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# Rare Disease Research Conference 2026

## Poster Presentations



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# From Mutation to Degeneration: Developing Novel Models to Understand Warburg Micro Syndrome

Ailbhe Conway[1], Niamh O'Sullivan[1]

[1] UCD School of Biomolecular and Biomedical Sciences, UCD Conway Institute of Biomedical and Biomolecular Research

Warburg Micro Syndrome (WARBM) is a very rare genetic condition that affects brain growth and development from birth. Typically, affected children have poor vision, experience progressive muscle stiffness, and generally fail to reach developmental milestones on time. Currently, there are no treatments available for this condition.

Research has shown that WARBM is caused by changes in the genes RAB3GAP1, RAB3GAP2 and TBC1D20 which regulate the levels of a protein called RAB18. However, it is not understood how loss of RAB18 causes neurons to malfunction in WARBM.

The goal of my research is to develop animal models that help us understand the biological causes of WARBM. Using gene-editing technology I created fruit flies carrying WARBM-causing gene abnormalities. These models enable me to study what is going wrong in neurons to make them stop working, in a way that is not possible in WARBM patients. These model flies show worsening movement and reduced survival over time, suggesting that they reproduce key features of the human condition. Current work is focused on understanding what happens inside neurons when these genes are disrupted, including changes in how cells store fats, recycle damaged components, and maintain normal cellular structure.

This project has been developed in collaboration with the Warburg Micro Research Foundation. As part of this work, I have produced lay summaries of WARBM research papers and explanatory resources covering key genetic concepts. These materials are published on the Foundation website to help make research findings more accessible to individuals and families affected by WARBM.

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# Beyond Growth Velocity: Child-Parent Discordance in Quality-of-Life Reporting under Vosoritide Treatment for Achondroplasia (A 10-Patient Cohort)

Alexandra-Aurora Dumitra[1,2], Ioana Streata[1,2], Rebecca-Cristiana Șerban[1,2], Andreea Mituț-Velişcu[1], Liana Maria Marica[1], Florin Burada[1,2]

[1]Regional Centre of Medical Genetics, Craiova County Emergency Clinical Hospital. [2]University of Medicine and Pharmacy of Craiova, Romania

**Introduction:** Achondroplasia (ACH), caused by a gain-of-function FGFR3 variant, is the most common skeletal dysplasia. Vosoritide, approved by EMA/FDA in 2021 and by Romanian ANMDM in 2024, is the first disease-modifying treatment for ACH. While its effect on growth velocity is established, its impact on patient-reported quality of life (QoL), and specifically on how child and parent perceptions align or diverge, remains poorly characterised.

**Methods:** Ten pediatric patients with molecularly confirmed ACH on subcutaneous vosoritide, followed at the Regional Centre of Medical Genetics, Craiova, were evaluated prospectively. Anthropometric parameters were recorded longitudinally. QoL was assessed using QoLISSY and APLES, administered separately in child-report and parent-proxy versions at standardised intervals, enabling direct comparison of paired responses within each domain. Patient and Public Involvement was incorporated through collaboration with a patient advocacy organisation, which contributed to shaping the study's quality-of-life focus.

**Results:** All patients showed positive height-SDS trajectories under vosoritide (best AGV 12.67 cm/year). Paired child-parent injection-burden assessments were available for 8/10 patients. Among the four patients followed ≥12 months, children reported higher injection burden than parents in all four (mean difference +0.62/5, scale 1–5); the pattern was inconsistent among patients followed <12 months.

**Conclusions:** Vosoritide delivers measurable anthropometric benefit, but QoL improvement is neither uniform nor linear with growth. Child-parent discordance constitutes an independent, actionable data point that should be tracked longitudinally and addressed directly in counselling. Dual-perspective, separately-administered PROMs should be standard practice in ACH follow-up, a framework transferable to other rare diseases entering disease-modifying treatment.

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# Defining the role of ATP-citrate lyase (ACLY) in Pulmonary Fibrosis

Atia Batool[1], Patricia Ogger[2], Lauren W.H. L[5], Philip Molyneaux[4,5], Helen O'Brien[1,3], Donal O'Malley[1,3], Niamh Boyle[1,3], Kathryn Duvall[1], Sarah H. Forde[1], Madita Hövel[1,3], Megan M. McKean[1], Lisha Joshi[1], Julie C. Worrell[1], Cormac McCarthy[1,3], Adam J. Byrne[1]

[1]University College Dublin, School of Medicine, Belfield, Dublin 4. [2]Max Planck Institute of Biochemistry, Am Klopferspitz 18, 82152 Martinsried, Bayern, Germany. [3]Department of Respiratory Medicine**, S**t. Vincent's University Hospital, Elm Park, Dublin 4, D04 T6F4. [4]NIHR Respiratory Biomedical Research Unit, Royal Brompton Hospital, Sydney Street, London, SW3 6NP, UK. [5]Inflammation, Repair & Development Section, National Heart and Lung Institute, Imperial College London SW7 2AZ, UK.

**Background:** Airway macrophages (AMs) are involved in dysregulated wound healing responses in Idiopathic Pulmonary Fibrosis (IPF). The metabolic enzyme, ATP Citrate Lyase (ACLY), involved in the conversion of citrate to acetyl-CoA, has been linked with macrophage phenotypes regulation in vitro, however its role in macrophage metabolism in IPF is not known. We hypothesize that ACLY controls the fibrotic phenotypes of AMs and manipulation of ACLY represents a potential therapeutic strategy for IPF.

**Methods:** We employed gene expression analysis in primary AMs to analyse expression of ACLY in healthy vs IPF lung. The expression of ACLY was also investigated at protein level using flow cytometry. To mechanistically investigate the role of Acly in bleomycin model, we utilised mice expressing or lacking Acly in CD11c+ cells (AclyΔCD11c mice).

**Results:** Gene expression of ACLY was significantly upregulated in AMs sorted from IPF patients versus controls. Higher ACLY expression in IPF-AMs was associated with poorer survival in patients. ACLY expression was upregulated at protein level in IPF AMs compared to controls. In bleomycin model of pulmonary fibrosis, expression of Acly was increased in Monocyte-derived (Mo)-AMs at day 21 (peak fibrosis) compared to day 1, in WT mice. AclyΔCD11c mice had a lower frequency of monocytes and Mo-AMs in the lung tissue in bleomycin model.

**Conclusion:** Taken together, these data suggest a key role for ACLY-expressing AMs in IPF pathogenesis. Future work will aim to delineate the mechanistic role of ACLY-expressing AMs and determine the effect of pharmacological blockade of ACLY, in lung fibrosis.

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# Developing New Therapeutic Strategies for Hereditary Spastic Paraplegia SPG3A

O'Leary AC[1], O'Sullivan NC[1]

[1] UCD Conway Institute of Biomolecular and Biomedical Research

Hereditary Spastic Paraplegia (HSP) is a group of rare neurological disorders that cause progressive muscle stiffness, weakness, and difficulties with walking. For children with severe forms of HSP, symptoms can significantly affect quality of life, and there are currently no treatments that slow or stop disease progression. Existing therapies focus on managing symptoms, highlighting the urgent need for disease-modifying treatments.

My research focuses on developing new therapeutic approaches for a severe form of HSP (SPG3A) caused by mutations in the Atlastin-1 (ATL1) gene. These mutations produce a harmful version of the ATL1 protein while the healthy copy of the gene remains functional. This presents an opportunity for a precision medicine approach that selectively reduces the disease-causing gene product while preserving the normal protein.

To achieve this, I have developed antisense oligonucleotides (ASOs), molecules designed to specifically silence the mutant ATL1 gene. Using human cell-based models, I established a screening platform that enables the rapid evaluation of ASO candidates and identified molecules capable of selectively reducing expression of the mutant gene segment while sparing the healthy gene segment. I validated these findings using full-length ATL1 constructs, confirming that the lead ASO selectively lowers levels of the mutant protein without affecting normal ATL1 expression.

The next stage of this work will evaluate whether this ASO can improve disease-related features in neuronal progenitor cells. By targeting the genetic cause of HSP rather than its symptoms, this research highlights the potential of allele-specific gene silencing as a treatment strategy for rare dominant genetic disorders.

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# Understanding the Cardiac Phenotype in Resistance to Thyroid Hormone beta

Benái Paponette[1, 2, 3], Muhammad Najmi Md Nor[1, 2, 3], Jane Noble[1, 2], Sebastian Flynn[2], Una Buckley[2], Martina Walsh[2], Jonathan Dodd[2], Krishna Chatterjee[4], Carla Moran[1,2,3,4]

[1] Endocrine Section, Beacon Hospital, Dublin, Ireland. [2] Endocrine Department, St. Vincent's University Hospital, Dublin, Ireland. [3] Royal College of Surgeons in Ireland, Dublin, Ireland. [4] Institute of Metabolic Science, University of Cambridge, UK

Resistance to thyroid hormone beta (RTHβ) is a rare genetic disorder caused by defective signaling through TRβ, causing a complex state of tissue-specific hypo- (TRb expressing tissues, e.g. liver) and hyperthyroidism (TRa-expressing tissues, e.g. myocardium). Dyslipidaemia and insulin resistance are known features; more recently, increased cardiovascular risk (heart failure, atrial fibrillation), with reduced healthy life expectancy, have been demonstrated. This study aims to perform prospective cardiac phenotyping in RTHβ to detect early structural, functional and/or rhythm dysfunction and advance mechanistic understanding of cardiac disease. Adults with genetically proven RTHβ attending the national Rare Thyroid Disease Clinic in Ireland are being invited to participate. Recruited individuals underwent advanced phenotyping (history, clinical, biochemical measurements, liver and cardiac MRI (CMR)). Quantitative liver assessment included region of interest hepatic proton-density fat fraction to quantify hepatic steatosis and Iron measurements. CMR included T1 mapping and extracellular volume (ECV) assessments. Five participants (4 females, 1male; average age 31.6years) were recruited. One participant had atrial fibrillation and cerebrovascular accident and three had dyslipidaemia. ECV values were within a non-elevated range (25.9-27.7%) and T1 measurements were relatively consistent (1207-1289ms). One participant had mild hepatic steatosis (8.8%). Planned analyses include ongoing recruitment (target cohort n=9-10), complete CMR analysis of cardiac anatomy, atrial and ventricular structure, comprehensive echocardiography and 14-day ambulatory rhythm monitoring to characterise atrial rhythms. Preliminary results have not yet shown an abnormality on cardiac MRI although further analyses are ongoing. Findings may provide clinically meaningful endpoints for future interventional trials, including studies of thyroid hormone analogues.

