The Unusual Suspects Report 2023

On Wednesday 15 February, emotive attended Medics4RareDiseases' (M4RD) 10th Annual Symposium, 'The Unusual Suspects: Rare disease in everyday medicine'. Following 2 years of virtual meetings, this year's meeting was held at the Royal Society of Medicine (RSM) in London, giving attendees the opportunity to engage face-to-face. Scientific Director, Emma Macleod; Account Manager, Charlotte Roe; and Associate Medical Writer, Ledicia Botas Pérez, joined the event to tell us more about what was discussed this year.

Meeting report

Held in association with the Medical Genetics Section of the RSM, the M4RD Annual Symposium has become a very popular event where healthcare professionals, medical trainees and students, patients and carers gather to raise awareness and emphasise the importance of a holistic approach to rare disease, providing tips to improve the diagnostic journey and management.

This year, the focus of the event was on mental health (MH), coinciding with the imminent launch of the **M4RD Learn MH module** co-written with **Rareminds**, whose founder participated as a speaker.

M4RD creates a nurturing environment to discuss rare diseases collectively and holistically

The event was opened by Dr Shwetha Ramachandrappa, Consultant Clinical Geneticist, President of the Medical Genetics Section at the RSM and Chair at **Unique**, a charity supporting, informing and networking families and individuals affected by rare chromosome and gene disorders. Shwetha opened the event by highlighting how the M4RD Annual Symposium has been one of the only spaces available to professionals, patients and industry partners to network and share stories in the rare disease community, providing an inclusive and nurturing environment to forge strong relationships, even during the pandemic.

Dr Lucy McKay, CEO and founder of **M4RD**, welcomed face-to-face and virtual attendees, introduced her team at M4RD and provided an overview of the afternoon's agenda and speakers.

‘Rare Disease 101’ provides healthcare professionals with the tools to recognise, support and manage patients living with rare conditions

Lucy began her ‘Rare Disease 101’ talk by describing the impact of the loss of her brother to a rare condition, highlighting that even if a condition dies out when a person is lost to it, the impact continues throughout the lives of their families and friends.

She explained that a rare disease is one experienced by <1 in 2000 people. However, there are more than 7000 rare diseases, affecting 3.5 million people in the UK, with an estimated 1 in 17 people affected in their lifetime – so, although the conditions are individually rare, they are collectively common and healthcare professionals should expect to encounter patients with them.

A high proportion of rare diseases present in childhood and 80% have a genetic origin; however, newborn genetic screening of only 10 conditions remains “a drop in the ocean”. Diagnosis of a rare disease takes an average of 4–6 years and patients are frequently ‘ping-ponged’ from one specialist to another, sometimes encountering disbelief, misdiagnosis, inappropriate treatment or no treatment at all. This so-called ‘diagnostic odyssey’ takes a toll on patients and families.

The UK Rare Diseases Framework, published in 2011, states that rare diseases are a priority in the UK; however, this is not yet reflected on the National Institute for Care Excellence or the National Health Service guidelines. Therefore, to help medical professionals integrate rare disease into everyday practice, Lucy shared some advice from the M4RD ‘Rare Disease 101’ e-learning course, including “thinking rare” and becoming a rare disease ally.

Lucy emphasised the overarching goals of M4RD – to ensure people living with a rare condition receive a timely diagnosis, mental health support and holistic specialist care, including excellent communication, as well as support from patient advocacy groups and hope from ongoing research projects.

Find more resources in M4RD Module:

Rare Disease 101 ›

Rare diseases can have a profound effect on identity, and mental health support is key to learning to live with a rare condition

The first invited speaker was Mr Dunstan Nicol-Wilson, patient and author of the Sickle Sagas column at **Sickle Cell Disease News** and Clinical Project Manager.

Dunstan was propelled into the rare disease arena with the publication of his column ‘It’s OK Not to be OK with Sickle Cell Disease (18 April 2022),’ in which he relayed his journey of accepting the truth of living with this condition and unapologetically being his whole self.

He opened his talk by reminding the audience that, although people with rare conditions go through individual experiences, their emotional realities are very similar. Dunstan was diagnosed with sickle cell disease from birth; a disorder without apparently visible symptoms, in which a genetic mutation alters the shape of red blood cells, causing blockages in blood vessels, affecting an estimated 15,000 people in the UK. During crises, patients can experience constant and unbearable pain.

