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ABSTRACT BOOK

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Ethnic Variation in Vitiligo: Characterising Epidemiological, Immunological and Proteomic Factors

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Scientific abstract

Background:

Vitiligo is a chronic depigmenting disorder primarily driven by T-cell mediated autoimmune destruction of melanocytes. Recent epidemiological data show a higher incidence and lifetime risk in Asian, Black, and mixed-ethnicity groups compared with White populations, suggesting that ethnic differences in biological susceptibility may underlie these disparities[1]. Evidence from other autoimmune and inflammatory skin diseases demonstrates ancestry-related variation in immune-cell phenotypes and cytokine profiles[2]. Emerging data in atopic dermatitis show that immune endotypes (Th1, Th2 and Th17 immune responses) vary by ancestry, influencing disease course and treatment response[3]. whether similar ancestry-related differences in biological signatures and immune responses exist in vitiligo remains largely unexplored.

Aims:

1. Explore epidemiological factors contributing to increased vitiligo susceptibility in minority ethnic populations.
2. To characterise circulating and tissue immunological profiles in vitiligo patients of Caucasian, African, and Asian origin.
3. To characterise circulating proteomic profiles reflecting Th1, Th2, Th17, and Treg immune responses across ethnic groups.
4. To integrate immunological and proteomic findings to identify immune endotypes that may explain ethnic variation in vitiligo susceptibility.
5. Enhance representation of ethnic minority in mechanistic vitiligo research.

Methods:

A mixed-methods epidemiological arm will assess environmental, socioeconomic, and behavioural risk factor differences using the UK Optimum Patient Care Research Database (OPCRD). Data supplemented by questionnaires and interviews, collected through a UK-based vitiligo registry, will capture cultural and social factors not routinely available. This will be accompanied by a translational pilot study (n=30; 10 Caucasian, 10 African, 10 Asian) that will compare differences in:

1. Circulating and skin T-cell phenotypes using multicolour flow cytometry on PBMCs and NanoString transcriptomics on paired peri-lesional and non-lesional skin biopsies.
2. Th1, Th2, Th17 and Treg-associated cytokines and chemokines using targeted multiplex immunoassays on plasma samples to evaluate variation in immune endotypes.

Impact:

By improving representation of ethnically diverse patients in vitiligo research, this study will evaluate ancestry-associated immune profiles, generate data to inform power calculations and design for larger studies, providing translational hypotheses to explain ethnic disparities in vitiligo incidence, guiding future personalised therapeutic strategies.

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Lay Summary

Vitiligo is a skin condition that causes white patches when the immune system mistakenly destroys pigment-producing cells. Studies show that the risk of developing vitiligo is higher in Asian, Black, and mixed-ethnicity groups than in White populations. Research in other skin and autoimmune conditions suggests that differences in immune responses between ancestry groups may explain these patterns, but this has not yet been explored in vitiligo.

This project will explore why these differences occur. We will use large UK health databases, along with questionnaires and interviews, to examine whether environmental, social or lifestyle factors vary between ethnic groups. We will also take blood samples and small skin biopsies from people with vitiligo of African, Asian, and Caucasian backgrounds to study how their immune systems behave and whether they differ by ancestry.

By including ethnically diverse participants, this study aims to improve understanding of vitiligo, explain why risk varies between groups, and support fairer and future personalised treatments.

Lauren Madden-Doyle **Pre-PhD Fellow talk**

Adipose tissue as a site of androgen generation in women: understanding the origins of androgen excess and metabolic disease in polycystic ovary syndrome and simple obesity

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Background: Polycystic ovary syndrome (PCOS) affects 10% of women of reproductive age. Biochemical hallmarks include insulin resistance and androgen excess (AE), with significant associations with metabolic dysfunction. AE is also observed in women with simple obesity in the absence of fulfilling diagnostic criteria for PCOS. Adipose tissue (AT) acts as a reservoir for peripheral androgen activation, but also as a target organ of androgen action. Resultant androgen-induced adipocyte lipotoxicity is hypothesised as a potential mediator of metabolic dysfunction in PCOS. Data is limited on the intrinsic differences in AT between women with PCOS and simple obesity, with respect to functional capacity and androgen-generating potential. We also have limited understanding of the potential role of androgens in AT dysfunction in women without PCOS.

Aims: This project aims to elucidate the differences between AT generation of 11-oxygenated and classic androgens in women with PCOS and simple obesity using *in vivo* and *ex vivo* models. I will also ascertain changes in systemic and local androgen metabolism and systemic fatty acid oxidation following glucagon-like peptide 1 receptor anologue (GLP1A) therapy.

Methods:

1. WP1: Oral androgen challenge to delineate differences in androgen metabolism using multisteroid profiling between 3 cohorts: (i) PCOS women with obesity, (ii) lean PCOS women (iii) women with simple obesity.
2. WP2: Generate novel adiposphere model using patient-derived biopsies from WP1. Examine baseline characteristics, then differential impact of exposure to culture medium containing classic and 11-oxygenated androgens. Explore impact of *siRNA* AKR1C3 on AT androgen generation. Lipidomics and live-cell imaging will establish cohort-specific differences in lipid droplet formation.
3. WP3: Compare differences in multi-steroid profiling, biometrics, grip strength and de novo lipogenesis using stable isotopes between cohorts following GLP1A treatment.

Impact: This project will provide foundations for further exploration of AT-derived androgens as a risk factor for metabolic dysfunction in PCOS and simple obesity. Understanding of pre-receptor androgen metabolism in adipocytes will have transferrable application for other metabolic disorders.

Lay Summary

Polycystic ovary syndrome (PCOS) is a common condition affecting about 1 in 10 women, and has been linked with increased risk of diabetes, cardiovascular disease and other metabolic conditions. One key feature is having too many androgens—"male-type" hormones—which can also be high in women with obesity without PCOS. Fat tissue plays an important role in producing and responding to these hormones, and this may contribute to poor metabolic health.

This project will compare how women with PCOS and women with simple obesity process different types of androgens, both in the body and in fat tissue samples taken during the study. It will also test how fat cells respond to specific androgens in the lab, and whether a diabetes medication (GLP-1 agonist therapy) can improve hormone processing and metabolism.
Overall, the research aims to uncover how fat-related hormone changes may drive health risks in PCOS and obesity.

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David Synnott **Pre-PhD Fellow talk**

IO Survivor: Exploring the impact of immunotherapy in patients who are long-term survivors in cancer

Background

Immune checkpoint inhibitors (ICIs) have revolutionised the treatment of cancer. Recent data estimates over half of all newly diagnosed cancer patients are now eligible for ICIs and ICIs have near doubled the survival outcomes for patients who respond to treatment(1, 2). ICIs can cause a spectrum of immune-related adverse events (irAEs) leading to patient morbidity and mortality(3, 4). While improvements in outcomes from ICIs are exciting for patients, the long-term toxicities and associated needs these survivors may expect to experience, are largely unknown. The median adverse event (AE) reporting period for immune checkpoint inhibitor (ICI) clinical trials is typically limited to 90 days, and safety data are often not collected for participants after they complete treatment(5, 6). In one organ-specific example, differentiating between true ICI-induced acute kidney injury (AKI) and AKI from other causes can be challenging but essential to avoid unnecessary dose reductions, discontinuations, and morbidity(7). As more patients survive, understanding long-term toxicities is essential for evidence-based survivorship care.

Aims

1. To investigate outcomes after immune checkpoint inhibitor (ICI) rechallenge in adults who survive ICI-associated kidney injury
2. To investigate the toxicity and quality of life of long-term survivors of ICI toxicity, including exploring novel blood- and urine-based metabolic and proteomic biomarkers of long-term toxicity
3. To explore genomic and immunologic insights of ICI toxicity of the kidney.

Methods

Study 1: Systematic Review and Meta-analysis. Outcomes After Rechallenge With Immune Checkpoint Inhibitors Following ICI-Associated Acute Kidney Injury.

Study 2: Prospective clinical trial recruiting 165 patients alive >1 year after first dose of ICI for non-small cell lung cancer (NSCLC) or melanoma across four of the Irish national cancer centres. Prospective assessment of clinical irAEs are graded by CTCAE/SITC(4, 8). Participants complete validated PROMs (EORTC-QLQ, FACIT-COST) and provide blood, urine, and surplus clinically-indicated tissue for proteomic/metabolomic profiling. Statistical modelling will link biomarkers, PROMs, and outcomes.

Study 3: Our findings and exploratory biomarkers will then be shared with the team at the Massachusetts General Hospital, Boston, USA, Severe Immunotherapy Complications (SIC) Service and Clinical-Translational Research Effort. For external validation with the large MGH biorepository of over 15,000 ICI patients(9).

Study 4: Utilising kidney tissue transcriptomics with same biorepository, we will explore to explore if T-cell mediated rejected of a transplanted kidney (TCMR) and ICI-AKI share similar transcriptomic signatures to provide a platform for future ICI-AKI research.

Impact

This programme will generate the first national, prospective characterisation of long-term immunotherapy survivorship in Ireland, defining the clinical, biological, and patient-reported burden of chronic irAEs. By integrating multi-omic biomarker exploration and external validation in one of the world's largest ICI biobanks, this work will lay the foundation for "precision survivorship" and directly inform national survivorship models, improve risk-stratification, and guide future clinical trials in immunotherapy toxicity.

Lay Summary

Immunotherapy has transformed cancer treatment, particularly through medications known as immune checkpoint inhibitors (ICIs). These medicines boost the immune system to attack cancer cells and have doubled survival for many patients. However, they can also cause the immune system to attack healthy organs, leading to immune-related side effects that may appear months

or years after treatment and can persist long-term. As more people live longer after immunotherapy, the number affected by long-term toxicities is rising, yet little is known about their frequency, severity, or impact.

The IO-Survivor study will recruit people with lung cancer and melanoma (a type of skin cancer) who are alive at least one year after starting immunotherapy. We will measure how many patients have persistent side effects and what type of side effects. We will also explore quality of life, financial and time burdens using validated questionnaires, while collecting blood, urine, and surplus tissue to identify biological markers of toxicity. By linking patient experiences with laboratory research, this study aims to improve long-term patient care and guide future treatment strategies.

