biomarkers for tuberculosis screening prior to anti-retroviral therapy initiation: A diagnostic accuracy study'
Dr Rishi Gupta, University College London

10:45 **Refreshments**

11:00 **Pre-doctoral plenary competition**
Each competitor will have five minutes to present their research, followed by five minutes of questions from the judges and audience

'Genetic variants associated with psychiatric disorders are enriched at epigenetically active sites in lymphoid cells'
Dr Mary-Ellen Lynall, University of Cambridge, Cambridgeshire and Peterborough NHS Foundation Trust and Addenbrooke's Hospital

'Genome-wide mutagenesis screens identify regulators of cellular iron metabolism and ferroptosis'
Dr Anthony Martinelli, University of Cambridge and Addenbrooke's Hospital

'Integrated analysis of preterm birth and socioeconomic status with neonatal brain structure within a cohort study'
Dr Katie Mckinnon, University of Edinburgh and Royal Infirmary of Edinburgh

'Using spatial epidemiology to measure geographic inequalities in sexual and reproductive outcomes among women aged 16-24 in England'
Dr Danielle Solomon, University College London

'Exploration of the relationship between social cognition and PTSD using longitudinal and cross-sectional methodology'
Dr Chantelle Wiseman, University of Bristol

'Prediction of prostate tumour hypoxia prior to radiotherapy using MRI-based radiomics machine learning models'
Jim Zhong, University of Leeds and Leeds Teaching Hospitals NHS Trust

12:00 **Lunch**

13:00 **Poster competitions**

14:00 **Parallel sessions**
Please attend one session of your choice

Future-proofing UK Health Research: a people-centred, coordinated approach
or
What does good patient and public involvement in research look like?

15:30 **Refreshments**

15:45 **Prize giving**
Professor Dame Anne Johnson DBE PMedSci

16:00 **Keynote**
Professor Mary Dixon-Woods FMedSci

16:45 **Closing remarks**
Professor Charlotte Summers

16.50 **Networking reception**

18:00 **Event ends**

Post-doctoral plenary competition

Dr Jienchi Dorward

University of Oxford
Jubilee Street Practice

Implementation and outcomes of dolutegravir-based first-line antiretroviral therapy for people with HIV in South Africa: a cohort study

Background
Since 2018 the World Health Organization (WHO) has recommended dolutegravir-based first-line antiretroviral therapy (ART), due to clinical trial evidence of increased efficacy compared to the previously recommended efavirenz. Initially, safety concerns regarding a potential increased risk of neural tube defects if dolutegravir was taken at conception, led the WHO to recommend restricted use among women of child-bearing potential. However, new data suggesting a lower risk of neural tube defects, led WHO to remove these restrictions in July 2019. We aimed to determine dolutegravir uptake in women, and the impact of dolutegravir on clinical outcomes in routine care in South Africa.

Methods
We analysed de-identified routinely collected data from people receiving first-line ART at 59 South African clinics from December 2019 to February 2022. We used Poisson regression, Cox proportional hazards models, and propensity score matching to assess initiation and transition to dolutegravir-based ART by gender, and associations with 12-month retention-in-care and viral suppression <50 copies/mL.

Findings
Of 45,392 adults initiating ART, 28,725 (63·3%) were women, median age was 31 years (IQR 26,38), and 31,264 (69·9%) initiated dolutegravir. Dolutegravir initiation was lower in non-pregnant (risk ratio [RR] 0·78 [95%CI 0·74,0·82], risk difference [RD] -18·4% [-21·6,-15·2]) and pregnant women (RR 0·57 [0·49,0·66], RD -35·4% [-42·3,-28·5]) versus men. At 12-months, retention-in-care (adjusted RR 1·09 [1·04,1·14], aRD 5·2% [2·2,8·4]) and viral suppression (aRR 1·04 [1·01,1·06], aRD 3·1% [1·2,5·1]) was higher in dolutegravir initiators.

Among 180,956 adults receiving first-line ART in December 2019, median age was 38 years (32,45), 124,168 (68·6%) were women and 98·6% received efavirenz. By February 2022, 121,210/158,999 (76·2%) of those in care were transitioned to first-line dolutegravir. Transition was lower in women (hazard ratio 0·56, [0·56,0·57]). Among 92,318 propensity score matched people, 12-month retention-in-care (aRR 1·02 [1·01,1·04], aRD 2·5% [2·1-2·9]) and viral suppression (1·01 [1·00,1·02], aRD 0.8% [0.3,1.4]) were slightly higher in the dolutegravir versus non-dolutegravir group.

Interpretation
Our study is significant as it is the first large study to evaluate dolutegravir uptake and compare subsequent treatment outcomes against non-dolutegravir based regimens in a public health programme in a low- and middle-income country. We used data from routine public sector clinics, which provide care according to South African Department of Health guidelines, and used programmatic outcome definitions, making our findings more generalisable to other public sector settings globally. We were unable to assess HIV drug resistance and adverse events such as weight gain, as these are not recorded in the routine dataset.

Implications

Our findings are important as they demonstrate the extent to which women were excluded from the early dolutegravir rollout. They also provide reassurance that in programmatic settings, dolutegravir is associated with similar or better outcomes than efavirenz, reflecting findings from clinical trials. While improvements in retention-in-care and viral suppression with dolutegravir were modest, incremental gains are important in reaching global HIV treatment targets. Our findings support ongoing efforts to continue the transition to dolutegravir globally. Efforts should particularly focus on ensuring that women receive updated safety information and are provided the opportunity to use dolutegravir without restrictions. More broadly, strategies to introduce newer antiretrovirals at scale should ensure that the necessary safety evidence is been generated as quickly as possible prior to rollout. Our methods also demonstrate how routinely collected data can be used to rigorously evaluate the impacts of public health interventions in low and middle income countries.

Dr Laura Goodfellow

University of Liverpool
Liverpool Women's Hospital

laura.goodfellow@liverpool.ac.uk
@DrLGoodfellow

Preterm Prelabour Rupture Of Membranes (PPROM) before 23 weeks' gestation: A prospective observational study

Background
When preterm prelabour rupture of membranes (PPROM) occurs under 23 weeks' gestation the burden of neonatal morbidity has been considered so high that termination of pregnancy for medical reasons (TFMR) is generally offered. There is a paucity of both research and clinical experience in expectant management of this condition, and parents report wide variations in care in seemingly similar clinical scenarios. Uncertainty of baseline pregnancy outcomes has hindered previous research.

The aim of this study was to provide UK population level data for pregnancies with PPROM between 16+0 and 22+6 weeks gestation, stratified according to gestation when PPROM occurred.

Methods
This prospective national population-based cohort study using UK Obstetric Surveillance System (UKOSS) identified 330 women with singleton and 38 with multiple pregnancies and PPROM 16+0 - 22+6 weeks gestation 1/9/19-28/2/21.

Infant outcomes: livebirth, survival to hospital discharge and severe morbidity, defined as intraventricular haemorrhage grade 3 or 4 and/or supplemental oxygen requirement at 36 weeks postmenstrual age.

Maternal outcomes: sepsis; surgery for placental removal; admission to intensive care and death.

Ethics approval was obtained from North London REC1. Cases were reported anonymously, as such consent from patients was neither required nor sought. Registration was through the UKOSS system only.

Findings
The estimated incidence was 0.04% of births nationally. 31% of women had a TFMR, to account for these three rates were calculated for infant outcomes: i) all TFMR excluded; ii) assuming that all TFMR and those with missing data would have died; iii) assuming that all TFMR and those with missing data would be liveborn. Rates are presented as i (ii-iii).

For singleton pregnancies the livebirth rate was 44% (30-62%), infant survival to discharge was 26% (16-54%) and 18% (12-49%) of infants survived without severe morbidity.

For twin pregnancies the rate of livebirth of both infants was 48% (43-52%). The rate of survival to hospital discharge of both infants was 26% (22-35%).

Maternal sepsis rate was 12% for singleton and 26% for twin pregnancies. Surgery for placental removal was 20% and 14%, respectively.

Five women became severely unwell with sepsis, 2 died and a further 3 required ITU care.

Interpretation
The UKOSS infrastructure has enabled the largest population-based study of PPROM prior to 23 weeks' gestation. We found that although significant numbers of pregnancies with very early PPROM have

favourable outcomes, morbidity and mortality rates in this cohort are high for mothers and infants. The data can now be used in counselling families facing this difficult situation.

There is unavoidable uncertainty concerning infant outcomes due to 31% of our population opting for TFMR and inability to follow up all infants. There is also a possibility of under reporting, particularly during the COVID-19 pandemic.

Implications

Women with PPROM prior to 23 weeks' gestation have some of the highest risks of infant and maternal morbidity that a clinician will face; moreover, the incidence is so low that an individual clinician is unlikely to develop a wealth of experience by clinical practice alone.

The authors are now working with national bodies to develop guidelines for care, as part of this we are developing a network of clinicians with an interest in this area to share best practice and optimise care. The authors are also working the patient support and advocacy group, Little Heartbeats, to develop resources to communicate the research findings to affected families.

The data provide a baseline upon which interventions aiming to improve outcomes can now be planned. Interventions may be novel treatments aimed at treating the pathology, or care bundles to optimise care using interventions already available.

Dr Haotian Gu

King's College London
Guy's and St Thomas' NHS Foundation Trust

haotian.gu@kcl.ac.uk
@espeaz

A randomised controlled trial of intensive compared to less intensive blood pressure control to prevent adverse cardiac remodelling in children with chronic kidney disease

Background
Blood pressure (BP) is a key determinant of major clinical outcomes in children with chronic kidney disease (CKD). Those with childhood-onset CKD are recognised to be predisposed to the development of left ventricular hypertrophy which is associated with adverse clinical outcomes in early adulthood.

Our previous work using auscultatory office BP highlighted that LVH was closely associated with BP and less likely in those with BP <50th percentile. We conducted the HOT-KID trial to assess whether intensive treatment (BP target <40th percentile) would prevent and reverse left ventricular remodelling compared to standard treatment (BP target 50th-75th percentile).

Methods
The HOT-KID RCT performed at 14 centres across the UK and was approved by the UK National Research Ethics Committee. Parents of children gave written informed consent.

Children with CKD were randomised (1:1) to standard treatment (systolic BP target 50th-75th percentiles) and intensive treatment (<40th percentile). Following randomisation, antihypertensive treatment in whom BP was not to target was commenced or up-titrated.

The primary outcome was the difference in left ventricular mass index (LVMi) between the two trial arms at 2 years.

The primary analysis was the comparison of the outcome measures, assessed according to allocation on an intention to treat basis.

Findings
Children were randomised to the intensive (n=64) and standard arms (n=60). The participants were followed for a median of 38.7 (IQR 28.1, 52.2) months. Throughout follow-up, mean systolic/diastolic (SD) BP in the intensive-treatment group was 103/60 (10/10) mmHg, z-score 0.06/-0.27 (0.88/1.09) and 107/64 (10/12) mmHg, z-score 0.19/0.004 (0.80/1.16) in the standard-treatment group (all P<0.001 for SBP, DBP). The average annual reduction in left ventricular mass index was similar for intensive and standard treatments: -1.9g/m2.7 (95% confidence interval [CI] -2.45 to -1.34) versus -1.2g/m2.7 (95% CI -1.54 to 0.82, P=0.76). However, at baseline elevated relative wall thickness was more marked than increased left ventricular mass index and a reduction in relative wall thickness was greater for the intensive compared to the standard treatment: -0.01 (95% CI -0.015 to -0.006) versus -0.004 (95% CI -0.0083 to 0.0011, P=0.002). Intensive treatment was not associated with significantly worse renal outcomes or greater adverse effects.

Interpretation
To our knowledge the HOT-KID study provides the first evidence from a RCT on the effects of differing BP targets on cardiac remodelling.

The main findings of the HOT-KID study are that allocation to a target below the 40th rather than above the 50th percentile does not result in a significant reduction in LVMI (although a trend to a reduction was seen) but does result in a greater reduction in concentric remodelling as measured by relative wall thickness. It suggests that 50th percentile BP target is close to the optimal target for preventing adverse cardiac remodelling in children with CKD.

Implications

Definitive evidence to determine the optimal BP target in children to reduce adverse events requires follow-up in sufficiently large numbers over many years to obtain data on clinical events. Such an undertaking is not regarded as feasible at present. The strong association of cardiac remodelling in children with CKD, left ventricular hypertrophy in particular, with adverse cardiac events in later adulthood has led to a focus on cardiac remodelling as a surrogate outcome in such children.

The HOT-KID study provides the first evidence from a RCT that cardiac re-modelling in children with CKD is closely related to BP control. This finding may lead to the change of current guidelines and providing evidence of the optimal BP target in children with CKD.

Dr Rishi Gupta

Institute of Health Informatics, University College London

r.gupta@ucl.ac.uk
@Rishi_K_Gupta

Blood transcriptomic biomarkers for tuberculosis screening prior to anti-retroviral therapy initiation: A diagnostic accuracy study

Background
Tuberculosis (TB) is a leading cause of death among people living with HIV (PLHIV). The WHO recommends systematic screening for TB among PLHIV, including using C-reactive protein (CRP). CRP has similar sensitivity but higher specificity for TB than the WHO 4-symptom screen (W4SS), but CRP performance falls short of the WHO triage test target parameters (≥90% sensitivity; ≥70% specificity). Multiple blood transcriptomic biomarkers have shown promise for TB diagnosis, but their diagnostic accuracy and clinical utility for pre-antiretroviral therapy (ART) TB screening has hitherto been untested. We sought to address this research gap among PLHIV commencing ART in South Africa.

Methods
We enrolled consecutive adults referred to start ART at a community health centre in Cape Town, irrespective of symptoms. Sputa were obtained (using induction if required) for two liquid cultures. Whole-blood RNA samples underwent transcriptional profiling using a custom Nanostring gene-panel. We measured the diagnostic accuracy of seven candidate RNA biomarkers for a TB-culture reference standard as areas under the receiver-operating characteristic curves (AUROCs), and sensitivities and specificities at pre-specified thresholds (two standard scores above the mean of healthy controls). Clinical utility was assessed using decision curve analysis. We compared performance to CRP, W4SS and the WHO target parameters.

Findings
89 (13%) of 707 participants (median CD4 count 306 cells/mm3) had culture-confirmed TB. The seven RNA biomarkers were moderately to highly correlated (Spearman rank coefficients 0.42-0.93) and discriminated TB culture-positivity with similar AUROCs (0.73-0.80). However, none of the RNA biomarkers were statistically better than CRP (AUROC 0.78; 95% CI 0.72-0.83). Diagnostic accuracy was similar between CD4 count strata, but lower among asymptomatic (AUROCs 0.56-0.65) compared to symptomatic participants (AUROCs 0.75-0.84). The RNA biomarker with the highest AUROC point estimate was a 4-gene signature (Suliman4; AUROC 0.8; 95% CI 0.75-0.86), with sensitivity 0.83 (0.74-0.9) and specificity 0.59 (0.55-0.63). In decision curve analysis, Suliman4 and CRP had similar clinical utility to guide confirmatory TB testing, but both had higher net benefit than W4SS. In exploratory analyses, multivariable models including (1) new gene combinations; and (2) CRP, Suliman4 and clinical predictors (age, gender, body-mass index, haemoglobin and CD4) did not further improve performance.

Interpretation
RNA biomarkers showed better clinical utility to guide confirmatory TB testing for PLHIV prior to ART initiation than symptom-based screening, but their performance did not exceed that of CRP, and fell short of WHO mandated targets.

Strengths of the study include the large, representative sample of consecutive participants referred for ART initiation. The cohort were extensively investigated for TB (including sputum induction), thus enabling evaluation of diagnostic accuracy compared to a culture-based reference standard. Seven RNA signatures were measured using a robust Nanostring pipeline. Limitations include the single-centre design, thus precluding assessments of generalisability across regions.

Implications
Our data demonstrate that blood RNA biomarkers do not perform any better than CRP as triage tests for TB among PLHIV prior to ART initiation. Since CRP is already widely available, including on point-of-care platforms, our findings support further evaluation of the clinical and health-economic impact of CRP-based triage for pre-ART TB screening, to inform policy.

An underlying mechanism that limits the diagnostic accuracy of RNA biomarkers for TB among PLHIV prior to ART may be upregulation of interferon signalling in untreated HIV. Since interferon activity underpins expression of TB biomarker genes, HIV-induced upregulation of interferon-stimulated genes may reduce the specificity of blood transcriptomic biomarkers for TB in this context. These findings highlight a wider need to develop interferon-independent approaches when developing host immune-response based biomarkers to support systematic infectious disease screening for PLHIV pre-ART initiation.

Pre-doctoral plenary competition

Dr Mary-Ellen Lynall

University of Cambridge
Cambridgeshire and Peterborough NHS Foundation Trust
Addenbrooke's Hospital

mel41@cam.ac.uk
@MLynall

Genetic variants associated with psychiatric disorders are enriched at epigenetically active sites in lymphoid cells

Background
Multiple psychiatric disorders have been associated with abnormalities in both the innate and adaptive immune systems. The role of these abnormalities in pathogenesis, and whether they are driven by psychiatric risk variants, remains unclear. It is also known that some genetic and environmental risks, including infections, operate trans-diagnostically across multiple psychiatric syndromes. We hypothesized that some psychiatric risk variants act via their effects on regulatory elements in specific immune cell subsets. We further hypothesized that some of these immunogenetic mechanisms may represent a common pathogenic pathway to multiple psychiatric disorders.

Methods
We tested for enrichment of psychiatric risk variants associated with multiple psychiatric disorders (trans-diagnostic risk), or 5 specific disorders (cis-diagnostic risk), in regulatory elements across multiple tissues and immune cells. We integrated genetic association data with three independent epigenetic datasets: a multi-tissue atlas (Roadmap/ENCODE), an atlas of 19 sorted immune cell subsets (Blueprint), and a dataset of ex vivo stimulated T cells and macrophages. To contextualise our results, we conducted parallel analyses of three "positive control" disorders: Alzheimer's disease, rheumatoid arthritis, and body mass index, a common comorbidity which may contribute to observed immune abnormalities in psychiatric disorders.