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# Duplication origin shapes paralog compensation in rare developmental disorders

Carlos Vivas Rodríguez[1] and Colm J. Ryan[1]

[1]School of Medicine, University College Dublin, Dublin, Ireland

Understanding why complete loss of some genes is tolerated, whereas loss of others causes severe developmental disorders, is crucial for explaining patterns of genetic variation and for prioritising likely causal variants in rare-disease cohorts. Duplicate genes (paralogs) provide a potentially rich source of genetic robustness, since almost 70% of human protein-coding genes have a paralog. We hypothesised that loss-of-function mutations might be better tolerated in genes with paralogs than in other genes, and that tolerance might vary between paralog classes. To test this, we analysed four large sequencing cohorts and identified more than 2,000 genes with biallelic loss-of-function variants in healthy individuals, termed natural knockout (KO) genes. Paralogs were enriched among KO genes (OR=1.47, $P=2.1\times10^{-9}$), consistent with their mutation being better tolerated. We then compared these natural KO genes with genes whose loss is annotated in the Gene2Phenotype database as causing a developmental disorder. Tolerance differed according to duplication origin: whole-genome duplicates (WGD) were less likely than small-scale duplicates (SSDs) to be observed as KO (OR=0.58, $P=6\times10^{-24}$). Among WGD genes, greater sequence identity to the closest paralog was associated with a lower probability of being observed as a KO (OR=0.74, $P=4.07\times10^{-11}$), and highly similar WGD pairs were over-represented among developmental-disorder genes. SSDs, by contrast, did not show the same pattern. Together, these findings establish duplication origin as a key determinant of paralog tolerance to mutations, revealing that WGD and SSD genes follow different buffering logics, a distinction with direct implications for interpreting variant pathogenicity in rare developmental disorders.

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# Blood-Brain Barrier Disruption in Tuberous Sclerosis Complex: A Patient-Oriented Multimodal Investigation into Epilepsy and TSC-associated neuropsychiatric disorders- The Pilot study

Claire Behan[1,2,3], Chris Greene[3,4], Mary Vasseghi[,6], Anne Gough[7], Isabelle Hunt[7,8], Colin Doherty[3,7,8], Damien Ferguson[7,8]

[1] School of Nursing and Midwifery, RCSI. [2] St. James's Hospital. [3] FutureNeuro. [4] Department of Physiology & Medical Physics, RCSI. [5] TSC Ireland. [6] Rare Disease Clinical Trial Network, University College Dublin. [7] St. James's Hospital. [8] School of Medicine, Trinity College Dublin

Tuberous sclerosis complex (TSC) often causes drug-resistant epilepsy and a broad spectrum of TSC-Associated Neuropsychiatric Disorders (TAND). Not all cortical tubers are epileptogenic, suggesting local microenvironmental factors beyond tuber load and genotype. Converging evidence from epilepsy studies and emerging TSC models indicates that BBB disruption amplifies neuronal hyperexcitability, impairs drug delivery, and promotes neuroinflammation. However, direct patient-level evidence for BBB involvement in TSC is lacking.

**Aim:** To determine whether BBB disruption is a tractable driver of seizures and TAND in TSC and to deliver translational tools for BBB-targeted therapy.

**Objectives:**

- In vivo localisation: Quantify BBB permeability with dynamic contrast-enhanced MRI, test co-localisation with epileptogenic tubers, and relate regional leakiness to seizure severity and TAND profiles.
- Fluid biomarkers: Develop and validate a composite blood-based BBB disruption index integrating vascular and inflammatory analytes, benchmarked against MRI-derived permeability and clinical outcomes.
- Mechanism/rescue: Use patient-derived iPSC BBB models to define cellular and molecular mechanisms of barrier failure, assess tight junction integrity and transporter function, and evaluate BBB-stabilising interventions for functional rescue.

The project will deliver:

- non-invasive imaging criteria to localise epileptogenic tissue,
- a blood-based score to stratify patients and monitor BBB health, and
- mechanistic evidence that BBB-targeted strategies restore barrier and transporter function.

Together, these outputs will establish BBB dysfunction as a measurable, therapeutically actionable axis in TSC, creating a foundation for precision interventions that complement seizure- and mTOR-directed treatments to improve seizure control, cognition, and quality of life.

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# Real-World Insights from the ERN-RND Registry at Tallaght University Hospital: Experience from a National Rare Neurological Disease Cohort

Colin Clarke, Edwin E. Pabilona Jr, Sean O'Dowd, Antoinette O'Connor, Allan McCarthy, Emmet Kelly, Karen O'Connell, Deirdre Ward, Mary Kearney, Richard Walsh, Petya Bogdanova-Mihaylova, Sinead Murphy.

Tallaght University Hospital, Dublin, Ireland.

**Background:** Rare diseases affect ~6% of the population, with most being genetic and over half involving the nervous system. Tallaght University Hospital (TUH) serves as Ireland's national lead site within the European Reference Network for Rare Neurological Diseases (ERN-RND), integrating genomic diagnostics, multidisciplinary subspecialist care, and international research participation across ataxia, movement disorder, and cognitive neurology services.

**Aims:** To characterise the demographic, clinical, and genetic profile of patients enrolled in the TUH ERN-RND registry and evaluate how participation in a European rare disease network enhances diagnosis, specialist care, and research integration.

**Methods:** A cross-sectional review was conducted of all patients registered in the TUH ERN-RND registry as of 11 February 2026. Diagnoses were grouped using coded registry entries. Demographic, genetic, and referral data were analysed descriptively.

**Results:** The registry included 289 patients (age 16–81) with balanced sex distribution. Most (238; 82.4%) had ataxia or hereditary spastic paraplegia (HSP). Molecular diagnoses demonstrated substantial heterogeneity, including Friedreich's ataxia, POLR3A-related leukodystrophy, SPAST, SPG7, RFC1, ANO10, AIFM1, and multiple spinocerebellar ataxias (SCA7, SCA14, SCA27B/FGF14). Forty-nine patients (17%) had atypical parkinsonian syndromes—corticobasal degeneration, progressive supranuclear palsy, or multiple system atrophy. Two patients (0.7%) remained undiagnosed. Referrals were received nationwide across public and private services.

**Conclusions:** The TUH ERN-RND registry demonstrates the value of embedding research within specialist clinical care. Participation has enabled Irish patients to join international natural history studies and trial-ready cohorts. Growing demand, longer waiting times, and limited allied health access highlight the need for further investment in rare neurological disease services.

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# Worldwide Cystinosis Community Advisory Board (CAB) – a model for meaningful patient partnership in rare disease research

Denise Dunne [1,2], Dr Tracey McCauley[1], Anne Marie O'Dowd [1,2]

[1] Cystinosis Ireland. [2] Cystinosis Network Europe

"CABs are international, independent groups of patient representatives selected by their community who meet regularly with health product companies [and academic and clinical sponsors of research] to discuss a wide range of topics, from study design to compassionate use of therapies."[1] CABs streamline cooperation between stakeholders, de-risk development and decrease costs, from basic research right through to therapy access in a global environment.

The key principles of the Cystinosis CAB are based on the EUROCAB model[2]: confidentiality; transparency; sharing; optimisation of research and development; and the development of joint action plans. Cystinosis CAB members are patients and parents/carers who offer their expertise to sponsors of clinical research and other areas of importance to the cystinosis community. They bring the lived experience of cystinosis to discussions as well as being trained in areas such as clinical research, clinical trials, drug development, market authorisation, access and reimbursement. The Cystinosis CAB also provides PPI for research-investing patient organisations.

Engagement with the CAB process can promote:

- Faster participant recruitment and better retention
- Shortened development time
- Fewer EMA/FDA dossier amendments
- Quicker market access
- Understanding of the rare disease environment
- Real-life expertise

The Cystinosis CAB has provided engagement with sponsors in areas such as:

- Patient information materials
- Review of clinical guidelines
- Clinical trial protocols
- Other issues relevant to the cystinosis patient community

The Worldwide Cystinosis CAB is an independent, autonomous body and offers an example of a sustainable, internationally connected and patient-led partnership model with transferable lessons to share with other rare disease networks.

[1] https://link.springer.com/article/10.1186/s40900-026-00866-9. [2] https://www.eurordis.org/get-involved/eurordis-community-advisory-board-programme/

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# An investigation of the utility of serial BMD measurement by DXA in patients with XLH

Emily Riordan[1], Katrina Mennie[1], Breeda Sweeney[1], Sarah H. Forde[2,3] and Rachel Crowley[1,2,3,4]

[1] St Vincent's University Hospital, Dublin, Ireland. [2] School of Medicine, University College Dublin, Dublin, Ireland. [3] Rare Disease Clinical Trial Network, University College Dublin, Dublin, Ireland. [4] Rare Disease Research Catalyst Consortium, University College Dublin, Dublin, Ireland.

X-linked hypophosphatemia (XLH) is a rare disease characterised by FGF3 hormone-induced renal phosphate excretion, with complications like pseudo- /fractures and osteomalacia. Two aspects of the disease process are ectopic ossification of the spinal ligaments and cortical bone thinning, both processes may be detectable on serial DXA. This study aims to assess whether Lumbar spine (LS) and Hip DXA scans can detect change in XLH, through observation of common trends in BMD rate of change.

