Spring 2024

AGSD UK
Association for Glycogen Storage Disease

GLISTEN

GLYCOGEN STORAGE DISEASE NEWS

Thanks to all our inspirational fundraisers! Find out more about their efforts inside - and how you could get involved

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Charity Number :1132271

Thank you!

Help raise money for our vital services

Do you have a close connection with an employer or business who might be interested in making a donation to our work or might organise some fundraising to support our services?

It can be challenging to raise funds for rare and little known conditions like GSD. When organisations have a personal connection they're much more likely to help.

If you feel able to approach a company that might be willing to get involved with our cause and would like a template letter, leaflets or tips on how to go about this, just email info@agsd.org.uk. Your contacts could make all the difference in ensuring we can continue to offer the support that people affected by GSD value so much.

Front cover images:

The montage of photos from the Ben Nevis climb includes four McArdle-ites: summit photo L to R: ***Taylor Adam, Jen Dickson, Rachel Walker, and Colin Dearden***

Bottom right photo L to R: ***Flo Osborne, James Bruce and Vanessa Bruce***

AGSD-UK recognises that not everyone is online and has access to a computer. In this edition of Glisten, if we mention a website or a link to information and you can't use that to get the information you want,

PLEASE PHONE 0300 123 2790

We do not want ANYONE to be excluded; we will print and post things to you.

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Message from the Chief Executive

Welcome to the Spring 2024 edition of Glisten.

We all know the challenges faced by rare conditions in getting the attention, action and understanding they deserve. Because few decision makers and funders have a connection to the cause, it's difficult to gain political interest or funding. Low prevalence can limit research focus and investment. Meanwhile people affected can find it hard to link with others who really understand their experiences.

This edition of Glisten picks up on some ways to help tackle this. It includes a piece about how the forthcoming general election can be a chance to gain political support for rare conditions from candidates looking for your vote. There's a story about how community members used the hook of ***Rare Disease Day*** to raise money and awareness, plus a fundraising call to action to think about whether a personal connection to a business or employer could encourage donations or involvement in fundraising activities.

Another article describes a speed-dating event that offered a forum for life sciences companies, clinicians and organisations like AGSD-UK to meet and explore potential to jump start the development of new treatments. Also featured is a focus group bringing members of the ultra-rare GSDIV and APBD community together globally to pool numbers and build international collaboration for change.

Closer to home there's news about new online support groups being offered by AGSD-UK to help people share experiences and relaxation techniques and a flyer for our next Main Event, which is a great opportunity to spend time together while getting the latest on research and approaches to living well.

Progress on improving life with rare conditions may be an uphill struggle at times. But as illustrated by this edition, with its cover picture of the intrepid McArdle community members at the summit of Ben Nevis, it's one that can be best tackled together.

Val Buxton

Fundraising Round-up

Thank you to all who have been raising awareness and funds for the charity over the last six months.

Frank and Irene Green raised £1043.16 with their regular display of festive Christmas lights and decorations.

Lee Jones raised £220 for dying his hair and beard green!

Sioned Williams has raised £938 while celebrating her 70th year.

On May 19th, nine family, friends and colleagues of AGSD-UK's Chair, ***Flo Osborne*** from Loughborough University took part in the Nottingham Outlaw Team Triathlon event to raise money for AGSD-UK. After some weeks of training (!!!) and on a gorgeous Sunday morning, three teams set off at 6am to complete 1.2mile swim, 56 mile bike ride and a half marathon run.

Great tri-ers: Natalie Pearson, Dale Esliger, Ellie McDermott

Seasoned tri-ers: David Fletcher, Hilary McDermott, Stacy Clemes

Desperately tri-ing: James Bruce, Florence Osborne, Vanessa Bruce.

The weather was on our side as we took part in the event at Nottingham Hulme Pierre Point Lakes and by 2pm we were all enjoying a well deserved cold drink on the banks of the lake. Everyone has been hugely generous and we have managed to raise over **£2,500** for the charity. We want to thank everyone who came to support and sent messages of support leading up to and on the day.

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The Rarest Day

As 2024 is a leap year, Rare Disease Day fell on the 29th of February.

It was an extra special day for Gary Thompsons' daughter who has GSD and was born on the 29th. Gary organised a charity bake sale on the day and raised a fantastic **£453** for AGSD-UK!

