MPS Matters 2025

MPS EXPERT MEETING

Title: Current challenges, pathways and solutions

Date: 27 June 2025

Time: 11:00–18:00

Venue: Hilton (Doubletree), Coventry, UK

Attendees: Medics and nurses from centres across the UK

Overview

Mucopolysaccharidoses (MPS) and related lysosomal storage disorders remain among the most complex conditions to manage, treat, and monitor. This expert meeting, held on the opening day of the 2025 MPS Conference, has been convened in response to ongoing concerns and challenges in key clinical areas, including airway management, cardiac disease, orthopaedic complications, and neurological involvement. In addition to exploring these pressing clinical issues, the meeting will provide a platform for dialogue on emerging topics such as research developments, innovation in care, childhood dementia, and in utero enzyme replacement therapy (ERT).

Purpose of the meeting

Hosted by the MPS Society, this expert meeting aims to facilitate focused discussion and knowledge exchange among leading clinicians, researchers, and nurses. The agenda is designed to promote critical review of current practices, share insights, and identify practical solutions and future directions in the management of MPS and related conditions.

Meeting Chairs: Dr Fiona Stewart and Professor Derralynn Hughes

11.00	**Arrivals – tea, coffee biscuits**	
11.15	Welcome, introductions, setting the scene	**Fiona Stewart, Derralynn Hughes and Bob Stevens**
Topic 1 – Current challenges pathways and solutions (11.30–13.45)		
Airway complications in MPS and related diseases		
11.30–11.45	Paediatric perspective	**Johnny Kenth**
11.45–12.00	Adult perspective	**Chai Gadepalli**
12.00–12.10	Developing an emergency airway plan	**Simon Jones**
Cardiac issues in MPS and related diseases		
12.10–12.30	Overview of cardiac issues in MPS	**Peter Woolfson**
12.30–12.50	Update from Cardiac service – UHS	**Nicola Viola and Tara Bharucha**

Discussion		
12.50–13.45	**Discussion** 1. How we standardise pathways 2. Sharing data between centres 3. Measuring outcomes 4. Research opportunities 5. Summary / next steps	**ALL**
13.45–14.25	**Lunch / Networking**	
Topic 2 Orthopaedic issues in MPS and related diseases (14.25–15.30)		
Orthopaedic issues		
14.25–14.45	**Orthopaedic issues MPS and related diseases** • Need for/timing of spinal surgery • Long term issues after spinal surgery • Emerging surgical issues in adults	**Neil Oxborrow**
How physiotherapy can help with orthopaedic issues		
14.45–14.55	Paediatric perspective	**Michelle Wood**
14.55–15.05	Adult perspective	**Andrew Oldham**
Discussion		
15.05–15.30	Discussion	
Topic 3 Neurology in MPS and related diseases (15.30–16.30)		
15.30–15.50	Early signs of cognitive decline– how to assess and monitor	**Jacqui Hussey**
15.50–16.10	Role of biomarkers in assessing efficacy of treatments	**Wendy Heywood and Simon Jones**
16.10–16.30	Use of a mixture of fatty acids taken as an oral liquid in the treatment of difficult epilepsy	**Simon Heales**
16.30–16.45	**Break**	
Topic 4 Research, Innovation and the challenges (16.45–17.50)		
16.45 –17.05	Childhood Dementia Initiative – expanding the global reach	**Gail Hilton**
17.05 –17.25	Pre–natal ERT study	**Emma Canepa University of California (online)**
17.25–17.50	Latest research and hot topics open floor discussion	**Open to people wishing to present**
17.50–18.00	**Summing up / End**	**Fiona Stewart and Derralynn Hughes**

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TOPIC 1

Current challenges, pathways and solutions

Airway complications in Paediatric MPS patients		
Speaker	**Johnny Kenth**	**Academic Paediatric Anaesthetist & Data Scientist** *Royal Manchester Children's Hospital*
Presentation Focus	Airway complications in MPS (Mucopolysaccharidoses), particularly MPS IVA, clinical decision-making, and new technologies supporting safer management.	

1. Clinical Context

- All MPS subtypes involve airway complications; MPS I/II affect the upper & lower airway, MPS IVA the central airway.
- Children with MPS face high anaesthetic risk due to small anatomy, disease burden, and frequent procedures.
- Difficult airway management includes face mask ventilation, intubation, and extubation.

2. Variation & Risk

- Airway problems vary by phenotype, even within subtypes.
- Despite therapies (ERT, gene therapy), airway risks remain.
- With increased survival, new complications are emerging in adolescents and young adults.