Twenty XLH patients had a median of four DXAs. An absolute least significant change (LSC) between BMD consecutive scans (LS = ±0.022g/cm2; hip ±0.028g/cm2) was observed in an average of 85.4% and 61.8% of LS and hip scans per patient, respectively.

Longitudinal changes in LS and hip BMD were analysed using linear mixed-effects models with patient-specific intercepts and time slopes. LS BMD increased by an estimated 0.0123 g/cm$^2$ per year (SE 0.0037, p = 0.0036). The estimated direction of change of hip BMD was negative (−0.0026 g/cm$^2$ per year), although this was not statistically significant evidence of a population-average change over time (p = 0.626). Substantial between-patient variability in BMD slopes was observed for LS and hip, indicating that rates of BMD change varied between individuals. There was no statistical evidence to suggest that baseline age, sex or medications modified the longitudinal LS or hip BMD slopes.

This analysis could justify further investigation into a larger cohort to establish the nature of DXA changes present in XLH. Detection of a common trend can help clinicians use DXA to predict the likelihood of complications and the nature of the patient's disease. XLH is a disease that would benefit from this due to the wide variation in presentation and disease progression.

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# One Gene, Two Paths: Divergent Outcomes of ATL1 Mutations in Hereditary Spastic Paraplegia

Emma Cadoria[1], Niamh O'Sullivan[1]

[1] UCD School of Biomolecular and Biomedical Sciences, UCD Conway Institute

Mutations in ATL1 are a common cause of hereditary spastic paraplegia (HSP), a genetic condition that leads to progressive stiffness and weakness of the legs. However, the severity of the disease varies widely between patients. Most people have a "pure" form that progresses slowly and mainly affects walking, while in rare cases individuals develop a more severe "complex" form early in life, with additional neurological problems. Why the same gene can cause such different disease patterns is still not well understood. To explore this, we used fruit fly models carrying disease-related changes in the same gene (ATL1). Flies with mutations linked to the complex form showed more severe movement problems, poorer development, and shorter lifespans than those with mutations linked to the pure form, reflecting the differences seen in patients. We then examined what was happening inside nerve cells. In the pure form, we found abnormal buildup of fat droplets inside long nerve fibres, which can be partly improved using a drug that targets fat regulation pathways. In contrast, flies with the complex form did not show these fat changes and did not respond to this treatment. Instead, they showed disruption of an important internal cell "network" called the endoplasmic reticulum, which is essential for producing and processing proteins. Overall, our findings show that different ATL1 mutations can damage nerve cells in different ways. This helps explain why HSP can look so different between patients and suggests that future treatments may need to be tailored to the specific underlying cellular problem in each form of the disease.

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# An Epidemiological Study of Friedreich's Ataxia in the Republic of Ireland

Eva Tallon[1], Edwin Pabilona[1], Mary Kearney[1], Colin Clarke[1], Richard Walsh[1], Sinead Murphy[1], Petya Bogdanova-Mihaylova[1]

[1] Tallaght University Hospital

Friedreich's ataxia (FRDA) is the most common inherited ataxia, causing progressive neurological and cardiac disease with onset typically in childhood. Patients are most commonly wheelchair-dependent by adulthood and have a significantly shortened life-expectancy with the mean age of death being 37-years. No reliable, systematically ascertained prevalence data exist for FRDA in the Republic of Ireland. A prior estimate based on informal patient-organisation data suggested a prevalence of 1:23,000 on the island of Ireland, however this predated the widespread availability of genetic diagnostics and potentially overestimated true disease-burden.

We describe the protocol for a national, population-based, cross-sectional epidemiological study to determine the point prevalence of FRDA in Ireland. Case ascertainment will use multiple overlapping sources: the National Ataxia Clinic (Tallaght University Hospital, the Irish ERN-RND expert site), direct notification of all Neurologists in Ireland, patient support organisations, national media, and clinical review of symptomatic relatives of confirmed cases. Inclusion requires genetically confirmed diagnosis of FRDA or an early-onset ataxia phenotype with a first-degree relative with confirmed FRDA through genetic testing. Based on international prevalence data (1:50,000) and patient-group estimates, approximately 130 individuals are anticipated with 85% case ascertainment targeted (~110 participants). Secondary outcomes include regional distribution, disease burden as determined by interview and validated assessment-scores, as well as patient-reported quality-of-life measures.

This will be the first systematic prevalence study of FRDA in Ireland, providing data to guide service planning, identify geographic and demographic inequities in care access, and estimate healthcare costs and savings relevant to future disease-modifying therapies.

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## BRIDGE-HD-IE: Changing How We Do Huntington's Disease Research

Eva Woods[1], Eoin O'Connor[1], Orla Russell[2], Derek Readman[3], Emma Grace[3], Jarlath Varley[3], Fiona Moran[3], Patricia Towey[3], Niall Pender[4,5], Roisin McMackin[1]

[1] Discipline of Physiology, School of Medicine, The University of Dublin, Trinity College, Dublin, Ireland. [2] Beaumont Hospital, Dublin, Ireland. [3] Irish Huntington's Disease Public Patient Involvement Panel, The University of Dublin, Trinity College, Dublin, Ireland. [4] Academic Unit of Neurology, School of Medicine, The University of Dublin, Trinity College, Dublin, Ireland. [5] Department of Health Psychology, Royal College of Surgeons, Dublin, Ireland.

Research participation by families affected by Huntington's disease (HD) is essential for improving understanding of the condition and supporting the development of future treatments. However, involvement in HD research can be influenced by practical, emotional, social, stigma and privacy-related concerns, as well as previous experiences and access to local services. These issues are particularly relevant in Ireland, where specialist HD services and research opportunities remain limited.

BRIDGE-HD-IE aims to understand why people affected by HD in Ireland choose to participate in research, decline participation, or feel uncertain about taking part. The study explores the barriers, motivators, concerns, and supports that shape research engagement.

This national survey was co-designed with HD families, clinicians, researchers, and patient and public involvement (PPI) contributors. PPI contributors reviewed the study materials and helped shape the survey language, topics, and questions to better reflect the experiences and priorities of the HD community. The survey is open and currently recruiting participants from across Ireland, including people living with symptoms of HD, premanifest gene expansion carriers, individuals at risk, family members, and caregivers. It explores previous research experiences, willingness to participate in different types of studies, perceived benefits and barriers, stigma, privacy and discrimination concerns, and views on HD clinical and research infrastructure in Ireland.

Data collection is ongoing, and preliminary findings will be presented at the November conference. The results will provide community-informed insights into the factors that facilitate or hinder research participation among people affected by HD in Ireland. BRIDGE-HD-IE aims to inform more inclusive recruitment strategies and research practices grounded in lived experience, with relevance for other regions where HD research infrastructure is continuing to develop.

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# A retrospective review of the prevalence of carpal tunnel syndrome (CTS) in Transthyretin amyloidosis patients in a Tallaght University Hospital (TUH) cohort.

Helen Connaughton[1], Jordan Wilkinson[2], Colin Clark[1], Marianna Kalaszi[1], Geoff Haughton[1], Emer Joyce[2], Mike Alexander[1], Claire Davidson[1], Sinead M Murphy[1].

[1] Tallaght University Hospital. [2] Mater Hospital

**Background:** Amyloidosis is a group of heterogeneous conditions characterised by infiltration of insoluble, fibrillar protein in tissues and organs. Transthyretin amyloidosis (ATTR) is the most common form of amyloidosis and can be either hereditary (variant) or acquired (wild-type). ATTR typically presents with peripheral neuropathy and cardiomyopathy. Without treatment survival is limited to 2-6 years from diagnosis. Several studies have highlighted the relationship between carpal tunnel syndrome (CTS) and ATTR. However biopsies taken during carpal tunnel decompression are not routinely sent.

**Methods:** Retrospective review of ATTR patients who attended TUH from 2018 to present. Information was obtained through patients' medical records and internal database systems.

**Results:** 88 individuals with ATTR were identified. 81 (92%) had hereditary ATTR (ATTRv) and 7 (8%) had wild-type (ATTRwt). Of ATTRv patients, mean age was 60 years; 38 (47%) were male; 51 (63%) had a history of CTS and 31 (61%) of these had CTS prior to ATTR diagnosis; 14 (17%) had decompression; mean duration from CTS symptoms to diagnosis of ATTR was 7.1 years. In ATTRwt patients, mean age was 81.5 years; 5 (71%) were male; 5 (71%) had a history of CTS and 100% of these had symptoms prior to ATTR diagnosis with a mean time to diagnosis of 7.2 years. 4 (57%) had decompression.

**Conclusion:** CTS is a frequent precursor of ATTR. ATTR is a progressive condition that, without treatment, leads to premature death. Initiation of disease-modifying therapy earlier, which is associated with slowing progression, improving outcomes and improved survival, highlights the importance of accurate diagnosis. Prospectively we are routinely sending specimens for amyloid testing at the time of CT decompression.

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# Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia is Associated with Systemic Immune and Metabolic Dysregulation

Julie C. Worrell[1], Helen O'Brien[1,2], Kathryn Duvall[1], Donal O'Malley[1,2] , Niamh Boyle[1,2], Janet McCormack[3], Lisha Joshi[1], Atia Batool[1], Megan McKean[1], Sarah H. Forde[1], Madita Hovel[1], Ronan Murray,[1] Michael P. Keane,[1,2] Aurelie Fabre[1,3], Adam J. Byrne[1] and Cormac Mc Carthy[1,2]

[1] UCD Conway Institute, School of Medicine, University College Dublin, Ireland. [2] Department of Respiratory Medicine, St. Vincent's University Hospital, Dublin, Ireland. [3] UCD Conway Institute, Research Pathology Core, University College Dublin, Ireland

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare lung disorder with limited therapeutic options and poorly defined pathogenesis. Abnormal proliferation of pulmonary neuroendocrine cells (PNECs) drives tumourlet formation and lymphocytic infiltrates, yet the role of immune cells in disease development is unclear.