Meanwhile Sioned Williams marked the day with a great video promoting awareness of McArdle disease, the work of AGSD-UK and how McArdle's has affected her life as a leading harpist. She writes:

'The rarest day in the calendar, 29th February was also international Rare Disease Day.

I produced a short video for YouTube, Facebook and other platforms. I do this every year to highlight the need to share information about McArdle disease to the masses. In this particular video I explained how AGSD-UK has such valuable resources for all. I personally would be lost without the help and information gained from this association. For me, to be able to access specialised services is vital but so too are the lifelong friendships I've made through AGSD-UK.

If you haven't had an opportunity to check out my 2024 Rare Disease Day video, now is your chance! If you could also share the link to the JustGiving page, both AGSD-UK and I would be very grateful'.

YouTube video https://tinyurl.com/4s5bnez5

JustGiving page https://justgiving.com/sioned-williams28

Five (minus one!) Go For It on Ben Nevis

Congratulations to ***Jen Dickson***, ***Rachel Walker***, ***Colin Dearden*** and ***Taylor Adam*** who all made the Ben Nevis summit on the 11th of May. Commiserations to ***David Thompson*** who couldn't join them due to a cycling injury the week before.

On 11th May a group of four McArdlers set off to climb Ben Nevis in Scotland. At 1345m it is the UK's highest mountain. It is a 16.6km hike and for a non-McArdle's person would typically take eight hours to get to the top and back.

Colin, Rachel and Jen have previously met a few times over the years whilst mountain walking in Snowdonia on trips organised by Andrew Wakelin. The fourth member of the group, Taylor, is the youngster of the group but he's a keen walker and was enthusiastic to take on Ben Nevis. Our ages range from early 20's to late 50's and the two main things we all have in common are: 1) we all have McArdle disease; and 2) we share an overwhelming desire not to let the condition define us or limit our goals.

We were all training in the lead up to this event and were hoping this would be enough for us all to be able to reach the summit.

'After all the effort we're so pleased we made it -this may be the first time that four McArdlers have stood together on the highest point in the UK. We are all looking forward to our next challenge!'

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THE MAIN EVENT

AGSD UK
Association for Glycogen Storage Disease

Feedback from 2023 event

'Fabulous weekend! ...Loved the whole conference. Great speakers and workshops.'

9th - 10th November 2024

Back at **Burleigh Court, Loughborough** *by popular demand!*

Whatever your GSD, join us for:

- Updates on latest research and treatment options
- Tips for living well
- New therapeutic activities to try
- Time to share experiences and make new friends
- Chance to hear from leading experts
- Fun for children and families

'100% valuable. Well organised. Would love an event in this place again.'

'Great organisation. Informative programme and social opportunity to connect with others. Venue and food spot on'

'Learnt more today than in the previous 50+ years since initial diagnosis'

Visit agsd.org.uk for more information and how to register

EXPLORING PHYSICAL ACTIVITY & EXERCISE AMONG PEOPLE LIVING WITH POMPE

My name is *Nicola Condon*, I am a physiotherapist, and I work with the *Inherited Metabolic Disorders* team at the *Queen Elizabeth Hospital* Birmingham. I have been with the team for over ten years and over this time I have observed the unique difficulties encountered by our patients when engaging in exercise and physical activities. I have recently completed a Master's in Clinical Health Research at the *University of Birmingham* and for my thesis I conducted a research study exploring the barriers and facilitators to physical activity and exercise for people living with Pompe disease.

Purpose of the study

The purpose of the study was to explore the perceptions and experiences of people living with Pompe disease when engaging in physical activity and exercise. Research shows that physiotherapy and exercise training (aerobic and strength training), is safe and beneficial for individuals with Pompe and can improve general functioning, however, little is known about the experiences and main barriers people encounter when engaging with exercise.

Methods

Seventeen study participants were recruited with support from the Association of Glycogen Storage Disease (AGSD UK) and Pompe Support Network. Participants were asked to take part in interviews which were conducted over Zoom. Interview questions aimed to explore the individuals' experiences with exercise, current and prior to diagnosis, their attitudes towards activity and exercise, what helps or hinders them in keeping active and what support and advice (if any) they had received from healthcare professionals. Interview transcripts were then analysed to identify common themes across participants.

Results

Participants reported a range of themes and the following were identified as factors influencing engagement in regular physical activity and exercise.