Findings
Trans-diagnostic risk variants were enriched at active regulatory sites in several adult and foetal brain tissue samples, as expected. Strikingly, we also found that trans-diagnostic risk variants were enriched at an independent set of regulatory elements in peripheral blood lymphoid cells (but were not enriched in myeloid cells). Our key results - enrichment of trans-risk in T cells and lack of enrichment in myeloid cells - were statistically robust to multiple comparisons and replicated in the three independent epigenetic datasets. Trans-risk for psychiatric disorders was especially enriched in stimulated T helper cells. Further investigation of risk variants for individual psychiatric disorders confirmed significant enrichment of genetic risk for schizophrenia and major depressive disorder at active promoters and enhancers in peripheral lymphoid cells, but not myeloid cells. These results were not driven by risk variants associated with body mass index.

Interpretation
These data suggest a previously unknown effect of psychiatric trans-diagnostic genetic risk on T cells. The enrichment seen in stimulated T cells suggests a possible model where environmental stimuli activate T cells to unmask the effects of psychiatric risk variants, contributing to the pathogenesis of mental health disorders. To our knowledge, this is the first in-depth investigation of the immunological implications of genetic variants conferring risk for psychiatric disorders. Future work should extend these analyses to non-European samples.

Dr Anthony Martinelli

University of Cambridge
Addenbrooke's Hospital

awm37@cam.ac.uk
@awmartinelli

Genome-wide mutagenesis screens identify regulators of cellular iron metabolism and ferroptosis

Background
Iron is essential for life, with diseases resulting from its deficiency or excess constituting a global health burden. On a cellular level, iron is incorporated into life-critical proteins, but also presents a challenge because of its ability to drive free radical formation. Despite major advances in our understanding of physiological iron homeostasis, how iron levels are tightly controlled within cells remains surprisingly poorly understood. With the recent identification of a distinct iron-dependent cell death pathway, ferroptosis, which contributes to cell death in neurological disease and may help kill tumour cells, it is essential to understand how cellular iron is regulated.

Methods
We generated fluorescent reporter cell lines that are highly sensitive to changes in cellular iron abundance by endogenously tagging Iron Regulatory Protein 2 (IRP2) to the GFP-like protein Clover. We then undertook parallel genome-wide CRISPR/Cas9 mutagenesis screens in HeLa and A549 IRP2-Clover cells to identify genes that when mutagenised disrupt normal iron homeostasis. After initial hit validation by flow cytometry and Western blot, mechanistic investigation was undertaken including using methods including qPCR, RNA-seq, ChIP-seq and analysis of alternative splicing. Susceptibility to ferroptosis was assessed by evaluating kidney cancer cell survival and lipid peroxidation after treatment with the ferroptosis-inducer erastin.

Findings
122 unique genes were identified as significant hits (FDR <0.25), of which 64 can be mapped to known pathways in cellular iron metabolism. These hits underline the importance of iron uptake via the transferrin receptor and its recycling to the cell surface, mitochondrial iron-sulfur cluster synthesis and ferritin breakdown in maintaining cellular iron homeostasis.

SETD2, a histone methyltransferase, was identified as a novel top hit, providing the first example of a chromatin modifier as a mediator of iron levels. SETD2 depletion leads increased levels of the cargo receptor NCOA4 (responsible for ferritin breakdown), intracellular iron depletion and activation of the IRP2 response to promote iron uptake. As a regulator of alternative splicing, SETD2 loss is further associated with the differential expression of NCOA4 isoforms. Finally, SETD2 mutant kidney cancer cell lines are more resistant to ferroptosis compared to wild type, whilst knockdown of SETD2 promotes resistance in wild type lines.

Interpretation
Here, we establish a robust reporting system for intracellular iron levels, definitively map the cellular pathways of iron metabolism, identify novel regulators of iron levels, and determine their impact on the induction of ferroptosis. SETD2, a novel hit in our screen, is commonly mutated in cancer, including in clear cell renal cell carcinomas where SETD2 loss of function mutations occur in up to 28% of cases. These tumours are known to be relatively resistant to induction of iron-dependent cell death and we show that this resistance corresponds to SETD2 expression, which may have implications for future therapies targeting ferroptosis.

Dr Katie Mckinnon

MRC Centre for Reproductive Health, University of Edinburgh
Neonatal Department, Simpson Centre for Reproductive Health, Royal Infirmary of Edinburgh

Integrated analysis of preterm birth and socioeconomic status with neonatal brain structure within a cohort study

Background
Preterm birth and socioeconomic status (SES) are associated with developmental outcomes and brain structure in childhood, but the relative contributions of each to brain development during the neonatal period are unknown. We investigated the associations of gestational age (GA) and SES with neonatal brain morphology, by testing three hypotheses: GA and SES are associated with brain morphology in mutually adjusted models; associations between SES and brain morphology vary across the GA range, and; associations between SES and brain development depend on how SES is operationalised.

Methods
Participants: 170 preterm and 91 term infants, median (range) GA 30+0 (22+1-32+6) and 39+4 (36+3-42+1) weeks recruited to a cohort study (Boardman, BMJ Open 2020, NRES 16/SS/0154). SES was operationalised at neighbourhood-level (Scottish Index of Multiple Deprivation [SIMD], primary measure), family-level (parent education/occupation), and subjectively (WHO Quality of Life). Brain volumes (85 parcels) and 5 whole-brain cortical measures (gyrification index [GI], sulcal depth, thickness, curvature, surface area [SA]) were calculated from MRIs at term-equivalent age. Associations of GA and SES with morphology were investigated with linear ridge regression models, including interaction (GA*SES) and covariates as per preregistration (Mckinnon, OSF 2022).

Findings
In adjusted models, low GA associated with more parcels (22/85 [26%], β range |-0.13| to |0.22|) than neighbourhood SES (1/85 [1%], β=0.17), p=<0.001. GA-associated parcels included grey/white matter and CSF. GA was associated with SA (β=0.10 [95% CI 0.02-0.18]) and GI (β = 0.16 [95% CI 0.07-0.25]); neighbourhood SES was not associated with any whole-cortex measure.

Correlations between SES measures ranged from very weak to strong. Family SES associated with more parcels than neighbourhood SES, but fewer than GA. Six parcels associated with SES measures; maternal education with left and right cerebella, left middle superior temporal gyrus, and left anterior lateral occipitotemporal gyrus/gyrus fusiformis, β range |0.09| to |-0.15|, p=0.01-0.0496; maternal occupation with right occipital lobe (grey matter), β=0.06, p=0.0496, and neighbourhood SES with right anterior medial and inferior temporal gyri (white matter), β=0.17, p=0.03. There were significant interactions between GA and family and subjective SES measures on brain structure.

Interpretation
In a UK cohort, GA and SES are both associated with neonatal brain morphology, but low GA has more widely distributed effects on neonatal brain structure than neighbourhood-level, family-level and subjective SES measures. Family-level measures (parental education and occupation) were associated with more alterations in brain structure than subjective SES and neighbourhood deprivation. Interventions designed to mitigate the adverse effects of family-level socioeconomic disadvantage during neonatal intensive care could promote healthier brain development in preterm infants. Further work is warranted to elucidate the mechanisms embedding GA and SES in neonatal brain development.

Dr Danielle Solomon

University College London

danielle.solomon@ucl.ac.uk
@df_solomon

Using spatial epidemiology to measure geographic inequalities in sexual and reproductive outcomes among women aged 16-24 in England

Background
Women aged 16-24 in England experience a significant burden of sexual and reproductive morbidity, a burden that disproportionately affects the most vulnerable populations. Addressing these health inequalities requires an understanding of unmet need within this population. To support the regional measurement of unmet need within sexual and reproductive health (SRH), we have created the Index of Unmet Need within Sexual and Reproductive Health (IUSRH). This tool combines a range of indicators within SRH (chlamydia testing and positivity rates, gonorrhoea testing and positivity rates, abortion rates, and repeat abortion rates), allowing levels of intraregional outcome disparity to be quantified and compared.

Methods
The IUSRH was created using data collected by UK Health Security Agency/Department of Health and Social Care from 2012-2019, and comprises three scores reflecting: (1) the absolute disparity of an outcome within a region, (2) a comparison of the level of disparity within a region to the mean level of disparity for England, and (3) the ranking of the region by size of outcome disparity. These scores were calculated for each NUTS2 region within England, then mapped using GIS software to describe the patterns of inequality within the population of interest during the study period.

Findings
Deprivation: On analysis of testing and abortion rates, the direction and size of intraregional outcome disparity varied between regions. The pattern of disparity was much more uniform for test positivity and repeat abortion – rates of chlamydia and gonorrhoea diagnosis, and repeat abortion, were highest in the most deprived 20% of areas within almost every region in England.

Ethnicity: There were also intraregional disparities when comparing outcomes between Black and White populations, although the pattern of inequality differed between regions: while some regions had higher testing, diagnosis, abortion and repeat abortion rates among the Black population, other regions had higher rates among the White population.

While there was no specific pattern of inequality nationally, Outer London (South) displayed the largest outcome disparities related to deprivation and ethnicity across almost all outcomes.

Interpretation
The IUSRH allowed us to assess the way that SRH-related inequalities varied between regions. Although there wasn't a national geographical pattern of outcome disparity, we were able to identify patterns of disparity at the regional level that may indicate unmet need. For example, higher testing rates in the less deprived areas of a region combined with higher diagnosis rates in more deprived areas may indicate testing need linked to deprivation. By quantifying patterns of outcome disparity at the regional level, the IUSRH should have utility for public health professionals, particularly those whose remit involves addressing inequalities within SRH.

Dr Chantelle Wiseman

University of Bristol

c.wiseman@bristol.ac.uk

Exploration of the relationship between social cognition and PTSD using longitudinal and cross-sectional methodology

Background
Social cognition is the ability to understand, process and interpret information on the social world, and includes emotion recognition and mentalisation. Three review papers have been published in the last five years that have found aspects of social cognition to be impaired in PTSD groups compared to controls. Sharp, Fonagy and Allen (2012) hypothesised that social cognitive deficits could increase the risk of PTSD developing. My doctorate focusses on whether extremes of social cognition (deficits and hypermentalisation) are risk factors for PTSD and whether social cognitive abilities affect recovery from PTSD.

Methods
Study 1: data from the ALSPAC cohort was used to measure whether social cognition in childhood is associated with outcomes of trauma and PTSD.

I designed a battery using five pre-existing social cognition measures. I developed this with feedback from a qualitative/PPI project and a pilot study. The battery was used in Study 2, a cross-sectional study using logistic regression techniques to determine if the odds of trauma and PTSD were associated with social cognition scores (n=171). Study 3: (data collection ongoing, target N=60, 56 enrolled currently) used the battery to assess if social cognition is associated with PTSD recovery.

Findings
For study 1, a parental report measure of the child's social cognition was associated with increased odds of trauma in later childhood (ORadjusted 1.32, 95% CI 1.13, 1.54, p value <0.001) and PTSD developing at age 24 years (ORadjusted 1.54, 95% CI 1.15, 2.05, p value 0.004).

For study 2, a self-report measure of hypomentalisation was associated with increased odds of PTSD (OR 4.50, 95% CI 2.79, 7.27, p value <0.001), whilst a hypermentalisation measure reduced the odds of PTSD occurring (OR 0.50, 95% CI 0.34, 0.73, p value <0.001). Little association was found with trauma as the outcome.

These associations persisted after adjusting for confounders (age, sex, verbal IQ, autism diagnosis) in both studies.

Interpretation
I found that self/ parent report measures of difficulties with social cognition are associated with increased odds of PTSD developing after adjusting for confounders. This result was found in both a longitudinal and cross-sectional study, triangulating the findings. I did not find a strong association for task-based measures of social cognition. Strengths of both of these studies are the sample size. Study 2 was limited by a cross-sectional design meaning the association found could be due to reverse causation (i.e. PTSD causing impairments in mentalising), but can be triangulated by the findings from Study 1.

Jim Zhong

University of Leeds
Leeds Teaching Hospitals NHS Trust

j.zhong@leeds.ac.uk
@DrJZed

Prediction of prostate tumour hypoxia prior to radiotherapy using MRI-based radiomics machine learning models

Background
Tumour hypoxia, a low oxygen environment, is associated with radiotherapy resistance and metastatic disease in prostate cancer. Identifying tumour hypoxia may help with patient selection for radiation boosting. Current methods of assessing hypoxia, such as using prostate biopsy samples to identify gene-based hypoxia biomarkers are invasive and hindered by sampling errors due to multi-focal tumours and intra-tumoral heterogeneity. Magnetic resonance imaging (MRI) is a potential non-invasive method of assessing hypoxia and utilising radiomics, a quantitative imaging analysis method, we aim to develop a machine learning (ML) model based on prostate MRI radiomics for prediction of tumour hypoxia.

Methods
This two centre retrospective study was ethically approved and written consent obtained (IRAS 15/NW/0559). All patients had histologically confirmed high-risk prostate cancer treated with radiotherapy. Cancers were dichotomised as normoxic or hypoxic using a validated biopsy-based 32-gene hypoxia signature. Prostate segmentation was performed on axial T2-weighted MRI sequences using RayStation. PyRadiomics was used to extract 1313 radiomic features for analysis. The cohort was split 80:20 into training and test sets. Six different ML classifiers for distinguishing hypoxia were trained and tuned using five feature selection models and five-fold cross validation with 20 repeats.

Findings
195 patients were included with 97 (49.7%) with signature determined tumour hypoxia. The model with highest mean validation area under the curve (AUC) receiver operating characteristic (ROC) curve was tested on the unseen set. The hypoxia-prediction model with best performance was derived using ridge regression and had a mean training AUC of 0.73 (SD 0.02), mean validation AUC of 0.71 (SD 0.10) and a test AUC of 0.69. For the best performing ML model the performance metrics were an overall model accuracy of 0.68, sensitivity of 0.68, specificity of 0.65, positive predictive value of 0.65, and a negative predictive value of 0.68. The five selected RFs included textural and wavelet-transformed features. This radiomics model outperformed the clinical variables only model with a mean validation AUC of 0.57 (SD 0.02).

Interpretation
Whole prostate MRI-radiomics has the potential to non-invasively predict tumour hypoxia. Identification of hypoxic prostate tumours using non-invasive imaging methods will allow for adapted and personalised treatment options in order to improve local tumour control.

A limitation to this retrospective imaging study is the lack of imaging protocol standardisation, which differ significantly among institutions. In this study, a harmonisation technique was applied to the MRI data to minimize issues related to imaging acquired on different scanners.

Using validated Ragnum hypoxia gene signature, we can provide biological validation of hypoxia for the radiomic features selected by the machine learning models.

Poster competition – Group A

Dr Daniel Whitehouse

University of Cambridge
Cambridge University Hospitals NHS Foundation Trust

A1

The relationship between proteomic biomarkers and lesion progression following traumatic brain injury: a CENTER - TBI study

Background
Progression of intracranial lesions following traumatic brain injury (TBI) is common and associated with increased mortality and morbidity. However, both clinical and radiological heterogeneity can present a significant challenge to clinicians for risk stratifying those at risk of lesion progression. Blood-based biomarkers, sampled acutely following injury, are known to associate with the burden of intracranial injury, however, the relation to the longitudinal lesion progression remains unclear.

Methods
The concentration of a panel consisting of six biomarkers (GFAP, NFL, NSE, S100B, t-tau and UCH-L1) were measured in 628 adult TBI patients with CT abnormality on acute imaging and at least one subsequent CT images within five days from injury. The volume of four lesion classes (intraparenchymal haemorrhage (IPH), oedema, intraventricular haemorrhage (IVH) and extra-axial haemorrhage (EAH)) was measured using the Brain Lesion Analysis and Segmentation Tool for CT (BLAST-CT). Descriptive, Receiver Operated Curve (ROC) analysis, univariate and multivariable regression analysis was used to assess the association between biomarker and lesion progression.

Findings
67% of subjects had progression of IPH, 57 % had progression of IVH, 42% had progression of EAH, and 68% had progression of post-traumatic oedema. GFAP ($p<0.001$), NFL ($p=0.033$), S100B ($p<0.001$), UCHL-1 ($p<0.001$) and tau ($p<0.001$) were all significantly raised in patients with progression of IPH. S100B ($p=0.035$) and NFL ($p=0.035$) were both significantly raised in patients with the progression of EAH. GFAP, NFL, NSE, S100B, t-tau and UCH-L1 were raised in patients with progression of oedema (all $p<0.001$). S100B and t-tau both had fair discrimination (AUC > 0.7) for the prediction of IPH progression, whilst GFAP, NFL, t-tau and UCH-L1 all had fair discrimination for oedema progression. On multivariable regression with adjustment for demographic, clinical, haematological, and radiological factors associated with lesion progression, there was a positive association between all six biomarkers and the volume change in IPH and oedema, with a weak association between t-tau and IVH volume.

Interpretation
These findings indicate that the acute biomarker concentration of GFAP, NFL, NSE, S100B, t-tau and UCH-L1 are acutely raised in patients who have subsequent progression of intra-axial pathology, but not extra-axial lesion types. These findings suggest the acute biomarker concentration can help inform future studies into the prediction of patients at risk of secondary injury following TBI, moving towards greater personalisation of TBI management.

Dr Ashleigh Hamilton

Queen's University Belfast
Belfast Health and Social Care Trust

A2

Understanding the Treatment Experiences of Adults Diagnosed with Early-Onset Colorectal Cancer: A Qualitative Study

Background
The incidence of early-onset colorectal cancer (defined as adults aged under 50) is increasing. A diagnosis of early-onset colorectal cancer and its treatment presents unique challenges for these patients and there is a need for better understanding of their supportive care needs.