3. Key Pathophysiology

- Upper airway: nasal polyps, enlarged tonsils/ tongue, redundant tissue can all pose obstruction risks.
- Skeletal: cervical spine and instability complicates positioning and intubation.
- Lower airway: tracheomalacia, extrinsic tracheal compression (notably in MPS IVA).

4. Red Flags for Anaesthetic Planning

- History of difficult extubation or ICU stay.
- Severe OSA, prior tracheostomy, facial dysmorphism, small mouth.
- Need for experienced teams and non-standard approaches (e.g. video laryngoscopy, CPAP, nasal high flow).

5. Advances in Airway Assessment

- CT remains key but is limited by static imaging.
- Newer tools like virtual endoscopy and 3D-printed airway models offer dynamic insights and surgical planning support.
- These reduce the need for high-risk diagnostic bronchoscopy.

6. Multidisciplinary Innovation

- Collaborative work enables safer care.
- 3D models show pre/post-surgery anatomy, aiding both anaesthetic and surgical teams.

Conclusion

- MPS airway management is complex and patient-specific, necessitating tailored, multidisciplinary care.
- Imaging innovation and multidisciplinary collaboration are improving outcomes and safety in this high-risk group.

Airway Assessment and Management in Adult Lysosomal Storage Disorders

Speaker	**Chai Gadepalli**	**ENT Consultant** *Salford Royal Hospital*
Presentation Focus	Outlined a comprehensive and collaborative approach to managing airway complications in adult patients with lysosomal storage disorders (LSDs), particularly those with Mucopolysaccharidoses (MPS), alpha-mannosidosis, and mucolipidosis. These conditions cause progressive multi-system involvement due to the accumulation of storage materials (e.g. GAGs), with the airway frequently affected from lips to lungs.	

Key Clinical Insights

- **Airway Involvement is Universal:** All MPS patients should be presumed to have airway abnormalities unless proven otherwise. Even subtypes previously thought to be low-risk (e.g. MPS III) can show subtle airway involvement.
- **Multisystem Complexity:** Airway disease coexists with musculoskeletal, cardiac, and neurological complications. A holistic, MDT approach is essential.
- **Adult Cohort:** Over 200 adult MPS patients are known in the UK. At Salford, 96 patients have been assessed, with detailed airway analysis in 81.

Airway Challenges

- **Problems span oral cavity to lungs:** limited mouth opening, macroglossia, high Mallampati grades, cervical spine instability, tracheomalacia, and bronchomalacia.
- **Endoscopic findings** show variable but often severe airway narrowing, abnormal epiglottis positioning, and high secretions.
- **Anaesthetic risk is high:** past literature reports numerous complications (558 anaesthetic episodes) including difficult mask ventilation, failed intubation, rapid desaturation, airway oedema, and CICV scenarios.
- **Spinal involvement:** Severe cervical abnormalities necessitate extreme caution in airway manoeuvres and favour fibreoptic or video-assisted techniques.

Innovations in Assessment

- Non-invasive assessment is preferred over bronchoscopy.
- Advanced imaging techniques should include:
  - CT and virtual endoscopy
  - 3D segmentation and airway modelling
  - 3D printing and custom device simulation (used successfully in high-risk cases)
- A custom airway scoring tool (15-point system) has been developed in Salford to assess and stratify risk across anatomical levels.

Clinical Practice Impact

- 3D modelling and virtual tools allow for airway rehearsal and pre-planning, significantly reducing anaesthetic risk.
- Multi-disciplinary care with anaesthetics, ENT, metabolic, and surgical teams is vital.
- Salford collaborates nationally (e.g. with Southampton, Liverpool) to standardise and improve care pathways.

Conclusion

Airway management in adult LSD patients requires meticulous planning, innovation, and interdisciplinary teamwork. Non-invasive assessments, patient-specific modelling, and custom planning tools are transforming outcomes. As patients live longer, shifting focus from paediatric to adult care demands continued adaptation and collaboration.

Emergency Airway Passport for MPS Patients

Speaker	**Simon Jones**	**Paediatric Consultant & Medical Director** *NIHR children's clinical research facility, Manchester*
Presentation Focus	This presentation outlined an urgent and ongoing initiative to develop a national "Emergency Airway Passport" for patients with Mucopolysaccharidoses (MPS).	

Background & Rationale

- MPS patients often have extremely complex and difficult airways.
- While elective procedures allow for careful MDT planning, emergencies do not.
- Emergency presentations frequently occur at local, non-specialist hospitals often at night or weekends posing high risk.
- Several cases, including fatalities, have led to coroner recommendations calling for a national solution.

The Emergency Airway Passport Concept

Aim: To provide instant, individualised guidance for airway management in MPS patients during emergencies.