- Participants engaged in a diverse range of exercise and physical activities which suited their interests and diverse physical capabilities (*Figure 1*). The most reported barriers to exercise were fatigue,

Figure 1: Range of activities participants engaged in

pain, mobility and balance issues and motivation. Facilitators were support (physical, practical, or emotional) from carers, family, friends, or healthcare professionals knowledgeable about LOPD, and enjoyment in the activity.

- Most participants achieved some regular physical activity. Over half of the participants required support to achieve this and often needed motivation to maintain it.
- Available resources and support across the health services were generally considered lacking, particularly when initially diagnosed.

Conclusions

This study provided valuable insights into factors important for physical activity behaviour for people living with Pompe disease and can guide healthcare professionals in supporting physically active lifestyles.

The results of this study further highlighted that factors influencing participation in exercise for people with Pompe disease are complex and require an individualised approach by healthcare professionals knowledgeable about the condition.

FINDINGS: Three main themes were identified as factors influencing engagement in regular physical activity and exercise: 'Perceptions, beliefs and preferences'; 'State of wellbeing' and 'Socio-environmental conditions'. There were also a number of sub-themes, as illustrated in *figure 2*.

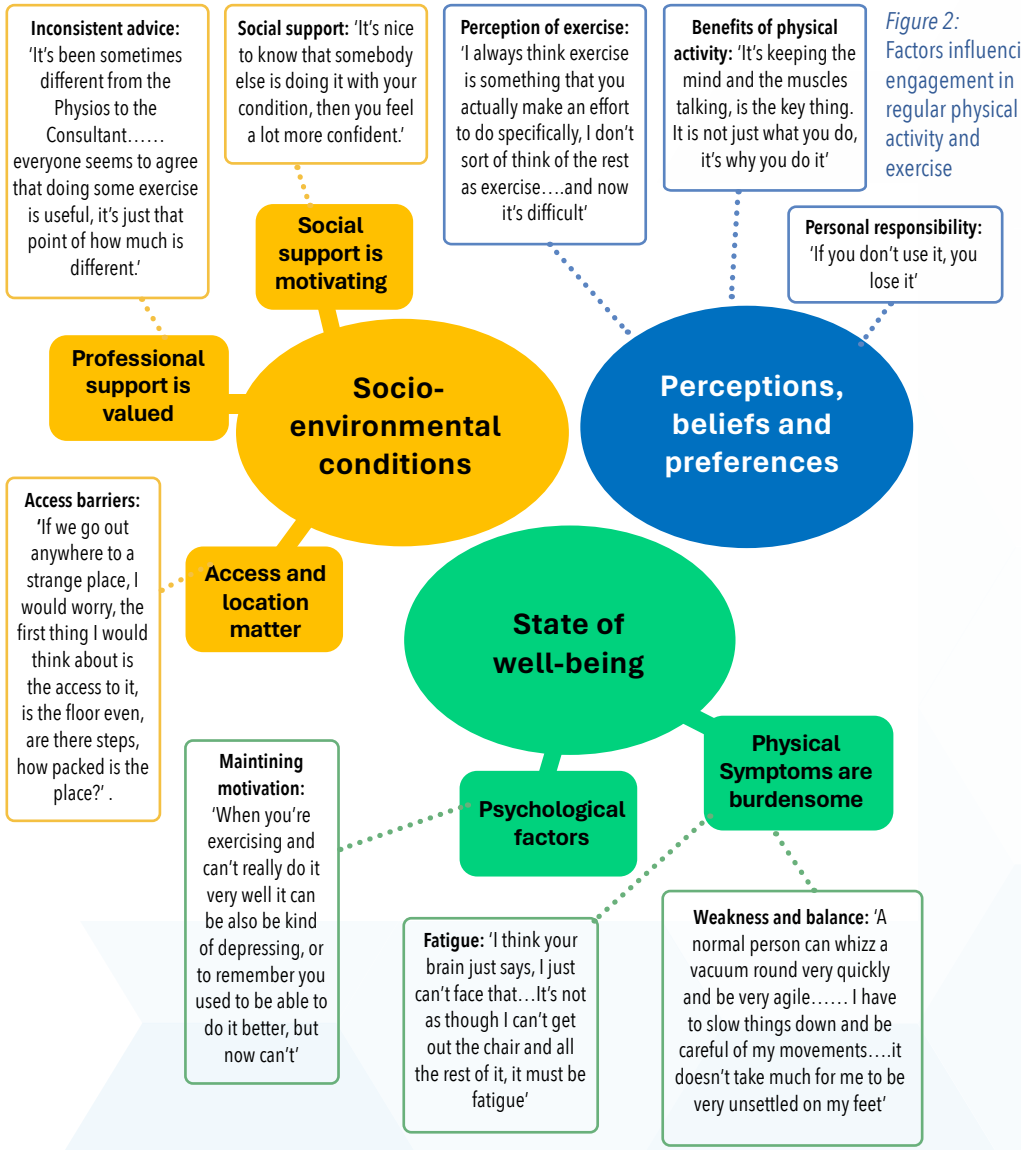

Figure 2: Factors influencing engagement in regular physical activity and exercise