We hypothesised that systemic immune perturbations and metabolically dysregulated lymphocytes shape the DIPNECH lung microenvironment and contribute to PNEC dysfunction.

Peripheral blood immune profiling showed preserved granulocyte and myeloid populations in DIPNECH patients (n=13), alongside a significant reduction in circulating T and B lymphocytes compared with age- and sex-matched controls (n=10). Despite reduced frequencies, DIPNECH T cells exhibited altered activation and metabolic phenotypes. $CD4^+$ T cells had increased expression of CD71, a key regulator of cellular iron uptake, while $CD8^+$ T cells expressed higher levels of CD69, consistent with early activation. Metabolic profiling using SCENITH revealed a significant shift in DIPNECH $CD8^+$ T cells towards increased fatty acid oxidation and reduced glucose dependence, indicating metabolic reprogramming relative to controls. In lung tissue, DIPNECH tumourlets ($CgA^+$) clustered around small bronchioles and were closely associated with lymphocytic infiltrates. Within these lesions, altered expression of proteins regulating cell proliferation, metabolism and mTOR signalling (RPS6 and 4EBP1) was observed, supporting a role for immune–epithelial crosstalk in promoting PNEC survival and proliferation.

Collectively, this suggests coordinated systemic and tissue-specific immune dysregulation in DIPNECH implicating immune-metabolic reprogramming as a potential driver of disease pathogenesis.

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# Evidence for Genetic Compensation in Intraflagellar Transport Pathways in *C. elegans*.

Kameshwari Tata[1], Oliver E Blacque[1].

[1] UCD School of Biomolecular and Biomedical Science, University College Dublin, Dublin, Ireland.

Primary cilia are microtubule-based organelles facilitating sensory and signaling roles for tissue development and homeostasis. Ciliary formation and function depend highly on intraflagellar transport (IFT), a conserved bidirectional protein delivery and removal system that operates along the ciliary microtubules. IFT trains are composed of three cargo-binding subcomplexes: IFT-A (6 proteins), IFT-B (12 proteins), and the BBSome (8 proteins). Mutations in IFT-related genes cause ciliopathies, a collection of over 20 distinct disorders affecting many tissues and organs. Despite progress, the mechanisms underpinning the extreme clinical heterogeneity and phenotypic penetrance observed in ciliopathies remains poorly understood.

To investigate conserved ciliopathy mechanisms, we performed whole-animal RNA-seq in the nematode *Caenorhabditis elegans* to assess transcriptomic changes resulting from ciliopathy gene disruption. Our data revealed that loss-of-function mutations in several ciliopathy genes cause broad-scale transcriptomic alterations. Of particular interest was that IFT gene disruption causes transcriptional upregulation of other IFT genes. For example, the *bbs-2(ok2053)* deletion mutant exhibits upregulation of eight IFT genes across the IFT-A, IFT-B and BBSome module (*ift-139*, *dyf-1*, *ift-40*, *ift-54*, *ift-81*, *ift-88*, *ift-80*, and *bbs-1*). These *bbs-2* mutant data were validated using qPCR, and an *osm-5::sl2::h2b::gfp* fluorescence knock-in allele that reports on endogenous *osm-5* expression levels within individual ciliated sensory neurons. Validated data was also obtained for worms carrying lof mutations in additional BBSome genes (*bbs-1*, *bbs-5*, *bbs-7*, and *bbs-8*) as well as *ift-81* (IFT-B). Using a knock-in GFP fusion reporter for *ift-74* (IFT-B), we show that mutants with increased levels of IFT gene transcript correlate with increased levels of the translated protein. Notably, in lof mutants for non-IFT ciliopathy genes (eg. those functioning at the ciliary base transition zone compartment), IFT gene mRNA and protein levels are not increased, indicating that the phenomenon we observe is specific to the IFT pathway.

Together, these data indicate that a transcriptional adaptation mechanism exists in *C. elegans* to potentially compensate for genetic lesions in IFT genes. Research is ongoing to investigate the mechanisms underpinning this compensation, and whether the adaptation impacts cilium structure and function.

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# Novel variants in ATP6V0a1 are associated with dysfunction of autophagy, nutrient sensing and mitochondria

Maria Borja-Gonzalez[1,2], Anthony Sannicandro[1,2], Brian McDonagh[1,2], Nicholas N Allen2,3, Katarzyna Goljanek-Whysall[1,2]

[1] School of Pharmacy and Biomedical Sciences, University of Galway, Galway, Ireland. [2] Galway RNA Research Cluster, University of Galway, Galway, Ireland. [3] School of Medicine, University of Galway, Galway, Ireland

The Vacuolar H+-ATPase is a multi-subunit proton pump involved in the acidification of lysosomes during autophagy. ATP6V0a1, a gene implicated in neurodevelopmental and neurodegenerative disease, encodes the a1 subunit of this proton pump. Whilst these disorders predominantly affect the nervous system, milder phenotypes may be associated with hypotonia and mobility impairments. The importance of variants of this gene outside of the nervous system is largely unknown, as well as processes affected by the variants associated with milder neurodevelopmental phenotypes.

We investigated the role of ATP6V0a1 in neuronal and muscle homeostasis by siRNA-mediated knockdown and overexpression of wild type or mutant ATP6V0a1 discovered in patients, in human myoblasts and neurons, as well as in patient-derived fibroblasts. In addition to lysosomal accumulation and changes in nutrient sensing pathways, changes in autophagy proteins, e.g. p62 and mitochondria-associated proteins, such as mitofusins, Pgc1a, or TOM20, were observed as a result of knockdown or mutation. Differences in morphology of mitochondria observed by Mitotracker staining and TEM were also observed in addition to mtDNA release. RNA-Seq revealed changes in proteins associated with innate immunity response. NFkB activation was also significantly reduced following ATP6V0a1 knockdown which may be associated with lysosome sensing of pro-inflammatory cytokines as a result of ineffective lysosomal acidification by Vacuolar H+-ATPases. Myogenic and neurogenic potential was negatively influenced by ATP6V0a1 knockdown or variant expression. Together, these data support the critical nature of ATP6V0a1 function in muscle and neuronal homeostasis and suggest another layer of pathogenesis in patients with V-ATPase conditions.

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# Assessing knockdown oligonucleotides in *Drosophila* as a therapeutic strategy for the treatment of severe ATL1-HSP

Lawless K[1], O'Sullivan NC[1]

[1] UCD Conway Institute of Biomolecular and Biomolecular Research, University College Dublin

Atlastin-1 associated Hereditary Spastic Paraplegia (HSP) is a rare inherited neurological disorder causing progressive lower-limb spasticity and weakness. It is the second most common form of autosomal dominant HSP and is caused by mutations in the Atlastin-1 (ATL-1) gene. Recently, several mutations in Atlastin-1 have been linked to a more severe form of the disease than is typically seen. Because a single faulty copy of the ATL-1 gene is sufficient to cause disease, my project aims to investigate whether it is possible to selectively silence the mutant copy while leaving the healthy copy unaffected. This approach uses small RNA molecules (siRNAs) designed to target the mutant copy in a fruit fly (*Drosophila melanogaster)* model of disease.

To identify siRNAs specifically targeting mutant ATL-1, I carried out a genetic screen using *Drosophila* S2 cells. These cells were engineered to contain fragments of both the mutant and the healthy versions of the Atlastin-1 gene. I used these cells to test the effect of multiple siRNAs on both the mutant and the healthy (wild-type) ATL-1 gene. I identified five promising siRNAs that silenced mutant but not wild-type ATL-1.

To further evaluate these five siRNAs, I examined their effect on protein levels in *Drosophila* S2 cells. Engineered constructs expressing Atlastin-1 proteins contained molecular tags that allowed the mutant and healthy proteins to be distinguished and measured separately. These findings identify candidate siRNAs for future testing and represent an important step towards developing allele-specific therapies for severe Atlastin-1 associated HSP.

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# Patient reported outcomes as a part of The Core Registry (European Registry for Rare Bone and Endocrine conditions) data collection.

Kyrylo Lebed[1], Rachel Crowley[1,2,3], Daniel Mikula[1], Anila Varghese[1,2], Athira Kurian[1,2]

[1] Rare Disease Research Catalyst Consortium, University College Dublin, Ireland. [2] St. Vincents University Hospital, Dublin, Ireland.
[3] Rare Disease Clinical Trial Network, University College Dublin, Dublin, Ireland.

A rare disease is defined as a life-threatening or chronic disease that impacts on fewer than 5 out of every 10,000 people. Rare diseases, estimated to number between 5,000 and 8,000, collectively affect 27-36 million individuals across the European Union. Due to the low prevalence of individual rare diseases and the small number of affected patients within each EU Member State, knowledge of their pathophysiology and natural history remains limited.

The twenty-four European Reference Networks (ERNs) were established to address these gaps by connecting healthcare professionals and researchers across Europe.

SVUH has participated in the Core Registry (European Registry for Rare Bone and Endocrine conditions) since January 2025. 157 patients with rare bone and endocrine conditions have given informed consent for registry inclusion (to July 2026). As a part of the informed consent procedure the patients were offered the choice to provide their email for patient access to the registry. 146 (92.9%) of SVUH patients provided their email in order to add their own patient reported outcomes to the registry; 47 (32.1%) of 146 have activated their account. This marker of engagement by patients with rare conditions to contribute their own experience indicates a need for wider implementation of, and need to support, patient centred approaches to data capture in ERN registries. This will be enabled by greater involvement of health care facilities of Ireland with rare disease networks.

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# An introduction to ASTRAL: The **A**ngelman **S**yndrome **Tra**ns**l**ational Research Study

LM Loughlin[1,2], R Hollinshead[1], H Scully[1], D Fahy[1], L Dooley[1], A Beegan[1], A Collins[1,3], S Byrne[1,2,4], S O' Connell[1,2,5], J McBrien[1,3]

[1] Paediatric Academic Health Science Centre, Children's Health Ireland, Dublin. [2] Department of Paediatrics, Royal College of Surgeons, Dublin. [3] Department of Neurodisability, Children's Health Ireland, Dublin. [4] Department of Neurology, Children's Health Ireland, Dublin. [5] Department of Endocrinology, Children's Health Ireland, Dublin.