- Dual-format proposal:
  - Cover page: Simple, essential instructions (e.g., airway precautions, emergency contact).
  - Detailed guide: Personalised, comprehensive airway plan.

The passport must be regularly updated as the patient ages and their clinical situation evolves.

Implementation presents challenges, especially around consistency, accessibility, and integration across disparate NHS IT systems. While formats such as QR codes and USB devices have been considered, practical issues like IT compatibility and data security must be addressed.

To address these challenges, a dedicated working group, comprising anaesthetists, ENT specialists, frontline clinicians, and representatives from patient advocacy organisations are drafting a proposed standardised national passport. The aims are to:

- Establish a consistent format usable across all regions and healthcare settings.
- Enhance the safety of MPS patients during unplanned emergency presentations.
- Support non-specialist staff, especially in district general hospitals (DGHs), by providing essential, patient-specific information and key contact details to enable safe, informed decision-making in time-critical situations.

Next steps include finalising the draft, consulting a broad range of stakeholders, testing the passport in real-world settings, and integrating feedback. Although not directly led by NHS England, this project is feeding into formal national workstreams and has a unique opportunity to leverage attention and resources due to the seriousness of recent incidents and the momentum from national inquiries.

Next Steps

- Finalise draft of the passport template.
- Consulting a broad range of stakeholders, testing the passport in real-world settings, particularly in DGH's integrating feedback and proposal for change

Although not directly led by NHS England, this project will feed into formal national workstreams.

Cardiac Issues and Surgical Considerations in MPS

Speaker	**Peter Woolfson**	**Consultant Cardiologist** *Salford Royal Hospital*
Presentation Focus	This presentation outlines the key cardiac complications seen in patients with Mucopolysaccharidoses (MPS) and related lysosomal storage disorders, with a focus on valvular heart disease, conduction abnormalities, and surgical planning. The presentation highlighted the need for early detection, multidisciplinary care, and tailored surgical approaches in this complex patient group.	

Prevalence & Pathophysiology

- Cardiac complications are common in MPS types I, II, and VI and are linked to dermatan sulphate accumulation.
- Glycosaminoglycan (GAG) deposits affect:
  - Heart valves, leading to thickening, fibrosis, and dysfunction.
  - Conduction system, increasing the risk of arrhythmias and heart block.
  - Coronary arteries, though typically not symptomatic (e.g. angina) due to patients' limited mobility.

Valvular Heart Disease

- Mitral and aortic valves most affected; often both need replacement.
- Right-sided valves rarely involved.
- Severe disease can occur even with mild systemic symptoms.
- Annual echocardiography is essential, as murmurs may be absent.

Conduction Abnormalities

- Risk of bradyarrhythmias and heart block; pacemakers may be needed.
- Symptoms (e.g. dizziness, syncope) require prompt investigation.
- Recommend annual ECGs and 24-hour Holter monitoring.

Coronary Artery Disease

- GAGs may mimic or worsen atherosclerosis.
- Often silent; CT coronary angiography is essential pre-op.

Diagnostic Challenges

- Physical examination may not reliably detect murmurs or arrhythmias due to patient anatomy.
- Imaging (especially transthoracic echo) is often technically difficult; expert interpretation is essential.

Enzyme Replacement Therapy (ERT) & Stem Cell Transplant

- While beneficial for systemic disease, ERT does not halt cardiac valve degeneration, likely due to poor vascularisation of valves.
- Cardiac monitoring must continue regardless of systemic response to therapy.

Surgical Considerations

- Cardiac surgery is feasible but requires:
  - Detailed pre-op planning.
  - Involvement of ENT, anaesthetics, spinal, and metabolic teams.
  - Consideration of small body size, airway management, and difficult vascular access.
- Pacemaker and valve surgeries are not routine and require specialist cardiac and anaesthetic support.

Multidisciplinary Approach

- Success hinges on early diagnosis, regular surveillance, and collaborative MDT input (cardiology, ENT, anaesthesia, metabolic, and surgical teams).

Shared care protocols and planned surgical pathways significantly improve outcomes

Conclusion

Airway management in adult LSD patients requires meticulous planning, innovation, and interdisciplinary teamwork. Non-invasive assessments, patient-specific modelling, and custom planning tools are transforming outcomes. As patients live longer, shifting focus from paediatric to adult care demands continued adaptation and collaboration.

New Interdisciplinary Cardiac Surgical Service for MPS Patients at University Hospital Southampton (UHS)

Speakers	**Tara Bharucha** **Nicola Viola**	**Cardiology Lead** **Cardiac Surgical Lead** *University Hospital Southampton*
Presentation Focus	Introduction to Southampton's emerging cardiac surgical service for Mucopolysaccharidosis (MPS) patients and explaining the rationale, structure, and early experience of delivering this care through an interdisciplinary congenital cardiac model. NHS England approached UHS to consider leading this service due to its ability to offer a unique colocation of services, including: paediatric and adult cardiac surgery, cardiology, ENT, anaesthesia, ICU, PICU and post-surgical care all under one roof. Since March 2025, they have successfully operated on their first two MPS patients.	