I would like to thank the participants for sharing their time and experiences and to the AGSD-UK and Pompe Support Network for their support.

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New personal McArdle's stories

Since the Autumn 2023 edition of Glisten, IamGSD has added personal stories to their website.

Bronte Thomas, UK

Rachel Thomas tells the story of her daughter *Bronte's* journey from an unhappy 2-year-old, through years of investigations to an eventual diagnosis of McArdle disease – an ultra-rare genetic condition, at age 14. Then finding good information from the doctors and the support networks and gradually learning how to manage well. Bronte now passes it on to others, having spoken at the 2023 Main Event and played a leading role in the walking courses in Wales.

One of Holly's series of photos representing what it's like to live with McArdle disease

Holly Goodwin, USA

Holly has produced a series of photographs which convey what McArdle's feels like. The photos show a visualisation of the "invisible extra weight" that she carries due to this genetic muscle disease. The letter "M" features for McArdle disease and the suitcases are concrete and represent the baggage that affects her mentally and physically during normal activities.

James and Ned Duggan, Australia

Jane Harris and Darcy Duggan tell the story of their twin boys, James and Ned. Now 16, they were diagnosed back in 2014 using a genetic test developed in Australia. They are doing very well, with support from the Children's Hospital Westmead and the international McArdle's community. They enjoyed time with many McArdleites on the walking course in Wales last summer.

Slow & steady work to treat GSDIII

On the other side of the channel, in France, scientists have been involved in a lengthy search for a treatment for GSDIII.

Some of you may remember *Giuseppe Ronzitti*, who came to our conferences at *Nottingham University* and *Wyboston Lakes* to present his research.

Giuseppe is now leading a team at *Genethon Laboratories* who specialise in gene therapy. They are looking at a gene therapy strategy involving a working version of the enzyme involved in GSDIII, that is small enough to be carried to diseased cells.

They demonstrated that when a recombinant adeno-associated virus expressing a truncated version of the enzyme was injected into mice and rats, a working enzyme was produced that significantly reduced accumulated and abnormal glycogen. This restored muscle and heart function and the same method corrected glycogen accumulation in a GSDIII model of human cells.

Jérémy Rouillon and *Antoine Gardin*, researchers who are part of the team have said:

"This breakthrough is an essential first step towards the development of a gene therapy for GSDIII patients, offering the hope of an innovative solution that should significantly improve their quality of life."

Here is a link to the academic article.

https://www.jci.org/articles/view/172018

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The next General Election
Something to talk about with your candidate

When your prospective parliamentary candidate knocks on your door and asks for your vote, what will you say?

You could say there are 3.5 million voters out there with a rare disease who are all looking for help. Help that starts in Parliament.

GSD is a rare disease, but there are 7,000 rare diseases and 3.5 million people in the UK are affected. Rare diseases aren't so rare and government figures show that they receive poorer than average care.

1 in 17 people will be affected by a rare disease at some stage in their life. They deserve far more attention than they are given.

But strength can be found in collaboration and making sure that people who can make a difference are aware.

You could direct your candidates to Rare diseases, common inequalities: bringing rare diseases into the health inequalities agenda. This was published last year by the *Specialist Healthcare Alliance* in collaboration with the rare disease charities, who they work with, and represent, at a parliamentary level. The link to this document is: https://tinyurl.com/36uwk6nt

The 8 key headings and areas for improvement are

1. **Lack of knowledge, understanding and awareness among Health Care Practitioners**
2. **Poorly coordinated care**
3. **Scarcity of specialised services/centres across the UK**
4. **Lack of funding for rare disease research**
5. **Accessing clinical trials**
6. **Delays in medicines approval**
7. **Mental health**
8. **The financial impact of a rare disease**

Genetic Alliance and the *Specialised Healthcare Alliance* have also published a Manifesto for rare diseases that has been sent to all political parties ahead of the next general election and can be accessed here: www.tinyurl.com/3z6457cp

Above all, let your candidates know your opinion. Your voice matters to them, and they want to listen.