Dunstan explained how, as a child, he made the conscious decision not to get excited in order to avoid crises. As an adult, he became reluctant to go to hospital as he encountered the reality that many healthcare professionals were unfamiliar with his condition and unprepared to provide appropriate care. This led to a profound breakdown in trust; he was expected to apply pain management techniques at the same time as having his pain minimised and dismissed by doctors (through inadequate treatment and verbal disbelief: “pain doesn’t kill you”). Hospital for Dunstan meant a very real fear for his life.

In the absence of genuine understanding of sickle cell disease or a role model, Dunstan felt lonely as a black man with a chronic condition. He pretended to be okay in order to be seen as the ‘strong independent man’ he felt he was supposed to be, generating an internal struggle between his two selves to the point where, during a severe crisis, he pretended to be recovering so he could be discharged from hospital, leading to a worsened crisis and mental breakdown.

Thanks to therapy, Dunstan was able to reconcile the opposite realities of his life (the patient and the strong man) and decided to share his personal experience as a patient with sickle cell disease to raise awareness, encourage others to share their stories and showcase all the ups and downs of living with a rare condition. Dunstan closed his talk by sharing a few takeaways for medical professionals: Believe your patient’s pain, follow their protocol, work collaboratively to make adjustments to care plans and, most importantly, be mindful of how you speak to them, since a few unfortunate words at the wrong time can stick with patients for years.

Hear more from Dunstan via the M4RD podcast:

Listening to the Sickle Cell community Parts 1 and 2 ›

Looking after emotional well-being is a win-win for patients, families and doctors

The subsequent talk was given by Ms Kym Winter, CEO, founder and Clinical Director at Rareminds, a non-profit organisation providing specialist online psychotherapy and counselling services to rare disease communities and collaborating with M4RD on their M4RD Learn MH module. Rareminds works in partnership with more than 20 patient organisations and provides unique insight into both the generic and the specific impact of rare conditions on mental health over time.

A counsellor is placed with a patient organisation to expand their understanding of a specific rare disease, and the team grows in clusters of specialist medical areas, which aim to:

- Provide tailored support to patients
- Train and educate patient organisations and healthcare professionals
- Build data and influence, and inform policy and practice to ensure appropriate mental health support becomes an integral part of rare disease care

Rareminds offers the first continuing professional development training programme for rare disease counselling, and 50% of the team have experienced living with a rare disease, which is part of their ethos.

Kym's teenage daughter and son were diagnosed with a rare genetic syndrome inherited from their father who, years earlier, had a rare cancer linked to this disorder. While her daughter was cared for by paediatric services, 'landing on a soft cushion', her son was directed to adult services, which she described as 'brutal'.

Kym described how living with a rare disease often feels like "being press-ganged into a ship: you cannot sail, you don't know where you're going and you didn't want to get on it anyway; but you have to get on with it, with little help, and find your own way".

This results in a very high proportion of patients and carers experiencing anxiety, stress, emotional exhaustion, suicidal thoughts and feeling like they're at their breaking point.

Kym highlighted that, **although patients may suggest things are going well, they can be doing a lot of emotional work in the background to maintain this impression**.

Just under 50% of patients/carers have never been asked about their mental health or that of their loved one/child, but most of them want to be asked and directed to sources of emotional support.

Kym provided a few tips to support the mental health of patients with rare diseases:

- Acknowledge distress
- Normalise conversations around mental health and emotional impact
- Recognise that helping as an ordinary human being goes a long way
- Think with and for someone about the support that might be helpful and available
- Signpost resources
- Focus on the quality of the interaction

In summary, Kym concluded that talking with patients about emotional health and well-being without overcomplication, in an ordinary way, is a win-win for patients, families and healthcare professionals.

Mental health is everyone's responsibility; and for people with learning disabilities, we should consider behaviour as their means of communication

Kym's talk was followed by a joint presentation by Dr Hayley Crawford, Associate Professor at University of Warwick Medical School, where she leads the Neurodevelopmental Conditions Research group; and Dr Jane Waite, Senior Lecturer in Psychology at Aston Universityw and Clinical Psychologist. Both Hayley and Jane are part of the team at the **Cerebra Network for Neurodevelopmental Disorders**, which was created to enable collaborative research across the UK to improve the lives of people with neurodevelopmental disorders and rare genetic syndromes.

Hayley explained that more than 50% of severe-profound learning disabilities (LDs) have a genetic cause and impact a large proportion of our population, generating both physical and mental health needs. Care for patients with these conditions should be considered 'everybody's responsibility', because medical professionals are likely to encounter them in their service.