The aim of this study was to explore the lived experiences of individuals receiving treatment for early-onset colorectal cancer, the resulting impact on their lives, and their supportive care needs.

Methods
Individuals diagnosed and treated for early-onset colorectal cancer in the UK in the last 5 years were recruited from social media. Virtual semi-structured interviews were held with participants from August 2021 to March 2022, which were recorded and transcribed verbatim. Data were analysed using thematic analysis. Ethical approval was granted by the Faculty of Medicine, Health and Life Sciences Research Ethics Committee at Queen's University Belfast.

Findings
Twenty-one individuals participated in interviews (n=16 females and n=5 males), with stage I-IV disease. Thematic analysis demonstrated five themes:

- The wide-ranging physical, psychological and social impacts of cancer treatment.
- Interaction with healthcare including the key role of healthcare professionals and frustration with the NHS.
- Support during treatment, with the main sources of support being online support and family/friends, with participants describing those around them as essential to coping.
- Areas of unmet need were identified, specifically the need for tailored information and support in the areas of mental health, sex, intimacy and fertility.
- The positive and negative impacts of COVID-19 on the treatment experience.

Interpretation
Our study highlights the unique issues experienced by this patient group during treatment, including the lack of specific care and recognition of younger adults with colorectal cancer. There is a need for more holistic care of these individuals, with service improvement particularly required in the areas of information needs, mental health, sexual health and fertility counselling.

Margaret Huang

University of Cambridge
Royal Papworth Hospital NHS Foundation Trust
Addenbrooke's Hospital

A3

Reprogramming mitochondrial metabolism to reduce organ transplant ischaemia reperfusion injury

Background
Oxidative damage following organ transplant ischaemia reperfusion injury (IRI) is initiated by a burst of reactive oxygen species (ROS) generated by reverse electron transport (RET) in mitochondria. RET is driven by complex II-mediated oxidation of the mitochondrial metabolite succinate, which accumulates extensively in ischaemic tissues. We use translational models of kidney transplantation to identify conserved metabolic changes between mice, pigs, and humans, and examine the efficacy and mechanism of protection afforded by inhibition of complex II using the small molecule inhibitor disodium malonate (DSM).

Methods
Mouse and pig kidney IRI (bilateral renal pedicle clamping) and pig and human ex vivo normothermic machine perfusion models were used to temporally resolve changes in succinate metabolism. Further experiments using the mouse model examined key metabolic pathways with and without DSM treatment through untargeted bulk metabolomics analysis, targeted temporospatial metabolomics analysis, and bulk RNA sequencing. Animal procedures were conducted under Home Office Project License number P7720A3D6 (mice) or PP3524891 (pigs). Human kidneys retrieved for transplantation but subsequently declined were used following obtaining informed consent (Research Ethics Committee number 15/NE/0408).

Findings
Kidney succinate metabolism was highly conserved between mice, pigs, and humans during IRI. Oxygen tension and metabolic substrate use varies between the kidney cortex and medulla; nevertheless, succinate metabolism was similar throughout the mouse kidney. Administration of DSM prior to kidney IRI in mice inhibited complex II (tissue malonate concentration 0.0132±0.0003 vs 14.49±4.21 nmol/mg p=0.0138; tissue succinate concentration 0.170±0.027 vs 1.591±0.255 nmol/mg p=0.0015; n=4) and was protective, ameliorating serum creatinine (24-hour serum creatinine following IRI; 211±23 vs 135±15 µmol/L p=0.0012; n=5-6) and oxidative marker rise. DSM treatment substantially increased the NAD+/NADH ratio prior to IRI onset, rapidly reprogrammed metabolism away from fatty acid oxidation, and reduced ROS generation upon reperfusion. Over-representation analysis of differentially expressed genes between untreated and treated mice indicated global changes in cellular processes including in the activity of the PI3k/Akt/mTOR, integrated stress response, and interleukin signalling pathways.

Interpretation
DSM not only ameliorates oxidative damage through inhibition of ROS production but also leads to protective metabolic rewiring via pharmacological preconditioning. It is not clear whether these transcriptomic changes are attributable to DSM-mediated complex II inhibition, therefore these analyses identify key enzyme targets for further investigation. Together, these data increase our understanding of the mitochondrial mechanisms underpinning IRI and facilitate clinical translation of DSM as a safe and effective therapy in organ transplantation.

Dr Maciej Debski

Norwich Medical School, University of East Anglia
Department of Cardiology, Norfolk and Norwich University Hospital

maciekdebski@gmail.com
@MaciejDebski

A4

Mitral valve repair versus replacement in minimally invasive mitral surgery: registry-based analysis from a large-volume cardiothoracic centre

Background
Mitral valve repair and mitral valve replacement may be done as an open-heart surgery procedure or as minimally invasive heart surgery (MIMVS). Multiple studies have suggested that patients with mitral valve replacement have worse outcomes than those with the repair. However, most of those studies reported on conventional sternotomy mitral valve surgery. Although MIMVS has been conducted for more than two decades, there is a paucity of data on characteristics and outcomes after this type of surgery. The present study aimed to review the departmental database on the clinical outcomes following minimally-invasive mitral valve repair compared to replacement.

Methods
We identified adult patients with MIMVS with or without tricuspid valve surgery (TVS) performed between 2007 and 2019. Patients with previous mitral valve surgery, concomitant coronary artery bypass graft surgery, aortic valve repair/replacement, and emergency or salvage procedure were excluded. The study outcome measure was time to all-cause mortality. Information on vital status as of May 14, 2020, and the date of death was obtained from the UK's Office for National Statistics. Logistic binary regression was used to identify the risk factors associated with MV replacement vs repair. A Cox proportional hazards model was fitted and adjusted for baseline characteristics.

Findings
We included a total of 417 patients. The mean (SD) follow-up time was 4.9 (3.4) years. All patients with rheumatic MV disease underwent MV replacement. Logistic regression identified the following covariates associated with the type of MV treatment (replacement versus repair): female sex (odds ratio 2.237, 95% CI, 1.017-4.922), previous cardiac surgery (OR 17.7, 95% CI, 4.409-71.188), NYHA 3 or 4 (OR 2.707, 95% CI, 1.248-5.871) and concomitant tricuspid valve surgery (OR 0.232, 95% CI, 0.069-0.777). In addition, Kaplan-Meier analysis revealed that replacement was associated with worse survival than MV repair (log-rank, p=0.008). In Cox multivariable regression adjusted to baseline differences, however, only age (HR 1.034, 95% CI, 1.005-1.064, for 1-yr increase), body mass index (HR 0.903, 95% CI, 0.851-0.959, for 1 kg/m2 increase), and logistic EuroSCORE (HR 1.082, 95% CI, 1.025-1.142) predicted long-term survival, whereas MV replacement vs repair did not (HR 1.531, 95% CI, 0.822-2.852).

Interpretation
It is the first study looking exclusively at minimally invasive mitral valve surgery. Female sex, previous cardiac surgery, NYHA 3 or 4, and TVS were independently associated with MV replacement. After adjustment for baseline covariates, a mitral valve replacement was not associated with long-term survival compared to repair. The limitation is a single-centre, retrospective, non-randomised design. As coronary artery bypass grafting is predominantly done via sternotomy, our sample was not representative of the general population with ischaemic MV pathology.

Dr John Reynolds-Wright

MRC Centre for Reproductive Health, University of Edinburgh
Chalmers Centre for Sexual Health, NHS Lothian

A5

UTAH: Using Telemedicine to improve early medical Abortion at Home – a randomised controlled trial

Background
Telemedicine has the potential to improve the patient experience of abortion and to alleviate staffing and service pressures. This was identified as an area requiring research and development by the National Institute of Health and Care Excellence (UK) in 2019. Prior to the COVID-19 pandemic, telemedicine-use was less common across all sectors of healthcare and due to the unique medicolegal framework surrounding abortion in Great Britain, some aspects of care required in-person contact to meet legislative requirements.

Methods
We conducted an unblinded non-inferiority randomised controlled trial comparing telemedicine consultations (by telephone) with in-person consultations for the provision of medical abortion to women <10 weeks pregnant (by ultrasound) and aged 16 years or over. Randomisation was via RedCap using independently generated randomisation lists. The primary outcome was efficacy of medical abortion (complete abortion without surgical intervention). We hypothesised that telemedicine consultations would be non-inferior to in-person consultations with a non-inferiority limit of 3%. Secondary outcomes included satisfaction with consultation type, preparedness, unscheduled contact with care, complication rate, time spent in clinical contact and uptake of long-acting contraception.

Findings
Recruitment opened on 13 January 2020, was suspended 31 March 2020 due to COVID-19 and formally closed 31 August 2021. A total of 125 participants were randomised, approximately 10% of the total planned (63 telemedicine and 62 in-person). Primary outcome was available for 115 participants (lost-to-follow-up telemedicine=2, in-person=8), secondary outcomes were available for 110 participants (n=5 and n= 10 in telemedicine and in-person groups did not complete questionnaires). There were no significant differences between groups in treatment efficacy (telemedicine 59/63 (93.6%), in-person 56/62 (90.3%) However non-inferiority was not demonstrated (+3.3% in favour of telemedicine, confidence interval -6.6% to +13.3%, lower than non-inferiority margin). There were no significant differences in most secondary outcomes, however, there was possibly more unscheduled contact with care in the telemedicine group (12(19%) vs 3(5%), p=0.01). The overall time spent in clinical contact was statistically significantly lower in the telemedicine group (mean (SD) 94 (24) minutes, p=0.0005).

Interpretation
Telemedicine for medical abortion appeared to be as effective, safe and acceptable to women as an in-person consultation but with less time spent in the clinic. However, due to the small sample size the study was underpowered to confirm this. These findings reflect and support findings of large scale observational studies conducted during COVID-19 (with a minimal ultrasound scanning protocol) and another randomised controlled trial conducted in South Africa (with ultrasound and/or abdominal palpation for participants).

Dr Mervyn Thomas

University of Leicester
University Hospitals of Leicester NHS Trust

A6

High resolution in vivo imaging in arrested retinal development establishes structure-function correlations to genotype and retinal expression patterns: A multicentre study

Background
Arrested retinal development (foveal hypoplasia (FH)) is genetically heterogenous and has debilitating lifelong consequences due to poor vision and infantile nystagmus. Defects within the melanin biosynthesis pathway are often implicated to FH and albinism. Approximately 19 genes, variants of which, have been identified to cause albinism and can be broadly grouped into non-syndromic oculocutaneous albinism (nOCA), syndromic OCA (sOCA; for example Hermansky Pudlak Syndrome) and ocular albinism (OA, due to GRP143 variants). We aimed to characterise the structural and functional consequences of FH and its relationship to genotype and early embryonic and foetal gene expression patterns in a multi-centre study.

Methods
Twelve centres across nine countries joined in a collaborative effort to establish the foveal development investigators group (FDIG). Foveal optical coherence tomography (OCT) scans, visual acuity (VA) and confirmed molecular diagnosis was obtained from each centre (n=523). Genotypes were determined using either targeted panel-based sequencing or exome sequencing. The Leicester Grading System for foveal hypoplasia (PMID: 21529956) was used to grade foveal OCTs. Using a consensus grading approach each scan was graded including the presence or absence of foveal cone photoreceptor specialisation (PRS). Embryonic and foetal retinal transcriptomic data was analysed to determine expression patterns of genes associated with FH.

Findings
The most common genetic aetiology for typical FH was albinism (67.5%), followed by PAX6 (21.8%), SLC38A8 (6.8%), and FRMD7 (3.5%) variants. There was a significant difference in the spectrum of FH grades based on the molecular diagnosis (chi-square = 60.4, $p < 0.0001$). All SLC38A8 cases were PRS– ($p = 0.003$), whereas all FRMD7 cases were PRS+ ($p < 0.0001$). Analysis of albinism subtypes revealed a significant difference in the grade of FH (chi-square = 31.4, $p < 0.0001$) and VA ($p = 0.0003$) between nOCA compared with OA and Hermansky–Pudlak syndrome (HPS). OA and HPS demonstrated higher grades of FH and worse VA than OCA. There was a significant difference ($p < 0.0001$) in VA between FRMD7 variants compared with other diagnoses associated with FH. Retinal transcriptomic data revealed early embryonic expression spikes with SLC38A8, GPR143 and HPS1. However, with FRMD7 later foetal expression spikes were observed.

Interpretation
This study represents the largest study on retinal development using high resolution in vivo imaging in a wide spectrum of genotypes. Using a multi-centre approach, we observe specific genotypes that are associated with higher grades of FH and lacking foveal cone photoreceptor specialisation (SLC38A8, GPR143, HPS1). This correlates with the worse visual prognosis seen in this cohort. Based on retinal expression patterns it suggests that developmental arrest occurs earlier in SLC38A8, GRP143 and HPS1. The retinal developmental arrest occurs later in those with FRMD7 variants and this corresponds to better visual prognosis and correlates with the retinal expression of FRMD7.

Dr Romit Samanta

Heart and Lung Research Institute, University of Cambridge
Cambridge University Hospitals NHS Foundation Trust

A7

Integrated data science methods identify a high ferritin sub-phenotype of acute respiratory distress syndrome

Background
No pharmacological agents have been shown to consistently improve the outcomes of patients with acute respiratory distress syndrome (ARDS) by addressing the underlying biological processes, despite over 50 years of research and many randomised controlled trials of therapies thought to show promise. Patients with ARDS continue to have a significant mortality and long-term morbidity burdens. Our aim was to identify mechanistic subtypes of ARDS using a combination of protein biomarkers and transcriptomics, and to validate these in independent patient cohorts.

Methods
We integrated results from bulk RNAseq of peripheral whole blood with protein biomarkers from patients recruited to a UK observational study of sepsis (GAinS) to identify subtypes of patients with sepsis-associated ARDS (REC: 05/MRE00/38, 08/H0505/78). To validate our findings, we subsequently measured ferritin concentrations in plasma samples from patients recruited to two ARDS randomised controlled trials (HARP-2; ISRCTN88244364 and ROSE; NCT02509078). Restricted cubic splines calculated the thresholds associated with 28-day mortality. We described the relationship between ferritin, other protein biomarkers, and patient outcomes using Bayesian mediation methods.

Findings
One of the proposed mechanisms we identified using an integrated network analysis and clustering approach was suggestive of phenomena observed in patients with haematophagocytic lymphohistiocytosis. Ferritin was associated with significantly increased 28-day mortality in both clinical trial cohorts. A pooled meta-analysis calculated the increased risk of 28-day mortality for a log-fold rise in ferritin (OR 1.71; 95% CI 1.01-2.9). Patients with raised ferritin had worse non-pulmonary organ failure, consistent with a dysregulated, systemic immune response. IL-18, a marker of inflammasome activation, was a significant mediator of the effect of ferritin on 28-day mortality (0.06, credible interval 0.01-0.13).

Interpretation
Patients with high-ferritin-associated ARDS can be identified in two large, independent patient cohorts. This is a potentially treatable trait, which could easily be identified. We calculated a threshold ferritin value to identify patients at increased risk of death, in the context of ARDS, to assist others in replicating our findings and potentially using this for a future stratified, randomised controlled trial.

Dr Sarah Leiter

University of Cambridge
Cambridge University Hospitals NHS Foundation Trust
Wellcome Sanger Institute

sarah.leiter1@nhs.net

A8

Introducing routine paired whole genome sequencing in paediatric cancer patients – a retrospective analysis

Background
Paediatric neoplasms are rare with an estimated 8-18% of children having a cancer predisposition syndrome. Over the past decade, whole genome sequencing (WGS) has been shown to be reliable and effective for investigating both somatic and germline mutations in cancer patients. In late 2020, NHS England commissioned paired (germline and tumour DNA) WGS for all children and young people with suspected neoplasms. Our aim is to assess the impact of WGS on the care of children with solid malignancies diagnosed at Cambridge University Hospitals (CUH) NHS Foundation Trust from the introduction of WGS up to 17th September 2022.

Methods
Following an initial run-in phase during which WGS was offered only to selected patients to establish feasibility, from 18th March 2021 WGS was available to all paediatric patients with a newly diagnosed or relapsed malignancy. Case records from all presentations of patients aged 0-16 years to the CUH Paediatric Oncology department over the following 18 months were reviewed to establish if WGS was offered, reasons for not being offered and turnaround time for data return to treating clinicians. The WGS data and impact of WGS on each case is currently being evaluated through case review where research consent is available.

Findings
During the run-in phase, 16 patients underwent WGS. Over the following 18 months, of 143 new/relapsed presentations, 98 were eligible for WGS. Patients were not eligible if they had a benign diagnosis (1), biopsies were performed elsewhere (6), tissue was unavailable (18) or inadequate for sequencing (20). Of the 98 patients, 87 (89%) were offered and accepted WGS. Turn-around time from available DNA to genomic tumour advisory board had a median of 27 days (13 - 69 days).

WGS has had a significant impact on some patients, ranging from escalation/de-escalation of treatment to modification of treatment approach. In one important example, uncertainty regarding the histological diagnosis of a fusion negative infantile fibrosarcoma in a newborn was resolved following discovery of a somatic 173bp internal tandem duplication in PDGFRB, characteristic of a benign lesion. This led to a dramatic alteration in management with observation only instead of surgery and chemotherapy.

Interpretation
Implementing paired WGS into routine care of paediatric patients with cancer can be achieved though cross-departmental collaboration. In our experience families are keen to participate with no family declining WGS during the routine phase. The information provided to the clinicians was clinically meaningful and in some cases led to significant changes to patient care as demonstrated by the aforementioned example.

In addition to providing novel findings, we envision that WGS will replace multiple standard of care investigations currently used as part of the diagnostic work up for children with suspected cancer.