Bannau Brycheiniog… The McArdleites are coming!

Our courses for 2024 are almost fully booked at the time of going to press. But if you'd like to see if we can squeeze you in, please urgently contact Andrew Wakelin on (01597) 860686, or email type5@agsd.org.uk.

We will be returning to the Bannau Brycheiniog (Brecon Beacons) National Park in South Wales, with accommodation near Hay-on-Wye. Walks along riversides, behind a waterfall and even up relatively easy hills and mountains will feature! For either course, all you need is to be able to get into second-wind and then we take it from there.

Under 21s course – Monday 29 July to Monday 5 August. Adults course – Monday 5 to Friday 9 August. Full details are on our website.

Our previous visit to BBNP, in 2018… setting off on the Wye Valley Walk, an iron suspension bridge around the corner then beside the River Wye.

Social groups you can get involved in

For more information and joining details for any of these groups just contact info@agsd.org.uk

Living Well socials

This group started a few months ago and aims to enhance overall well-being and emotional health. So far we've explored approaches like positive thinking, affirmations, meditation, and relaxation. Everyone's welcome at these friendly, online sessions where participants shape the agenda and their voice is always valued. It would be great to see you at our next ***Living Well*** social on 18th July, at 7pm.

'I'm writing to follow up on our session... I thoroughly enjoyed it! The positive atmosphere left me feeling uplifted afterwards. It's amazing how much seeing other humans can brighten a dull day. Zainib and Elizabeth really brought the people together. Their engagement with us, listening to our inner feelings and thoughts, created a safe space to open up. The energy everyone brought was fantastic, and the discussion topic was particularly engaging. I'm eagerly anticipating our next session. Thank you'

'I very much enjoyed being part of an AGSD-UK gathering of lovely people to share friendship and experience, on Zoom... Elizabeth and Zainib led us brilliantly and let us share some thoughts with each other, and both brought such fun and energy to us all. We were led into positive thinking and positive affirmations, and the time went too quickly. An hour later, we'd made new friends, re-acquainted ourselves with others, and we know there's always someone there for us, and that we are well supported. I certainly think many would enjoy this type of meeting...'

'I very much enjoyed the Zoom meeting... It was very informative and uplifting...I feel I gained a lot and am looking forward to the next meeting'.

'I am absolutely thrilled and immensely grateful for the positive mindset social meeting. It was truly a wonderful experience. Managing life while dealing with a child who has no cure can be incredibly challenging, and having this support system is like a breath of fresh air. I felt rejuvenated and uplifted after attending. Zainib even assigned us homework, which is quite exciting! This has prompted me to reflect on how I think and the consequent impact on my feelings. The training was remarkably powerful. Thank you so much, AGSD-UK!'

Parents' group

Our new online parents' group will run every few months according to demand and will offer all parents the opportunity to meet others and hopefully gain support and share experiences. Each meeting will have a theme, previously decided by parents and will we also have online speakers. We're looking forward to running a face-to-face session at the Main Event.

Men with GSD

We're excited to tell you about our latest virtual group, which is for men with GSD and male carers. We have asked a very experienced facilitator to run these for us and here is some information about him. If you would like to know more, or get involved, then please let us know.

'Hi, my name is David, and I was diagnosed with a rare disease as an adult in 2017. Soon after my diagnosis I reached out for support and found that whilst there were many amazing females in the community there was nothing for men.

So, in 2020 I set up a mental health support group for rare disease patients and caregivers around the world on Zoom with the purpose being to provide a safe space where men could share their experiences, seek support, and listen to others.

I am very excited to be given the opportunity to support AGSD-UK in setting up a men's group. I feel I have the proven experience to make it work and I also feel that this is something that is definitely needed for guys. Having a group like this can also support men but also celebrate their strengths which are both important when you are impacted by a rare disease!'

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Speed dating event aims to kick-start development of new treatments

Aspire Biosciences invited AGSD-UK to engage with a "speed dating" event in December 2023. Entitled _Collaborating for Change_, it was for companies and support groups involved with rare metabolic and liver diseases.

For this particular event AGSD-UK fielded a team representing McArdle's, though there will be an opportunity to focus on different GSDs at a future event. We are grateful to ***Prof Ros Quinlivan*** and ***Dr Richard Godfrey*** for representing GSDs on this occasion, together with ***Andrew Wakelin***, our McArdle's Coordinator.