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Aine Varley

Pre-PhD Fellow talk

The economic burden of TB and the cost effectiveness of models of care to diagnose and manage latent TB infection.

Background

There has been a global resurgence in tuberculosis (TB) since COVID-19 (1). In Ireland, migrants from high-incidence countries experience disproportionately high rates of disease (72% of cases in 2024 were in people born outside of Ireland) (2). Given the context of broader global migration trends, TB in this population represents an important and ongoing threat to population health.

There is a paucity of evidence on the growing economic burden of TB among migrants from high-TB-incidence countries in Ireland; without this, health care decision-makers are unable to quantify the scale of the problem, or prioritise resource allocation accordingly. Furthermore, although economic evaluations of TB-related interventions have been conducted in several countries, existing models are often context-specific, proprietary, or have a narrow methodological scope, limiting their adaptability to new settings or emerging policy questions (3-5).

Aims

1. To evaluate the economic and health burden of TB among migrants from high-incidence countries in Ireland.
2. To develop a reusable, open-source model to investigate the cost effectiveness of models applicable to care for the diagnosis and management of latent TB infection that can inform policy and guide resource allocation.

Methods

1. Estimate the economic and health burden of TB among migrants in Ireland.
2. Identify and appraise care pathways for the diagnosis and management of latent TB infection among migrants in Ireland.
3. Development of an open-source, epidemiologic-economic model to investigate the cost effectiveness of care pathways for the diagnosis and management of latent TB infection among migrants in Ireland.

Impact

This work is timely and directly relevant to Ireland, and will generate actionable insights to inform national TB policy and health system resource allocation. Internationally, this research has wider relevance to other high-income, low-incidence countries facing similar challenges. The reusable, open-source epidemiologic–economic model generated will enable others to answer comparable research and policy-relevant questions.

Lay Summary

Tuberculosis (TB) is a serious bacterial infection. Not everyone with TB gets sick immediately; it can lay dormant in the body for years. Finding and treating TB early reduces the risk of illness, and stops spread to other people.

TB cases are increasing in Ireland, and these are mostly in people who have lived in countries where TB is very common. This research will measure the health and cost-related impact of TB in this population in Ireland. It will also investigate if programmes to find and treat latent (dormant) TB would be good value-for-money.

This research is important because it will allow us to fully understand the scale of the problem of TB in Ireland, and provide health decision-makers with options to address it that make good use of limited health resources. The model will be reusable and free-to-access, so that researchers from other countries can also use it.

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Brian Maloney **Pre-PhD Fellow talk**

Nano-Engineered Chiral Hydroxyapatite for Targeted Tooth Regeneration (NEXT-GEN)

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Scientific Abstract

Background

Dental caries is the most prevalent non-communicable disease worldwide.[1] Left unabated, the carious process will lead to irreversible loss of enamel, invading the dentine, compromising the dental pulp and its innate capacity for repair.[2] Gold standard materials are reliant on the body's natural healing processes, rather than actively directing them, leading to low-quality hard and soft tissue responses, which do not replicate the hierarchical organisation of native dental hard tissues.[3,4] Advances in tissue engineering mark a potential paradigm shift in the treatment of decay and its consequences.[5] Chiral hydroxyapatite combines the familiar structure of the main inorganic constituent of dental tissues with a novel tunable surface architecture that may be exploited to actively guide enamel and dentine regeneration.[6]

Aim and objectives

The overarching goal of this work is to establish whether *chirality* may act as a controllable design variable in the design and formulation of next-generation dental biomaterials.

Methods

- To review and appraise the pertinent literature regarding the use of hydroxyapatite-based biomaterials in dental tissue regeneration and to examine the application of chiral forms in non-dental contexts.
- To synthesise, characterise chiral hydroxyapatite (CHAp) for dental applications.
- To investigate the remineralisation potential of CHAp on artificially demineralised enamel using various structural recovery characterisation techniques (Micro-CT, Scanning Electron Microscopy [SEM], Energy-Dispersive X-ray Spectroscopy [EDX] and XRD analysis).
- To investigate the effect of CHAp on the viability, proliferation, cytocompatibility, mineralisation, gene, and protein expression (e.g., dentinogenic/osteogenic markers) of human dental pulp stem cells (hDPSCs) in 2D monolayer culture in vitro.
- To incorporate CHAp nanoparticles into natural polymers (e.g., collagen) bioengineered scaffolds and evaluate their ability to influence mechanical and biological properties, including hDPSC viability, proliferation, cytocompatibility, mineralisation, gene expression, protein expression, and functional regeneration.

Impact
Through the development of this next-generation chiral biomaterial, the potential to recapitulate the hierarchical structure and multifunctional interfaces of native dental tissues may become a reality, allowing unification of currently disparate strategies for the management of dental decay into a single, comprehensive approach to minimally invasive dental care.

Lay summary

Dental decay is a prevalent condition which can progress to pain, infection and tooth loss if not treated.[7] Recent advances in dental treatment have been directed at tissue repair and regeneration rather than the traditional doctrine of 'drill and fill'. As new research emerges, conventional approaches to treat decay, such as dental restorations in the case of early decay, or root canal treatment in advanced decay, are being slowly replaced by less invasive techniques focused on assisting teeth to repair themselves.[5]

While there are effective materials to aid in these techniques, there is a need for improved, targeted solutions to treat these conditions and regenerate lost tissue. Additionally, there is a lack of emphasis on halting decay at its earliest stage in enamel. This project aims to investigate, in a lab setting, the use of a specific modification of hydroxyapatite, the main component of teeth. We will examine whether developing a dental material with this compound will help to remineralise early decay in enamel, and in cases where disease progresses further, to examine whether we can stimulate the dental pulp to protect itself against future harm.

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Identifying targets for early intervention in personality disorder

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Background:
Personality disorders affect around 2-7% of the population(1,2) and are associated with high use of services(3) despite both patients and staff describing these treatment experiences negatively(4). Patients believe earlier intervention would have been of great benefit(5). Of those diagnosed with personality disorder in adulthood, half previously attended child and adolescent psychiatry(1). Scattershot interventions can cause iatrogenic harm(6). Personality disorders are perceived as particularly stigmatized which indicates additional caution around overdiagnosis(7). Precision in screening is particularly key in this area. Identifying epidemiologically informed risk systems could facilitate the development of precise screening(8).

Aims:
1) What risk systems capture those with or likely to develop personality disorders in young adulthood
2) What features mediate the development of subsequent symptoms from early risk
3) Whether there are novel methods available to us that could aid in identifying these patients.

Methods:
Study 1: Use registry data to establish whether young adult Emergency Department self-harm attendances, substance misuse attendances and primary care mental health appointments capture a significant percentage of patients with subsequent adult personality disorders
Study 2: Use cohort study data to establish important mediators between self-harm and help-seeking in adolescence and positive personality disorder screening in adulthood
Study 3: Develop a NLP tool assessing free text descriptions of psychotic experiences and identify patterns associated with positive personality disorder screening
Study 4*: Develop a NLP tool assessing free text descriptions from primary care assessments of patients describing psychotic symptoms who are subsequently diagnosed with personality disorders
Study 5*: A qualitative study of personality disorder symptoms and functioning in patients attending psychiatric services following referral with psychotic symptoms

Impact:
Studies 1-2 identify targets for screening and early intervention in personality disorder. Studies 3-4 develop tools for primary care and community-based support services flagging need to screen for personality disorder. Study 5 characterises patient experiences to guide subsequent screening and intervention research.

Lay summary
Personality disorders are mental health conditions that affect a person's thoughts, feelings, perceptions and behaviours in ways that affect their perceptions of and behaviour towards themselves and others. They make it difficult for them to adapt to or respond to everyday tasks and experiences. This research aims to find where people who are developing personality disorders are most likely to first seek help and how they describe the experiences they are having. This work will set a foundation from which we can develop screening and eventually an early treatment that will prevent severe personality disorder from developing.

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Alice Talbot

Pre-PhD Fellow talk

Cell-free DNA Fragmentomics in Hereditary Cancer Predisposition Syndromes

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Background

Hereditary cancers are an uncommon but clinically significant subset of cancers, accounting for up to 10% of all cases. These cancers are caused by pathogenic genetic variants that substantially increase lifetime cancer risk. In Ireland, hereditary cancer services remain underdeveloped and under-resourced, despite a rapid increase in demand. Recent research has explored genomic liquid biopsy techniques as a less invasive and potentially more sensitive screening option in some cases. DELFI (*DNA Evaluation of Fragments for Early Interception*), uses low-coverage whole-genome next-generation sequencing followed by machine learning to analyse genome-wide fragmentomic patterns in cell-free DNA (cfDNA).

Aims

To investigate the correlation between blood-based cell free DNA fragmentomics in affected and unaffected patients with CPS.

Methods

This is a prospective observational study on patients identified from the cancer genetics service in SJH. The study will include 3 cohorts; 1) Subjects with a pathologically confirmed cancer diagnosis and a known CPS 2) Subjects with a known CPS and no cancer diagnosis, 3) Subjects who do not have the CPS present in their family and have no cancer diagnosis.

Primary outcome:

1. Difference in fragmentomic patterns between affected patients with CPS and unaffected patients with CPS

Secondary outcomes

2. Difference in fragmontomic patterns between unaffected patients with CPS and negative predictive patients
3. Changes in cfDNA over time in affected patients with CPS, unaffected patients with CPS and negative predictive patients
4. Sensitivity and specificity of fragmentomic samples in patients with evidence of disease on screening in patients with CPS

Impact

If differences in cell-free fragmentomics can be consistently demonstrated between cohorts, further studies may compare this to current screening methods to become an adjunct to screening in the future. This would be a less invasive screening method for malignancy and could result in increased compliance and earlier diagnoses for hereditary cancer patients.

Lay summary

This study will be used to test whether a blood test can be used to identify cancer in patients with a cancer predisposition syndrome (CPS). About 5 – 10% of cancers will be linked with a genetic change. A CPS is a condition where people have genetic changes that increases their cancer risk (vs the general population).