The Interdisciplinary Model

UHS core strength lies in functioning not just as a multidisciplinary team but as an interdisciplinary team training, meeting, and treating together, which increases shared knowledge and improves outcomes. This tight integration benefits patients significantly, particularly those with rare and complex conditions like MPS.

How the Service Works

- **MDT Process:** Patients are discussed at quarterly national MDT meetings, with input from their metabolic and local cardiology teams.
- **Pre-Admission:** A "one-stop" pre-assessment clinic includes all key specialists to minimise travel and streamline planning.

- **Surgery:** Aortic and mitral valve replacements are carried out using existing congenital expertise. So far, MPS anatomy hasn't required deviation from standard AVR/MVR methods.
- **Recovery & Follow-Up:** Patients transition smoothly from ICU to HDU to ward, all within close physical proximity, ensuring rapid response and continuity.
- **Feedback Loop:** Post-op cases are reviewed to inform referrers and share learning.

Technology & Innovation

We have embraced airway imaging and 3D printing (led by Chai and the ENT team at Salford), integrating these into our planning and intraoperative processes. This technology is now routinely used in our congenital service for MPS patient.

Patient Tracking & Safety

All MPS surgical patients are proactively followed on our waiting list using the ARM (Active Risk Management) system, ensuring risk is continuously monitored and prioritised based on clinical need.

Service launch

The service formally launched in March 2025. So far, 12 patients have been discussed, 2 surgeries successfully completed, and several more are either accepted or awaiting pre-assessment.

Conclusion

Southampton is building a coordinated, centrally based service for MPS patients requiring cardiac surgery. While still in its early stages, the team is committed to working collaboratively, sharing insights, and continuously strengthening their integrated approach to provide safe, specialist care for this complex patient group.

Discussion Summary

MPS Airway and Cardiac Management	
1. Standardising Care Pathways	• Strong support for creating national, standardised clinical pathways • Recognition of inequitable access to high-quality airway support across centres. • Calls for development of shared documentation (e.g., “airway passports”) and protocols to support consistent care across the UK.
2. Data Sharing and Collaboration	• Acknowledged excellence in current collaboration across centres, for both airway and cardiac MDTs. • Emphasis on the need for national or even international registries to track patient data and outcomes over time. • Recognised value of mutual learning between centres and between paediatric and adult services.
3. Measuring Outcomes	• A need to define meaningful clinical outcomes and to systematically collect and analyse them (e.g. surgical success, long-term survival, cardiac complications). • Discussion around predicting deterioration and identifying patients earlier, with potential for AI or big data models. • Suggestion to advocate collectively as a group to influence national policy. • Proposal to support training and upskilling of clinical teams outside of specialist centres. • Continued support for collaborative MDTs and joint working between paediatric and adult services.
4. Research Opportunities	• Potential to study disease progression from childhood through to adulthood, particularly in relation to cardiac and airway deterioration. • Interest in exploring early intervention (e.g., timing of valve surgery) and long-term effects of current therapies. • Questions raised about metabolic markers (e.g., glycosaminoglycan burden) and their relationship to clinical decisions.
5. Next Steps / Action Items	• Push for formal commissioning and funding from NHS England for complex airway and surgical services in MPS.

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TOPIC 2

Orthopaedic issues in MPS and related diseases

Spinal Issues in MPS

Speaker	**Neil Oxborrow**	**Consultant Spinal Surgeon** *Royal Manchester Children's Hospital*
Presentation Focus	focused on spinal issues in Mucopolysaccharidosis (MPS) based on over 20 years of experience in Manchester and reviews of more than 90 MPS I (post HSCT) patients, both surgical and non-surgical cases. This exposure has informed a cautious and conservative surgical approach, emphasising function and quality of life over radiological appearances.	