Nikesh Jathanna

School of Medicine, University of Nottingham
Department of Cardiology and Cardiothoracic Surgery, Nottingham University Hospitals NHS Trust

nikesh.jathanna@nhs.net

A9

A Reproducibility Study of Radiomics feature analysis on segmented ischaemic scar from Cardiac Magnetic Resonance Imaging

Background
Left ventricular scar on Cardiac Magnetic Resonance imaging (CMR) is intricately linked to arrhythmic events but the ability to delineate those scar characteristics posing this risk remains limited. Radiomics feature assessment allows objective quantification of latent scar imaging features with some features correlating with arrhythmic events in CMR. While acquisition settings and feature extraction can be standardised, manual scar segmentation has significant inter-operator variability even when the same method is utilised. This could affect feature reproducibility though CMR data is scant. We tested the impact of 5% per slice variability on radiomic features reproducibility in manual ischaemic scar segmentations.

Methods
Retrospective, clinically indicated, late-gadolinium enhanced CMR scans demonstrating ischaemic scar were collected. Images were obtained on a 1.5T Philips Ingenia or Siemens Aera utilising society recommended protocols and underwent manual scar segmentation.

Comparative segmentations were generated by randomly eroding or dilating the manual segmentation scar border of each CMR slice by 5%.

Pyradiomic features were extracted from both segmentations. Data was compared utilising intra-class correlation co-efficient (ICC). Scar volume from both segmentations were compared using the Wilcoxon signed rank test. Segmentation similarity was assessed using Dice co-efficient.

This analysis is part of a study with HRA approval (IRAS 290340).

Findings
400 ischaemic CMR scans were included from 2017-2021. The median patient age was 66 (56-74). Sixty-four (16%) had previous cardiac surgery and 153 (38.3%) had previous percutaneous coronary intervention. Only 144 of 4515 (3.19%) slices were considered non-diagnostic or uninterpretable in image quality.

Scar volume was significantly different between the original segmentation and the comparative segmentation (16.8 vs 22.08, $p<0.01$). Mean (SD) DICE between the scar segmentations was 0.571 (0.09).

An ICC of >0.9 (“excellent”) was seen in 74/107 (69.2%) features. In the Pyradiomic feature subgroupings, 15/18 1st order, 11/14 Shape, 16/24 GLCM, 10/14 GLDM, 12/16 GLRLM, 5/16 GLSZM and 5/5 NGTDM variables had ICC>0.9. Eight of the 107 (7.48%) features had “poor” correlation (<0.5) including 1 shape, 2 GLDM and 5 GLSZM variables.

Interpretation
Many Pyradiomic features show excellent reproducibility despite a random 5% border erosion or dilation, a Dice of only 0.571 and significantly different scar volume between masks. This may suggest that Pyradiomic features are not drastically affected by variations in scar border segmentation. Previously published arrhythmia-associated features such as entropy, kurtosis and skewness all had at least good reproducibility in our dataset.

This study of reproducibility may support the development of radiomic-based biomarkers for ischaemic heart disease in CMR, though comparison with other human operators and segmentation methods are required for confirmation.

Dr Mohamed Mohamed

University College London

mohamedosama@hotmail.co.uk
@dr_mosama

A10

A registry-based analysis of the impact of intracoronary imaging-guided percutaneous coronary intervention on procedural outcomes among complex patient groups

Background
Intracoronary imaging (ICI) has been previously shown to improve survival and clinical outcomes after percutaneous coronary intervention (PCI). However, whether this prognostic benefit is sustained across different indications/patient groups remains unclear.

Methods
All PCI procedures performed in England and Wales between 1st April 2014 and 31st March 2020 were retrospectively analysed. The association between ICI use and in-hospital MACCE (major adverse cardiovascular and cerebrovascular outcomes; composite of all-cause mortality, stroke and reinfarction) and mortality was examined using multivariable logistic regression analysis for each imaging-recommended indication as defined by the European Association for Percutaneous Coronary Intervention (stent thrombosis (ST), in-stent restenosis, renal failure, bioresorbable vascular scaffolds (BVS), stent length>60mm, acute coronary syndrome (ACS) indications, chronic total occlusion and left main stem (LMS) intervention).

Findings
Of 555,398 PCI procedures, 10.8% (n=59,752) were performed under ICI guidance. ICI use doubled between 2014 (7.8%) and 2020 (17.5%). ICI use was highest for BVS (44.7%) and LMS PCI (41.2%) cases and lowest in ACS (9%). Overall, the odds ratios (OR) of in-hospital MACCE and mortality were only reduced with ICI-guided PCI in cases with an imaging-recommended indication (OR 0.75 95% confidence interval (CI) 0.69-0.81 and OR 0.69 95%CI 0.63-0.76, respectively). Only specific imaging-recommended indications were associated with reduced MACCE and mortality, including LMS PCI (OR 0.45 95%CI 0.39-0.52 and 0.41 95%CI 0.35-0.48, respectively), ACS (OR 0.76 95%CI 0.70-0.82 and 0.70 95%CI 0.63-0.77), stent length>60mm (OR 0.75 95%CI 0.59-0.94 and 0.72 95%CI 0.54-0.95). ST was only associated with lower mortality (OR: 0.69 95%CI 0.52-0.91) while renal failure was associated with reduced MACCE (OR 0.77 95%CI 0.60-0.99) but not mortality.

Interpretation
This is the first analysis to systematically examine the utility and benefits of intracoronary imaging according to individual indications as defined by expert consensus. In the absence of previous literature, it is unclear whether the prognostic benefit of ICI guidance holds true across different indications for PCI. The present study provides important insights into specific patient groups that are most likely to benefit from ICI-guided PCI in terms of mortality reduction. Despite the inherent limitation of observational registry data, our findings were consistent in a national cohort of procedures over a six-year period.

Poster competition – Group B

Dr Hanya Mahmood

Academic Unit of Oral & Maxillofacial Surgery, School of Clinical Dentistry, University of Sheffield

h.mahmood@sheffield.ac.uk
@HanyaMahmood

B1

Development and validation of a multivariable model for prediction of malignant transformation and recurrence of oral epithelial dysplasia

Background
Oral epithelial dysplasia (OED) is the precursor to oral squamous cell carcinoma which is amongst the top ten cancers worldwide. Prognostic significance of conventional histological features in OED is not well established. Many additional cytological and architectural abnormalities are seen in OED; but are insufficiently investigated and have not been correlated to clinical outcomes. This study conducts a digital quantitative analysis of epithelial cellularity, nuclear geometry, staining intensity and lesion architecture/thickness in OED to develop a multivariable model for prediction of malignant transformation and OED recurrence.

Methods
Digitised whole-slide images of 75 OED (252 regions of interest) and 25 non-dysplastic/control cases (from School of Clinical Dentistry, University of Sheffield, dating 2008-2013) were quantitatively analysed to assess: cell number, nucleus circularity, nucleus eccentricity, nucleus haematoxylin optical density (OD), cytoplasm eosin OD, nuclear to cell area ratio and epithelial thickness/perimeter using a bioimage analysis software. Five-year clinical follow-up data was obtained to enable correlation to clinical outcomes. Statistical analyses were conducted to evaluate feature-specific differences between OED grades and against non-dysplastic/control cases control. Multivariable models were developed to evaluate prediction of OED recurrence and malignant transformation.

Findings
Grade-related differences were seen for cytoplasm eosin, nucleus eccentricity and nucleus circularity in basal epithelial cells of OED ($p < 0.05$). Individually, nucleus circularity in OED was associated with recurrence ($p=0.018$) and epithelial perimeter was associated with malignant transformation ($p=0.016$). Cellularity in the basal epithelial layer in OED was significantly different compared to controls ($p=0.0110$). The developed model demonstrated superior predictive potential for malignant transformation (AUROC 0.77, 95% CI 0.64 to 0.90, $p= 0.0004$) and OED recurrence (AUROC 0.74, 95% CI 0.61 to 0.86, $p= 0.0006$) as compared with conventional WHO grading (AUROC 0.68 and 0.71, respectively). External validation supported the predictive performance of the proposed model (AUROC 0.76 and 0.93, respectively).

Interpretation
This study provides new insight into OED progression, by identifying novel histological predictors that are not routinely considered in diagnostic practice, supporting a predictive model that may be useful for prognostication of OED lesions. Further analysis and validation on larger independent datasets are needed to establish the significance of these features for wider clinical application.

Dr Negin Holland

University of Cambridge
Cambridge University Hospitals NHS Foundation Trust

nda26@medschl.cam.ac.uk
@HollandNegin

B2

Longitudinal synaptic loss in primary tauopathies: an in vivo observational [11C]UCB-J PET study

Background
The primary tauopathies of Progressive Supranuclear Palsy (PSP) and Corticobasal Degeneration (CBD), are rapidly progressive neurodegenerative diseases with a poor prognosis, and diagnostic delays. PSP/CBD cause a combination of movement and cognitive impairment, and are pathologically associated with accumulation of hyperphosphorylated 4-repeat tau, inflammation, and severe synaptic loss, all leading to neuronal loss. Synaptic loss is a pathological hall-mark in neurodegeneration; it occurs early and is strongly related to functional deficits. In this longitudinal observational study, we determine the rate at which synaptic density is reduced in the primary tauopathies of PSP/CBD and test the relationship with disease progression.

Methods
Our cross-sectional cohort included 32 participants with probable PSP and 16 with probable CBD, recruited from UK tertiary care centres, and 33 sex-/age-matched healthy controls. Synaptic density was estimated by PET imaging with the synaptic vesicle 2A radioligand [11C]UCB-J. Clinical severity and cognition were assessed by the PSP rating scale and the Addenbrooke's cognitive examination. Regional [11C]UCB-J non-displaceable binding potential (BPND) was estimated in Hammersmith Atlas regions of interest.
22 participants with PSP/CBD had a follow-up [11C]UCB-J PET scan after 1 year. We calculated the annualised change in [11C]UCB-J BPND, and correlated this with the change in clinical severity.

Findings
At baseline, patients had significant widespread (cortical and sub-cortical) synaptic loss (up-to 30%) compared to controls, correlating with poor cognition and worse scores on the PSP rating scale ($p<0.05$, FDR adjusted). Synaptic loss was more severe and widespread than neuronal loss. At follow-up, there was significant annual synaptic loss within the frontal lobe (-3.5%, $p=0.03$), and the right caudate nucleus (-3.9%, $p=0.046$). The degree of longitudinal synaptic loss within the frontal lobe correlated with the rate of change in the PSP-rating scale ($R= 0.47$, $p=0.03$), and cognition (Addenbrooke's Cognitive Examination-Revised, $R= -0.62$, $p=0.003$). Although progressive neuronal loss was also observed, this did not correlate with a progression in clinical symptoms.

Interpretation
We found severe and progressive synaptic loss (-3 to -4% per year) in PSP/CBD in disease-related areas. The individual variability in the rate of synaptic loss is associated with how quickly patients deteriorate over-time. Future studies are required to examine the in vivo relationship between longitudinal changes in synaptic loss and the temporal distribution of the underlying tau pathology. With the pathogenic conversion of toxic tau oligomers, mitochondrial stress and inflammation on synaptic toxicity, we propose that synaptic loss is a functionally relevant intermediate marker of disease severity and suitable as a target or outcome measure in future disease-modifying trials.

Dr Mary Ni Lochlainn

King's College London
Guy's and St Thomas' NHS Foundation Trust

mary.ni_lochlainn@kcl.ac.uk
@younggeris

B3

The PROMOTe Study: A randomised trial of prebiotic and protein supplementation in older twins for cognitive and physical performance

Background
There is a growing body of evidence linking the microbiota in the human gut, to muscle and brain health, including cognition. Animal and human studies have shown that inducing changes in the microbiota can alter cognitive behaviour, suggestive of causative pathways. Indeed evidence exists of improvement in frailty index amongst older adults, in response to a prebiotic supplement.

The PROMOTe trial aimed to test whether the gut microbiome mediates anabolic resistance of skeletal muscle to protein supplementation in older adults, using a prebiotic food supplement intervention. A secondary objective was to test whether gut microbiome modulation improved cognition versus placebo.

Methods
Double blinded randomised placebo controlled trial using twin pairs, recruited from TwinsUK cohort. We recruited those aged >=60, with low protein intake, and access to a computer to take part (due to remote trial delivery). Each twin pair was randomised; one twin received protein supplementation plus placebo and the other received protein supplementation plus a gut microbiome modulator (prebiotic). Intervention period was 12 weeks, with participants advised to take 1 sachet of supplement daily. All were advised to undertake regular resistance exercises. The primary outcome was muscle strength (chair-rise time). Cognition, measured by CANTAB cognitive battery was a secondary outcome.

Findings
Target sample size was 70 individuals. 626 were screened 72 randomised (36 pairs). More adverse events occurred in the prebiotic group (n=8 versus n=2 in placebo group; p=0.041), but compliance remained high in both groups (% adherence based on sachet count at study end >78% in each group; p=0.37).

A factor analysis score was used to combine results of the five cognitive tests carried out. Linear mixed effects regression models were used to compare intervention groups (arm 1 vs arm 2; blinded) on their change in cognition score at 12 weeks. Twin clustering was considered as random effects, both family identifier and zygosity, and treatment group as fixed effect.

There was no significant difference between arms for the primary outcome of chair rise time (coefficient 0.184; 95% CI -0.569-0.938; p=0.631). The prebiotic intervention arm had an improved cognition factor score versus the placebo group (coefficient 0.482; 95% CI 0.823-0.141; p=0.014).

Interpretation
Overall, participants' muscle strength improved in response to the protein and exercise intervention. Significantly, this shows that a remotely delivered intervention in older adults can successfully improve physical performance measures. However, prebiotic food supplementation did not improve muscle strength versus placebo in this 12-week time frame.

Importantly, prebiotic food supplementation improved cognition versus placebo in a cohort of healthy older twins. This cheap and scaleable intervention holds huge promise for improving cognition and/or preventing cognitive decline in our ageing population.

Limitations include relatively small sample size. Strengths of this study include placebo control, fully blinded randomisation, and twin design.

Dr Nina Rzechorzek

University of Cambridge
MRC Laboratory of Molecular Biology

ninar@mrc-lmb.cam.ac.uk
@Neurocool

B4

Daily brain temperature rhythms predict survival after traumatic brain injury—a prospective and retrospective cohort study

Background
Patients undergo Targeted Temperature Management interventions to achieve a 'normal' brain temperature (TBr), yet this parameter remains undefined for humans. The profound sensitivity of neuronal function to temperature implies the brain should be isothermal, but observations from patients and non-human primates suggest significant spatiotemporal variation. Such controversy demands better evidence-based approaches in neurocritical care. We aimed to determine the clinical value of TBr in patients with traumatic brain injury (TBI) by establishing how much it varies in healthy adults.

Methods
We retrospectively screened data for all patients recruited to the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) High Resolution ICU Sub-Study. Only patients with direct brain temperature measurements and without Targeted Temperature Management were included. To interpret patient analyses, we prospectively recruited 40 healthy adults (20 males, 20 females, 20-40 years) for chronotype-controlled brain thermometry using magnetic resonance spectroscopy. Participants were scanned in the morning, afternoon, and late evening of a single day. A linear mixed model was applied to determine healthy TBr variation. A generalized linear mixed model was used to test for predictors of patient outcome.

Findings
In patients (n=114), TBr ranged from 32.6 to 42.3°C and mean TBr (38.5±0.8°C) exceeded body temperature (37.5±0.5°C, P<0.0001). Only 25/100 patients displayed a daily rhythm in TBr. In healthy adults, TBr ranged from 36.1 to 40.9°C; mean TBr (38.5±0.4°C) exceeded oral temperature (36.0±0.5°C), and was higher in luteal females relative to follicular females and males. TBr increased with age, notably in deep regions (0.6°C over 20 years, P=0.0002), and varied spatially by 2.41±0.46°C. TBr varied by time of day, especially in deep regions (0.86°C, P=0.0001, lowest at night). From these data we built HEATWAVE—a 4-dimensional map of normal TBr. Testing the relevance of HEATWAVE to patients, we found that lack of a daily TBr rhythm increased the odds of death 21-fold (P=0.016), whilst absolute temperature extremes did not predict outcome. Ageing by 10 years increased the odds of death 11-fold (P=0.0002) and a warmer mean TBr correlated with survival (P=0.035).

Interpretation
Human TBr is higher and varies more than previously assumed—by age, sex, menstrual cycle, brain region, and time of day. This has major implications for temperature monitoring and management, and for understanding how the brain works. Sequential MR thermometry is impractical for routine use in most clinical settings, underpinning the urgency for cost-effective, non-invasive technologies that can capture longitudinal variations in TBr. Whilst larger prospective studies are needed to validate our outcome model, daily TBr rhythmicity is emerging as the strongest single predictor of survival after TBI. We conclude that TBr variation—not absolute TBr—better distinguishes brain physiology from pathophysiology.

Dr Shahnaz Jamil-Copley

School of Medicine, University of Nottingham
Department of Cardiology and Cardiothoracic Surgery, Nottingham University Hospitals NHS Trust

B5

Developing a biventricular geometry and scar segmentation neural network from cardiac magnetic resonance imaging using transformers

Background
3D models derived from late gadolinium-enhanced cardiac magnetic resonance imaging (LGE-CMR) reduce ventricular tachycardia ablation procedure times and improve outcomes. Routine adoption into clinical practice is limited by the significant time required for accurate manual, or semi-automated, scar segmentation combined with lack of reproducibility.

Neural networks can mimic clinician decisions, operating at a fraction of the time, with no inter-operator variability. Published segmentation models are limited by small developmental datasets, limited available labels and often lack correlating clinical information. We aimed to develop and assess an artificial intelligence biventricular geometry & scar segmentation model addressing these limitations.