**Background:** Angelman Syndrome (AS) is a rare neurodevelopmental, congenital imprinting disorder that affects 1 in 10,000-25,000 births. It is characterised by developmental delay (particularly expressive language), epilepsy, movement disorders, maladaptive behaviours, sleep and gastrointestinal manifestations. Limited information exists on AS prevalence among Irish children, the care and supports accessed by families, or the broader experience of living with the condition in Ireland including the economic impact.

**Proposed Study Design:** ASTRAL is a cross-sectional study enrolling children and young people aged 0-18 years living in the Republic of Ireland with a confirmed diagnosis of AS. Data are collected prospectively via questionnaires across domains including: demographics; household and care provision; diagnostic journey; medical history; sleep; behaviour; resource utilisation and quality of life using validated instruments. Data are entered directly into REDCap, a secure online research platform, by families and the research team. CHI REC study approval (REC-656-25). ASTRAL operates as a silo within the CINDI registry.

**Barriers Imposed by GDPR to Rare Disease Research:** Strict applications of EU GDPR legislation to the design of research for individuals living with rare genetic disorders translates to stricter interpretations of data access and an increased burden for researchers and participating families alike.

Small RD populations and scare research resources, make efficient research, cross-border collaboration, and knowledge sharing essential. Thoughtful study design, early PPI involvement and engagement with international academic collaborators are critical. Our experience of securing a data sharing agreement for the use of an AS-specific assessment "MOOD-AS" is demonstrative of this challenge.

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# Retrospective Review of Bleeding Outcomes in Patients with Jacobsen Syndrome

Luke Myers[1,2], Dr. Saad Ahmed[1,2], Dr. Beatrice Nolan[1]

[1] Paediatric Coagulation Centre, Children's Health Ireland. [2] School of Medicine, University College Dublin, Dublin, Ireland.

**Background:** Jacobsen syndrome (JBS) is a rare (1/100,000) disorder caused by partial deletions of the long arm of chromosome 11. More than 90% of affected individuals have Paris-Trousseau syndrome (PTS), a thrombocytopenia/platelet disorder predisposing to both spontaneous and perioperative bleeding. The identification and management of Paris-Trousseau syndrome is a key component of the management of Jacobsen syndrome.

**Objectives:** To review the incidence and management of spontaneous and surgical bleeds in patients with PTS.

**Methods:** We reviewed the records of all patients with JBS and documented key clinical features, laboratory results, bleeding scores using the International Society of Thrombosis and Haemostasis Bleeding Assessment Tool (ISTH BAT), as well as incidence and management of surgical and non-surgical bleeding.

**Results:** 10/12 patients with JBS had PTS with 11/12 having thrombocytopenia. Only 9/12 had abnormal platelet function/nucleotide studies. 8/12 had documented significant bleeding with epistaxis being commonest. Across 30 surgical/procedural episodes, only 3 (in 2/12 patients) had a bleed. DDAVP was the most common choice for haemostatic prophylaxis (12/30). All 3 bleeding episodes occurred in procedures where haemostatic prophylaxis had been administered. The median ISTH-BAT score was 2.5 with 6/12 meeting the paediatric abnormal cut-off of ≥3.

**Conclusions:** Despite frequent laboratory abnormalities, severe bleeding was relatively uncommon, suggesting laboratory abnormality alone is an imperfect predictor of clinically significant bleeding. All documented procedural bleeds occurred despite prior haemostatic prophylaxis, possibly suggesting that standard cover may not fully mitigate bleeding risk in higher-risk procedures.

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# Retrospective Review of Haematological Abnormalities and Bleeding Outcomes in Patients with Noonan Syndrome

Luke Myers[1,2], Dr. Saad Ahmed[1,2], Dr. Beatrice Nolan[1]

[1] Paediatric Coagulation Centre, Children's Health Ireland. [2] School of Medicine, University College Dublin, Dublin, Ireland.

**Background:** Noonan syndrome (NS) can be associated with haematological abnormalities and bleeding diathesis. Detection of coagulopathy and appropriate intervention is a crucial part of management.

**Objectives:** To review the incidence and management of haematological abnormalities, spontaneous and surgical bleeds in paediatric NS patients.

**Methods:** We reviewed the records of patients with NS with haematological abnormalities and documented clinical features, laboratory results, bleeding scores by International Society of Thrombosis and Haemostasis Bleeding Assessment Tool (ISTH –BAT), surgical and non-surgical bleeding events, and their management.

**Results:** 17 NS patients with haematological abnormalities were identified. Coagulation profile was abnormal in 12/17 and 10/17 had at least one clotting factor deficiency. FBC was abnormal in 11/15 that were tested, platelet function studies abnormal in 7/15 that were tested, and VWF screen abnormal in 3/17. 7/17 had significant bleeding. There were 22 procedures performed in 10 patients, with 1 bleeding complication. Only 2 of 22 procedures had haemostatic cover with tranexamic acid. The single documented bleeding complication occurred in an uncovered procedure. The median ISTH-BAT score was 1. Only 3/17 met the paediatric abnormal cut-off of ≥3.

**Conclusions:** Laboratory findings were poorly associated with bleeding, with no single laboratory abnormality reliably predicting bleeding. Procedural haemostatic cover was rarely used despite high rates of laboratory abnormality. The only bleeding complication occurred in an uncovered procedure, which may warrant prospective evaluation of prophylactic tranexamic acid.

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# Methods for Incorporating Lived Experience Perspectives in Rare Disease Core Outcome Set Long-List Development: A Descriptive Narrative Review

Marci Kay Livingston[1-4], Rachel Crowley[4,5], Brona Kearney[4,6], Eva Lally[4,6], Stephanie Skeffington[4,6], Katie Robinson[1-3,7], Elaine Toomey[8,9], Cassandra Dinius[4,5,10]

[1] Health Research Board, Trials Methodology Research Network. [2] School of Allied Health, University of Limerick. [3] Health Research Institute, University of Limerick. [4] Rare Disease Clinical Trial Network. [5] School of Medicine, University College Dublin. [6] PPI Partner. [7] Ageing Research Centre, University of Limerick. [8] Centre for Health Research Methodology, School of Nursing and Midwifery, University of Galway. [9] Institute for Clinical Trials, College of Medicine, Nursing, and Health Sciences, University of Galway. [10] Health Research Charities Ireland (HRCI)

**Background:** Core Outcome Sets (COS) are agreed, standardised minimum outcome sets for clinical trials. Development typically begins by generating a comprehensive long-list of potential outcomes through literature reviews and, in some cases, qualitative research or primary studies involving people with lived experience (PWLE). Although methodological guidance emphasises PWLE involvement throughout COS development, how their perspectives inform long-list generation remains unclear. Rare diseases provide a practical starting point. Because clinical evidence is limited, researchers often rely on patient experience, which can provide real-world examples of how PWLE shape early outcome lists. This review aims to map and describe how PWLE perspectives have been incorporated into rare disease COS long-list development and the extent to which their contributions can be identified.

**Methods:** A descriptive narrative review will examine rare disease COS registered in the Core Outcome Measures in Effectiveness Trials (COMET) Initiative database. Rare diseases will be identified using European Union definitions and Orphanet classification. Two independent reviewers will extract data on study characteristics, long-list development methods, and mechanisms of PWLE involvement.

**Results:** The review will describe the characteristics of rare disease COS, the methods used to generate long-lists, and the extent and of PWLE involvement. Where reported, examples of outcomes specifically attributed to PWLE input will be presented.

**Conclusions:** Currently in progress, this review will comprehensively map the reporting and practice of PWLE involvement during early-stage COS development for rare diseases. Findings will contribute to the methodological evidence base for incorporating lived-experience perspectives into long-list generation and inform future COS development.

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# Irish National Hereditary Transthyretin Amyloidosis Epidemiological Study

Marianna Kalaszi[1], Helen Connaughton[1], Smitha Samuel[1], Colin Clarke[1], Emer Joyce[2], Sinéad M Murphy[1,3]

[1]Department of Neurology, Tallaght University Hospital, Dublin. [2]Department of Cardiology, Mater Misericordiae University Hospital, Dublin. [3]Academic Unit of Neurology, School of Medicine, Trinity College Dublin

**Background**: Hereditary transthyretin amyloidosis (ATTRv) is a late-onset, progressive, multisystem disorder. The T60A (p.T80A) variant is the most prevalent mutation in Ireland and is considered a founder ATTRv mutation of Irish origin. However, the true prevalence of ATTRv in Ireland is poorly defined and almost certainly underestimated, as the only previous epidemiological study was conducted in 1995 in Northwest Donegal. With a recognised founder variant, evidence of regional clustering, and frequent underdiagnosis due to its heterogeneous clinical presentation, there is a clear need for contemporary population-based data to support timely diagnosis and early access to treatment.

**Methods**: This national, population-based, cross-sectional study will include adults aged ≥18 years resident in the Republic of Ireland. Cases will comprise individuals with known genetically confirmed TTR variants and clinically diagnosed ATTRv, as well as newly identified mutation carriers, including asymptomatic relatives detected through cascade family screening. Case ascertainment will use multiple overlapping sources: the Irish Expert Amyloidosis Network, tertiary neuromuscular and regional neurology services, clinician referrals from hospital and community settings, patient support organisations, and structured family-based genetic screening. Standardised case-report forms will collect demographics, phenotype, diagnostic pathway, treatment, and family history. Prevalence will be expressed per 100,000 adults, and age- and sex-specific penetrance will be estimated as the proportion of mutation carriers with clinical disease.

**Conclusion**: This study will provide robust national estimates of ATTRv prevalence and penetrance in Ireland, and define the geographic and clinical spectrum of disease, thereby informing service planning, genetic counselling, and early intervention strategies.