Key points:

- **Unique clinical setup:** All MPS patients are seen by the spinal team, providing insight into the natural history of both surgical and non-surgical cases.
- **Importance of radiology led decision making:** Surgeons unfamiliar with MPS may overinterpret imaging, leading to unnecessary or inappropriate surgeries.
- **Lack of Evidence and Guidelines:** Spinal surgery in MPS suffers from weak evidence bases, with most studies amalgamating diverse MPS types and minimal guidance outside thoracolumbar kyphosis.
- **Indications for Surgery:** No absolute indications exist beyond neurological compromise, and even that is sometimes managed conservatively. Decisions must be inter-multidisciplinary, factoring in development, hip condition, and functional potential.
- **Surgical Approach:** Procedures are generally posterior-only with a high complication rate (~30% failure), though patients often remain asymptomatic. Revision surgery is avoided unless functionally justified.
- **Kyphosis and Scoliosis:** Thoracolumbar kyphosis is the most commonly addressed deformity; scoliosis surgery is mostly cosmetic unless respiratory compromise exists. There is little data on adult outcomes.
- **Emerging Concerns in Adults:** As patients live longer, they are increasingly presenting to adult services unfamiliar with MPS, creating risks of mismanagement.
- **Hip-Spine Interaction:** The relationship between spinal deformity and hip pathology is critical. Surgical decisions should prioritise overall function and balance, not just radiographic correction.

The overarching message was one of caution: spinal surgery in MPS should be undertaken only when clearly beneficial, acknowledging high risks, limited evidence, and the complex interplay of multiple factors.

How physiotherapy can help with orthopaedic issues - a paediatric perspective

Speaker	**Michelle Wood**	**Specialist Physiotherapy** *Great Ormond Street Hospital, London*
Presentation Focus	Michelle reflected on nearly 30 years of experience in physiotherapy, highlighting significant advancements in treatment approaches, particularly in the care of children with complex orthopaedic and musculoskeletal conditions. Central to this progress is the shift toward more integrated, multidisciplinary care especially between physiotherapy and orthopaedics to improve function and quality of life for patients.	

Key developments include:

- **Shift in Focus:** While the core aim remains achieving pain-free, functional movement, there's a greater emphasis today on individualised, condition-specific assessment and timing of intervention.
- **Understanding Disease Mechanisms:** Physiotherapists must account for the underlying disease process, especially in conditions with storage disorders like MPS, which uniquely affect joint and muscle function.
- **Paediatric Considerations:** Treatment must adapt to a growing skeleton and the unique developmental stages of children.
- **Advances in Gait Assessment:** Technology such as electronic gait mats enables objective analysis of walking patterns, supports more precise interventions, and facilitates collaboration with orthopaedics.
- **Active vs. Passive Treatment:**
  - Active exercises and stretches performed by the child are most effective.
  - Passive stretches and splints generally show poor outcomes in storage disorders and may cause discomfort, though supportive orthotics may improve function without forcing range gains.
- **Hydrotherapy:** Movement in water is considered a gold standard due to its safety, pain-free environment, and therapeutic benefits.
- **Equipment Use:** Custom orthotics and splints are carefully chosen to support, not restrict, function, tailored to individual gait and joint needs.
- **Surgical Interventions:** Physios now play a larger advocacy role in multidisciplinary discussions about the appropriateness and timing of surgeries, especially given mixed surgical outcomes (e.g. toe walking corrections).

Conclusion

The presentation concluded by emphasising the importance of realistic expectations, careful timing of interventions, and a holistic, interdisciplinary approach to treatment planning. Ultimately, the goal is not just to prolong life, but to add quality to life, ensuring children remain active, pain-free, and engaged.

Orthopaedic issues: Rehabilitation of adult MPS patients

Speaker	**Andrew Oldham**	**Highly Specialised Metabolic Physiotherapist** *Salford Royal Hospital*

Presentation Focus

Andrew presented on orthopaedic issues in adults with MPS, particularly focusing on rehabilitation and pain management. Building on earlier paediatric insights, the speaker highlighted the persistent and often complex musculoskeletal pain faced by adult patients, including in the hips, knees, ankles, and spine. Despite the use of analgesics, pain often remains inadequately controlled, with side effects and limited efficacy.

Conventional physiotherapy techniques such as acupuncture and land-based exercises have shown limited benefit in this population. However, hydrotherapy was identified as a particularly valuable intervention due to its ability to reduce joint loading, relieve pain, and improve mobility through buoyancy, resistance, and warmth.

A pilot study conducted at Salford Royal explored the impact of hydrotherapy in adults with MPS II (Hunter syndrome). Five male patients participated in a 24-week crossover study, half starting with observation followed by hydrotherapy, and vice versa. Each underwent six fortnightly hydrotherapy sessions (up to 50 minutes each).

Hydrotherapy exercises included warm up, hip knee, shoulder flexion, hip, horizontal and shoulder abduction, step ups, squats, bicep curls, spinal rotation and warm down.