People with a CPS are often in screening programmes to attempt to discover a cancer earlier. However, no screening programme is 100% effective and some methods can be intrusive (e.g. colonoscopy), or involve radiation (e.g. CT scans). As such there is great interest in finding new screening methods.

A liquid biopsy is a blood sample which looks for changes in patterns of cancer DNA, rather than normal tissue biopsy. Studies have shown that liquid biopsy can notice cancers before a change is seen on imaging. The goal of our study is to find ways to diagnose cancer earlier in patients that have a CPS.

Development of Machine Learning Clinical Prediction Models and a Utility Score for Prehospital Differentiation of Ischaemic and Haemorrhagic Stroke

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Scientific Abstract

Background:
Stroke is a leading cause of death worldwide and leaves most survivors with permanent disability. Currently, stroke is diagnosed by the combination of clinical symptoms and signs, and neuroimaging. The aim of this study was to develop clinical prediction tools (CPT), for differentiating acute ischaemic stroke (AIS) and intracerebral haemorrhage (ICH) in the pre-hospital setting without neuroimaging, utilizing machine learning (ML).

Methods:
We included patients with confirmed acute stroke who presented within 6 hours of symptom onset, from the INTERSTROKE study. Twenty-five variables were selected as inputs for the primary machine learning (ML) models based on their feasibility for pre-hospital acquisition, including in patients who were confused, aphasic, had reduced consciousness, or lacked an available proxy. Six classification algorithms were used namely, multivariate logistic regression (MLR), KNN, SVM, neural network (NN), random forest (RF), and XGBoost. Model performance was estimated using bootstrap resampling. To quantify the potential clinical impact of model-guided intravenous thrombolysis (IVT) decisions, we developed a utility score to estimate the theoretical balance of benefit and harm associated with applying each model's results.

Results:
The primary cohort included 4,571 patients (AIS=3,281, ICH=1,290). The AUCs for each of the ML classification models were: MLR 0.832, KNN 0.787, SVM 0.719, NN 0.825, RF 0.801, and XGBoost 0.781. Net utility, expressed as the number of lives improved per 1,000 patients treated, was evaluated across a range of decision thresholds. Maximum utility occurred at thresholds of 20–25%. The CPT only yielded no net benefit if one erroneously thrombolysed ICH were valued as worse than withholding IVT from 36 true AIS who would otherwise have benefited.

Conclusions:
ML models showed great potential to predict stroke type at the prehospital stage. When combined with a simple utility framework, this may help guide thrombolysis decisions in settings without neuroimaging, potentially improving point-of-care decision-making and pre-hospital stroke management.

Lay Summary

Stroke is a major cause of death and disability. It is difficult to determine whether a stroke is caused by a blocked blood vessel (ischaemic stroke) or bleeding in the brain (haemorrhagic stroke). This distinction is crucial because the main treatment for ischaemic stroke, is dangerous if given to someone with bleeding. Currently, doctors rely on brain scans to make this decision, which are not available in ambulances or many remote settings.

In this study, we used information that can be collected before arriving at hospital to train computer models to predict stroke type. Using data from over 4,500 patients, machine-learning models were able to distinguish between the two stroke types with good accuracy. We also developed a "utility score" to estimate the potential benefit or harm of using these models to guide treatment. These findings suggest that such tools could support safer, faster decision-making in the pre-hospital setting.

Morphea in Ireland: Demographic Data from the IMAGINE Study Cohort

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Morphea is a rare sclerosing disorder associated with significant cosmetic and functional morbidity. To date, no large Irish cohort has previously been reported.

Aim:
To describe the demographic and clinical characteristics of adult and paediatric morphea patients in Ireland, within the IMAGINE study.

Methods:
We conducted a multicentre, cross-sectional study of adults and children with morphea across Ireland. Recruitment occurred over a 6-month period through dermatology clinics in Cork, Galway, Mayo, and Dublin, supplemented by national dermatology networks and social media outreach. Data were collected on demographics, clinical features, potential triggers, and treatment history using REDCap, adapted from the Morphea in Adults and Children (MAC) cohort to enable international comparison. Analyses were performed in R. Ethical approval was obtained at all sites.

Results:
Forty-nine patients were enrolled: 32 adults and 17 children. Patients were recruited from Cork (22), Galway (19), Mayo (6), Dublin (2). Subtypes included 27 linear (12 En coup de sabre), 13 plaque and 15 generalised. The female-to-male ratio was 6:1. Mean age of paediatric onset was 9.6 years. One-third had a personal autoimmune history, while over half reported a family history of autoimmunity. Over two-thirds required systemic therapy, most commonly methotrexate ± corticosteroids. Extracutaneous involvement occurred in 40%, with functional impairment reported in 16%.

Discussion:
This is the first national, multicentre study of morphea in Ireland and represents the largest Irish cohort to date. Despite its rarity, morphea carries significant morbidity. These findings highlight the importance of early recognition and timely intervention.

Lay Summary

Morphea is a rare condition that causes areas of hard, tight skin and can lead to visible changes and reduced movement. Until now, Ireland has never had a large study describing who is affected or how the disease presents.
As part of the IMAGINE study, we collected information from adults and children with morphea across Ireland over six months. People were recruited through dermatology clinics and national networks. We gathered details on symptoms, possible triggers, family history, and treatments.
Forty-nine people took part: 32 adults and 17 children. Most had the linear form of morphea, including a subtype affecting the face and scalp. The majority were female, and many had personal or family histories of autoimmune conditions. More than two-thirds needed systemic treatment such as methotrexate, and 40% had deeper tissue involvement, sometimes affecting movement. This is the largest Irish study of morphea to date and highlights the need for early diagnosis and treatment.

Development and optimisation of a caprine claw removal model for the investigation of musculoskeletal loading conditions during development.

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Background
The musculoskeletal (MSK) systems of both humans and animals are reliant on complex interactions between the bones and their associated soft tissue supporting structures. The importance of load in the development and maintenance of the MSK system has been known for well over a century [1]. An array of models have been utilised to study the effects of unloading or microgravity including prolonged bed rest [2], paralysis, limb immobilization [3], hind-limb unloading [4,5], and spaceflight [6]. However, none of these models are particularly effective in delivering translatable results over prolonged study periods. The goat has been recognised to translate very well to humans due to its similarities in joint anatomy and joint loading.

Aims & Objectives
The aim of this study is to develop a novel, caprine unilateral claw removal model utilising a refinement of a well-established clinical technique that can be utilised to study the effects of various loading conditions on the MSK system whilst minimising impact on the animal.

Methods
A 2-phase approach was used with initial *ex vivo* work performed using a 100N load cell and jig to confirm the proposed effects of unilateral claw removal on loading before progressing to *in vivo* surgical model development. The model design integrates a within-animal contralateral limb control. Pre-mortem radiography and pressure plate gait analysis have been used, followed by post-mortem computed tomography, histology and biochemistry to quantify the effects of the model on cartilage, bone, and associated soft tissues.

Interim Results
Preliminary findings show a clear effect of the different loading conditions of the model, with a marked reduction (~75%) in bone density on the unloaded series of bones, and an overloading of force on the side having undergone claw removal. The goats in this study have displayed no evidence of lameness following claw removal and have exhibited normal behaviour with comparable growth rates and weight gain. Further analysis is ongoing.

Lay Summary:
The musculoskeletal system which is made up of bone, cartilage, muscles, tendons and ligaments is essential to our everyday existence. The importance of load in the development and maintenance of this system has been known for well over a century, yet we do not fully understand the role load plays and the implications of altered load such as that seen following injury or during space travel. This study aims to develop a novel, welfare friendly model utilising a well-established clinical technique that can be used to study the effects of various loading conditions on the musculoskeletal system and in particular during development and repair of orthopaedic disease conditions. The goat has been recognised to translate very well to humans due to its similarities in joint anatomy and loading. Preliminary findings clearly show the model successfully created a large and measurable effect, resulting in a significant reduction (~75%) in bone density in the unloaded limbs. Importantly, the goats showed no signs of persistent lameness and displayed normal behaviour, confirming that this model is both effective and welfare friendly. Further analysis is ongoing.

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Characterising the Impact of Atopic Dermatitis on Dual X-Ray Absorptiometry derived Bone Mineral Density Outcomes.

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Introduction

Atopic dermatitis (AD) affects ~5% of adults worldwide and has been increasingly linked to impaired bone health, including low bone mineral density (BMD) and osteoporosis. Population-based cohort studies to date suggest the greatest risk in severe AD, but may be limited by under-diagnosis, assignment and selection bias.[1–4] Addressing the above issues requires methodological approaches that do not rely on presence of diagnostic codes for bone health outcomes.

Aim

To evaluate the association between AD severity and dual X-ray absorptiometry (DXA) measured BMD T-scores using international reference standards.

Methods

Using the UK Biobank cohort, AD was defined and severity stratified via a validated algorithm requiring ≥1 diagnostic code and ≥2 prescriptions for AD therapies.[5] Analyses were restricted to postmenopausal women and men ≥50 years with DXA imaging and T-scores were calculated in line with World Health Organisation/International Society for Clinical Densitometry guidelines.[6] AD cases were matched to controls without replacement (1:5) by age and sex using nearest-neighbour propensity scores. Linear mixed-effects modelling was used to assess associations between AD severity and T-scores at the femoral neck, total hip, and lumbar spine, adjusting for age, sex, and matching.

Results

Of 229,860 participants with primary care records, 13,255 (5.7%) met AD criteria: mild 81.2%, moderate 14.4%, severe 4.4%. After DXA, age, and menopause filtering, 852 mild, 155 moderate, and 40 severe AD cases remained, alongside 42,465 controls. Mean cohort age 66.8; 51.2% female. Mild and moderate AD showed no association with BMD. Severe AD demonstrated consistent negative effects across sites: -0.323 (femoral neck), -0.355 (total hip), -0.173 (lumbar spine). Only left total hip reached statistical significance (estimate: -0.367; 95% CI –0.725 to –0.009, p = 0.04), reflecting the small severe AD sample size.