People with these conditions are often unable to follow a regular routine and need future-proof plans put in place for them, with a higher proportion of individuals with rare genetic syndromes experiencing anxiety compared with the general population and individuals with LDs of unknown origin [73% vs 4–5%].

Jane expanded on how to improve mental health for those with rare diseases. Research shows that there are a number of risk factors for poor mental health (with an emphasis on anxiety) in individuals with rare genetic disorders. These include environmental factors, such as poverty, loneliness or stressful family circumstances, and personal characteristics, such as low-level information processing and adapted skills, reduced executive functions, attentional deficits, sensory differences and intolerance of uncertainty. Access to appropriate mental health support can also be blocked due to systemic issues, such as the outdated and unfounded belief that language and high IQ are needed to experience psychological distress; 'diagnostic overshadowing' by considering challenging behaviour as part of the genetic syndrome; and therapeutic nihilism, the belief that little can be achieved in therapy for those who are non-verbal.

Hayley highlighted how people living with these disabilities are often unable to self-report, so understanding the behavioural profile is key to understanding what these patients are communicating. Physical avoidance, seeking the proximity of a trusted caregiver and repetitive or challenging behaviour can be signs of anxiety. Hayley used a case study of a patient with Fragile X syndrome to showcase how, by addressing their profile-specific needs, it is possible to provide adequate mental health support to people living with LDs and their families.

She emphasised that nobody with a learning disability and/or is non-verbal should be getting 'bounced' on the basis of challenging behaviour, because behaviour can be their only way of communicating. She encouraged healthcare professionals to ask the relevant questions around low mood, anxiety and distress, to understand the full impact of each condition.

Useful resources are available, including:

- **'The anxiety guide for parents'**
- **'The Be-Well Checklist'**
- **'Further Inform Neurogenetic Disorders (FIND)'**

Coming soon:
A toolkit including a validated assessment for few or no words for anxiety, more screening tools, a pathway of scores and a list of behavioural indicators

We should aim to provide timely and accurate diagnoses to minimise the impact of uncertainty and maximise the chances of empowering patients living with a rare condition

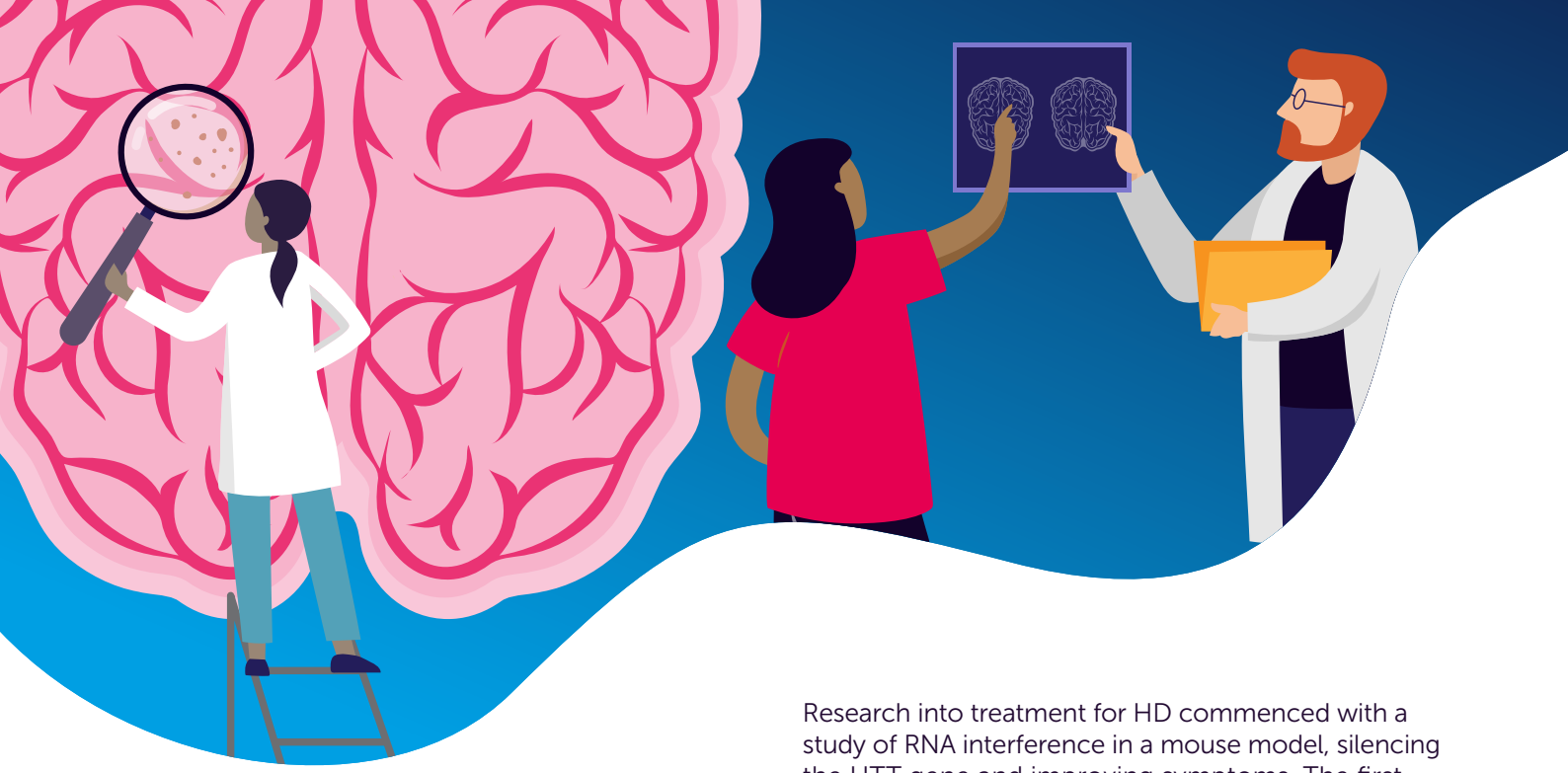
Lucy then introduced the winner of the Student Voice Prize 2022, Zheqing Zhang, third-year medical student at the University of Oxford, who partnered with Sarah, a patient with vascular Ehlers-Danlos syndrome (VEDS). 'The Invisible Kingdom,' by Meghan O'Rourke, told the story of a patient's journey to being diagnosed with post-treatment Lyme disease syndrome and inspired Zheqing to learn more about rare diseases.