Key outcomes:

- **Functional improvements** were seen in the six-minute walk test and 10 metre walk time
- **Pain and psychological outcomes also improved:** the GAD-7 (anxiety), PHQ-9 (depression), Tampa Scale (fear of movement), Pain Catastrophising Scale, and Brief Pain Inventory all showed clinical benefit and improvement.
- **Muscle strength,** measured via handheld dynamometry, improved by an average of 6.1 lbs in all patients across 8 muscle groups

Conclusion

Although small in scale, this study is one of the first to demonstrate clinically meaningful benefits of hydrotherapy in MPS II adults. It supports its broader and longer-term use as a safe, well-tolerated, and effective addition to conventional care, addressing a previously unmet need in symptom management.

Discussion Summary

Surgical Considerations, Physiotherapy, Hydrotherapy and Access in MPS Care	
1. Surgery for Stability	Some people with MPS need spinal fusion surgery to stabilise the spine and improve posture or mobility. For some, this helps make future treatments like hip replacements more straight forward
2. Bone Health and Medication	MPS patients don't usually have fragile bones or fractures. Treatments like bisphosphonates (used in osteoporosis) aren't typically used here.
3. Positive Outcomes	Most patients do well after surgery, spending only 5–6 days in hospital and getting up and moving the day after surgery. Families report better posture, reduced pain, and improved quality of life.
4. When Surgery Helps and What Can Go Wrong	Surgeons aim to carry out spinal fusion at the right time (often around age 7–8), using materials that help the bones fuse and post-surgery bracing to support healing. While outcomes are often good, some risks remain, such as loosening of screws due to body weight or movement, and instability developing above or below the fused area over time.
5. Physiotherapy Innovation & Education	Suggestions included creating physio-led video resources for home or community use and engaging local gyms and charities to provide support.
6. Hydrotherapy Value & Access	Strong consensus on the benefits of hydrotherapy for patients with MPS, though access remains highly unequal. Many hospitals lack pools; financial pressures threaten existing facilities. Medical conditions like heart issues or epilepsy can limit who can safely use hydrotherapy.
7. Alternative Solutions	Use of warm public pools, hot tubs, gym-based aqua.

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TOPIC 3

Neurology in MPS and related diseases

Early signs of cognitive decline - how to assess and monitor

Speaker	**Jacqueline Hussey**	**Consultant Old Age Psychiatrist** *Berkshire Healthcare NHS Trust YPWD CIO*

Presentation Focus

Jacqui discussed how dementia presents and is diagnosed in adults under 65, particularly those with long-term conditions such as mucopolysaccharidoses (MPS). Drawing on experience from a memory clinic serving individuals aged 35–65, the presentation highlighted key diagnostic challenges and tools.

Young-onset dementia affects around 70,000 people in the UK, but fewer than 50% receive a diagnosis. Memory loss is not always the main symptom in younger people. Changes may instead affect language, decision-making, behaviour, or social awareness.

The talk emphasised the importance of:

- Identifying a clear change in cognitive ability or behaviour
- Ruling out other causes such as depression, sleep disorders (e.g. sleep apnoea), or medication effects
- Considering the possibility of co-existing dementia in patients with existing conditions (such as MPS) who are now living longer

What to Look For

- Cognitive or behavioural changes lasting over 6 months
- Symptoms beyond memory loss: language issues, social withdrawal, executive dysfunction
- Rule out reversible causes like depression or sleep apnoea

Assessment Tools

- Addenbrooke's Cognitive Examination (ACE-III): tests memory, attention, language, and executive function
- IQCODE: carer questionnaire tracking change over 10 years
- Imaging: MRI and CT scans help detect patterns of brain change

Considerations in MPS

- Adults with MPS may show new cognitive changes as they age
- Important to differentiate between progression of MPS and new-onset dementia
- Increased longevity means greater need for dementia screening in this group

Formal testing (e.g. neuropsychology) is valuable but early screening and functional assessment is encouraged. Future developments may include biomarker blood tests and genetic screening for younger patients with a strong family history.

Conclusion

There is a need for greater awareness of young-onset dementia, particularly with complex medical needs, and the value of practical tools that can support early detection and management in non-specialist settings.

Why We Need Biomarkers in Paediatric Neurodegenerative Disease Trials

Speaker	**Simon Jones**	**Paediatric Consultant & Medical Director** *NIHR children's clinical research facility, Manchester Children's Hospital & Manchester University*
	Wendy Heywood	**Principal Research Fellow, Hon Clinical Biochemist & Executive Director and Founder** *Guilford St Laboratories Great Ormond Street Hospital*

Overview & Clinical perspective

Presented by Simon Jones

Current clinical approaches to treating neuropathic lysosomal storage diseases (LSDs) such as MPS III have failed to deliver effective therapies despite over two decades of trials. A key limitation has been the reliance on clinical outcome measures which are slow to change, highly variable, and ethically and logistically difficult to use in trials. This has led to wasted time, inconclusive results, and unmet needs for affected children and families.