Interpretation

Despite limited power, the consistent direction across skeletal sites suggests a biologically plausible reduction in BMD among individuals with severe AD, in line with previous studies. A hip T-score difference of –0.355 is comparable to established risk factors such as current smoking and is clinically meaningful.[7]

Future work will incorporate additional confounders (e.g. ethnicity, vitamin D, smoking, alcohol), compare AD with psoriasis, and utilise the upcoming UK Biobank November 2025 data release (~30,000 additional participants with DXA imaging) for greater statistical power.

Lay Summary

Atopic dermatitis (AD), (also known as eczema) affects approximately 1 in 20 adults. Recent data has shown a plausible link between eczema and development of osteoporosis – a condition where bones become brittle and are more likely to break. Using UK Biobank data, we assessed bone density using bone scan data in adults with and without AD. Mild and moderate AD were not associated with lower bone density, but those with severe AD showed consistently lower bone density scores, particularly at the hip. Although numbers of severe AD were small in this study, this pattern aligns with previous research and may represent a meaningful, measureable link between AD and bone health.

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ATLANTIS - Identification of AutoimmuniTy reversaL in ANca vasculiTIS

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Scientific abstract

Background

ANCA associated vasculitis (AAV) is an archetypal autoimmune disease, resulting in immune-mediated organ damage. Immunosuppressive drugs (ISDs) have transformed AAV from a progressively fatal condition into chronic relapsing-remitting disease. However, infection post ISDs is now the primary cause of death among patients with autoimmune diseases. The greatest unmet need in AAV is to devise personalised strategies for precise tailoring of ISDs. ISDs could be reduced if it were possible to quantify relapse risk and to identify patients in whom treatment could be stopped safely.

Aims

The aim of this study is to quantify the immunological state in AAV remission and to identify factors that signify a return to normal, with re-establishment of tolerance to the relevant autoantigens, myeloperoxidase (MPO) or proteinase-3 (PR3).

The objectives are to:
1. Perform an in-depth comparison of the immune status of AAV patients in long-term remission off therapy (LTROT) with (a) patients with active disease, (b) patients with anti-GBM disease, a monophasic “one-hit” autoimmune disease, and (c) healthy controls.

2. Test whether the cluster of “tolerance markers” are present at various time points in the AAV disease course in LTROT patients.

3. Build a statistical model, incorporating a longitudinal dataset and the parameters identified above, and assess whether this identifies those remaining in remission when applied at the point of treatment discontinuation.

Methods

The RITA-Ireland Vasculitis RIV Registry and Biobank includes over 900 patients with vasculitis, approximately 50 meet LTROT criteria. This longitudinal dataset has serial biological samples obtained at diagnosis, remission and relapse (PBMC, serum, plasma, urine, DNA, Paxgene).
The experimental methods to define LTROT immune tolerance signature include high dimensional flow cytometry using stored PBMCs, including identification of antigen specific B cells (Aurora cytometer, proteomic screening (o-link), single cell RNA sequencing, PCR and measurement of Torque Teno Virus levels. Validation will be performed by testing international cohorts e.g. UCL, IDIBELL, Barcelona and Czech vasculitis biobank.
Impact

Tailored ISD use will benefit low-relapse-risk patients, enhance societal productivity, and reduce healthcare costs, patient/carer burden, and physician clinical time.

Lay Summary

Autoimmune disease affects 10% of adults, most of whom are women, and two of the top five medications with the highest cost globally are used to keep these recurring conditions in remission. These medications suppress the immune system, leaving the patient exposed to increased infection and cancer risk. Patients have highlighted a desire to tailor these treatments to each patient and to stop these medications where safe.

What is the aim of ATLANTIS?
ATLANTIS delivers a practical response to this challenge.
We aim to closely examine the immune system characteristics of patients who have infrequent disease flares by performing tests in laboratories. This may help us identify patients in which immunosuppressant medications can be stopped.

We use systemic vasculitis as a typical autoimmune disease to answer these questions.

gEnomic chaRacterizAtion and DisinfectIon of CPE from humAn hospiTal Environments (ERADICATE)

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Scientific Abstract

Background
Carbapenemase-producing Enterobacterales (CPE) remain a major infection prevention and control challenge. Increasing evidence shows that hospital water systems, particularly sinks and drains, act as persistent reservoirs where biofilms protect CPE from conventional disinfectants. As carbapenemase genes are largely plasmid-borne, environmental persistence provides opportunities for horizontal gene transfer and the amplification of resistance. Novel disinfection approaches that can disrupt both bacterial survival and plasmid integrity are urgently required.

Aims & Objectives
1. Characterise the genomic, phenotypic and plasmid features of environmental CPE isolated from hospital sinks and drains in Ireland and Trinidad.
2. Compare population structure, carbapenemase gene distribution and plasmid incompatibility groups across contrasting healthcare systems.
3. Evaluate the efficacy of conventional disinfectants and photodynamic disinfection (PDD) against planktonic and biofilm-associated CPE, and assess their impact on plasmid stability and conjugation.

Methods
All CPE isolates will undergo whole-genome sequencing, with a subset sequenced using hybrid long- and short-read approaches to resolve plasmids. Comparative genomics will be used to identify resistance genes, plasmid incompatibility groups and accessory genome content. Clonal relatedness will be assessed through MLST, core-genome MLST and SNP-based phylogenies, enabling comparison of environmental lineages across Ireland and Trinidad. Plasmid analysis will examine structure, mobility and co-carriage of additional resistance genes. Representative isolates spanning key sequence types and plasmid groups will then be selected for time-kill and biofilm assays using conventional disinfectants and photodynamic disinfection, alongside plasmid stability and conjugation testing to determine the impact of each intervention on plasmid integrity.

Preliminary Results
Environmental sampling from two Irish hospitals yielded 35 CPE isolates at Site A and 21 at Site B. Site A showed a heterogeneous carbapenemase profile comprising IMP (3%), KPC (31%), NDM (29%), VIM (6%) and OXA-48-like enzymes (31%). Site B was dominated by OXA-48-like producers (95%), with only a single KPC isolate. These data confirm the feasibility of environmental recovery and demonstrate substantial inter-site variation, suggesting differing plasmid backgrounds and selective pressures. Sampling in Trinidad later this year will add an essential comparative dimension.

Impact
This project will generate the first comparative genomic dataset of environmental CPE from Ireland and the Caribbean, while evaluating a sustainable, non-chemical intervention with potential to overcome limitations of current disinfection strategies. Findings will inform future IPC policy and contribute to global AMR mitigation efforts.

Lay Abstract

Antibiotic resistance is a growing threat to healthcare. Some bacteria can break down antibiotics and share this ability with other bacteria, making infections harder to treat. These resistant bacteria are not only found in patients but also in hospital sinks and drains, where they form protective biofilms that standard disinfectants struggle to remove. My PhD project, ERADICATE, focuses on these resistant bacteria, known as carbapenemase-producing Enterobacterales (CPE). Early sampling in two Irish hospitals recovered 35 CPE isolates at one site and 21 at another, with very different resistance types present at each location. Later this year, similar sampling in Trinidad will allow comparison with a contrasting healthcare setting. Using genome sequencing and laboratory testing, I will study how these bacteria survive in the hospital environment and which disinfectants work best—including a light-based method called photodynamic disinfection. The aim is to identify effective cleaning strategies that reduce the spread of resistant bacteria and help protect patients.

John Mark O'Leary **Research Blitz 2**

Molecular Approaches to Diagnosing and Managing Pulpitis in Equine hypsodont teeth ('DAMPEN')

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Scientific Abstract

Background
Pulpitis is a common disease in equine hypsodont teeth (EHT) that is traditionally managed by extraction[(1,2)]. Vital pulp treatment (VPT) is a conservative alternative that has been promoted recently in humans, but is complicated in EHT by complex root canal systems and the lifelong juvenile state of eruption[(3)]. In order to improve VPT strategies and outcomes in diseased EHT it is critical to understand the molecular mechanisms of dental pulp cell (DPC) inflammation, mineralisation and repair in comparison with both brachydont and human teeth. There is currently a lack of available information on this subject.

Aims
The overarching aim of this project is to investigate the pulpitic response in EHT to microbial challenge with the aim of identifying potential diagnostic and therapeutic targets for use in regenerative VPT.

Methods
- To review the molecular characterization of pulpitis in equine teeth, highlighting current methodological issues as well as key mediators, pathways and focus areas for future research.
- To experimentally establish the molecular changes occurring in LPS stimulated stem cell (DPSCs) and primary cell lines of DPCs from healthy EHT / brachydont teeth and compare with inflamed/ uninflamed DPCs from healthy human teeth, by using RNAseq analysis, candidate marker confirmation, bioinformatic analysis and proteomic array. Current work is validating the inflammatory response of in vitro cultured human and equine DPSCs to LPS with qPCR for classical markers of inflammation (IL-1β & TNF-α) and refining cell culture techniques for the establishment of primary dental pulp cell lines.
- To clinically characterise candidate mediators, molecules and pathways in inflamed EHT *ex vivo* by clinical collection of pulp tissue and teeth from veterinary clinics and abattoir by using gene/ protein expression, histology and immunohistochemistry.
- In combination with recombinant proteins (e.g. growth factors) and pharmacological inhibitors, siRNA knockdown to investigate the potential therapeutic benefits in inflamed equine DPCs of inhibiting key inflammatory mediators in pulpitis and repair as part of a topical VPT.

Impact
Understanding EHT pulpal inflammation and repair pathways will help to advance clinical equine endodontic diagnosis, regenerative treatment and horse welfare. From a ONE HEALTH perspective 'DAMPEN' may also act as a translational model to improve human VPT strategies.

Lay Summary

Dental decay is the main cause of inflammation, infection and toothache (called pulpitis). Pulpitis affects half the World's population[(3-5)]. Traditional treatment includes extraction and root canal treatment (RCT). RCT is technically challenging in horses' teeth and predisposes teeth to fracture. Vital pulp treatment (VPT) preserves the cells in a tooth, while overcoming the limitations of RCT and is recommended in humans[(6,7)]. The centre of horses' cheek teeth contain dental pulp cells (DPCs). These cells contribute to repair and to a unique feature of horse's cheek teeth, their continual growth throughout life, a feature required for dietary reasons [(3)]. The mechanisms underlying inflammation and repair in horses' teeth is currently unknown. Within this study we plan to compare the response in human and horse teeth with a view to identifying targets and pathways that may benefit our understanding of the disease and improve our therapies in the future.