Methods
Clinically indicated LGE-CMR in those with ischaemic scar were retrospectively identified. Clinical data was extracted from healthcare records and ground-truth manual CMR segmentation of 7 labels was undertaken – left ventricular (LV) myocardium, LV blood pool, LV scar, aorta, LV papillary muscles, right ventricular (RV) myocardium and RV blood pool.

A neural network was developed utilising transformers, zero-centre normalisation, average of dice loss and weighted cross entropy. LGE-CMR datasets were separated 70:10:20 for training, validation and testing respectively. Results were assessed using Dice co-efficient and average symmetric surface distance (ASSD).

The study has received HRA approval (IRAS 290340).

Findings
400 LGE-CMR were labelled, 360 obtained from a 1.5T Philips Ingenia and 40 from a 1.5T Siemens Aera. Median slice number per scan was 11 with 10mm slice thickness. This resulted in a total of 4515 slices of which 2373 (52.6%) were labelled "optimal" quality and only 144 (3.19%) "uninterpretable". All images were 2D and did not utilise compressed sense (or equivalent).

Median age was 66 (56-74) with a male predominance (80.5%). 12 (3%) had cardiac devices consisting of implantable cardioverter defibrillators (7/12) and pacemakers (5/12). 114 (28.5%) had diabetes and 153 (38.3%) had previous cardiac stenting. A history of previous, confirmed ventricular arrhythmia was present in 15 (3.8%).

Overall mean Dice was 0.667 and mean ASSD was 1.52. The left ventricular blood pool had the highest mean dice (0.888) and second lowest mean ASSD (0.818). Scar had the lowest mean dice (0.439) and a mean ASSD of 2.416

Interpretation
Utilising, to our knowledge, the largest dataset for the training and testing of an AI segmentation model in ischaemic heart disease, scar labelling performance is similar to previously published data. However, it demonstrates the benefit of additional structure segmentation and was undertaken with image quality and patient characteristics representative of the clinical population.

Despite this, variations compared to ground-truth remain and further clinical studies are needed to assess clinical impact. External validation and re-training with other CMR manufacturers and acquisition settings are required to assess and improve generalisation. This forms ongoing work at our institute -the NotIs CMR study (IRAS:298151).

Ana-Catarina Pinho-Gomes

University College London

a.pinho-gomes@ucl.ac.uk
@Ana_Cat_PG

B6

Gender equality and the gender gap in life expectancy in the European Union

Background
Life expectancy (LE) is influenced by the wider determinants of health, such as housing and working conditions, money, education. There are stark gender inequalities related to those wider determinants of health, as illustrated, for instance, by women's representation in the workforce, the gender pay gap, or the gendered societal roles that place the burden of informal care on women. However, it was unclear if and how gender equality might be correlated with LE. Therefore, this study aimed to investigate whether gender equality across different domains was correlated with LE for women and men and the gender gap in LE.

Methods
This ecological study estimated gender equality using a modified gender equality index (mGEI), based on the index developed by the European Institute for Gender Equality for the 27 European Union countries between 2010 and 2019. This index is calculated as a weighted average of the scores in six domains (work, money, knowledge, time, power, and health) and ranges from 0 to 100, where 100 represents gender parity. The mGEI does not include LE in the health domain. The correlation between this mGEI and LE and the gender gap in LE was calculated using the spearman correlation coefficient.

Findings
Between 2010 and 2019, LE increased more for men than women, which resulted in a narrowing of the gender gap in LE from 6.1 to 5.5 years in the EU. There was also an improvement in gender equality, as shown by the increase in the mGEI from 63 to 68 between 2010 and 2019, which was mainly driven by an increase in gender equality in the domains of power, money, and knowledge. There was substantial heterogeneity between countries for both LE and the mGEI. There was a strong correlation between the mGEI and the gender gap in LE (-0.880), which was explained by a stronger correlation between the mGEI and longer LE in men than women (0.655 versus 0.629, respectively). The domains of the mGEI most strongly correlated with a narrowing of the gender gap in LE were health, money, and knowledge, whilst power had the weakest correlation.

Interpretation
The narrower gender gap in LE in more gender equal countries was explained by the stronger correlation between the mGEI and longer LE in men than in women. Therefore, gender equality appears to be at least as beneficial to men's as to women's LE. The longer LE observed in countries with greater gender equality may be mediated by greater socioeconomic development, thus suggesting gender equality may not only improve population health and longevity but also enhance national wealth and prosperity.

Dr Taryn Treger

Wellcome Sanger Institute
Addenbrooke's Hospital

tt6@sanger.ac.uk

B7

Somatic genetic alterations leading from cancer predisposition via normal tissue to Wilms tumour

Background
Some children are at increased risk of developing paediatric cancers, through mutations in genes that are intimately linked to organogenesis. A classical example is mutations in the Wilms Tumour 1 (WT1) gene, a key regulator of mesodermal and urogenital development, predisposing to Wilms tumour. Whether cancer predispositions affect the clonal architecture of surrounding histologically normal tissue remains unknown, as does whether somatic driver alterations differ in tumours arising within this context.

Methods
To investigate this, we assembled a primary cohort of 140 children with Wilms tumour from three archives: the UK UMBRELLA study, the German Wilms tumour registry and the tissue archives of the Princess Maxima Centre (Netherlands). The cohort was enriched for children more likely to have a predisposition, including those with Wilms-associated syndromes, with bilateral tumours or younger than 2 years of age. We obtained a total of 270 neoplasms which, alongside matched normal kidney and blood, underwent whole genome sequencing, methylation arrays and messenger RNA sequencing. We determined all classes of mutations, subdivided into germline, mosaic, or tumour-somatic.

Findings
We identified 77/140 children with a predisposition including germline alterations (n=51), mosaicism in blood and normal kidney (n=5), and in 16 cases, mosaicism confined to kidney. This included methylation changes, substitutions, indels, copy number and structural variation, some of which would not have been detectable by common clinical assays. In addition to bonafide predispositions, we found evidence that CTCF may represent a Wilms tumour gene.

We assessed somatic features across the two groups of cases vs. controls. There were no significant differences in mutation burden of primary tumours and equally, signatures of substitutions were comparable. We found clonal expansions enriched in predispositions, such as in mosaic chromosome 11p LOH and hypermethylation of H19, but not in cases with mutations in WT1. In children with predisposing WT1 mutations, tumours exhibited a recurrent constellation of driver events, comprising secondary WT1 hits, via 11p LOH, and a CTNNB1 mutation.

Interpretation
In summary, we found an enrichment of normal tissue clonal expansions in children with specific germline or mosaic predispositions, most of whom had not been previously diagnosed with a predisposition. This, along with a preordained constellation of driver mutations in some groups, then raises the possibility of secondary cancer prevention; by devising treatments that interfere with the milieu that promotes clonal expansions or the selection of highly recurrent somatic driver events.

Adam Galloway

University of Leeds
Leeds Children's Hospital

adamgalloway@nhs.net

B8

"If you know when it's going to go, you're waiting for the best day of your life". A qualitative study of key stakeholders' experiences of NON-STOP (Non-Surgical Treatment of Perthes' Disease)

Background
Perthes' Disease is idiopathic avascular necrosis of the developing femoral head, and often causes hip deformities that impair physical function of the child. Current treatment for the condition aims to maintain the best possible environment within the hip joint for the disease process to run its natural course. Recent work demonstrated variation in care and no clinical consensus exists. Despite over 100 years passing since it was first described, the experiences of those affected have never been reported, until now. This study investigated key stakeholders' experiences and understanding of non-surgical treatment of Perthes' Disease (NON-STOP).

Methods
Children with Perthes' Disease and their families were interviewed, as were treating clinicians. The interviews followed a coding framework and interview schedule that was informed by behavioural theory and patient and public involvement. Health Research Authority and NHS Research Ethics Committee approval was gained for this study.

Findings
24 participants were interviewed in this study. 12 Child/family dyads and 12 clinicians from UK NHS centres. A number of themes were derived and yielded responses relating to experiences of key stakeholders. The key themes described outlined:

- Widespread variation of care exists, both in the lived experience of children and their families, as well as self-reported disagreement amongst clinicians.
- Children with Perthes' Disease and their families recounted positive experiences when included in the decision-making process for treatment.
- There is a strong desire from clinicians and children/their families for consistent evidence for everyone involved, and this should be based on clinical consensus.

Interpretation
This study is the first to describe the experiences of NON-STOP. The results of indicate a clear need for robust evidence to support clinicians' treatment decisions. Findings from this study will inform a future consensus study aiming to develop clinical consensus on NON-STOP. It was valuable for children with Perthes' Disease and their families to feel involved and included in the clinical decision-making process. Moving forward, this is something that clinicians should strive to achieve in their care of children with Perthes' Disease.

Rebecca Grossman

Oxford Centre for Diabetes, Endocrinology and Metabolism, Radcliffe Department of Medicine, Churchill Hospital, University of Oxford

@rebgross

B9

Circadian regulation of liver energy metabolism: translational studies in diabetes and obesity

Background
Obesity-related conditions are linked to perturbations of the circadian clock, but studies of how fat affects liver clock function examined whole in vivo livers rather than isolated hepatocytes, and were thus confounded by external cues from organs such as the suprachiasmic nucleus (SCN). In addition, the role of ceramides (bioactive sphingolipids that are implicated in the pathogenesis of non-alcoholic fatty liver disease) in circadian clock function is under-explored. The aim of this project was to investigate the effect on isolated murine hepatocyte circadian clock of high fat diet-induced obesity and explore the intersection of clock gene function and ceramide metabolism.

Methods
Transgenic PER2::LUC C57BL6 mice (n=24) were fed high fat versus normal chow for approximately 18 weeks. Primary mouse hepatocytes (PMHs) were isolated via collagenase perfusion and seeded on collagen-coated plates for luciferase activity measurement. PMHs were also seeded in 3D on ultra-low attachment plates to form spheroids for qPCR. PMHs were also given high lipid media in vitro.

To assess the role of ceramides, Huh7 cell lines and PMHs (high fat and normal chow) were used. The CRY stabiliser KL001 modelled core clock dysfunction. Ceramide content was increased with ceramide analogue C2 and decreased with ceramide synthase inhibitor fumonisin B1.

Findings
PER2::LUC oscillations of cells from mice fed high fat demonstrated suppressed amplitude compared with normal chow (53.80 luminosity units versus 192.2, p = 0.0368). qPCR showed Per2 and Bmal1 expression was suppressed in spheroids from mice fed high fat (multiple 8-hourly time points) and in spheroids subjected to in vitro lipid loading (single time point) compared with control conditions.

KL001 suppressed Per2 expression and altered expression of the majority of ceramide pathway enzymes (Sptlc1 increased; Cers2 and Sphk1 decreased). In high fat conditions, KL001 did not impact Per2 expression; ceramide enzymes were still altered, but Sphk1 expression was increased with KL001. C2 ceramide suppressed single time point clock gene expression in normal diet and high fat conditions; fumonisin B1 suppressed clock gene expression only in high fat conditions. Real time luciferase reporting of PER2::LUC PMHs revealed that ceramide increase induced a phase advance.

Interpretation
This is the first study showing a direct impact of lipid loading on hepatocyte clock function, independent of non-parenchymal liver cells and neuro-humoral inputs from organs such as the SCN, as isolated hepatocytes were used. Furthermore, clock gene disruption affects expression of ceramide pathway enzymes, and ceramide content in turn affects hepatic clock gene function. Future experiments will explore the mechanisms linking lipids and clock function, and whether the effects of ceramides are via signalling or membrane function. The study was limited by the use of mouse hepatocytes and cell lines, and should be repeated in primary human hepatocytes.

Clare MacRae

University of Edinburgh

B10

Comparison of diagnostic ascertainment and associations with adverse outcomes in primary and secondary care records for 47 long-term conditions: cross-sectional study of 2.3 million individuals in the Welsh National Health Service

Background

The widespread use of electronic health records presents many new opportunities for medical research, and their use in epidemiological studies has rapidly increased over the past two decades. However, records of events captured by one part of the health system might not reflect those found in other parts, and use of single data sources can result in underestimation of disease. This study compares diagnostic ascertainment of 47 long-term conditions (LTCs) and associations with health outcomes for multiple LTCs, using two different national health data sources, primary and secondary care records.

Methods

This cross-sectional study of 2,340,027 individuals used routinely collected anonymised electronic health records data available in the SAIL Databank on 1 January 2019. Data from primary care (PC), derived from the Welsh Longitudinal General Practice Dataset, secondary care (SC), derived from the Patient Episode Database for Wales, and linked PC-HI records for all individuals living in Wales were included. Prevalence of 47 LTCs was ascertained and associations between condition count and 12-month mortality was examined. Choice of LTCs was based on a recent Delphi study that developed international consensus on multimorbidity.

Findings

Using linked PC-HI compared with only HI data, multimorbidity was more prevalent (32.2% versus 16.4%), and the population of people identified as having multimorbidity was younger (mean age 62.5 versus 66.8 years) and included more women (54.2% versus 52.6%). Individuals with multimorbidity in both PC and HI data had stronger associations with mortality than those with multimorbidity only in HI data (adjusted odds ratio 7.93 [95%CI 7.62-8.25] versus 4.70 [95%CI 4.55-4.85] in people with ≥4 conditions). Prevalence of conditions identified using only PC versus only HI data were significantly higher for 37/47 and significantly lower for 10/47: the highest PC/HI ratio was for post-traumatic stress disorder (PTSD) (27.7 [95%CI 26.0-31.8]) and lowest for aneurysm (0.51 [95%CI 0.48-0.53]). Agreement in ascertainment of conditions between the two data sources varied considerably, being slight for five (Kappa <0.20), fair for 13 (Kappa 0.21-0.40), moderate for 17 (Kappa 0.41-0.60), and substantial for 12 (Kappa 0.61-0.80) conditions. Agreement was lowest for mental and behavioural disorders. The percentage of all individuals with a condition identified in both PC and HI data was lowest in PTSD (0.2%) and highest in coronary artery disease (62.9%).

Interpretation

Use of single data sources may underestimate prevalence when measuring multimorbidity and many important conditions (especially mental and behavioural disorders). Caution should be used when interpreting findings of research examining individual and multiple long-term conditions using single data sources. Where available, researchers using electronic health data should link primary care and hospital inpatient data to generate more robust evidence to support evidence-based healthcare planning decisions for people with multiple long-term conditions.

Poster competition – Group C

Dr Hamish Foster

University of Glasgow

hamish.foster@glasgow.ac.uk
@hamishfoster

C1

Associations and interactions between dimensions of social isolation and loneliness with mortality: a prospective analysis of the UK Biobank cohort

Background
Both social isolation and loneliness are associated with all-cause mortality and cardiovascular disease (CVD). Different dimensions of social isolation (eg, living alone) and loneliness (eg, self-reported loneliness), may interact in their combined associations with adverse health outcomes and could indicate high-risk groups. Yet these interactions remain unexplored. We aimed to explore the strength of association between dimensions of social isolation and loneliness – friends and family visit frequency (FFVF), participation in weekly group activities, living alone, and perceived loneliness – and all-cause and CVD mortality, and to examine how these factors interact with one another to modify associations with adverse health outcomes.

Methods
Data: UK Biobank - 502,536 adults recruited 2006–10, age 37-73. Baseline self-reported exposures: three social isolation dimensions - FFVF (6 category ordinal variable), weekly group activity (yes/no), and living alone (yes/no); 2 loneliness dimensions: frequency of ability to confide (6 category ordinal variable), and often feels lonely (yes/no). Outcomes: all-cause (ACM) and CVD mortality (CVDM) ascertained via linked national registries. Cox proportional hazard models, adjusted for sociodemographic and health confounders, used to examine combined associations and interactions for outcomes. Sensitivity analyses excluded those with prior CVD/cancer or who died within 2 years of recruitment.

Findings
Participants with full data (458,136 [91.2%]) were included. After median 12.6 years follow-up, there were 33,135 (7.2%) deaths, of which 5,112 (1.1%) were CVD deaths. Each dimension was independently associated with both outcomes. For FFVF, incrementally stronger associations were seen from a level of less than monthly and lower. In combined associations, compared to least isolated and not lonely, the association with outcomes generally strengthened stepwise with each additional dimension. Those with lowest FFVF, no weekly group activity, lived alone, and not lonely had strongest associations with ACM (HR 95%CI 2.34 [1.65-3.30]). However, there was considerable overlap of mortality estimates for all those with lowest FFVF irrespective of other dimensions. Exploring interactions between dimensions revealed an interaction between FFVF and living alone for ACM; compared to highest FFVF, HRs (95% CIs) for lowest FFVF was 1.33 (1.22-1.46) in those not living alone and 1.77 (1.61-1.95) in those living alone.

Interpretation
Each dimension of isolation or loneliness is important. However, lowest FFVF and living alone were associated with greatest mortality. The interaction between FFVF and living alone indicates that those with no friends or family contacts who also live alone are at particularly high risk and could benefit from targeted intervention. FFVF of less than monthly may represent a threshold effect which could inform interventions. While UK Biobank is a large and rich prospective data set it is not representative of the UK population. Associations may not be causal although similar results for the sensitivity analyses add weight against reverse causality.

Dr Jonathan Wan

University College Hospital
Guy's Cancer Centre

C2

Detection of early-stage non-small cell lung cancer using circulating bacterial DNA: a metagenomics proof-of-concept study

Background
In individuals with cancer, circulating tumour DNA (ctDNA) is released from tumour cells into the circulation. ctDNA can be detected using blood tests and DNA sequencing, termed liquid biopsy. However, the sensitivity for detection of early-stage cancers is limited due to low concentrations of ctDNA molecules in the bloodstream.

The human microbiome comprises trillions of cells and may provide an abundant source of cell-free DNA, termed circulating bacterial DNA (cbDNA). Recent studies demonstrate differences in cbDNA profiles between individuals with cancer vs. healthy controls, although the sources of cbDNA driving these differences are unclear.