Clinical Perspective: The Challenge of Outcome Measures

- **Natural history data** for MPS III shows early normal development, followed by plateau and gradual decline. Even within "classical" phenotypes, there is wide heterogeneity.
- **Early intervention is ideal**, but diagnosis typically occurs too late due to symptom onset, making early-stage recruitment extremely difficult.
- **Late-stage intervention** brings ethical and measurement challenges: it's unclear how to define success, especially when patients are already declining.
- **Perfect trials** need earlier diagnosis, early treatment, clear comparator groups, long-term follow-up and are nearly impossible to conduct under current models.

Conclusion

Without better tools to track neurological disease progression, clinical trials are likely to continue failing, regardless of therapeutic promise

Scientific Perspective: Biomarkers as a Solution

Presented by Wendy Heywood

Wendy emphasised the critical role of biomarkers in enabling timely and interpretable trial outcomes.

Neurofilament light chain (NFL)

- Widely used as a non-specific marker of axonal injury.
- Can be measured in CSF (central) or serum (includes peripheral), though interpretation depends on disease context.
- **Challenges:**
  - Raised NFL can reflect peripheral neuropathy (e.g. in Fabry disease).
  - In some severe neurodegenerative diseases, NFL declines as neurons are lost.
  - NFL shows very slow turnover: one study demonstrated it can take 3–6 months to reflect changes in CSF, and persist over 18+ months in brain tissue.
  - Unsuitable for short-term monitoring of treatment response in clinical trials.

Proteomics Approach: Identifying Faster, Relevant Biomarkers

A study on CLN2 (Batten disease) treated with Brineura (enzyme therapy) demonstrated:

- CSF proteomics can identify biomarkers with faster responses than NFL.
- In short-term treatment (2–12 weeks), significant and consistent reductions in neuroinflammation markers were observed.
- In long-term treatment (1–2 years), increases in proteins associated with neuronal development and synapse formation were noted.

This suggests potential for identifying disease- and age-relevant biomarkers reflecting both treatment response and natural neurodevelopment.

Key Recommendations

- Biomarkers are not a luxury, they are essential.
- Regulators are increasingly open to biomarker-informed trials, as seen in recent workshops with FDA and EMA.
- Future trials should be designed with:
  - Early biomarker readouts (6–12 months)
  - Long-term clinical follow-up (5–10 years)
  - Acceptance that biomarkers may offer the clearest early indicators of efficacy.

Conclusion

Using only clinical outcomes to evaluate neurodegenerative treatments in children is unethical, impractical, and ineffective. A shift toward biomarker-integrated trial design is necessary to generate meaningful results, reduce patient burden, and accelerate therapy approval.

Biochemical Approaches to Drug-Resistant Epilepsy

Speaker	**Simon Heales**	**Consultant Clinical Scientist & Professor** *Neurometabolic Unit, National Hospital, Queen Square & UCL Great Ormond Street Institute of Child Health, London*
Presentation Focus	Professor Simon Heales delivered a presentation on the use of a biochemical approach using medium chain fatty acids to improve the treatment of drug-resistant epilepsy in children and adults. Drawing on over 15 years of research, Professor Heales explored the limitations of conventional ketogenic diets and proposed an innovative reformulation to improve efficacy and patient compliance.	

Background & Aim

Ketogenic diets, used since the 1920s to manage refractory epilepsy, rely on high-fat intake to produce ketone bodies as alternative brain fuel. While effective, these diets are highly restrictive and difficult to maintain, especially in children. Heales' research aimed to identify the active therapeutic components of the diet and develop a more practical alternative.

Key Findings:

- **Fatty Acids Over Ketone Bodies:** Cellular studies revealed that ketone bodies alone had limited impact on mitochondrial function. In contrast, the medium-chain fatty acid decanoic acid (C10) significantly increased mitochondrial content and activity as indicated by elevated levels of the enzyme citrate synthase and improved complex I function, supported by electron microscopy and fibroblast studies.
- **Mechanism of Action:** C10 activates the PPAR-γ receptor, promoting mitochondrial biogenesis and antioxidant activity (e.g., catalase). It is slowly metabolised in the brain, allowing accumulation at therapeutic levels, unlike the faster-metabolised octanoic acid (C8).
- **Optimised Formulation:** An 80:20 mix of C10:C8 was identified as optimal. C8 slows C10 breakdown via competitive inhibition. In a mouse model of Dravet syndrome, this mix improved seizure control, survival, and biochemical markers compared to standard MCT diets.
- **Clinical Translation:** A human tolerability trial (with Great Ormond Street Hospital and the National Hospital for Neurology) showed that the new formulation—requiring only moderate carbohydrate restriction—was well tolerated and effective in reducing seizures, even in patients unresponsive to traditional therapies. Seizure reduction correlated with C10 blood levels, not ketones, indicating a novel non-ketotic mechanism.
- **Product Development:** This work led to the creation of K.Vita, a prescribed nutritional therapy now available in select countries for managing drug-resistant epilepsy.