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InterrOgation of Peritumoural Mechanisms of Hyper-Excitability in GliomA (OMEGA)

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Scientific Abstract

Introduction
Brain tumours are increasing in incidence and lead youth cancer mortality in the UK and USA.[1-4] Brain-tumour related epilepsy (BTRE) is a common, debilitating and frequently drug-refractory comorbidity.[5-8] Peritumoural hyperexcitability is conducive to both BTRE and tumour progression.[9-13]

Objective
To characterise peritumoural hyperexcitability across network, cellular, and proteomic levels, to identify novel and targetable mechanisms relevant to BTRE and tumour progression.

Methods
Multimodal analysis was performed on live peritumoural tissue obtained from the National Neurosurgery Centre. Clinical and neuropathological features were recorded. Acute peritumoural brain slice local field potential (LFP) recordings assessed network excitability under baseline, provoked and pharmacologically manipulated conditions. Tissue underwent histopathological and immunohistochemistry interrogation. Global and phospho-proteomic profiling was performed using a modified high-throughput LFQ-DIA workflow, ThermoScientific™ Orbitrap™ Exploris 480 system, DIA-NN v2.2.0 Academia to process raw data, and Perseus for downstream analysis.[14-16] In parallel, an international Delphi consensus study is underway to define and classify the peritumoural zone.

Results
To date, 29/48 patients have been recruited (mean age 50; 62% with epilepsy). Pathologies include glioblastoma, diffuse astrocytoma, oligodendroglioma, ganglioglioma, and non-tumoural epilepsy. LFP recordings from N=89 slices reveal emerging tumour subtype-specific differences. Slices from patients with clinical epilepsy exhibited more frequent epileptiform discharges and a significantly shorter latency to first event (IED/SLE), both in baseline and pro-convulsant conditions (Kaplan–Meier, p=0.017), indicating a distinct hyperexcitable phenotype. Pilot proteomic assessment of N=2 patients demonstrates distinct inter-patient and inter-tumour signatures, with only 1% overlap in upregulated phosphoproteins (6/592) between low-grade astrocytoma and glioblastoma peritumoural tissue, suggesting divergent mechanisms driving hyperexcitability. Lastly, the Delphi study is underway with 51 international participants completing round 1/2.

Conclusion
Early findings reveal marked electrophysiological and proteomic heterogeneity across tumour types, suggesting distinct mechanisms of peritumoural hyperexcitability. Integrated multimodal profiling aims to identify actionable targets to mitigate both tumour progression and BTRE.

Lay Abstract

This project explores why brain tumours cause seizures and how this abnormal activity may also support tumour growth. Using human brain tissue removed during surgery, we study the tumour and the surrounding "peritumoural" brain using electrical recordings, microscopy, and detailed protein analysis.

So far, we have collected tissue from 29 patients and recorded activity from 89 living brain slices. Early findings show differences in seizure-like activity and protein signatures between different tumour types, suggesting that each tumour creates its own pattern of brain hyperexcitability.

We are also leading an international consensus study to better define and classify the 'peritumoural zone', which is crucial for understanding and treating tumour-related epilepsy.

Overall, this work is revealing how tumour biology and seizures interact, with the goal of identifying new treatment targets that could reduce seizures and slow tumour progression.

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Invasive Group A Streptococcus: changing Epidemiology and Optimising Management (iGAS-EpitOMe)

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Scientific Abstract

Background

Group A Streptococcus (GAS) causes over 500,000 deaths annually[1]. In 2023, Ireland saw a fivefold increase in invasive GAS (iGAS) cases[2], a global trend with unclear causes[3]. In the absence of a vaccine, treatment relies on antimicrobials and adjuvant immune-modulatory therapies, though the effectiveness and clinical use of these adjuvants vary widely.

Primary Aim

Investigate the molecular epidemiology of iGAS in Ireland using laboratory and clinical data.

Secondary Aims

- Identify genomic markers that correlate with severity, complications and outcomes in iGAS cases.
- Evaluate the role of intravenous immunoglobulin (IVIG) use in iGAS treatment.
- Investigate the efficacy of clindamycin as an anti-toxin agent in clindamycin-resistant GAS isolates.

Methods

Study 1: An observational study using clinical data from the Health Protection Surveillance Centre (HPSC) and isolate data from the Irish Meningitis and Sepsis Reference Laboratory (IMSRL). Statistical and bioinformatic analysis will be employed to establish the molecular epidemiology, genomic diversity and emerging lineages of iGAS in Ireland and how this compares internationally.

Study 2: An observational study which will build upon the dataset from Study 1 to determine if genomic markers correlate with iGAS severity, complications, and outcomes. Genomic analysis will include genome assembly, read mapping and phylodynamic analysis, conducted in collaboration with Dr. Mark Davies at the University of Melbourne.

Study 3: A systematic review and meta-analysis to assess the impact of adjunctive IVIG therapy on mortality in iGAS infections, using data from MEDLINE, EMBASE, and Web of Science. The primary outcome is the odds ratio for mortality.

Study 4: A laboratory-based study using an in vitro human whole blood model of streptococcal toxic shock syndrome to establish if the anti-toxin effect of clindamycin therapy is maintained in clindamycin-resistant GAS isolates. This has been completed at the Murdoch Children's Research Institute at the University of Melbourne.

Conclusion

My PhD addresses the significant surge in iGAS cases, which increased fivefold in Ireland in 2023 and has been mirrored globally. By focusing on the evolution of GAS and optimising treatment strategies, this work aims to enhance patient outcomes and inform responses to this pressing public health concern in the absence of a vaccine.

Lay Summary

Group A streptococcus (GAS) is a germ which can be found in the throat and on the skin of healthy people causing no harm. When it does cause infection, it usually causes a mild illness such as a “strep throat” or a minor skin infection. Much less commonly GAS can cause serious, life-threatening infections. Invasive GAS (iGAS) is an infection where GAS is found in parts of the body that should usually be germ-free such as in the bloodstream. In Ireland, since October 2022, iGAS infections have occurred more often than expected and no-one understands why. Our study aims to discover why this sudden increase has happened. We will be looking at the GAS germ in more detail using special DNA tests. We aim to discover if new and/or specific types of GAS are circulating in Ireland recently. We will also look at how good some of the treatments for iGAS are such as immunoglobulin and an antibiotic called clindamycin. To do this we will read and summarise all the research published about immunoglobulin treatment and we will also investigate if the antibiotic clindamycin stops GAS from producing toxins by doing laboratory testing ourselves.

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Real-World Insights into Young-Onset Gastroesophageal Adenocarcinoma: All-Ireland Population Based Analysis

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Background

Population-based studies have reported a rising incidence of young-onset (YO) oesophageal and gastric cancer. In this study we examined diagnosis age-specific differences in clinicopathological features, treatment and outcomes in YO (18-49 yr), average-onset (AO, 50–70 yr), and late-onset (LO, >70 yr) oesophageal and gastric adenocarcinoma.

Methods

Population-based data were collected from the National Cancer Registry Ireland (NCRI) and Northern Ireland Cancer Registry (NICR). We analysed 21,706 patients diagnosed with incident oesophageal or gastric adenocarcinoma, (ICD10 C15.0-C16.9) from 1999 to 2022 (censored 31.12.22). Categorical variables were compared by Chi-squared tests and trends by Cohrane-Armitage. Kaplan–Meier curves and log-rank tests were used to assess survival differences. Multivariate Cox regression adjusted for key clinical covariates; analyses used complete cases, excluding patients with missing covariates (including stage). Analyses used R v4.4.2; average annual percentage change (AAPC) was calculated in JoinPoint v5.3.0.

Results

The YO cohort accounted for 6.8% of cases. YO gastric cancer patients had significantly more diffuse and poorly differentiated tumours ($p<0.0001$). YO patients also presented more frequently with stage IV disease in lower oesophageal and gastric adenocarcinoma subsites ($p<0.0001$). Incidence increased significantly across YO (AAPC 2.6%), AO (AAPC 3.3%) and LO (AAPC 2.1%) age groups for oesophageal cancer. Gastric cancer incidence was stable in YO but declined in AO (AAPC -2.6%) and LO (AAPC -2.1%) groups. LO had poorer overall survival vs YO (HR 1.23, 95% CI 1.13–1.33, $p<0.001$, multivariable Cox analysis).

Conclusion

We identified rising incidence of oesophageal cancer across all age groups, while gastric cancer is stable in the young and declining in older adults. Despite more advanced and aggressive disease at presentation, young-onset patients had better adjusted survival, highlighting the need for dedicated studies to clarify mechanisms and optimise care.

Lay Summary

Cancers of the food pipe and stomach are increasingly being diagnosed in younger adults. In this All-Ireland study, we analysed over 21,000 patients (1999–2022), comparing people diagnosed at 18–49, 50–70 and over 70 years. Younger adults (<50) were more likely to have aggressive tumour types and to be diagnosed with advanced disease, especially for cancers of the lower oesophagus and stomach. Rates of lower oesophageal cancer rose in all age groups. Stomach cancer rates stayed stable in younger adults but fell in older adults (50–70 and >70). Although younger patients often had more advanced disease, they lived longer than older adults after accounting for stage and other key factors. These results show important age-related differences and highlight the need for further research to understand causes and improve care for younger patients.

Laura Graham **Research Blitz 4**

Immune Cell Heterogeneity and Tertiary Lymphoid Structures in Oral Squamous Cell Carcinoma: Preliminary Insights from Multiplex Immunofluorescence

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Background
Oral squamous cell carcinoma (OSCC) exhibits variation in immune infiltration, influencing prognosis and immunotherapy response. Tertiary lymphoid structures (TLS) are emerging biomarkers, but their formation and functional relevance in OSCC remains unclear. Histological examination of OSCC frequently reveals dense lymphoid aggregates it is not clear if any of these are in fact TLS. TLS with a Germinal centre (GC TLS) are visible on H&E sections, however the frequency of non-GC TLS is unclear. Understanding the pattern and type of TLS present in OSCC is important as they function differently.