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# The role of the ERN Hub in supporting rare disease care in paediatric hospitals in Ireland

Mariya Stepanova[1], Cathy Bergin[1], Anthony Ryan[1], Hamdi Hassan [1], Monique Saclolo [1], Chiamaka Maduako [1], Jennifer Keogh [1], Aoife Dillon [1], Jenny McNulty [1], Joana Campos [1], Suzanne Bradley [1], Caitriona O'Connor [1], Ciara McDonnell [1]

[1] Children's Health Ireland, Dublin, Ireland

Children's Health Ireland (CHI) is committed to delivering state-of-the art care for children living with rare diseases in Ireland. As part of its commitment, CHI has launched the European Reference Networks (ERNs) Hub and is an active member in ERN initiatives.

CHI currently represents paediatric patients in 16 of the 24 ERNs and is actively striving to expand its membership to better paediatric rare disease care in Ireland.

To support CHI's mission at a national and European level, 6 ERN data managers and 6 ERN clinical care coordinators have been recruited into the new CHI ERN Hub. Significant advancements have been made towards increasing CHI's involvement in the ERN registries to represent Ireland's paediatric patient cohort at a European level. The CHI ERN Hub identified the core datasets for all paediatric rare disease conditions within the scope of the 13 ERN Registries, and implemented ongoing surveys on registry readiness and percentage dataset completion.

As part of the CHI ORPHAcode integration project, the ERN Hub has assigned ORPHAcodes to 90% of rare diseases to-date to support standardised rare disease reporting, including diagnosis cross-mapping to SNOMED. Unified procedures, policies and templates have also been developed.

The ERN Hub has completed the implementation of the Clinical Patient Management System (CPMS) in CHI and cross-border complex case discussion with partner hospitals has commenced.

In conclusion, the CHI ERN Hub is designing and implementing new policies and procedures to improve clinical care for children with rare diseases in Ireland.

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# Natural History of Friedreich's Ataxia in the Irish Population

Mary Kearney, Edwin E. Pabilona Jr, Colin Clarke, Petya Bogdanova-Mihaylova, Richard Walsh, Sinead M Murphy.

Department of Neurology, National Ataxia Centre, Tallaght University Hospital

**Background:** Friedreich's ataxia (FRDA) is the most common autosomal recessive ataxia worldwide. Symptoms typically begin around puberty, although approximately one-third of individuals are diagnosed after 20 years of age.

The National Ataxia Clinic at Tallaght University Hospital (TUH) provides a combined Neurology and Cardiology service for individuals with FRDA. It is the only Irish site participating in the international Friedreich Ataxia Global Clinical Consortium UNIFIED Natural History Study (UNIFAI).

**Aims:** The UNIFAI study seeks to standardise disease documentation, characterise disease progression, identify predictors or modifiers of disease, define meaningful outcome measures, and improve readiness for future clinical trials.

**Methods:** We performed a cross-sectional review of UNIFAI participants. We collected variables including age at symptom onset, clinical and genetic diagnosis. We reviewed disease severity, rate of disease progression.

**Results:** Sixty-six participants are currently registered, with longitudinal observational data extending up to 12 years (13 annual visits) for 19 individuals. Thirty-four participants (51%) are female and 32 (49%) male, with an age range of 17–72 years. Twelve participants (18.2%) were diagnosed after the age of 20. In this subgroup, the mean time to diagnosis was 13.3 years, compared with 1.5 years among those diagnosed between 11 and 20 years.

**Conclusions:** The registry provides a valuable insight into natural history of FA.

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# Tuberous Sclerosis Complex (TSC) Making the Invisible Visible

Mary Vasseghi[1,2,5,6] Claire Behan[1,2,3], Catherine Darker,[4] Eilish Burke[1], Miriam Galvin[1] & Colin P. Doherty[1,2,3].

[1] Academic Unit of Neurology, School of Medicine, Trinity College Dublin (The University of Dublin), Dublin, Ireland. [2] St James's Hospital, Dublin, Ireland. [3] FutureNeuro, SFI Research Centre, Dublin, Ireland. [4] Discipline of Public Health & Primary Care, School of Medicine, Trinity College Dublin. [5] TAND,Consortium (Vrije Universiteit Brussel (VUB), Belgium. [6] Rare Disease Clinical Trial Network, University College Dublin, Ireland

Tuberous Sclerosis Complex (TSC) is a rare approximate 1:6,000 birth incidence, genetic disease with a wide variability of physical and neuropsychiatric symptoms. Patients require lifelong care from multiple healthcare specialities, for which International TSC consensus recommendations exist. There is a paucity of information regarding the healthcare of this group in The Republic of Ireland (ROI).

**Purpose:** To identify the gaps in, barriers to, and facilitators of access to standardised healthcare in people living with TSC (PLW TSC) in the ROI.

**Methods**:

1. Clinical audits in twelve epilepsy centres in the ROI measured baseline care of eighty-three PLW TSC against UK, TSC clinical guidelines.
2. The lived experience of (PLW TSC) and their families was explored through thirty-four semi structured interviews.
3. The perspectives of twenty-four healthcare professionals caring for PLW TSC was explored through semi structured interviews.
4. The burden of illness and quality of life of PLW TSC was recorded through an anonymous survey.

Data was anonymised and analysed in Trinity College Dublin.

**Results:** The severity and extent of TSC symptoms especially epilepsy and Tuberous Sclerosis Associated neuropsychiatric symptoms, influenced the lives of PLW TSC and their families. The burden was frequently high while the quality of life was low. The healthcare of PLW TSC appeared fragmented and challenging for those affected by TSC and their healthcare providers. There was no evidence of formal coordinated disease surveillance except in one adult service. There was consensus that a coordinated approach to the delivery of personalised care, adhering to TSC international recommendations was required.

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# CD163$^{-}$HLA-Dr$^{low}$ Monocytes and Alveolar Macrophages are increased in frequency in Idiopathic Pulmonary Fibrosis

Megan McKean[1,2], Kathryn Duvall[1], Julie C. Worrell[1], Niamh Boyle[1,2], Helen O'Brien[1,2], Donal O'Malley[1,2], Atia Batool[1], Lisha Joshi[1], Ronan Murray[1], Sarah H. Forde[1], Cormac McCarthy[1,2], Adam J. Byrne[1], Peter Doran[1,2]

[1]School of Medicine, University College Dublin, Ireland. [2]UCD Clinical Research Centre, St Vincent's University Hospital, Dublin 4, Ireland.

**Introduction:** Idiopathic Pulmonary Fibrosis (IPF) is an interstitial lung disease with poor survival outcomes. Monocytes have shown utility as prognostic biomarkers of IPF progression [1] and phenotyping of the monocyte subsets and alveolar macrophages may provide insight into their mechanistic relevance to IPF.

**Aims:** The objective of this study is to phenotype monocyte subsets and alveolar macrophages to identify their mechanistic role in IPF pathogenesis.

**Methods:** Blood leukocytes from IPF patients (n = 17) and healthy controls (n = 11), and bronchoalveolar lavage (BAL) cells from IPF patients (n = 5) and healthy controls (n = 5) were obtained from St Vincent's University Hospital in Dublin and were analysed using flow cytometry. Data was analysed in R software using Mann-Whitney U-tests and two-sample t-tests.

**Results:** Of the monocyte subsets, classical and intermediate monocytes with a CD163$^{-}$HLA-Dr$^{low}$ phenotype were increased in IPF patients compared to healthy control subjects ($p = 0.022$ and $p = 0.0029$, respectively). This agrees with a recent study by Karampitsakos, et al. (2025), which showed an increase in CD14$^{+}$CD163$^{-}$HLA-Dr$^{low}$ monocytes in IPF. In addition to this, the present study showed an increase in CD206$^{+}$CD163$^{-}$HLA-Dr$^{low}$ alveolar macrophages ($p = 0.02$).

**Conclusion:** Further studies will be focus on assessing the role of this alveolar macrophage phenotype in IPF pathogenesis.

[1] Kreuter M, Lee JS, Tzouvelekis A, Oldham JM, et al. (2021). Monocyte Count as a Prognostic Biomarker in Patients with Idiopathic Pulmonary Fibrosis. *American Journal of Respiratory Critical Care Medicine*, 204(1):74-81.

[2] Karampitsakos T, Jia M, Tourki B, Fatima Z, et al. (2025). The transcriptome of CD14$^{+}$CD163$^{-}$HLA-Dr$^{low}$ monocytes predicts mortality in Idiopathic Pulmonary Fibrosis. *European Respiratory Journal*, 2500804.

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# Patient-centred care, the patient voice and professional identity formation – our students reflect on their 'Rare Genetic Disease' learning journey.

Niamh Banville[1], Paula Byrne[1]

[1] UCD School of Medicine, Dublin, Ireland

Rare disease education and training, including that for undergraduate medical students, is a key area addressed by the National Rare Disease Strategy 2025-2030, which aims to improve the care of the estimated 300,000 people living with a rare disease in Ireland. The School of Medicine at University College Dublin offers an optional module on 'Rare Genetic Diseases' to third-year undergraduate medical students. This module provides a reflective learning experience and incorporates presentations delivered by stakeholders from the rare disease world, including patients, patient advocacy groups, clinicians, researchers, and the pharmaceutical industry. The module is GPA neutral, limited to 35 students per cohort, and is consistently oversubscribed. Students complete a journal, reflecting on their learning journey. The overall sentiment of student feedback is consistently positive.

We performed content analysis of anonymised student reflective diaries, including a thematic analysis, (Braun and Clarke, 2006) using Nvivo software, to explore the educational impact of the module.

Following completion of the module, students demonstrated increased awareness of how common rare diseases are collectively. They also show an enhanced understanding of the challenges faced by patients and families impacted by rare diseases, the resources available to support patients and clinicians, and the broader rare disease landscape including issues around drug development, clinical trials and pharmacoeconomics.