Relevance to Lysosomal Storage Disorders (LSDs):

Although initially developed for epilepsy, the mechanisms underpinning this research improving mitochondrial function, reducing oxidative stress, and promoting autophagy may have therapeutic implications for LSDs, where similar biochemical dysfunctions are present.

Conclusion

This work represents a significant advancement in epilepsy treatment, shifting focus from restrictive ketogenic diets to targeted biochemical interventions. His team's work not only improves patient quality of life but opens promising avenues for treating other metabolic and neurological disorders, including LSD's

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TOPIC 4

Research, Innovation and the challenges

Understanding and Responding to Childhood Dementia

Speaker	**Gail Hilton**	**Head of Programmes** *Childhood Dementia initiative, Australia*
Presentation Focus	This presentation focused on the urgent need to recognise, understand, and act on childhood dementia, a group of over 100 rare genetic conditions that cause progressive brain damage in children. Like adult dementia, childhood dementia leads to memory loss, confusion, communication challenges, disturbed sleep, and behavioural changes. Unlike adults, however, children also lose developmental milestones, motor skills, and, ultimately, vital functions, often leading to death before adulthood. The speaker highlighted the shocking statistic that 1 in 2,900 babies is born with a condition that causes childhood dementia a similar incidence to cystic fibrosis and that, in Australia, annual deaths from childhood dementia are on par with childhood cancer. Despite this, childhood dementia remains severely under-recognised in health policy, care systems, and research agendas globally.	

The Childhood Dementia Initiative, launched in Australia during the COVID-19 pandemic, aims to drive awareness, accelerate therapeutic development, and improve care and quality of life. Over the past five years, the Initiative has:

- Secured major national media attention and political engagement.
- Achieved the inclusion of children in Australia's National Dementia Action Plan.
- Catalysed new research funding and system change, including a specialist disability care pathway.
- Supported the creation of a Scottish Childhood Dementia Action Group and sparked interest from countries such as Denmark, Sweden, Norway, and New Zealand.

Next Steps

Launch a Global Consensus Project to refine the definition and diagnostic criteria for childhood dementia, enabling harmonised international data collection and the development of a global research blueprint.

Pearl Trial – Prenatal Enzyme Replacement Therapy for Lysosomal Storage Disorders

Speaker	**Emma Canepa**	**Clinical Trial Programme Manager** *Centre for Maternal Foetal Precision Medicine at UCSF*
Presentation Focus	This presentation provided an update on the Pearl Trial, a phase I clinical study investigating prenatal enzyme replacement therapy (ERT) for lysosomal storage disorders (LSDs). Led by Dr. Tippi MacKenzie at UCSF, the study explores the use of FDA-approved ERTs administered in utero to prevent early disease manifestations, including organ damage and in utero demise, and to promote immune tolerance to the enzyme.	

Preclinical data in MPSVII mice showed promising results, including reduced storage pathology, improved survival, and enzyme delivery to the brain. A subsequent survey confirmed patient and family interest in foetal ERT, supporting the trial's launch.

The protocol involves:

- Diagnosis via amniocentesis or CVS
- Treatment from 18–36 weeks gestation via umbilical vein injection every 2–4 weeks
- Monitoring for safety, pharmacokinetics, and immune response
- Postnatal follow-up for 5 years

To date, six foetuses have been treated for various LSDs including IOPD, MPS I, MPS II, and neuronopathic Gaucher disease. Key interim findings include:

- No preterm labour or major procedural complications
- No anti-drug antibodies in 5 of 6 cases
- Favourable biochemical and imaging outcomes, including improvement of cardiac hypertrophy and normalized biomarkers
- Electron microscopy of placental tissue showed reduced substrate accumulation in treated patients

Conclusion

Although still early, the results suggest that in utero ERT may mitigate prenatal organ damage and facilitate better outcomes postnatally. The team emphasises this approach as a bridge to definitive postnatal therapies and encourages collaboration and registry participation.

Final Note

This summary reflects the key messages and structure of the original presentation but does not capture all of the detail, discussion, or clinical nuance shared. For full context and comprehensive understanding, please contact the MPS Society directly.

We would like to express our sincere gratitude to all speakers and attendees for their valuable contributions, which were instrumental in shaping the discussions and insights presented in this report.

For further information, please contact: The MPS Society

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