Methods
We extracted microbial sequencing reads from publicly available tumour and plasma whole-genome sequencing data from 39 patients with early-stage non-small cell lung cancer (NSCLC) and 38 healthy controls. Plasma samples were obtained at pre- and post-surgery (median 2.5 weeks) time points. 27 out of 39 had stage I disease (69.2%), and only one patient had stage IV disease.

cbDNA data were filtered, transformed to log2-counts per million, and then normalised for age and sex. We performed pairwise comparisons of genus abundance between plasma samples from cases vs. controls, and between plasma samples taken pre-and post-surgery.

Findings
There were significant differences in plasma abundance of multiple genera between cases and controls (FDR corrected $p < 0.05$, Wilcoxon test). Streptococcus, Staphylococcus and Corynebacterium were enriched in cbDNA in the blood of NSCLC patients, which were previously identified in NSCLC tumour sequencing. When pre- and post-surgery samples were compared, there was no significant difference in abundance in any genus (FDR corrected $p > 0.05$, Wilcoxon test).

A machine learning model was used to classify patient plasma vs. healthy control plasma for cancer detection using 10-fold cross-validation. This showed accurate cancer detection in both pre-surgery samples (Area Under the Curve, AUC 0.94) and also after tumour resection (AUC 0.98).

Interpretation
Altered cbDNA profiles persisted in the weeks following cancer surgery, suggesting a role for non-tumour release of cbDNA, such as lung-resident bacteria. Thus, cancer-associated alterations in cbDNA released from an altered lung microbiome might enable earlier detection of lung cancer.

Dr Andrej Corovic

Section of CardioRespiratory Medicine, University of Cambridge

C3

Imaging of Post-Infarct Myocardial Inflammation with 68Ga-DOTATATE PET/MRI; a Prospective Observational Cohort Study

Background
Inflammation and its resolution modulate post-infarct myocardial injury. Specifically, an excessive or prolonged inflammatory phase after myocardial infarction (MI) may contribute to adverse cardiac remodelling.

Hybrid PET/MR imaging using PET tracers that are more specific for highlighting immune cells may offer the opportunity to non-invasively monitor post-MI inflammation and remodelling.

68Ga-DOTATATE is a tracer with high affinity for the somatostatin receptor subtype 2, which has been shown to be up-regulated in pro-inflammatory macrophages and thus may offer greater specificity for highlighting myocardial inflammation and with minimal background myocardial uptake.

We aimed to investigate 68Ga-DOTATATE PET/MRI for quantifying post-infarct myocardial inflammation.

Methods
In this prospective observational cohort study, participants with MI underwent 68Ga-DOTATATE PET/MRI at baseline (t0: <2 weeks post-MI) and 3 months (t3M). Patients with prior MI, heart failure, coronary revascularisation, or contraindication to PET/MRI, were excluded. Blood samples were taken at the time of imaging for high sensitivity CRP (hsCRP), high sensitivity troponin I (hsTnI), NTproBNP and peripheral blood monocyte subset counts measured by mass cytometry. 68Ga-DOTATATE maximum Standardised Uptake Values (SUV) and Tissue-to-Background Ratios (TBR) adjusted for blood pool activity were compared in the infarct defined by late gadolinium enhancement (LGE) MRI to remote myocardium at t0 and t3M.

Findings
Thirty-two patients (mean age 59y; 81% male; 19% female), comprised of 56% patients with STEMI and 44% with NSTEMI, were enrolled.

68Ga-DOTATATE PET signal co-localised with myocardial LGE and focal oedema on T2-weighted MRI and had excellent ability to discriminate infarct from remote regions (t0: infarct TBR 5.08 vs. remote 3.35, $p<0.0001$).

At 100 (SD 13) days after MI (n=23), residual 68Ga-DOTATATE uptake in the infarct remained higher than remote myocardium (t3M: infarct TBR 3.96 vs. remote 2.73, $p<0.0001$), but was reduced compared to baseline (TBR -22%, $p=0.002$).

Reduction in infarct 68Ga-DOTATATE uptake was consistent with overall decreases in hsCRP, hsTnI and NTproBNP levels at t3M vs. t0 ($p<0.05$). Focal oedema on MRI was resolved in 74% patients at t3M. Infarct-to-remote TBR ratio at t0 was correlated with hsTnI ($r=0.35$, $p<0.05$). At t3M (n=9 samples) vs. t0 (n=20 samples), there was a reduction in % classical-to-non-classical ratio of peripheral monocytes.

Interpretation
This is the first prospective study of serial cardiac 68Ga-DOTATATE PET/MRI in patients after MI. Here we show that 68Ga-DOTATATE can highlight acute, and track resolving, myocardial inflammation after MI.

This approach holds great promise as a novel imaging tool for identifying people with residual myocardial inflammation after MI who would stand to gain the greatest benefit from emerging immunomodulatory therapies for cardiovascular disease.

Dr Jakub Scaber

University of Oxford
Oxford University Hospitals NHS Foundation Trust

jakub.scaber@ndcn.ox.ac.uk

C4

Studying cell-specific vulnerability in C9orf72-positive Amyotrophic Lateral Sclerosis in vitro using induced pluripotent stem cell derived motor and sensory neurons

Background
Induced pluripotent stem cell (iPSC)-derived from patients with Amyotrophic Lateral Sclerosis (ALS) who are carriers of the C9orf72 hexanucleotide repeat expansion (HRE) have multiple cellular phenotypes in motor neurons, but it remains unknown whether these phenotypes contribute to the cell-specific vulnerability seen in this disease. The aim of this study was to compare the phenotypes of C9orf72 HRE positive iPSC-derived motor neurons with sensory neurons, which are relatively spared in ALS, to provide insights into cell-specific vulnerability.

Methods
In this study, we differentiated sensory and motor neurons from five controls and three patients carrying the C9orf72 HRE and confirmed their cellular identity using immunofluorescence, western blotting, and RNA sequencing analysis. Direct consequences of the C9orf72 HRE including RNA foci formation (fluorescence in situ hybridisation) and GA and GP dipeptide repeat abundance (ELISA) were assessed. Downstream cellular phenotypes including stress granule formation and TDP mislocalisation were assessed with and without 0.5 mM sodium arsenite treatment for one hour. Axonal transport using Lysotracker, Mitotracker and Syto RNA select was studied using microfluidic devices.

Findings
RNA sequencing confirmed the divergent identity of iPSC-derived motor and sensory neurons. Nkx6.1 and ChAT were confirmed as motor neuron specific markers using western blotting and immunofluorescence analysis. The presence of sense and antisense RNA foci and dipeptide protein synthesis were confirmed in both motor and sensory neurons from C9orf72 patients, with no differences between the two cell types. No significant differences in TDP-43 distribution and stress granule frequency were observed between C9orf72 HRE patient samples and controls, but differences were seen between motor neurons and sensory neurons, with motor neurons forming fewer stress granules and having a higher relative cytoplasmic concentration of TDP-43. The speed of lysosomal transport was reduced in C9orf72 motor neurons and sensory neurons compared to controls and the speed of mitochondrial transport was reduced in motor neurons only.

Interpretation
Motor and sensory neurons derived from iPSCs carrying the C9orf72 HRE have similar levels of expression of RNA foci and dipeptides, and therefore are both affected by early manifestations of the C9orf72 HRE. Slowing of axonal transport, which is seen in C9orf72 HRE-positive motor neurons can also be seen in sensory neurons, indicating that axonal transport deficits may not be the driver of selective vulnerability. The differences in cellular physiology between motor and sensory neurons, such as TDP-43 distribution and stress granule formation, could however be of significance for selective vulnerability to neurodegeneration later in life.

Cathal McCague

University of Cambridge
Addenbrooke's Hospital

C5

Evaluating the clinical utility of artificial intelligence (AI) based segmentation-models for medical image analysis using a novel framework called AUGMENT (Assessing Utility of seGMENtation Tools), created using the categories of error in 3D-medical-imaging

Background
Segmentation is the identification of a region-of-interest, such as a tumour, and the delineation of its boundaries. It is an essential, time-consuming step in radiotherapy planning or the development of prognostic radiomic biomarkers.

Currently, performance of AI-based segmentation tools is measured using quantitative metrics like the Dice-Similarity-Coefficient (DSC). These metrics do not give information on the types of errors the tool makes, and can overestimate clinical utility, mask serious errors or be manipulated.

This study aims to assess if poor DSC score translates to a poor segmentation, and develop a better measure for clinical-utility.

Methods
We use ovarian-carcinoma to show AUGMENT's potential.

An nnU-Net model for segmenting pelvic/ovarian-disease(POD) and omental-disease(OD) achieved mean DSC of 72±19(POD) and 64±24(OD) on external test-set.

First, to assess if the AI-segmentations were noticeably different to manual-segmentations, we conducted a visual-Turing-test(VTT) with 20 independent-observers (from medical-student to genitourinary-radiologist).

To assess its clinical-utility we conducted a quality-comparison study. 27 scans had 3 separate segmentations created (for POD and OD) by: i) AI, ii) 3 radiologists (9 scans each), and iii) collaborative-segmentation, where 3 radiologists amended AI-segmentations. Segmentation time was also recorded. An expert genitourinary-radiologist scored each unlabelled segmentation using the AUGMENT-framework.

Findings
VTT – Classification accuracy for AI-segmentations: 63.8%, not meeting the 50% required for AI-tool to pass the VTT. No statistical difference in performance between experience-groups (Likelihood Ratio Test p=0.39). Written-feedback showed assessors detected AI-segmentations by their sometimes "unnatural" borders.

Quality-comparison study – Segmentation rankings: human+AI=1st place (or joint 1st) in 19/27 scans (70%); AI=1st place (or joint 1st) in 11/27 scans (41%); human segmentations=1st place (or joint 1st) in 6/27 scans (22%). Difference between AUGMENT score of AI-segmentation and human-segmentation at the 5% level (p-value = 0.46). Difference between AUGMENT score of human+AI-segmentation and human-segmentation at the 5% level (p-value = 0.00047). Mean additive effect of using the AI as a segmentation aid, in terms of the AUGMENT score, was 1.37. Segmentation time saving for human+AI vs. human: average decrease in segmentation time, compared to the baseline, of 57.23% overall, significant at the 5% level (p-value=0.000012).

Interpretation

Our study shows how a model with modest DSC scores has utility in i) improving the quality of radiologist curated segmentations, and ii) reducing segmentation time.

Using a qualitative framework like AUGMENT, which incorporates the views of clinical experts, alongside a quantitative metric, may give a better estimation of practical, clinical utility.

AUGMENT provides information on the types of errors a segmentation-model is producing, and fosters closer collaboration with clinical domain-experts during the model development process, which could aid transparency and build clinician trust in the tools. Its use, however, necessitates access to clinicians and commitment of their time.

Dr Rebecca Spencer

University of Leeds
Leeds Teaching Hospitals NHS Trust

r.n.spencer@leeds.ac.uk
@bekahspencer

C6

Discovery and validation of ultrasound and biochemical models to predict pregnancy outcomes from a case series of early-onset fetal growth restriction

Background
Fetal growth restriction (FGR) is diagnosed antenatally by ultrasound and most often results from placental insufficiency. Early-onset FGR, occurring before 32 weeks of gestation, carries significant risks of stillbirth, neonatal morbidity and mortality, neurodevelopmental impairment, and long-term health problems. Predicting the outcome of affected pregnancies at the time of diagnosis is difficult, preventing accurate patient counselling.

The aim of this study was to identify and validate ultrasound and serum biochemical factors that could be used to predict (1) fetal or neonatal death and (2) fetal death or delivery ≤28+0 weeks of gestation in pregnancies diagnosed with severe early-onset FGR.

Methods
Women with singleton pregnancies (n=142, estimated fetal weights [EFWs] <3rd centile, <600g 20+0-26+6 weeks of gestation, no known chromosomal, genetic or major structural abnormalities), were recruited from four European centres. Maternal serum from the discovery set (n=63) was analysed for seven proteins linked to angiogenesis, 90 additional proteins associated with cardiovascular disease and five proteins identified through pooled liquid chromatography tandem mass spectrometry. The resulting measurements were used for model construction and underwent parenclitic and functional network analysis. Patient and clinician stakeholder priorities were used to select models tested in the validation set (n=60).

ClinicalTrials.gov NCT02097667, REC reference: 13/LO/1254

Findings
Forty two (34%) of the pregnancies ended in fetal or neonatal death. The most discriminative predictive model included EFW z-score (Hadlock 3 formula/Marsal chart), gestational age and umbilical artery Doppler category (AUC 0.91, 95%CI 0.86-0.97) but the model containing EFW z-score (Hadlock3/Marsal) alone was better calibrated. Maternal serum placental growth factor (PlGF) concentration <14.2 pg/ml predicted fetal or neonatal death with a positive likelihood ratio of 18.3, sensitivity of 45% and specificity of 98% and correctly classified 80% of participants.

Fifty eight (47%) of the pregnancies ended in fetal death or delivery ≤28+0 weeks of gestation. The most discriminative predictive model included PlGF and umbilical artery Doppler category (AUC 0.89, 95%CI 0.83-0.94). Serum PlGF concentration <14.5 pg/ml predicted death or delivery ≤28+0 weeks with a positive likelihood ratio of 24.7, sensitivity of 38% and specificity of 98% and correctly classified 70% of participants.

Interpretation
This is the first study to use a discovery science approach, combining ultrasound and biochemical parameters, to identify and validate prognostic markers at the time of diagnosis of severe early-onset FGR. These findings can be used to inform personalised counselling and management of affected pregnancies with outcomes of importance to patients and clinicians.

The strengths of this study include its prospective multi-centre design, involvement of stakeholders in model selection and temporal validation of pre-specified models. The narrow inclusion criteria and high-income settings limit the generalisability of these results and clinician awareness of ultrasound findings could have introduced bias.

Petra Hanson

University of Warwick
University Hospital of Coventry and Warwickshire

C7

Sodium in the dermis colocates to glycosaminoglycan scaffold, with diminishment in type 2 diabetes mellitus, an experimental study

Background
Established dogma states that urinary sodium output matches dietary sodium intake in normal human physiology. This traditional model of sodium homeostasis locates sodium ions primarily within the extracellular fluid (ECF) compartment, and forms the traditional "2-space" model for sodium homeostasis. Dietary sodium intake mismatches urinary sodium excretion over prolonged periods, suggesting that a third space for sodium storage may exist. Our aims were to localize and quantify electrostatically bound sodium within human skin using triple-quantum-filtered (TQF) protocols for MRI and magnetic resonance spectroscopy (MRS) and to explore dermal sodium in type 2 diabetes mellitus (T2D).

Methods
This was an experimental study. We recruited adult participants with T2D (n = 9) and euglycemic participants with no history of diabetes mellitus (n = 8). All had undergone lower limb amputations or abdominal skin reduction surgery for clinical purposes. We used 20 µm in-plane resolution 1H MRI to visualize anatomical skin regions ex vivo from skin biopsies taken intraoperatively, 23Na TQF MRI/MRS to explore distribution and quantification of freely dissolved and bound sodium, and inductively coupled plasma mass spectrometry to quantify sodium in selected skin samples.

Findings
As demonstrated from the images, about 90% of sodium recorded by the standard 23Na GE MRI protocol was localized in the dermis layer. Therefore, the highlighted sodium dynamics most likely originate from the dermal layer of the skin. Both free and bound sodium colocalize with the dermis layer in the MRI slide, where glycosaminoglycans (GAGs) are typically located, as determined by histological staining. We observed similar patterns for both free and bound sodium in nondiabetic skin biopsies. However, T2D associates with a severely reduced dermal bound sodium capacity.

Interpretation
We provide the first evidence to our knowledge for high levels of bound sodium within human dermis, collocating to the GAG scaffold, consistent with a dermal "third space repository" for sodium. T2D associates with diminished dermal electrostatic binding capacity for sodium. This could explain the increased likelihood of sodium overload, and subsequently fluid overload and heart failure, among people living with type 2 diabetes.

Dr Simon Bell

Sheffield Institute for Translational Neuroscience, University of Sheffield
Department of Neurology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Trust

s.m.bell@sheffield.ac.uk
@NeuroSimon

C8

Astrocytes derived from patients with sporadic and familial Alzheimer's disease show deficits in hexokinase 1 expression which when corrected improves astrocyte glycolysis and mitochondrial stress

Background
Astrocytes have multiple roles including providing neurons with metabolic substrates and maintaining neurotransmitters at neuronal synapses. Astrocyte glucose metabolism plays a key role in learning and memory with astrocytic glycogen a key substrate supporting memory encoding. The homeostatic role the astrocyte provides for neurons leads to metabolic demands, meaning that abnormalities in the function of astrocyte mitochondria and glycolysis could affect this relationship. Changes to cellular metabolism are seen early in Alzheimer's disease (AD). Understanding cellular metabolism changes in AD astrocytes could be exploited as a new biomarker or synergistic therapeutic agent when combined with anti-amyloid treatments in AD.

Methods
In this project, we characterised mitochondrial and glycolytic dysfunction in astrocytes derived from patients with sporadic (sAD) (n=6), familial (fAD) (n=3), and associated controls (n=9). Astrocytes were derived using direct reprogramming technology. Astrocyte metabolic outputs; total cellular adenosine triphosphate (ATP) levels, and extracellular lactate levels were measured using luminescent and fluorescent protocols. Mitochondrial respiration and glycolytic function were measured using a Seahorse XF Analyzer. Hexokinase deficits identified where corrected by transfecting astrocytes with an adenovirus viral vector containing the hexokinase 1 gene. All sporadic patients had detailed neuropsychological assessment performed allowing for correlation of metabolic and neuropsychological phenotypes.