It was a whole day event held at the ***Royal Society of Medicine*** in London, with representatives from nine life sciences companies and nine patient groups.

An introduction by ***Aspire*** explained the goal of jump-starting the development of new treatments through leveraging the companies' platform technologies, de-novo developments based on identifying new targets, or by repositioning existing and parked assets.

Speed dating session where bioscience companies rotate around the tables of the patient support groups.

Aspire Biosciences

Systematic Serendipity for Rare Disease

The patient groups brought:

- a vast amount of knowledge and experience about their diseases;
- a clinical or scientific expert;
- and a variety of resources – from registries to biomarkers, patient-generated lists of unmet needs, and custom-made animal models.

The day began with short pitches by the patient group teams, followed by the company teams, just five minutes each. It was quite a challenge to put across something about GSDs in such a short space of time. This was achieved by Andrew and Richard presenting to an audience of about 50 in the lecture hall of the Royal Society.

After lunch came the speed dating part. Each patient group had a table at which to meet the various companies in turn, each for just twelve minutes. We needed to get to know each other and to understand what each side had to offer. The whistle would blow and the companies moved on to the next group in the rota.

After a short break, we were able to follow up on the most promising relationships and meet those companies again. Several interesting avenues developed and we are now following up with those companies.

Many thanks to Aspire BioSciences for organising this novel and worthwhile event. You can read more about what they do on their website at:

www.aspire-biosciences.com

Discussing Pain & Tiredness with your Health Professionals

You, your child or someone you know has glycogen storage disease. You may have googled or asked about it and found out about missing enzymes, large livers, special diets, weakened muscles and even metabolic pathways. But did anyone ever tell you about two symptoms that loom large, yet are rarely discussed - pain and tiredness.

Aurel Tankeu and *Cristel Tran*, researchers at the medical genetic centre in Lausanne, France have noted that chronic fatigue is common with diseases such as glycogen storage disease and is often exacerbated by physical exertion, infection, fasting or cold. The tiredness is real.

Health professionals see tired and hurt people every working day and these kindly and concerned people will offer pain killers, sympathy, and walking aids. They no doubt will worry about how best to help. You have an appointment and are told that your blood results are good/not good and what the scan showed. But as you walk away with a smile maybe you are thinking, '*do they really know how I feel?*'

There are so many questions that could be asked.

- What do you not do because of the pain and tiredness?
- How do you sleep?
- How did you find the journey here?
- You were OK yesterday, but are you OK today?
- Did one day's activities affect you for the rest of the week?
- Are there days when you can't think too clearly?
- Are pain and tiredness affecting your school or work?
- Are you missing out on what could be considered a normal life because it easier to stay at home and rest?
- How is your mood and how do you cope when you are feeling low?

An endless list of questions and everyone will have their own, unique thoughts.

What can be done?

There are many answers such as eating and sleeping well, being kind to yourself, but one path is sometimes overlooked, communication. But just how can communication be done effectively? Think how your life is affected. Talk about how you manage on an everyday basis. If you want, write down your thoughts before you meet them for your regular appointment and remember it is always possible to phone or write after the appointment if you feel an important topic has not been covered or use whatever method works best for you. Plan with your health practitioner. You have a partnership, and they want to help you. The pain and tiredness you are feeling is not small. Be strong while you represent yourself. Don't dismiss pain and fatigue as symptoms that '*have to be put up with*'. The benefits could be immense with possible improvements to every single area of your life.

Advice to health practitioners

You are there to make people better. This often can't be done with GSD and that is difficult, even frustrating when you came into a job to diagnose and provide a solution. Don't withdraw; empathise and then go one step further by engaging and asking simple questions such as '*What is the worst part for you*" "*What is important to you?*" Repeat back what has been said to you, but in different words, it is a demonstration that you are listening and understanding. Form a partnership with the patient, the care you give will only get better as your understanding of how pain and fatigue affect every aspect of their life, both physical and mental. Learn about a person's unique coping strategies and make a plan. Support and communicate and a solution for an individual may happen. Then gather these statistics together, if the true size of the problem is known then services may improve.

This article was written by a health practitioner and a mother of child with a hepatic GSD.

"Pain, tiredness and good communication are issues I grapple with every day. I am aware how difficult it is to reach a good level of understanding, but I do know that it is something that must consistently be worked at by everyone."