Aims and Objectives
To assess the spatial distribution and type of TLS present in OSCC cases with lymphoid aggregates, but no GC-TL S on H&E, using multiplex immunofluorescence (mIF).

Methods
Primary OSCC resection specimens were provided by HNSCC SPORE, Hillman Cancer Centre. OSCC cases (n=11) were included based on the presence of lymphoid aggregates, but no visible germinal centre (GC) TLS on histological evaluation of H&E sections. Unstained 5um sections were stained using a validated mIF TLS maturity panel (CD4, CD20, Ki67, PNAd, CD21, AID). Quantitative image analysis (QuPath v0.6.0) evaluated immune cell density, localization, and TLS type.

Preliminary Results
Immune infiltrates varied across cases. CD20+ B cells were distributed along the invasive front and closely associated with tumour islands. TLS were identified in 10/11 cases; two of these cases contained GC TLS. Multiplex IF confirmed TLS characteristics, with PNAd+ high endothelial venules present and variable AID and Ki67 expression.

Conclusion
OSCC frequently contain TLS which may only be visible as lymphoid aggregates on H&E. The pattern and location of TLS distribution and immune cell infiltration differ from other more characterised tumour types. TLS state may influence immune activation and immunotherapy responsiveness. Ongoing work will correlate spatial immune architecture and TLS classification with clinical outcomes.

Lay Summary
Oral cancers often contain clusters of immune cells called lymphoid aggregates. Orchestrated immune structures called Tertiary Lymphoid Structures (TLS) can form around many tumour types and they have been associated with improved prognosis. Our understanding of their type and distribution in oral cancers is limited. Improving this knowledge has the potential to allow us to apply treatments and insights from other cancer types to management of oral cancers. There are a range of types of TLS, some have a distinct feature, called a Germinal Centre and these can be identified when viewed under a microscope with a standard, H&E stain. When Germinal Centre TLS (GC TLS) form we think the immune system is functioning differently. Many oral cancers, when viewed under a microscope have numerous immune cells surrounding the tumour, but no obvious signs of a GC TLS. We wanted to determine what proportion of cases without a GC TLS had another form of TLS, and how these were related to the tumour. We found that many cases had a type of TLS that is not easily identifiable on H&E alone and that these TLS are distributed differently to what has been previously shown in other cancer types. Understanding these differences in the immune cells in oral cancer is important for increasing options for treatment, particularly utilising existing immunotherapies.

Feline oral Squamous cell carcinoma and the IMpact of toll-like receptors 2 and 4 and feline oral BActeria on tumour cell behaviour and growth (SIMBA)

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Scientific Abstract

Background

Feline oral squamous cell carcinoma (FOSCC) is a devastating disease of cats due to its invasive growth and lack of effective treatments. Its biologic behaviour is similar to human oral squamous cell carcinoma (HOSCC). In humans, periodontal disease is a risk factor for HOSCC and various studies have investigated oral bacteria in this context. In cats, the contribution of oral inflammation/bacteria to FOSCC remains unstudied. This work aims to address this knowledge gap.

Aims and objectives

To investigate the effects of clinical isolates of feline oral bacteria (*Porphyromonas gulae*, *F. canifelinum*) on proliferation and motility of FOSCC cell lines (SCCF2 and SCCF3).

Methods

Oral swabs were collected from cats at the UCD Veterinary Hospital and cultured anaerobically. Colonies morphologically consistent with *Porphyromonas* and *Fusobacterium* were selected for subculture and speciated using 16s rRNA sequencing. FOSCC cell lines were co-cultured with bacteria and Alamar blue and *in vitro* scratch assays were conducted.

Results

Porphyromonas gulae and *Fusobacterium canifelinum* were isolated from five and two cats respectively using 16S rRNA sequencing. In the Alamar blue assay, co-culture of SCCF2 with *P. gulae* and *F. canifelinum* in combination resulted in significantly increased cell proliferation compared to uninfected control cells at 24 hours (P=0.0128, 95% CI=0.07887 to 0.4010). For SCCF3, co-culture with *P. gulae* alone caused significantly increased cell proliferation at 72 hours compared to 24 or 48 hours (P=0.0297 and 0.0223, 95% CI=-0.6149 to -0.06003 and -0.6409 to -0.09566). Co-culture with *P. gulae* and *F. canifelinum* in combination caused significantly increased cell proliferation at 72 hours compared to 48 hours (P=0.0197, 95% CI= -0.3808 to -0.06517). Preliminary results from the *in-vitro* scratch assay suggested that, for SCCF2, *P. gulae* and *F. canifelinum* caused increased cell motility and proliferation compared to noninfected controls. For SCCF3, *P. gulae* enhanced cell proliferation and motility whereas *F. canifelinum* suppressed these effects compared to noninfected controls.

Conclusions

Based on these initial results, feline oral bacteria appeared to affect the growth and motility of FOSCC cell lines. *Porphyromonas gulae* tended to enhance proliferation and motility in both cell lines. The results regarding *F. canifelinum* are mixed, depending on the cell line and assay.

Future work

Cell invasion and migration assays will be carried out to further investigate these effects. RNAseq will be used to investigate genes up/downregulated in FOSCC cell lines due to bacterial infection, and results will be confirmed with RT-PCR and ELISA.

Lay summary

Feline oral squamous cell carcinoma (FOSCC) is the most common oral tumour of cats. It is usually incurable and affected animals are often euthanised at diagnosis. Periodontal disease (inflammation around the gums and teeth) may contribute to the development of a similar tumour in humans, but it is unknown if the same is true in cats. However, almost all cats develop periodontal disease as they age, so this possibility should be investigated.

Swabs were taken from cats mouths and bacteria were grown in the lab. DNA sequencing found that these were Porphyromonas and Fusobacterium. FOSCC cancer cells were grown in the lab and infected with these bacteria. It was shown that Porphyromonas bacteria increased the growth of both types of cancer cell. The results regarding Fusobacterium were mixed. Further lab tests will be carried out to investigate the effects of these bacteria in more detail.

PRIME-COMPASS: Paediatric Risk Integration and Modelling for Enhanced Clinical Outcomes, mapping Perioperative Anaesthesia and Surgical Safety

WP1: A Systematic Review and Pilot Analysis of Paediatric Perioperative Risk Prediction Tools

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Scientific Abstract

Background:

Despite increasing surgical complexity and case volumes, perioperative risk stratification tools in paediatric anaesthesia remain underdeveloped, poorly validated, and rarely integrated into routine practice. Existing clinical decision support tools (CDSTs) are often static, focused narrowly on mortality, and lack dynamic, explainable outputs that clinicians can use in real time. To address these limitations, this research aims to explore, evaluate, and inform the development of a dynamic, data-driven CDST that incorporates patient, procedure, and provider-level predictors to improve preoperative risk triage and assessment.

Methods:

A systematic review of perioperative paediatric risk prediction models was conducted across multiple outcomes (e.g. PRAEs, ICU admission, readmission) using PRISMA guidelines. Of 4,900 screened records, 13 studies met inclusion criteria. Data extraction and PROBAST analysis were performed.

In parallel, a pilot study and retrospective analysis was performed on a numeric triage tool used in the Pre-Anaesthetic Assessment Clinic at The Hospital for Sick Children, Toronto, across 3,579 cases. Triage decisions generated by the tool were compared to final clinician-assigned levels.

Results:

Included studies ranged from 2014 to 2023, mostly retrospective, with varied modelling approaches (logistic regression, machine learning, score-based). AUC values ranged from 0.65-0.94, with only two studies performing external validation. Predictor sets varied widely but commonly included age, ASA status, surgery type and respiratory comorbidity.

In the triage pilot study, overall tool accuracy was 47% ($\kappa = 0.22$), improving to 65% ($\kappa = 0.33$) when excluding patients who required no further review. Over-triage of low-risk patients was the primary source of misclassification.

Conclusion:

While some existing paediatric prediction models show promise, lack of validation and inconsistent definitions limit their clinical use. The initial pilot triage tool analysis highlights both the potential and pitfalls of decision support systems in paediatric anaesthesia. Together, these studies justify the need for a dynamic, interpretable, and validated risk prediction framework.

This PhD project, titled PRIME-COMPASS, aims to develop a Bayesian hierarchical model as a foundation for such a tool, to improve clinical safety, efficiency, and personalised care for children undergoing surgery.

Lay Summary

Children coming in for surgery have very different levels of risk depending on their age, medical conditions, and the type of operation they need. Right now, most hospitals rely on doctors and nurses to judge that risk, but the tools available to help them are not always reliable, especially for children. Many existing tools were never tested properly in real-life hospital settings.

As part of this research, we looked at what tools are currently used to predict complications in children before surgery. We found that most tools were not well validated, and often missed important details. We also reviewed a triage tool used at a large children's hospital to decide who should see a nurse or doctor before surgery. It was only correct about half the time.

This shows a clear need for better, smarter tools. PRIME-COMPASS will use hospital data and expert input to build more accurate, dynamic and useful ways of assessing risk before surgery.

Harnessing the Molecular Signature of Extramedullary Multiple Myeloma for Novel Targeted Therapy Design.

Dr Catherine Duane, ICAT Fellow: 2nd year PhD

Background:
Extramedullary disease (EMD) is an aggressive manifestation of multiple myeloma (MM), defined by the ability of clonal plasma cells to survive as discrete lesions outside the bone marrow (BM). EMD is associated with treatment resistance, inferior overall survival, and is a frequent manifestation of relapse following advanced cellular therapies, such as Chimeric Antigen Receptor T Cell therapy (CAR-T). Molecular drivers of this condition remain poorly understood but are critical to developing targeted treatment strategies.

In this study, genomic and transcriptomic profiling of paired BM-EMD sites identified key molecular features, subsequently evaluated in-vitro for clinical or therapeutic significance.