Importantly, student diary entries reveal that learning goes beyond knowledge acquisition and demonstrate an appreciation for patient-centred care, the importance of the patient voice and the influence of these on their professional identity formation in the preclinical stage of the curriculum.

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# The Role of CCL2 and IL-6 in Fibroblast–Macrophage Crosstalk During Fibrosis.

Oriana Henry[1], Kathryn Duvall[1], Adam Byrne[1], and Cormac McCarthy[1,2]

[1] UCD School of Medicine, Dublin, Ireland. [2] St Vincent's University Hospital, Dublin 4, Ireland

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic lung disease characterised by excessive extracellular matrix deposition and irreversible loss of lung function(1). Although fibroblasts and macrophages contribute to IPF pathogenesis, the role of fibroblast-derived soluble mediators in regulating macrophage phenotype remains incompletely understood(2). This study investigated whether conditioned media from fibrotic cocktail-stimulated primary human lung fibroblasts (HLFs) altered human airway macrophage-like (hAMLs) cells. HLFs were stimulated with a fibrotic cocktail for 72 hours. Morphology, viability, cytotoxicity, IL-6 and CCL2 secretion, and profibrotic gene expression were assessed using microscopy, MTT and LDH assays, ELISA, and RT-qPCR. Conditioned media were subsequently applied to hAML cells to evaluate morphology, IL-6, CCL2 and MMP7 secretion, and metabolic and functional gene expression. Fibrotic cocktail stimulation altered HLF morphology and induced a significant but transient increase in IL-6 secretion without affecting viability or cytotoxicity. CCL2 secretion and profibrotic gene expression were not significantly altered, although COL1A1 expression was higher following stimulation. The study was underpowered to determine whether this represented a true biological effect. Conditioned media from stimulated HLFs did not significantly alter hAML morphology, cytokine secretion, or metabolic and functional gene expression. Under the experimental conditions used, fibroblast-derived soluble mediators alone did not induce measurable macrophage changes. These findings highlight the complexity of fibroblast-macrophage communication in IPF and the need for more physiologically relevant models incorporating robust fibroblast activation and direct cell-cell interactions.

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# Developing a Microfluidic Organ-On-Chip Platform for Duchenne Muscular Dystrophy and Scoping an Art+Science Protocol for Public Patient Involvement.

Rucha Benare[1], Dympna Mulroy[2], Oran D. Kennedy[1]

[1] Royal College of Surgeons in Ireland, Tissue Engineering Research Group. [2] Muscular Dystrophy Ireland

**Background:** In Duchenne Muscular Dystrophy (DMD), dystrophin loss alters muscle tissue, compromising movement. New drugs are in the pipeline, but preclinical models often translate poorly, and conventional culture cannot recreate the disease environment. Organ-on-chip (OoC) models offer physiologically relevant platforms for drug-testing. Their technical complexity, however, can stall patient involvement and knowledge of these developments. Public Patient Involvement (PPI) is now seen as an important contribution in these early developmental stages of new technology.

**Methods:** OoC models were designed and fabricated in-house using 3D-printing technology and soft lithography with PDMS (a biocompatible polymer), developing a 2.5-week design-to-device timeline. This enabled iteration across a 52-design library that varied channel geometry, wall configuration, pillar arrangement and chamber architecture. Human bone marrow stromal cells were seeded in the device to test robustness and biocompatibility, with attachment and morphology assessed by brightfield microscopy. In parallel, Exploratory PPI art+science salons were scoped via PPI Ignite engagement and MDI gatherings, and feedback on developing them further was collected.

**Results:** OoC devices were fabricated reproducibly, with independently addressable inlets maintaining fluid compartments across a micropillar barrier. Cells remained attached and morphologically intact for eight days, establishing the muscle-culture window. In parallel, PPI activities were initiated, through which contributors will shape how this work is discussed, developed, and disseminated within the MD community.

**Conclusion:** We report in-house fabrication capability, a design library for rare-disease OoC, and an involvement protocol running across the research cycle. Engagements have started, and work will continue on understanding how to build DMD-patient-specific input into the process.

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# Autosomal recessive disorders in the Sinti population of Lombardy: a single-centre experience

Simone Carbonera[1], Marta Carboni[1], Gaia Visani[1], Marta Melfa[1], Gabriela Anaya[1], Maria Chiara Montalbano[1], Benedetta Inzoli[1], Silvia Kalantari[1,2], Enza Maria Valente[1,3], Fabio Sirchia[1,2]

[1] Department of Molecular Medicine, University of Pavia, Pavia, Italy. [2] Medical Genetics Unit, Department of Diagnostic Medicine, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. [3] Neurogenetics Research Center, IRCCS Mondino Foundation, Pavia, Italy

Sinti is the self-assigned name for a large subgroup of the Romani, the largest ethnic minority in Europe. Traditionally, Sinti communities practice endogamy and consanguineous marriage, which makes them uniquely vulnerable to autosomal recessive disorders. While other populations with similar customs, like Ashkenazi, have long been the focus of scientific attention, there are few studies about autosomal recessive disorders in Sinti communities. We aimed to share our experience treating Sinti patients to help clinicians develop a population-specific approach.

We reviewed clinical and genetic data about 28 Sinti patients who underwent genetic consultation in our centre from 2022 to 2026, comprising 10 couples presented for pre-conception screening.

We outlined our process to create a gene panel specific for the Lombard Sinti population, which currently includes two missense variants in ATP8B1 and HINT1, two intragenic deletions in MLC1 and MLYCD and a frameshift variant in ZNF469. The panel was gradually expanded as our experience with this population grew: each variant was included either after learning about it through family history and consulting genetic results provided by the families, or after it was found through genetic testing in our centre. Sinti patients that wish to undergo pre-conception screening in our centre are tested via Sanger sequencing for the single nucleotide variants and via MLPA for the intragenic deletions.

We believe sharing knowledge of population-specific variants may limit costs and time to diagnose inherited disorders which are rare in the general population but can be exceedingly common in closed communities.

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# Navigating Narrow Windows: A Researcher-Caregiver Perspective on Delayed Diagnosis and Invisible Burden in Rare Biliary Malignancy

Simrah Binte Sadique[1]

[1] UCD/MMUH and Family Caregiver

**Background:** Rare diseases frequently present with diagnostic uncertainty, fragmented referral pathways and limited evidence to guide urgent clinical decisions. A previously active 70-year-old man presenting with painless jaundice was diagnosed with advance cholangiocarcinoma. Interventional bottlenecks, specifically two failed ERCPs over two weeks before successful biliary drainage through PTBD, prolonged severe hyperbilirubinaemia and jeopardising eligibility for palliative chemotherapy.

**Objective:** To examine how interventional delays affected treatment eligibility and caregiver burden, evaluating structural gaps in rare-disease clinical pathways.

**Methods:** A reflective case study combined with a first-person caregiver narrative was used to examine the clinical pathway, treatment-related consequences and lived experience of care. The case was considered through the dual perspective of a rare-disease researcher and primary family caregiver.

**Key Findings:**

*Researcher perspective*: Procedural delays caused rapid health deterioration and consumed time-sensitive treatment windows, making the patient ineligible for palliative chemotherapy. The case highlights how patient access to systemic oncology is governed by interventional care coordination rather than disease biology alone.

*Caregiver perspective:* Managing complex post-procedural care, emergency transfers and fragmented communication created substantial emotional and financial burden. These impacts were largely invisible within conventional clinical documentation.

*Intersection:* Combining research expertise with lived experience enabled real-time patient advocacy while identifying critical patient- and caregiver-reported outcomes (PCROs) absent from routine clinical datasets.

**Conclusion:** Rare-disease research should examine pathway-related treatment delays alongside disease outcomes. Establishing rapid multidisciplinary referral networks and structured caregiver involvement is essential to prevent avoidable loss of treatment opportunities. Patient and caregiver perspectives should inform the outcomes measured in future clinical research and trial design.

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# Clinical characteristics of patients with Fibrous Dysplasia/McCune Albright syndrome: an international, multicenter cohort study using the European Registries for Rare Endocrine and Bone Conditions

Huisman SA[1], Bulaicon OO[1], Chapurlat R[2], Gensburger D[2], Cherenko M[1], Grasemann C[3], Iotova V[4], Javaid MK[5], Kassi E[6], Makras P[7], van der Meeren S[8], Soucek O[9], van Velsen EFS[10], van de Ven AC[11], Verroken C[12], de Witte PB[13], Yavropoulou M[14], Priego Zurita AL[1], Appelman-Dijkstra NM[1]

[1] Department of Internal Medicine, Division of Endocrinology, Leiden University Medical Center, Albinusdreef 2, Post box 9600, 2300 RC, Leiden, The Netherlands. [2] INSERM UMR 1033, Université Claude Bernard-Lyon 1, Service de Rhumatologie, Chu Edouard-Herriot, Lyon, France. [3] Department of Paediatrics-Katholisches Klinikum Bochum, Ruhr-University Bochum, Bochum, Germany. [4] Department of Pediatrics, Medical University of Varna, UMHAT "Sv. Marina", Varna, Bulgaria. [5] Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom. [6] Department of Biological Chemistry, Medical School, National University of Athens, 75 Mikras Asias Str., Goudi, Athens, 11521, Greece. [7] Department of Medical Research, 251 Hellenic Air Force & VA General Hospital, Athens 115 25, Greece. [8] Department of Ophthalmology, Leiden University Medical Center, Leiden, The Netherlands. [9] Department of Paediatrics, Second Faculty of Medicine, Charles University in Prague and Motol University Hospital, Prague, Czech Republic. [10] Department of Internal Medicine, Erasmus Medical Center, 3015 GD, Rotterdam, The Netherlands. [11] Department of Internal Medicine, Division of Endocrinology, Radboud University Medical Center, Nijmegen, The Netherlands. [12] Department of Endocrinology, Unit for Osteoporosis and Metabolic Bone Diseases, Ghent University Hospital, Ghent, Belgium. [13] Department of Orthopaedics, Leiden University Medical Center, Leiden, The Netherlands. [14] Endocrinology Unit, First Department of Propaedeutic and Internal Medicine, Medical School, National and Kapodistrian University of Athens, Athens 11527, Greece.