APBD Research Foundation Focus Group Brings APBD & GSD IV Communities Together

By Natacha Pires, MS, MBBS, Executive Director, APBD Research Foundation

On May 6, 2024, the ***APBD Research Foundation*** hosted a virtual focus group that brought together, for the first time, over 50 participants representing the ***Adult Polyglucosan Body Disease*** (APBD) and ***Glycogen Storage Disease Type IV*** (GSD IV) communities. The participants included patients, family members, patient advocacy organisation leaders, clinicians, and researchers from 13 countries. Among the participants were AGSD-UK, along with two UK community representatives.

Founded in 2005, the APBD Research Foundation (APBDRF) is the only US-based patient advocacy and research organization committed to finding treatments and a cure for APBD while improving the lives of those affected.

According to the scientific literature, just 200 cases of APBD and 146 cases of GSD IV have been diagnosed worldwide. Given patient reports of their lengthy diagnostic odyssey and multiple misdiagnoses, we assert that both groups of patients are likely under-diagnosed.

A recently completed study by the ***Broad Institute of MIT and Harvard*** estimates the global genetic prevalence of all GBE1 diseases, including APBD and GSD IV, at 26,000. To advance therapeutic development, the APBDRF believes it is imperative to build bridges between the APBD and GSD IV communities.

As ***Felix Nitschke***, PhD - a basic science researcher at UT Southwestern Medical Center and co-chair of the APBDRF's Scientific and Medical Advisory Board - shared, "*The fact that APBD and GSD IV are essentially different manifestations of the same biochemical problem provides a powerful argument for the patient communities to join forces and face the battle against glycogen branching deficiency diseases together.*"

The first challenge to convening the focus group was to identify and connect with GSD IV families and community members living around the globe. The APBDRF accomplished that by partnering with Humanized Solutions, a Portugal-based company that supports healthcare stakeholders by implementing solutions co-created with the patient voice.

During the focus group's first session, participants heard from patients and their physicians about the challenges in the diagnostic journey, as well as from researchers about the link between APBD and GSD IV, global genetic prevalence, natural history studies, and clinical practice resources. These presentations built on the focus group's narrative - building community, and strength and power in numbers.

The focus group's second session was set up as a Q&A panel discussion among GSD IV and APBD family members, patients, and leaders of patient advocacy organizations. The 12-person panel was moderated by ***Vanessa Ferreira***, PhD, MBA, co-founder of ***Humanized Solutions***, and a leader in the ***Congenital Disorders of Glycosylation***

community. The panellists discussed the challenges to receiving a correct diagnosis; the importance of helping families connect with each other, health professionals, and patient advocacy organizations; and the need for stronger global collaborations. The focus group is seen as a launching pad for strengthened collaborations among APBD and GSD IV community members as we work toward making therapies a reality.

The APBD Research Foundation and Humanized Solutions are developing a Summary Report that sheds light on the needs of the GSD IV community, highlights best practices from both GSD IV and APBD families and representatives, and identifies priority areas of possible near-term and future collaborations. To learn more about APBD and the APBDRF's work, visit: www.apbdrf.org.

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Gene therapy trial town hall meeting

On the 1st of April this year Ultragenyx staged a virtual town hall aimed at a US audience, in response to questions submitted by the GSDIa community about their DTX401 gene therapy trial.

The data presented in the session related to the stage 1/2 global study[i] and was collected up until March 10th 2023. All data presented was already in the public domain. Data from the first 48 weeks of the larger phase 3 global study[ii] in ages 8+, which is now in progress, will be presented later in the year. The company stressed that the safety and efficacy of DTX401 has not yet been established and it has therefore not yet been reviewed or approved by any regulatory body.

An overview of the design of the study was given by *Dr Rebecca Riba-Wolman* from *Connecticut Children's Medical Centre*. Twelve adult subjects were enrolled in the phase 1/2 study with three subjects in each of four treatment cohorts. The cohorts varied in terms of the dosage given and treatment regimen, including the way steroids were used to manage potential immune reactions from the adeno-associated virus (AAV) vector.

Figure 1 summarises the criteria for the study participants. Dr Riba-Wolman commented that while the number of participants was very small, there was diversity in terms of their genotype, the level and frequency of their cornstarch intake and how long they were able to fast at baseline before treatment. *Figure 2* shows what researchers were looking for from this phase 1/2 safety study and *Figure 3* shows what other patient experience data was being collected.