Methods:
Paired BM and EMD biopsy samples from 10 patients were obtained following informed consent. DNA and RNA sequencing was performed using *Illumina* NovaSeq-6000 and *TWIST* Bioscience RNA-Exome platform. In-vitro evaluation of clinical findings included CRISPR-Cas9 knockout (KO) of target genes, performed using multi-target Guide RNA in a MM cell line.
A novel CAR-T construct, targeting BCMA, with reduced susceptibility to a glycoimmune checkpoint was generated using gammaretroviral transduction of CRISPR edited activated T cells. In vitro evaluation of CAR-T-mediated killing was performed using the OPM-2 MM cell line.

Results:
Genomic Analysis revealed substantial EMD vs BM heterogeneity. EMD samples exhibited consistent CN gains, particularly in chromosomes 1 and 7, which were not prevalent in corresponding BM samples. In chromosome 1, *MUC1*, encoding a mucin glycoprotein, which is sialylated by ST3GAL1, demonstrated CN gain in 75% of EMD. Aberrantly glycosylated overexpressed MUC1 may contribute to immune evasion via interaction with immune inhibitory receptor Siglec-9. CRISPR-Cas9 KO of ST3GAL1 influenced therapeutic response, with increased susceptibility to CAR-T cell-mediated killing, supporting a role for hyper-sialylation in treatment resistance. A novel Siglec-9 gene edited CAR-T demonstrated significantly greater MM cell killing efficacy and efficiency

Conclusion:
This study demonstrates the distinct molecular profile of EMD in MM. Dysregulated glycosylation may facilitate immune evasion and therapeutic resistance. Modification of CAR-T design to reduce susceptibility to immune evasion via glycoimmune checkpoint may improve therapeutic efficacy.

Lay Summary

Multiple myeloma (MM) is an incurable blood cancer, diagnosed in up to 400 patients in Ireland each year. Extramedullary disease (EMD) is aggressive manifestation of the disease in which the cancer cells escape from the patient's bone marrow and form solid tumours at organ sites elsewhere in the body.

There have been major therapeutic advances in the treatment of MM in recent decades, significantly improving patient outcomes and survival. This includes the recent introduction of cell-based therapies, such as Chimeric Antigen Receptor T-cell therapy (CAR-T). However, for patients who develop EMD, the prognosis remains poor, with a limited response to treatment. One likely reason underlying this is that CAR-T treatments, like all MM therapies to date, have been developed using analyses of 'classic' bone-marrow based MM. Given the targeted nature of CAR-T cell therapy, it is crucial that EMD-specific treatment targets are identified. Detailed molecular characterisation of EMD is needed. In this study we have used genomic testing of patients' EMD tumour sites to identify potential therapeutic targets. This molecular profile was then harnessed to generate a CAR-T therapy which demonstrates enhanced therapeutic efficacy in a laboratory setting.

Sophie Duignan **Research Blitz 4**

Placental Signatures of Risk in Congenital Heart Disease: A Multimodal Study

Background

Congenital heart disease (CHD) is the most common congenital anomaly, affecting almost 1% of live births[1]. Current antenatal screening detects just over half of critical CHD[2].

Neurodevelopmental complications are the most common co-morbidity and have a profound effect on quality of life[3] . Although postnatal factors including neonatal bypass surgery are important, we now know that insults to the brain start in utero; fetuses with CHD demonstrate reduced fetal brain volumes and impaired metabolism compared to healthy controls[4]. Emerging evidence implicates the placenta, which is structurally and functionally abnormal in pregnancies complicated by CHD[5]. A recent study demonstrated an association between placental pathology and reduced neonatal brain volumes on MRI[6]. However, the pathophysiological mechanisms and relative contribution of placental dysfunction remain unknown.

Until recently, our understanding of the fetal circulation was largely derived from seminal studies of catheterized fetal lambs[7]. The advent of fetal cardiac MRI now enables detailed quantitative study of blood flow and oxygenation in the human feto-placental circulation. Novel techniques such as T1/T2 mapping and T2* exploit magnetic properties of oxyhaemoglobin to estimate oxygen saturation. Acute maternal hyperoxygenation allows us to test the circulation's ability to increase oxygen delivery to the brain and how autoregulation may affect this.

Aims

1) To delineate the feto-placental circulation in CHD, including response to maternal hyperoxygenation, and how this changes throughout gestation
2) To identify imaging and biochemical markers of placental dysfunction which correlate with neonatal and neurodevelopmental outcomes
3) To improve antentatal detection of CHD

Methods

Work package A: Prospective recruitment of CHD and healthy control pregnancies to undergo paired fetal MRI (including brain, placenta and cardiac imaging) and US with maternal hyperoxygenation at 2 gestational time points.

Work package B: Prospectively perform advanced placental functional ultrasound and correlate this with placental pathology, maternal and neonatal serum biomarkers, neonatal outcomes and infant neurodevelopmental assessments.

Work package C: Develop and evaluate the accuracy of a multimodal AI model to improve antenatal detection of CHD using clinical details, serum biomarkers and ultrasound images of the placenta.

Impact:
This research aims to improve detection of CHD antenatally and to identify high-risk patients with significant placental dysfunction who may benefit from modified delivery planning, neuroprotective measures, and delayed neonatal bypass strategies.

Lay Summary

Congenital heart disease (CHD) affects about 1 in 100 babies but many cases are not detected during routine antenatal screening. Children with CHD are at higher risk of developmental difficulties. Research shows that these problems begin during pregnancy, but we still do not fully understand why. Recent studies suggest that the placenta—the organ that supplies oxygen and nutrients to the baby—may not function normally in some CHD pregnancies. This could affect blood flow and oxygen delivery to the developing brain and other vital organs.

This project will study how the baby's circulation and placenta work in CHD using advanced MRI, ultrasound, and blood tests during pregnancy. We will also follow babies after birth to see how these findings relate to early outcomes and development.

By identifying which babies experience the greatest placental dysfunction, this research aims to guide personalised care to better protect the newborn brain. We also aim to use artificial intelligence to improve detection of congenital heart disease during pregnancy.

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Early OCT Indicators Are Associated with Degree of Vision Loss in Acute NAION

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Purpose:
We aim to characterize longitudinal structural changes in non-arteritic anterior ischemic optic neuropathy (NAION) using optical coherence tomography (OCT) and evaluate their relationship with visual outcomes in a large clinical trial cohort.

Methods:
We used OCT data including peripapillary retinal nerve fiber layer thickness (pRNFLT), peripapillary total retinal thickness (pTRT), optic nerve head volume (pONHV), and segmentation of the macular ganglion cell-inner plexiform layer (GCIPL) thicknesses from 715 participants in the QRK207 trial imaged within 14 days of NAION onset (mean: 8.0 ±SD: 3.2). Imaging was performed at Screening, Enrollment, Month 2, Month 6, and Month 12. We analyzed relative differences in study and fellow eye ONH, sectoral correlations, and rates of early OCT metric increase. Associations with best-corrected visual acuity (BCVA) and visual field (VF) outcomes were assessed with regression analyses.

Results:
Study eyes had ONH swelling at Screening (mean pRNFLT 241.0 ±74.8 µm; pONHV 6.70 ±1.27 mm^3), followed by marked thinning (pRNFLT 56.7 ±14.9 µm; pONHV 2.74 ±0.41 mm^3 at Month 6). For study eyes without prior NAION in the fellow eye, increased differences in baseline inter-eye ONH OCT metrics were associated with worse VF sensitivity and BCVA (e.g., inferior pRNFLT vs superior VF: rho = -0.35, $p<0.001$). Sub-analysis of participants with measurements between Screening and Enrollment (n=267; mean: 2.5 ±1.9 days) showed that GCIPL thinning (-3.0 µm, $p<0.001$) was detectable at an early stage. An initial rate of pONHV thickening of 0.15 mm^3/day conferred a 4.0-fold higher odds of VF decline by Month 2 (CI 2.8-8.5, $p < 0.001$).

Conclusions:
Macular GCIPL thinning is evident at an early stage following NAION onset. Increased baseline inter-eye pRNFLT asymmetry and early ONH volumetric increases in the first days of NAION onset are associated with worse BCVA and VF outcomes.

Lay Abstract

This study looked at how the eye changes in the first year after non-arteritic anterior ischemic optic neuropathy (NAION), a condition that suddenly damages the optic nerve and can cause lasting vision loss. Using optical coherence tomography (OCT), we followed more than 700 patients who were scanned within two weeks of symptom onset. At the first visit, affected eyes showed significant optic nerve swelling. Over time, this swelling shifted to thinning of the nerve layers, reflecting permanent damage. The study found that larger early differences between the affected and unaffected eyes were linked to worse vision and visual field loss later on. Importantly, thinning of a critical retinal layer (GCIPL) was detectable just a few days after symptoms began. Additionally, rapid early swelling of the optic nerve greatly increased the risk of vision decline. Our findings suggest that early OCT measurements can help predict visual outcomes after NAION.

Why do kidney transplants fail so early in young people?

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Scientific Abstract

Background
The burden of End-Stage Kidney Disease in young people is severe. Renal transplantation is the gold-standard treatment. Recipients <30 years old have the best short-term outcomes following transplantation but paradoxically have the worst long-term graft survival rates. Why kidney transplant fail so early in young people is poorly understood.

Aim
To explore whether the difference in long-term kidney transplant outcomes between younger (< 30 years old) vs older (≥30 years old) recipients is associated with variations in epidemiological risk factors, proteomic profiles and subsets of immunological cell types.

Objectives
1.) Identify epidemiological factors associated with long-term kidney transplant outcomes and variation in these between younger and older recipients.

2.) Investigate variation in proteomic profiles between younger recipients with/without evidence of immunological injury and comparing with older recipients with/without evidence of immunological injury.

3.) Investigation of subset variance of T- regulatory, B-regulatory and natural killer cells between recipients <30 and ≥30 years old with functioning transplants.

Methods
Study-1: Data will be extracted from a prospective clinical database of renal transplant recipients. Statistical analysis will identify variation in transplant graft outcome and demographic associations with graft loss.

Study-2: Using two OLINK 384 inflammation platforms, proteomic profiling of stored samples from young recipients with (n=50) and without (n=50) evidence of immunological injury will be performed. A control group of older recipients with (n=50) and without immunological injury (n=50) will enable cross-sectional comparisons to identify proteins associated with immunological injury in both age categories. This analysis will be further supplemented with genome wide sequencing to enable genotype phenotype linking.