In her essay, 'Diagnosing Rare Diseases and Mental Well-being: A Family's Story', Zheqing recounted how Sarah's brother died suddenly of an aortic dissection at 15 years old. 8 and 9 years later, Sarah suffered neurological and pulmonary crises, respectively. She was misdiagnosed with multiple sclerosis and was not offered genetic testing; her brother's death was not considered relevant or included in her medical history.

10 years after her brother's death, within days of giving birth to a baby girl, Sarah's sister died of an aortic rupture. Only then was Sarah genetically tested and diagnosed with VEDS, a life-threatening, connective tissue condition that makes arteries, muscles and organs fragile. She was told her mother was a carrier for this condition, which her siblings had likely also inherited and died from. In Sarah's words, "I cannot believe we had to lose another person to get an answer."

Pregnancy is contraindicated in patients with VEDS so, had there been a thorough family history review and genetic testing, her sister's death could have been prevented. A plethora of feelings inundated Sarah, including grief, survivor's guilt, regret, anger, confusion, fear and anxiety. Receiving a diagnosis also brought relief and empowered her to own her VEDS management by putting together her 'dream team' - a cardiologist, pulmonologist, neurologist, psychologist and nutritionist, accompanied by massage and acupuncture sessions - and reaching out to educate others about this condition.

Zheqing concluded that receiving an accurate diagnosis is key for people with a rare conditions to have a clearer outlook on their future. She encouraged medical professionals to self-educate themselves on rare diseases, work in multidisciplinary teams and provide patients with the necessary tools to navigate the impact of these conditions; she emphasised the importance of research and collaboration with funding bodies to identify novel diagnostic biomarkers.



Hunginton's disease is the most curable incurable brain disease

The final talk was given by Prof. Ed Wild, Professor of Neurology and Consultant Neurologist at the National Hospital for Neurology and Neurosurgery, Associate Director at the University College London Huntington's Disease (HD) Centre.

Ed described the impact of HD in voluntary movement and explained there is a progressive decrease in cognitive function, leading to dementia in elderly patients, with a Parkinson's disease-like presentation in juvenile patients. Huntington's disease was described by George Huntington in 1872 but it was Nancy Wexler, whose mother was diagnosed with the disease after a long 'diagnostic odyssey', who together with her sister Alice created the foundation that, in 1993, identified the region of chromosome 4 where the HTT gene lives.