Findings
In sAD astrocytes a 20% reduction ($p=0.05$) and in fAD a 48% ($p<0.01$) reduction in total cellular ATP was seen. A 44% reduction ($p<0.05$), and 80% reduction in Mitochondrial spare capacity was seen in sAD and fAD respectively. Reactive oxygen species (ROS) where increased in both AD astrocyte types ($p=0.05$). Mitochondrial complex I and II was significantly increased in sAD ($p<0.05$) but not in fAD. Astrocyte glycolytic reserve and extracellular lactate was significantly reduced when compared to controls in both sAD and fAD ($p<0.05$). The glycolytic pathway enzyme hexokinase1 had significantly reduced expression and activity in both AD astrocyte types. Correcting this deficit restored total cellular ATP levels, extracellular lactate and reduced ROS in sAD but not fAD astrocytes. In the sAD cohort, total cellular ATP and extracellular lactate levels correlated significantly with immediate and delayed recall. ROS showed a significant negative correlation using the same neuropsychological tests.

Interpretation
AD astrocytes have abnormalities in functional capacity of mitochondria and the process of glycolysis. AD astrocytes also have a reduction in metabolic output markers. These deficits are likely to impede metabolic support for neurons. Metabolic output markers such as total cellular ATP and extracellular lactate correlate significantly with neuropsychological assessments shown to be abnormal early in sAD. These functional deficits can be improved by correcting hexokinase deficits. This suggests that hexokinase 1 deficiency could potentially be exploited as a new therapeutic target for AD and neuropsychological assessment could be used as a biomarker for treatment.

Sarah James

University of Cambridge

slj38@cam.ac.uk

C9

Resolving inconsistencies in the computational analysis of large influenza antigenic datasets

Background

Understanding and tracking antigenic variation is a key aspect of disease control. Influenza vaccine strain selection relies on global influenza antigenic data, produced through testing virus strains with post-infection ferret antisera and recording patterns of reactivity. Antigenic cartography quantitatively visualises the results of laboratory antigenic assays using metric multidimensional scaling. The antigenic map is optimised by moving the points to better fit the antigenic distances between viruses and sera. As new data is integrated into large antigenic maps, there is sometimes an abrupt loss of accuracy. My aim is to develop new methods to make large, reliable antigenic maps.

Methods

Data science techniques were applied to an existing influenza B/Victoria CDC virological surveillance dataset (2013-2020, 5032 viruses, 125 ferret sera, haemagglutination inhibition assay with turkey erythrocytes). This dataset was segmented to identify tractably small subsets that demonstrated degeneration and could be split into two correct submaps.

An automated series of tests were developed to identify the underlying causes of these incorrect antigenic maps, including:

- Removing each antigen or serum
- Removing poorly fitting data
- Changing the serum normalisation constants for calculating antigenic distance
- Changing the threshold for excluding variable repeat data
- Using different optimisation methods

Findings

A total of four maps were analysed (two which met the criteria and two where only one of the submaps were incorrect). An ideal map should show antigenically similar viruses clustering close to each and antigenically different viruses far apart on the map, and should be robust to the addition of new data.

Two maps had a major shift in overall shape with linear degeneration. A single serum could be moved or removed to produce the correct map.

One map showed antigenically similar virus points spread out in two clusters instead of one. Decreasing the normalisation factor for calculating antigenic distance for several sera improved this map.

One map was twisted, with viruses and sera on the wrong side of the map. Using the default threshold for excluding variable data had removed a titre that was essential in holding the map in the correct shape.

Interpretation

This work shows that there are several different classes of incorrect map when new data is added to a large surveillance antigenic map. There are different causes for the different classes. By targeting these causes, we can develop methods make larger, more reliable antigenic maps.

This analysis used data from a single laboratory for a single lineage of influenza B. Further work is required to expand this analysis to other laboratories and other types and subtypes, notably A/H3N2. This will improve our understanding of the genetic basis of antigenic change and support vaccine strain selection.

Dr Radoslaw Debiec

Department of Cardiology and NIHR Leicester Biomedical Research Centre, University of Leicester
East Midlands Congenital Heart Centre, Glenfield Hospital, University Hospitals of Leicester NHS Trust

C10

Whole exome sequencing identifies risk variants in planar cell polarity pathway genes contributing to bicuspid aortic valve disease

Background
Bicuspid aortic valve (BAV) is a common congenital valvular malformation associated with significant morbidity. BAV disease clusters in families and additional family members are found in 15% of probands. Several genes have been identified and fully validated as causative for non-syndromic disease (GATA4, NOTCH1, ROBO4, SMAD6) but explain only a small proportion of the overall heritability. It is hypothesized that the underlying genetic defect may in part explain predisposition to valve dysfunction and aortic disease. The aim of the study was identification of novel genes associated with BAV thorough genetic segregation analysis in affected families.

Methods
Study subject were patients recruited the University of Leicester and Leicester NIHR Biomedical research Centre, Bicuspid aoRtic vAlVe gEnetic research (BRAVE) study (approved by the East Midlands Research Ethics Committee- Ref: 15/EM/0250). Segregation of rare, deleterious (CADD score>20) genetic variants, identified through whole exome sequencing (WES), was performed in 20 extended pedigrees (51 affected subjects) who underwent whole exome sequencing.

Independent exome wide genetic association analysis was performed in probands from 255 pedigrees with early onset complications of BAV disease, by researchers from the UTHealth BAV Research Registry (EBAV), Huston, US.

Findings
Analysis in the BRAVE study revealed rare deleterious genetic variants segregating with BAV in six of 20 families: a loss of function (LOF) variant p.Gln259Ter in PTK7 (three subjects) the missense variants: p.His411Arg in WNT9B (two subjects), p.Arg241His in PRICKLE1 (two subjects) and p.Asp2456Val, p.Arg2497His and p.Val1518Phe in CELSR1. Notably, each of these genes encodes members of the planar cell polarity (PCP) pathway.

Analysis in the EBAV cohort detected high burden of LOF (e.g. nonsense, frame-shift, splice) variants in PCP genes: seven individuals with LOF in DAAM2, one with LOF variant in FZD7, one with LOF variant in RYK, two with LOF variants in CELSR1, one LOF variant in GPC5 and four with LOF variants in FMNL2, eight with LOF variants in FMN2. Altogether 24/255 (9.4%) subjects from the EBAV cohort had LOF variants in genes of the PCP pathway in comparison to 41/282,912 of gnomAD controls (p=<0.001).

Interpretation
The PCP pathway is an evolutionary conserved pathway involved in spatial polarizing of cells in the plane of the tissue and necessary for cell migration during embryonic development. Previous work in animal models revealed an essential role for PCP signalling in heart development. Mice deficient for core PCP pathway genes (Dvl, Prickle1, Vangl2, Ptk7) demonstrate a range of congenital cardiac defects, including BAV.
Our study highlights rare deleterious genetic variants in the PCP pathway as a cause of BAV in humans. We have observed several events of incomplete penetrance (DAAM2) which have to be further validated in biological models.

Dr Emanuele Osimo

Institute of Clinical Sciences, Imperial College London
MRC London Institute of Medical Sciences

eosimo@ic.ac.uk
@eosimo

C11

Predicting treatment-resistance from first-episode psychosis using routinely collected clinical information: risk prediction model development and external validation

Background
23% of people who experience a first episode of psychosis (FEP) will develop treatment-resistant schizophrenia (TRS). TRS is associated with reduced quality of life, substantial societal burden, and up to tenfold higher healthcare costs. It is not currently possible to predict accurately whether someone with FEP will develop TRS. This is important because there is evidence that clozapine, the only treatment licensed for TRS, is more effective the sooner it is prescribed. Yet, in clinical practice there are often long delays before clozapine is considered. This highlights the need to identify treatment resistance as soon as possible.

Methods
We aimed to explore the predictive potential for TRS of routinely collected, objective biomedical predictors at FEP onset, and to externally validate the model in a separate clinical sample of people with FEP. We developed and externally validated a forced-entry logistic regression risk prediction Model fOr cloZApine tReaTment, or MOZART, to predict up to 8-year risk of TRS from FEP using routinely recorded information including age, sex, ethnicity, triglycerides, alkaline phosphatase levels, and lymphocyte counts. MOZART was developed in 785 patients, and validated externally in 1,110 patients from UK-based early intervention in psychosis teams.

Findings
MOZART predicted TRS well at internal validation (C statistic: 0.70; 95%CI 0.63,0.76). At external validation, discrimina-tion performance reduced (C: 0.63; 0.58,0.69) but recovered after re-estimation of the lymphocyte predictor (C: 0.67; 0.62,0.73). Calibration plots showed good agreement between observed and predicted risk in the forced-entry model.

Decision curve analysis for MOZART suggests that at propensity to intervene thresholds greater than 0.05 (revised model) or 0.06 (original model), the models provided greater net benefit than the competing extremes of treating all patients or none. The recalibrated model provided higher net benefit at most, if not all, thresholds over 0.05 than the original model.

We also present a data visualisation tool for both the original and recalibrated models (https://eosimo.shinyapps.io/trs_app/), which allows to interactively explore the effect of each predictor and their combinations on the risk of TRS based on the predictors included in this study.

Interpretation
This model cannot yet be recommended for clinical use. However, subject to several steps, in future MOZART could allow to implement low-risk strategies, e.g., stratifying patients at higher-than-average risk of developing antipsychotic resistance for closer psychiatric monitoring for the presence of TRS. These strategies have very low risk of causing harm, and might show potential at earlier recognition and treatment of TRS.

Further, the use of routinely collected clinical information including blood-based biomarkers taken at FEP onset can help to predict the individual risk of TRS, and should be considered alongside others in efforts to predict psychiatric outcomes.

Poster competition – Group D

Dr Kate Burley

University of Bristol

kb14162@bristol.ac.uk
@KateBurley6

D1

CRISPR-Cas9 gene editing of ZFPM2 suggests critical role in megakaryocyte proliferation, differentiation and granulogenesis

Background
ZFPM2 encodes zinc finger protein ZFPM2 (FOG2), a GATA transcription cofactor implicated in Tetrology of Fallot, congenital diaphragmatic hernia and sex-reversal disorders. ZFPM2 also has megakaryocyte (MK)-restricted gene expression in bone marrow. Common variants in ZFPM2 associate with both platelet count (PLT) and side scatter, a proxy of platelet granularity (Akbari et al. 2020). Although these observations suggest a role for ZFPM2 in megakaryopoiesis, there is currently little experimental evidence for this. Here we explore the clinical associations of common variants in ZFPM2 and describe the first in-depth functional characterisation of this gene in a MK cell model.

Methods
Variant-phenotype associations were examined through a Mendelian randomisation (MR) phenome-wide association study of genetic and health outcome data from UK Biobank. A cell model of reduced ZFPM2 expression was developed using RNP-based CRISPR-Cas9 gene editing in immortalised MK progenitor (imMKCL) cells in which differentiation to mature MK can be induced by suppression of doxycycline-dependant transgenes.

Findings
Of the common ZFPM2 variants associated with platelet traits in prior GWAS, intronic SNP rs6993770 was within an epigenetically active area and was a pQTL for multiple platelet alpha granule-derived plasma proteins. MR analysis revealed that the association between rs6993770 and reduced PLT was causal and that there were further causal associations with a reduced risk of venous thromboembolism and cardiovascular disease. CRISPR-Cas9 knockdown of ZFPM2 in progenitor imMKCL cells reduced proliferation compared to scrambled controls and increased the proportion of cells in S phase suggesting cell cycle arrest. Following differentiation, mature ZFPM2 knockdown imMKCL cells were smaller, had lower DNA ploidy and reduced surface expression of MK-maturity marker CD42b compared with controls. The knockdown imMKCL cells also had lower side scatter, altered abundance of transcripts associated with platelet alpha granules and abnormal ultrastructure with conspicuous areas of cytoplasm devoid of organelles. Proplatelet formation was reduced compared to controls.

Interpretation
The effect of ZFPM2 knockdown in imMKCL cells indicates a critical role for ZFPM2 in the proliferation and differentiation of MK with manifestations that include abnormal granulogenesis. These observations are consistent with the prior GWAS associations between common ZFPM2 variants and platelet traits and provide potential mechanistic explanations for the causal clinical associations between the common ZFPM2 variant rs6993770 and thrombotic disease.

Krit Dwivedi

University of Sheffield
Sheffield Teaching Hospitals NHS Foundation Trust

krit.dwivedi1@nhs.net
@kritdw

D2

Combining the strengths of AI and radiologists for prognostic quantification of lung disease on CT in pulmonary hypertension: a retrospective multicentre validation study

Background
The gold standard for Computed Tomography (CT) assessment is visual scoring by specialist radiologists, but it has significant inter-observer variability. Recent breakthroughs in Artificial Intelligence (AI) approaches enable automated quantification of imaging features. Distinguishing between Pulmonary Hypertension phenotypes, Idiopathic Pulmonary Arterial Hypertension (IPAH) and PH associated with Chronic Lung Disease (PH-CLD) is challenging in patients with 'mild' lung disease due to overlapping clinical characteristics. Phenotyping informs management, with novel therapeutic agents only indicated in IPAH. This multicentre study develops and deploys an automated AI model to quantify and establish the prognostic value of lung parenchymal patterns on routine chest CT.

Methods
521 consecutive patients between 2001-19 were included from the ASPIRE registry. A novel deep-learning AI model which automatically segments and classifies the lung parenchyma on chest CT was developed. The model quantified percentage of normal lung, ground glass, ground glass with reticulation (GGR), emphysema, honeycombing and fibrosis. Fibrosis severity was also visually scored by sub-specialist radiologists. Multivariate cox regression adjusting for age, sex, WHO function class, and diffusing capacity of carbon monoxide (DLCO) was performed. Findings were externally validated in 246 patients from 33 centres and 37 scanners. Ethical approval was granted by National Research Ethics Service.

Findings
AI quantified lung disease correlated well with DLCO and radiological scoring. All AI quantified patterns were prognostic univariate predictors. GGR% (HR 1.02, p=0.015) and fibrosis% (HR 1.01, p=0.05) were continuous (HR indicates single percentage point increase in disease severity) prognostic multivariate predictors. 2% GGR and 4% fibrosis corresponded to 20% 1-year mortality. In the external cohort, these thresholds were multivariate prognostic predictors (2% GGR HR 1.74, p=0.011 and 4% fibrosis HR 1.85, p=0.004). In 300 patients scored by radiologists as having 'no' fibrosis, AI identi-fied minor disease (1.2% GGR) which was prognostic (HR 1.03, p=0.006). Adding GGR to a predictive model of radiologi-cally scored disease significantly improved the model (c-index 0.763 vs 0.742, p=0.038).

Interpretation
This is the most representative AI study in this domain (521 vs 125 patients for second largest study), and the first with external validation (246 patients, 33 centres, 37 scanners). AI quantified GGR and fibrosis are independent prognostic markers for survival. AI is sensitive to minor lung disease changes, and when used in combination with radiological reporting, provides additional predictive value. We acknowledge limitations inherent to chest CT, imaging AI studies and in the retrospective setting. Prospective international studies are warranted. These findings have implications for patient phenotyping, management, and radiological reporting.

Dr Ahmed Alboksmaty

University of Cambridge

ahmed.alboksmaty@thisinstitute.cam.ac.uk
@alboksmaty

D3

Remote patient monitoring at home using ambient sensors: a systematic review

Background
The world population is ageing, and their health needs imply substantial demands on health systems. Remote Patient Monitoring (RPM) may help elderly patients live independently in their homes for longer. The essence of RPM is the continuity of use, which is challenging for wearable devices and patient-led technologies. Unobtrusive (ambient) sensors could be an innovative solution, such as motion detectors and similar technologies. This study aims to review the evidence on the effect of ambient sensors on healthcare use by the elderly.

Methods
This is a systematic review for narrative synthesis, searching five databases, Medline, Embase, CINHAL, Scopus and Web of Science, on 21 Feb 2022 without setting a lower time limit. No restrictions on the design of studies were applied. A meta-analysis was not feasible due to the heterogenicity of the studies.

Findings
Out of 5,653 search results, 180 studies were subjected to full-text review, of which 6 studies were included in the final synthesis. All the included studies were conducted in the USA. Four studies assessed the technology's cost-efficiency, while only one reported significant cost savings. One study reported a significant reduction in hospital days and visits to a physician among the users. Using ambient sensors was associated with an increased length of stay in facilities where the elderly can live independently, including at home. The impact on the number of hospitalisations or emergency room visits was unclear.

Interpretation
Our review identified limited evidence on the effect of ambient sensors on healthcare use by the elderly. The potential has been demonstrated for ambient sensor technologies to result in cost savings; however, further research is needed to assess the impact on health outcomes. Using ambient sensors for remote home monitoring has the potential to save healthcare resources and to help the elderly live independently for longer in their preferred environments.

Anna Rose

Department of Paediatrics, University of Oxford
Oxford University Hospitals NHS Foundation Trust

@DrAnnaMRose

D4

Reactive oxygen species, protein trapping and cancer: novel insights from in vitro studies

Background
Telomere maintenance is a hallmark of cancer, allowing cells to endlessly divide. In most cancers, this is achieved through telomerase re-expression, however, in 15% of malignancies, it is attained through a telomerase-independent pathway, termed alternative lengthening of telomeres (ALT). ALT is particularly prevalent in solid tumours affecting children and young adults (e.g. osteosarcoma, glioma). ALT cancers have a poor prognosis and novel therapeutic approaches are needed. Whilst loss of ATRX is a universal feature of ALT-cancers, it is insufficient in isolation. As such, other cellular events must be necessary, but the nature of the second factor(s) has remained elusive.