Study-3: Patients with functioning transplants will be recruited (n=25 <30 years old, n=25 ≥ 30 years old) to provide serum samples. High-dimensional multi-colour flow cytometry will enable subset analysis of T-regulatory, B-regulatory and Natural Killer cells identifying variation between younger and older recipients.

Conclusion
This study will assist in the understanding of why long-term outcomes in younger transplant recipients are poorer. The research may help identify ways of risk stratifying for immunologically mediated transplant loss.

Lay Summary

Kidney transplantation is the best treatment for people with end-stage kidney disease, providing improved quality of life and much longer survival. Unfortunately, younger people appear to be at higher risk of losing their transplant, having a devastating impact on their health. It remains unclear why kidney transplants fail so early in young people. The aims of my PhD are: 1.) Identify the reasons for kidney transplant loss in younger people and determine whether other details about their health can be linked to their increased risk of transplant loss. 2.) Use new technology to measure difference in proteins (proteomics) in transplant recipients to better understand their increased risk of transplant failure. 3.) Measure different types of cells that affect transplant outcomes to see if their expression varies between younger and older transplanted patients I hope by better understanding why young people suffer from earlier transplant loss we will be able to improve their care and ultimately reduce transplant loss.

Louise Rabbitt

Final year PhD

Biochemical Detection and Psychosocial Correlates of Antihypertensive Adherence in Hypertension: Initial Observations from a Cross-Sectional Study in Two Irish Tertiary Care Centres

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Background:
Non-adherence to antihypertensive drugs (AHDs) is a key contributor to poor blood pressure control, yet adherence measures are often unreliable. Chemical adherence testing (CAT) using liquid chromatography–high resolution mass spectrometry (LC-HRMS) provides objective, point-in-time assessment, but the integration of biochemical results with psychosocial profiling remains limited.

Objective:
To assess the extent and patterns of antihypertensive non-adherence in two Irish tertiary hypertension centres and explore associated psychosocial and demographic characteristics.

Methods:
In this prospective cross-sectional study, 171 patients attending specialist hypertension clinics at St James's Hospital and Galway University Hospital underwent CAT on unannounced spot urine samples. Participants completed validated questionnaires assessing self-reported adherence (MARS-5), beliefs about medicines (BMQ), health literacy, anxiety and depression (HADS), and perceptions of patient–provider communication.

Results:
Among 171 participants, only two self-reported non-adherence. LC-HRMS detected all prescribed AHDs in 132 (77%), partial detection in 32 (19%), and no detection in 7 (4%). Using the absence of ≥2 prescribed AHDs as a clinically significant threshold, 12 of 145 participants on ≥2 agents were non-adherent. Self-reported adherence did not correspond to CAT results; MARS-5 scores did not differ between adherent and non-adherent groups. No demographic predictors of adherence were detected.
BMQ results showed indifference as the most common attitudinal category (55%), followed by acceptance (39%). Beliefs about medicines were associated with adherence: the Sceptical group had markedly higher odds of non-adherence compared with the Accepting group (OR≈12, 95% CI 1.4–104). Illness coherence, physician communication style, and anxiety showed no association with adherence. Non-adherent participants demonstrated a trend toward higher depression scores.
Amlodipine was the most frequently prescribed AHD and had 96% detection, while spironolactone had the lowest detection rate (76%).

Conclusion:
CAT revealed substantial partial or complete non-adherence (23%). These initial findings underscore the need for multifaceted adherence assessment integrating objective testing with psychosocial insights to guide personalised management in hypertension.

Lay Summary

High blood pressure is common, and taking medication regularly is essential for keeping it under control. However, many people do not take their blood pressure tablets as prescribed, and doctors often have no reliable way to know this. In this study, patients from two Irish hospitals provided a urine sample that was tested in the laboratory to check whether their prescribed medicines were present. They also completed questionnaires about their views on medicines, mood, and communication with their doctors. The tests showed that nearly one in four patients were missing some or all of their blood pressure medicines, even though almost everyone reported taking them. People's beliefs about medicines were linked to how well they took them: those who were doubtful or worried about medications were more likely not to take them as prescribed. Mood, age, and gender did not appear to influence adherence. These findings highlight the importance of understanding both behaviour and beliefs when helping patients manage high blood pressure.

Maria Tomkins

Final year PhD

Impaired glucocorticoid metabolism is an independent predictor of cardiovascular risk in chronic kidney disease.

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Abstract:

Patients with chronic kidney disease (CKD) have an elevated risk of cardiovascular disease (CVD) potentiated by mineralocorticoid receptor (MR) overactivation. MR activation occurs from both mineralocorticoid and inappropriate glucocorticoid binding. The enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) converts active cortisol (F) to inactive cortisone (E) thereby protecting the MR, and its activity has been shown to be impaired in CKD.

To investigate the contribution of disrupted adrenal steroid metabolism to CVD risk in CKD we performed multi-steroid profiling via liquid chromatography–tandem mass spectrometry on paired serum and 24-hour urine samples from non-diabetic patients with CKD (n=103) and age-, sex-, and BMI-matched healthy controls (n=39) alongside detailed cardiometabolic phenotyping, including pulse wave velocity (PWV) and body composition analysis.

Despite elevated plasma aldosterone concentrations [357pmol/l vs 235pmol/l, p=0.01], patients with CKD had significantly lower urinary excretion of total mineralocorticoid metabolites [398nmol/l vs 882nmol/l, p<0.0001], suggesting impaired renal clearance. 11β-HSD2 activity declined with worsening renal function evidenced by an elevated F/E ratio [11.1 in CKD vs 5.7 in controls, p<0.0001]. Multivariable regression identified elevated plasma aldosterone, lower urinary mineralocorticoid metabolites and increased F/E ratio as independent predictors of lower eGFR when accounting for age, sex, antihypertensives, urine volume and urine creatinine concentration.

Multiple regression revealed an independent association of both the F/E ratio (β=0.1, p=0.04) and total urinary glucocorticoid metabolites (β=0.09, p=0.007) with arterial stiffness (PWV), controlling for age, sex, renal function, blood pressure, and antihypertensive use. Mineralocorticoid markers showed no independent associations with cardiometabolic outcomes.

This is the first study to interrogate the complete steroid metabolome in CKD providing an insight into renal determinants of steroid metabolism. Our findings highlight the important role of impaired 11β-HSD2 activity in driving glucocorticoid-mediated MR activation and arterial stiffness. Overall, our study provides novel evidence that disruptions in glucocorticoid metabolism, rather than mineralocorticoid excess alone, contribute substantially to cardiovascular pathophysiology in CKD emerging as a previously unrecognized therapeutic opportunity.

Lay summary:

Patients with chronic kidney disease (CKD) have an excess risk of cardiovascular disease. Arterial stiffness is a hallmark of cardiovascular disease in CKD. Previous research in this area has focused on the contribution of excess aldosterone, a mineralocorticoid steroid, to cardiovascular risk. It is important, however, to consider glucocorticoid steroids. Glucocorticoid metabolism is impaired in CKD allowing it to cause mineralocorticoid-like effects. In this study we measured arterial stiffness and cardiovascular risks in patients with CKD alongside complete measurement of adrenal steroids and their metabolites in serum and urine. We found significant perturbations in steroid metabolism in CKD. Additionally, glucocorticoid metabolism is a greater contributor to cardiovascular disease risk than aldosterone and should be considered as a potential therapeutic target in CKD.

Introduction
Hypertension remains a major health challenge, particularly in patients with resistant hypertension, blood pressure (BP) variability, and orthostatic hypotension. Adherence to oral antihypertensives is a key issue, and dynamic BP targets are difficult to achieve manually. Intravenous (IV) esmolol hydrochloride, a short-acting β_1-selective blocker, can rapidly lower BP; its use in a closed-loop system incorporating real-time feedback could enable more precise and automated BP management. This study aimed to demonstrate the feasibility of using a closed-loop system to control systolic blood pressure (SBP) with esmolol in swine.

Methods
Two anaesthetised female Yorkshire swine (20 kg) were instrumented with femoral arterial catheters for continuous SBP and heart rate monitoring. A custom-built Proportional-Integral-Derivative (PID) controller in MATLAB regulated IV esmolol hydrochloride (10 mg/mL) infusion via syringe pump. The system aimed to reduce and maintain SBP within 15–22% below baseline.

Preliminary dose–response experiments identified suitable loading and maintenance rates. The final protocol used a 2000 mcg/kg/min loading dose over one minute, followed by a 900 mcg/kg/min infusion. The PID algorithm adjusted the infusion every 60 seconds using a rolling SBP average. Controller gains (Kp, Ki, Kd) were tuned during open-loop trials and finalised based on haemodynamic responses. Safety features included manual override and an automatic cutoff if hypotension was detected.

Results
The PID-controlled infusion reached target SBP in 129 seconds. During the treated window, 51.7% of SBP readings were within the target range. Maximum undershoot was +8.4 mmHg; no excess hypotension occurred. Diastolic BP fell by 6.01%, heart rate by 9.09% with parameters recovering rapidly after infusion cessation.

Conclusions
A closed-loop PID system achieved stable, real-time BP control with esmolol in swine. The system was responsive and safe, supporting further investigation into autonomous antihypertensive delivery for patients with resistant hypertension and high BP variability.

Lay Summary
High blood pressure is a leading cause of heart attack and stroke, yet many people struggle to keep it under control, even with multiple medications. One reason is that blood pressure changes constantly, and it's difficult for doctors or patients to adjust treatment fast enough.

This research explores a new "closed-loop" system that automatically adjusts blood pressure medication in real time. Using a short-acting drug called esmolol and a computer-controlled pump, the system continuously monitors blood pressure and fine-tunes the dose every minute.

In laboratory studies using an animal model, the system safely and accurately reduced blood pressure to a target level within two minutes and maintained stable control without causing dangerously low readings.

These findings show the potential for future smart drug-delivery systems that could provide more precise, personalised treatment for people with difficult-to-control or fluctuating blood pressure.