Too many CAG nucleotide repeats (in DNA) lead to too many glutamine amino acids (in protein), resulting in the mutant (changed) huntingtin protein. The altered protein aggregates, rendering many neuronal pathways dysfunctional, and can be observed by magnetic resonance imaging before the manifestation of any symptoms, which mostly occur around the age of 40–50 years.

Ed explained that diagnostic and predictive tests are available; however, around 80% of at-risk patients decide not to get tested, likely because there are no treatments yet approved for the prevention of HD. One of the reasons for this is difficulty recruiting people with rare conditions for clinical trials; Ed highlighted that people telling their story, via books or social media, helps recruit people for clinical trials and secure funding. Science is cumulative, meaning that even negative results bring us closer to an effective treatment.

Research into treatment for HD commenced with a study of RNA interference in a mouse model, silencing the HTT gene and improving symptoms. The first preventive therapies tested in humans were the so-called anti-sense oligonucleotides, which chemically modify DNA so the cellular system disables any further process, leading to protein synthesis. Ed made worldwide headlines by performing the first spinal injection, sharing the patient's journey as she "stepped onto a rocket without knowing the outcome".

The topline trial results made him cry – the drug (Tominersen) held the potential to decrease huntingtin aggregates in proportion to the dose administered. However, Phase 3 trials had to be halted due to worsening HD symptoms.

From these negative results, however, the scientists learnt that the drug had been administered too quickly and at too high a dose, causing inflammation and damage to vulnerable neurons. It's now clear that the best population to target with this treatment are young people with the smallest number of CAG nucleotide repeats and who have not yet developed symptoms. Hence, the Phase 2 trial will be testing lower doses of the drug in younger patients.

In the last couple of years, gene therapy using an adeno-associated virus to inject RNA into the brain and reduce the generation of huntingtin has been tested, with the first patients treated in the US and Europe tolerating the drug. Additionally, RNA splicing modulators, which also result in lower expression of huntingtin, have been delivered as an oral drug.

Ed emphasised that science needs to be directed by the people affected. The Enroll HD study is a good example; patients commissioned a group to conduct research, which resulted in the largest registry of patients with HD worldwide and a magnet for pharma companies looking to sponsor clinical trials.

Ed closed by encouraging the audience to work collaboratively: "if you want to go fast, go alone; if you want to go far, go together."

Key takeaways

A final panel discussion provided presenters with the opportunity to share one final tip regarding mental well-being:

Ask how patients are coping and ensure they are given the space to be brave enough to share their true experience (Kym)

Listen to and believe patients (Zheqing)

Remember to think of behaviour as a form of communication, especially in those who are non-verbal (Hayley)**, and the protective role of social connections** (Jane)

Take a break to prevent burnout (Dunstan)

Remember that drugs are very effective in mental health conditions and patients may lack insights, so by understanding what is not working in their lives we can help them get on the journey to accepting appropriate medication (Ed)

There was a consensus on the responsibility of healthcare professionals to take care of their own mental health so they can take care of their patients'. Speakers agreed that the individual profiles of rare conditions are very important to the identity of each family experiencing a rare disease but should not be a barrier in them joining the collective rare diseases space. The rare disease community, together, can make a much stronger impact in the future of all individual rare diseases.

Reflections

Following the event, Emma commented:

"I believe that this vibrant community of patients, students and healthcare professionals, brought together by M4RD, are truly changing the world with their stories, passion and dedicated work. For those with rare diseases, this meeting was a showcase of hope, underpinned by practical information and clear pathways to facilitate meaningful change on an individual and societal level."

Charlotte shared her thoughts on the afternoon:

"I'm honoured to have had the opportunity to attend this meeting after 2 years in the virtual space. I had two person highlights. The first was Sarah's diagnostic journey to VEDS told by Zheqing. This story was very emotional and if it doesn't show the desperate need for us to include rare diseases in medical education then I don't know what does. The second was Ed Wild's incredibly engaging presentation on Huntington's disease and the hope and ambition for a treatment in our lifetime."

Reflecting on the meeting, Ledicia said:

"Whether you have come across a rare disease in your immediate circle or not, I'm sure listening to Dunstan's story made everybody resonate with the range of emotions experienced by people living with a rare condition. Speakers at this meeting fully excelled at making the emotional journey these patients and their caregivers face understood, and this will most assuredly translate into broader mental health support from healthcare professionals and the general public."

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