Methods
A cellular system was generated, allowing in vitro study of ALT-induction, with particular focus on the role of trapping of protein on DNA and reactive oxygen species (ROS). The HeLa-LT cell line is a HeLa subclone with long telomeres that is amenable to ALT-induction. The ATRX gene was knocked out using CRISPR-Cas9, allowing comparison of otherwise isogenic cell pairings (ATRX-wildtype and ATRX-mutant). The cells were treated with various chemical and chemotherapeutic agents, and induction of ALT was assessed. The mechanism of ALT induction was further explored through gene silencing approaches, as well as cellular imaging and immunoblotting based techniques.

Findings
Camptothecin (TOP1-poison), etoposide (TOP2) and talazoparib (PARP1) trap DNA-interacting proteins onto the double-helix. Treatment with these drugs led to a strong induction of ALT in ATRX-mutant (but not ATRX-wildtype) cells. Induction of ALT was strongly correlated to the trapping potency of the drugs ($R^2=0.971$, $p=0.0003$). Knockdown of TOP1/TOP2/PARP1 expression by siRNA failed to yield ALT, confirming that the mechanism was protein trapping rather than loss of catalytic activity. It was demonstrated that protein-trapping leads to DNA replication fork stalling and aberrant telomere recombination.

Next, we explored the endogenous origin of protein-trapping in ALT-cancers. It was found that ALT-cells have higher levels of trapped TOP1 and ROS as compared to non-ALT cancer cells. It was shown that excessive ROS led to trapping of TOP1 on DNA, and that this process was dependent on formation of R-loops. R-loops are abnormal RNA:DNA structures that arise under conditions of cellular stress during gene transcription.

Interpretation
ATRX loss has long been described as a central event in the pathogenesis of ALT-cancers, but the second necessary factor has remained obscure. Here, we provide the first cogent model of ALT-cancer biology, whereby accumulation of ROS leads to generation of R-loops, which subsequently causes trapping of protein on DNA. This, in turn, causes replication fork stalling and collapse, providing the genetic substrate for ALT-telomere elongation. These novel insights in ALT-cell biology highlight new therapeutic approaches to specifically impair key pathways in these difficult-to-treat cancer types. Future work will explore the translational potential of these findings.

Dr Rose Penfold

Edinburgh Delirium Research Group, Ageing and Health, Usher Institute, University of Edinburgh
Royal Infirmary of Edinburgh
Scottish Hip Fracture Audit

rose.penfold@ed.ac.uk
@rosespenfold

D5

Delirium in hip fracture patients admitted from home is associated with higher mortality, longer total length of stay, need for post-acute inpatient rehabilitation and readmission to acute services: *The IMPACT Delirium study*

Background
Delirium is associated with adverse outcomes following hip fracture, but the prevalence and significance of delirium for the prognosis and ongoing rehabilitation needs of patients admitted from home is less well studied. Here we analysed relationships between delirium in patients admitted from home with: (i) mortality; (ii) total length of hospital stay; (iii) need for post-acute inpatient rehabilitation, and (iv) hospital readmission within 180 days.

Methods
This observational study utilised routine clinical data in a consecutive sample of hip fracture patients aged ≥50 years admitted to a single large trauma centre during the COVID-19 pandemic between 01/03/20-30/11/21. Delirium was prospectively assessed as part of routine care by the 4'A's Test (4AT), with most assessments performed in the emergency department. Associations were determined using logistic regression adjusted for age, sex, level of social deprivation, COVID-19 infection within 30 days, and American Society of Anesthesiologists grade.

Findings
A total of 1821 patients (mean age 80.7 years; 71.7% female) were admitted, with 1383 (mean age 79.5; 72.1% female) directly from home. 87 patients (4.8%) were excluded due to missing 4AT scores. Delirium prevalence in the whole cohort was 26.5% (460/1734): 14.1% (189/1340) in the subgroup of patients admitted from home, and 68.8% (271/394) in the remaining patients (comprising care home residents and inpatients when fracture occurred). In patients admitted from home, delirium was associated with a 20 day longer total length of stay ($p<0.001$). In multivariable analyses, delirium was associated with higher mortality at 180 days (Odds Ratio (OR) 1.69, 95% Confidence Interval (CI) 1.13-2.54; $p=0.013$), requirement for post-acute inpatient rehabilitation (OR 2.80, CI 1.97-3.96, $p<0.001$), and readmission to hospital within 180 days (OR 1.79, CI 1.02-3.15, $p= 0.041$).

Interpretation
Delirium affects 1 in 7 patients with a hip fracture admitted directly from home and is associated with adverse outcomes in these patients. Delirium assessment and effective management should be a mandatory part of standard hip fracture care.

Dr Rubika Balendra

University College London

r.balendra@ucl.ac.uk
@RubikaBalendra

D6

Dipeptide repeat proteins in C9orf72 motor neuron disease & frontotemporal dementia bind to specific RNAs: A transcriptome-wide RNA binding analysis

Background
Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are fatal neurodegenerative diseases. ALS affects 1 in 300 people and FTD is a common cause of young-onset dementia, but there are no curative treatments. A hexanucleotide GGGGCC repeat expansion in the C9orf72 gene is the commonest genetic cause of both diseases. Despite being intronic, the hexanucleotide repeat is translated into five dipeptide-repeat proteins (DPRs): poly(Glycine-Alanine/GA), poly(Glycine-Proline/GP), poly(Glycine-Arginine/GR), poly(Proline- Alanine/PA) and poly(Proline-Arginine/PR). Arginine-containing DPRs are highly toxic in models and affect mRNA splicing in vitro. I hypothesised that there is a direct interaction between arginine-DPRs and RNA, representing a novel disease mechanism.

Methods
To date the interaction of DPRs with specific RNAs has not been studied, and this is of key relevance to understand mechanisms in C9orf72-ALS/FTD. We investigated this using a novel technique, individual nucleotide resolution UV-crosslinking and immunoprecipitation (iCLIP). We expressed poly(PR) and relevant control proteins in human embryonic kidney (HEK) cells, then UV-crosslinked poly(PR)-RNA interactions, and immunoprecipitated poly(PR)-RNA complexes. Using reverse transcription and high-throughput sequencing, we quantitatively identified poly(PR)-RNA crosslink sites transcriptome-wide, interrogating sequence specificity. We investigated the affinity of interactions of poly(PR) with specific RNA sequences using biolayer inferometry. We investigated the effect of specific RNAs on poly(PR) phase-separation.

Findings
We found that poly(PR) directly binds to RNA in human cells, and used the iCLIP high-throughput sequencing dataset to show that poly(PR) had >1,200,000 unique crosslinks compared to <74,000 in the control condition. Poly(PR) specifically binds to 558 RNAs in HEK cells. Intriguingly, the sequence GAAGA was particularly enriched at these binding sites. We used biolayer inferometry to show in vitro that poly(PR) had a stronger affinity for the polyGAAGA RNA with an apparent Kd of 2 ± 0.7 nM compared to the control polyUAUAA RNA, with an apparent Kd of 27 ± 6 nM, confirming the binding enrichment from the transcriptome-wide iCLIP dataset. We found that poly(PR) binds to specific transcripts, including ALS/FTD-relevant mRNAs such as Neurofilament Medium Chain and Nucleolin. We also studied the phase separation properties of poly(PR), and demonstrated that polyGAAGA RNA displays an enhanced ability to induce poly(PR) condensation compared to the control polyUAUAA RNA.

Interpretation
We have demonstrated direct and specific interactions between the arginine-rich DPR poly(PR) and GAAGA-containing RNAs, using a transcriptome-wide approach. Arginine-rich DPRs have been shown to exert deleterious effects on several cellular functions, some of which may be caused by interactions of these DPRs with other proteins. Our study now suggests a new mechanism in C9orf72-ALS/FTD, that DPR-RNA interactions might also contribute to these effects. Using biolayer inferometry we confirmed that poly(PR) has very strong RNA affinities in the nanomolar range, especially for polyGAAGA RNA. Intriguingly, RNA sequences that tightly bind to poly(PR) with high affinity also promote poly(PR) phase separation.

Anthony Yong Kheng Cordero Ng

University of Cambridge
Cambridge University Hospitals NHS Foundation Trust

aykcng@doctors.org.uk
@aykcng

D7

Efficient Genetic Modification of Primary Human Neutrophils

Background
Neutrophils are abundant immune cells and critical first responders to infectious pathogens. Genetic modification of mature human neutrophils has been technically impossible due to their short lifespan and tendency to 'prime' in response to chemical and physical treatments. Current approaches used to study genes involved in neutrophil functions include mouse models and the HL-60 promyelocytic cell line, neither of which fully recapitulate human neutrophil functions. We have established a model of genetically modified primary human neutrophils to investigate genetic contributions to neutrophil functional capacities.

Methods
CD34+ progenitors were isolated from leukapheresis cones and cultured with recombinant human G-CSF to produce a population of morphologically segmented neutrophils which recapitulate highly specific neutrophil functions such as priming, phagocytosis, oxidative burst, and NET formation. Differentiating progenitors were efficiently and stably modified by Cas9-gRNP nucleofection to produce potent and activation-free gene knockdown in mature neutrophils, which were viable for use in functional assays.

Findings
We knocked down ITGAM, a highly expressed myeloid gene that produces CD11b. CD11b-CD18 heterodimers form the complement receptor CR3 which is important for phagocytosis and bacterial killing, while also being a sensitive marker for the detection of off-target activation. Cas9-gRNP produced a potent knockdown in the unselected neutrophil population without concurrent activation in methodological control experiments. Neutrophils lacking CD11b had equivalent phagocytic capacity to serum-opsonised Staphylococcus aureus and Escherichia coli bioparticles, suggesting functional redundancy in complement-mediated phagocytosis of bacteria.

Interpretation
We present the first comprehensively phenotyped model of activation-neutral, genetically modified neutrophils by genetic modification of haematopoietic progenitor cells prior to the acquisition of sensitive activation capacities. This represents a novel avenue to dissect the roles of individual genes in key neutrophil functions in a scalable, efficient, and highly reproducible manner.

Dr Kelechi Njoku

**Division of Cancer Sciences, Faculty of Biology, Medicine and Health,
School of Medical Sciences, University of Manchester
Saint Mary's Hospital**

D8

Detection of endometrial cancer in urine and blood plasma: Leveraging proteomics and machine learning for biomarker discovery

Background
The quest for simple, non-invasive, painless and convenient tests was voted the most important research priority for detecting cancer early, representing the views of patients, the general public and healthcare professionals. Voided self-collected urine is an attractive biofluid for cancer biomarker discovery due to its simplicity, low-cost and ease of collection. Blood sampling is easily accessible and acceptable to patients, qualities that make it attractive for cancer biomarker discovery and validation. The aim of this study was to identify proteomic signatures in urine and blood plasma that accurately discriminate endometrial cancer from symptomatic controls.

Methods
Matched self-collected voided urine samples and blood plasma samples were obtained from symptomatic women with (n=53) and without (n=65) endometrial cancer. A bespoke spectral library comprising 19,394 peptides and 2,425 endometrial cancer-related proteins was developed and validated for use in relatively quantifying and characterising putative uterine derived biomarkers contaminating urine. In a prospective case-control study, digitised proteomic maps were derived for urine and plasma samples using sequential window acquisition of all theoretical mass spectra (SWATH-MS). Machine learning techniques were used to identify important discriminatory proteins, which were subsequently combined in multi-marker panels using logistic regression.

Findings
The top discriminatory proteins individually showed moderate accuracy (AUC>0.70) for endometrial cancer detection. However, algorithms combining the most discriminatory proteins performed well with AUC's >0.90. The best performing diagnostic model for urine was a 10- marker panel combining SPRR1B, CRNN, CALML3, TXN, FABP5, C1RL, MMP9, ECM1, S100A7 and CFI and predicted endometrial cancer with an AUC of 0.92 (0.96-0.97), while a 6-marker panel of plasma proteins (APOD, PSMA7, HPT, APOA2, FA10 and SELL) predicted endometrial cancer with an AUC of 0.85(0.79-0.91. Urine based protein signatures showed better accuracy for the detection of early-stage endometrial cancers (AUC 0.92) compared to plasma (AUC 0.85).

Interpretation
A validated urine multi-protein biomarker assay can lead to rapid discrimination of symptomatic women with and without endometrial cancer, with substantial cost-saving implications for health service providers, whilst saving healthy women from invasive tests that are distressing and avoidable in over 90% of cases. Our multi-marker panels demonstrated sufficient accuracy (AUC>0.90) to warrant clinical utility and several of the identified biomarkers have mechanistic links with the malignant transformation process. These data can inform the development of innovative point of care diagnostic tests that can transform patient care. Confirmatory studies using immunoassays or targeted proteomics in a larger study are needed.

Dr Nikolina Skandali

Department of Psychiatry, University of Cambridge
Cambridgeshire and Peterborough NHS Foundation Trust

nikolina.skandali@gmail.com
@nikolinaskandal

D9

Neural circuit mapping of waiting impulsivity and proactive inhibition with convergent evidence from fMRI and TMS

Background
Waiting and stopping are essential and distinct elements of appropriate behavioural control. Although rodent and human studies have investigated both phenomena, the role of preparing to stop in waiting impulsivity has rarely been investigated. Here, we conducted two separate, but hierarchical studies, using functional magnetic resonance imaging (fMRI) to map the neural circuit involved in waiting impulsivity and proactive stopping, and subsequently provide mechanistic and causal evidence of disruption of this circuit by transcranial magnetic stimulation (TMS). We used a validated human version of the 5-Choice Serial Reaction Time (5CSRT) task and developed a novel proactive stopping task.

Methods
41 healthy volunteers performed a waiting impulsivity task (1CSRTT) adapted to closely model the one used in rodent studies within and outside the fMRI scanner. We also designed a proactive inhibition task to directly compare proactive inhibition and waiting impulsivity. Our fMRI data showed a strong association between left inferior frontal gyrus (LIFG) activity and waiting impulsivity on the 1CSRTT. In the second study we attempted to investigate on 51 healthy volunteers possible causation between LIFG and waiting impulsivity by modulating LIFG with an inhibitory transcranial magnetic stimulation (TMS) protocol called continuous theta burst stimulation (cTBS).

Findings
In the proactive inhibition task, premature responses decreased in proactive inhibition compared to baseline trials (mean ± S.D.; 3.1% ± 3.0 vs. 1.3% ± 1.7, $p < 0.001$, paired t-test). fMRI results show a shared neural network comprising pre-supplementary motor area and bilateral anterior insula underlying both waiting impulsivity and proactive stopping. We then found activity in dorsomedial prefrontal cortex and left inferior frontal gyrus negatively correlated with waiting impulsivity in trials with additional target onset delay. Participants in the stimulation group made significantly more premature responses than sham group during testing session ($t(49)= -2.46$, $p = .02$, paired t-test).

Interpretation
We addressed the neural correlates of waiting impulsivity and directly compared with proacting stopping using two novel tasks with highly conserved structure. Our data point toward the relevance of task design in understanding the neural encoding of waiting impulsivity both behaviourally and with neuroimaging. Our findings enhance our understanding of waiting impulsivity with tasks of translational significance among animal and human studies, guide the selection of appropriate cognitive tasks as potential biomarkers in clinical populations displaying or prone to impulsive behaviours and provide support to neurostimulation as a tool for establishing causal connection of cognitive constructs and implicated brain regions.

Deborah Critoph

University of Cambridge
Cambridge University Hospitals NHS Foundation Trust

D10

How can healthcare professionals communicate effectively with teenagers and young adults with cancer? Results of a scoping review and patient survey

Background
How healthcare professionals (HCPs) communicate effectively with teenagers and young adults with cancer (TYACs) is a research priority. A UK-wide survey of TYACs' research priorities found communication was a striking cross-cutting theme. It is recognised that TYACs have different communication needs from younger children and older adults. These communication challenges are recognised by TYACs and HCPs. Effective communication is critical for TYACs health outcomes, engagement, decision making, future self-management and reducing psychosocial sequalae. This work was designed to gain knowledge to write an evidence-based good practice guideline on communicating with TYACs, funded by the United Kingdom's professional association TYAC.

Methods
1. Scoping review: A literature search was conducted in February 2022 to identify and map the available evidence to get an overview of the literature, identify knowledge gaps and clarify concepts. The searches yielded 2481 records, generating 1706 unique articles. Twenty-five articles met the inclusion criteria and narrative synthesis was undertaken in relation to each of the research questions by four researchers.
2. Patient survey: A patient questionnaire was sent nationally to ask TYACs about their communication experiences. We had 24 survey respondents from England, Wales, Scotland, and Northern Ireland and across various haematological and solid tumour sites.

Findings
Three core themes were found in the data from the scoping review, and these were mirrored in the findings of the patient survey.

- Being an adolescent/young adult. TYAC need to feel that HCP understand their unique perspective and how it relates to their cancer experience.
- Supporters (most often parents) are a central tenant in TYAC care and undertake several roles. TYAC need and choose parental support, however parents can be more involved than the young person wants and time to speak with HCPs without supporters is crucial.
- Healthcare professionals must actively engender and promote the involvement of TYACs. TYACs involvement preferences vary over time and HCPs must assess and reassess.

The data is clear, there are core components of effective communication. Often young people are not involved in communication at the level they want affecting their ability and willingness to engage with healthcare systems.

Interpretation
Communication with TYAC is complex and at times challenging. We present a conceptual framework illuminating the multiple dimensions of communication with TYAC's. HCPs must be aware of the pivotal role they have to empower young people to be involved rather than bystanders in their own cancer experience.

We have identified a knowledge gap, how to enable optimal involvement of TYACs (at the level they choose) in a triadic encounter. Further research may help to understand how HCP can navigate communication to meet the needs of all involved. Future efforts must be made to educate HCPs to communicate effectively with TYAC's.

The Academy of Medical Sciences

Academy of Medical Sciences
41 Portland Place
London W1B 1QH

@acmedsci
Academy of Medical Sciences
acmedsci
The Academy of Medical Sciences

+44 (0)20 3141 3200
info@acmedsci.ac.uk
www.acmedsci.ac.uk

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