Fibrous dysplasia/McCune Albright Syndrome (FD/MAS) is a rare, non-hereditary genetic bone disorder with limited large-scale data on clinical characteristics.

This international, multicenter cohort study aimed to characterize a large FD/MAS cohort using data from the European Registries for Rare Endocrine and Bone conditions (EuRREB).

Between January 2023-September 2025, data was collected in a condition-specific module within EuRREB, including 694 patients (638 adults, 56 children) from 8 countries.

Monostotic FD (MFD) was most prevalent in adults (49.0%), whereas MAS predominated in children (36.8%). Median (IQR) age at diagnosis was the highest in monostotic FD (28.7 (17.8-44.9) years) followed by polyostotic FD (PFD) (22.8 (13.5-35.4) years) and MAS (6.7 (2.9-14.2) years). Median (IQR) diagnostic delay was 1.3 (0.4-4.6) years occurring mainly before first presentation at an expertise center. Craniofacial lesions were most common in MFD (47.6%), lower extremity was mostly affected in PFD (67.6%). Among craniofacial FD patients, 6.3% had impaired vision and 1.3% had optic nerve compression.

At first presentation, all bone turnover markers were elevated in 46.2% of MAS, 21.3% of PFD and 4.5% of MFD patients. Early age at diagnosis (OR 1.05, 95%CI 1.03-1.08), PFD (OR 2.59, 95%CI 1.41-4.76) and MAS (OR 3.02, 95%CI 1.34-6.76) were associated with fractures before first presentation, whereas female sex (OR 2.57, 95%CI 1.56-4.25) and PFD (OR 2.43, 95% CI 1.42-4.17) were associated with pain. Pain was more common for spine (83.3%) and rib lesions (77.8%) than craniofacial lesions (42.6%).

These results offer valuable insights into FD/MAS and can improve screening, diagnosing and therapeutic decision-making.

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# Development and testing of a Patient-Reported Experience Measure for rare diseases – Preliminary findings from the RD-PREM Project Phase 3 (a mixed methods study)

Suja Somanadhan[1], Stephanie Sangalang[1], Lucy Collins Stack[2], Jessie Dubief[3], Simone Dunn[2], Vicky McGrath[2]

[1] University College Dublin, School of Nursing, Midwifery and Health Systems. [2] Rare Diseases Ireland. [3] EURORDIS – Rare Diseases Europe

**Background:** People living with rare diseases (PLWRD) and carers may experience health inequalities due to delayed diagnoses, fragmented healthcare, and unmet psychosocial needs. One possible solution for addressing rare disease (RD) healthcare gaps is patient-reported experience measures (PREMs). These are standardised tools that assess what matters most to people with lived experience.

**Aim:** The aim of the larger RD-PREM project is to develop PREMs for assessing secondary and tertiary care for RDs, which could regularly be sent to PLWRD and carers by hospitals or states. The aim of Phase 3 is to test the RD-PREM questionnaire in Ireland.

**Methods:** We used a mixed method, multi-phase approach. Phase 1 (March – April 2025) was an online consultation with international experts and a prioritisation exercise to identify and rank healthcare domains relevant for RD care. Phase 2 (June 2025) involved focus groups with PLWRD and carers from Ireland. We used findings from Phase 1 and 2 to refine a PREM questionnaire for PLWRDs and carers. Phase 3 (April – September 2026) involves testing the new PREM questionnaire in Ireland. The questionnaire is anonymous, contains 70-80 questions, and is hosted on the Qualtrics© online survey platform. Participants, recruited via social media and signposting by hospitals and clinics, will rank each question using a five-point Likert scale.

**Expected Results:** Questionnaire testing and validation results will determine if the RD-PREM is a useful tool that can be upscaled for assessing RD care in Ireland. Findings will identify top-priority domains that should be addressed for RD care improvements.

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# Use of patient-centred outcome measures in orphan medicinal product reimbursement: Case studies from Ireland

Suja Somanadhan[1], Stephanie Sangalang[1], Lucy Collins Stack[2], Simone Dunn[2], Vicky McGrath[2]

[1] University College Dublin, School of Nursing, Midwifery and Health Systems. [2] Rare Diseases Ireland

**Background:** Reimbursement of orphan medicinal products (OMP) involves stakeholders working across sectors and being influenced by informal and formal factors. Much progress has been made in policy and practice, but OMP reimbursement remains fragmented and access to treatment is still limited for millions of people living with rare diseases (PLWRD). Understanding key players and their roles and interactions with each other during OMP reimbursement in Ireland is limited. One approach to closing this knowledge gap is to use patient-centred outcome measures (PCOMs), which allow for standardised assessment from the perspective of people with lived experience of rare diseases (RDs).

**Aim:** We aimed to deepen understanding about this topic by creating case studies on OMP reimbursement in Ireland.

**Methods:** We conducted 15 structured interviews from September 2025 to May 2026 with three stakeholder groups based in Ireland, i.e. representatives from patient organisations, pharmaceutical companies, and government. We used Braun and Clarke's (2006) six-step approach to thematic analysis to identify themes and understand patterns from interview transcripts. In July - August 2026 we conducted a survey to assess interviewees' opinions about the usefulness of PCOMs for four RDs: Friedreich's ataxia (FA), epidermolysis bullosa (EB), neurofibromatosis (NF), and Phenylketonuria (PKU).

**Results:** Four main themes emerged: the OMP reimbursement ecosystem is complex and dynamic; the reimbursement process is context-specific; patient's voice in reimbursement decision-making; untapped potential of PCOMs.

**Conclusion:** OMP reimbursement in Ireland benefits from policies that are inclusive of patient participation. PCOMs can further ensure reimbursement decisions are in line with person-centred care.

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# Role and reach of the Neuromuscular Service at Tallaght University Hospital: A two-year service evaluation

Anwar Al Abri, Smitha Samuel, Michael Alexander, Susanne Ledesma, Leanne Mooney, Sinéad M Murphy

Department of Neurology, Tallaght University Hospital. Academic Unit of Neurology, Trinity College Dublin

**Background:** Neuromuscular disorders are complex, heterogeneous conditions requiring subspecialist expertise with dedicated access to neurophysiology. A multi-disciplinary tertiary level clinic operates at Tallaght University Hospital (TUH), cohorted into neuromuscular and neuropathy clinics.

**Methods:** We conducted a retrospective service evaluation of all patients attending the TUH neuromuscular/neuropathy clinics over a two-year period (2023–2024). Demographic data, referral source, travel distance, diagnostic categories, investigations, and follow-up requirements were analysed.

**Results:** 643 patients were reviewed: 466 return and 168 new patients. Among new referrals, 77 (46%) were referred from other neurology services for subspecialty opinion or advice regarding diagnosis or management. The median waiting time for new patients was 10.5 months, 74 (44%) waiting longer than 12 months. The majority required additional investigations and/or long-term follow up.

Patients travelled significant distances to access specialist care, with 186 return patients (40%) travelling more than 100 km and 63 (14%) travelling more than 200 km to attend clinic.

Among return patients, neuropathies were the most frequent diagnostic category (256, 55%), including inherited, immune-mediated, paraproteinaemic, and other acquired aetiologies. Myopathic disorders accounted for 98 (21%), largely inherited. Neuromuscular junction disorders were identified in 31 (7%), predominantly myasthenia gravis, with rarer congenital and paraneoplastic syndromes.

Additional diagnostic categories included mitochondrial disorders (20, 4%), anterior horn cell disorders (15, 3%), and a range of other rare neuromuscular conditions, mostly genetic.

**Conclusions:** In the context of rapid advances in neuromuscular diagnostics and disease-modifying therapies, these findings highlight a clear need to develop and strengthen neuromuscular services in Ireland.

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# Emerging Biomarkers and Artificial Intelligence in the Early Laboratory Diagnosis of Wilson Disease: A Mini Review

Zia Ullah Shah[1]

[1] Department of Medical Laboratory Sciences, Kohat University of Science and Technology (KUST), Kohat, Khyber Pakhtunkhwa, Pakistan

**Background**: Wilson disease is a rare autosomal recessive disorder of copper metabolism caused by pathogenic variants in the ATP7B gene. Delayed recognition remains common because of its heterogeneous clinical manifestations and the limited diagnostic accuracy of conventional laboratory investigations during the early stages of disease.

**Objective**: This mini review critically evaluates established laboratory biomarkers, emerging diagnostic indicators, and the potential integration of artificial intelligence (AI) to enhance the early detection of Wilson disease.

**Methods**: A focused literature review was conducted using peer-reviewed publications addressing laboratory diagnosis, copper metabolism, molecular genetics, novel biomarkers, and AI-assisted diagnostic strategies in Wilson disease.

**Results**: Conventional diagnostic approaches, including serum ceruloplasmin, 24-hour urinary copper excretion, hepatic copper quantification, and slit-lamp examination for Kayser–Fleischer rings, remain clinically valuable but demonstrate important limitations in sensitivity and specificity. Recent evidence indicates that exchangeable copper, relative exchangeable copper, ATP7B molecular analysis, and multi-omics approaches may improve diagnostic precision, particularly in presymptomatic and atypical presentations. Furthermore, AI-driven predictive algorithms integrating biochemical, genetic, and clinical datasets show promise for supporting earlier and more accurate diagnostic decision-making.

**Conclusion**: Advances in laboratory biomarkers combined with AI-assisted analytical frameworks have the potential to transform the diagnostic pathway for Wilson disease. Future multicentre validation studies and standardized diagnostic algorithms are required before widespread clinical implementation, with the ultimate goal of enabling earlier diagnosis, timely therapeutic intervention, and improved long-term patient outcomes.

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