Only people without antibodies to the vector AAV8 were eligible for the study and a number of the questions submitted related to this issue. In terms of AAV8 antibody prevalence, Dr Riba-Wolman explained that while data was not available from this study, research in other disease populations points to significant geographical variations. It was stressed that DTX401 was currently a one-time infusion, as the development of antibodies in response to the therapy would prevent re-dosing. It was highlighted that while the study didn't consider what the options might be for people who do have antibodies, this is an area of active focus for Ultragenyx and other organisations working in the gene therapy field.

Safety data

In his presentation of the emerging safety data *Dr John Mitchell* from *Montreal Children's Hospital* highlighted that there had been no serious related treatment-emergent adverse events or dose limiting toxicities by the data cut off point and no patients were discontinued from the study. While, as expected, levels of liver enzymes AST/ALT increased in all participants, this resolved with steroids. These were given reactively as enzyme levels went up in the first cohorts then prophylactically in the final cohort, with the dose being gradually reduced as indicated. This preventative approach to managing the vector-associated inflammatory immune response has continued into the phase 3 study.

Giving an overview of the nutritional data, dietician *Heather Saavedra* from the *University of Texas* explained that all study participants had been able to reduce their cornstarch intake at the one year point.

Figure 1

Safety and Dose-Finding Study of DTX401 (AAV8G6PC) in Adults With Glycogen Storage Disease Type Ia (GSDIa)

Who Participated?

- Males and females ≥18 years of age
- Documented GSDIa with confirmation by molecular testing
- Documented history of ≥1 hypoglycemic event with blood glucose <60 mg/dL (<3.33 mmol/L)
- Patient's GSDIa disease was stable as evidenced by no hospitalization for severe hypoglycemia during the 4-week period preceding the screening visit

What investigational product was studied?

DTX401 is an investigational adeno-associated virus serotype 8 (AAV8) vector designed to express the human *G6PC1* gene under transcriptional control of the human G6Pase promoter

Figure 2

What were researchers looking for?

The primary endpoint was to evaluate the **safety** by examining the incidence of adverse events (AEs), including dose-limiting toxicities (DLTs) at each dose level, treatment-emergent AEs (TEAEs), and serious AEs (SAEs) for each cohort, assessed by severity and relationship to DTX401.

Key study assessments included:

- Time to hypoglycemia (TTH) assessed by a controlled fasting challenge (CFC): assess symptom-free, fasting time in euglycemia
- Average cornstarch dose and frequency
- From Cohort 3 onwards: percentage of time in euglycemia (60-120 mg/dL) by continuous glucose monitoring (CGM)
- Corticosteroid therapy (prednisone) when suspected vector-induced immune response (administered prophylactically for Cohort 4)

Figure 3

Was any other data collected?

- Clinical interviews were conducted interviews among 7 subjects
  - 5 participated at week 25
  - 7 participated at weeks 52 and 104
- These interviews assisted the Ultragenyx team to define the outcomes that are most meaningful to people with GSDIa and their families.
  - This type of research allowed them to describe their experiences in their own words, which goes beyond the information that can be captured in a survey or other trial assessment
- Questions included but were not limited to:
  - Did you experience any changes due to the study treatment?
  - What did you expect from the study treatment?
  - What did you like about the study treatment? Why?
  - What did you not like about the study treatment? Why?
  - How does your GSDIa treatment now compare to when you started the clinical study?

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Nutrition results are summarised in *Figure 4.*

There was encouraging data on the durability of the effects which had lasted over four years in the first cohort, with more to be learned from follow up of the remaining cohorts.

Speaking about metabolic control, Dr Mitchell referred to an increase in the percentage of time the blood sugar of those in the later cohorts remained within the desired range and an improvement or stabilisation of fasting time to hypoglycaemia, despite the reductions in cornstarch intake. Longer term data would allow more insight into the way the different steroid regimes have an impact on the efficacy of the therapy.

In response to further questions ***Dr. Richard Collis*** from ***Ultragenyx*** explained that treatment with this therapy may not necessarily preclude being treated with any other therapy that might be developed in the future. However this would depend on the eligibility criteria for any future clinical trials and the prescribing information for any treatment that had been approved.

While data on patient experience of the trial gathered though interviews was not yet available, it was noted that all subjects had opted to enrol in the ongoing five year extension study evaluating the long term safety and efficacy of DTX401 over a total of six years from dosing. All those involved with the study were thanked for their participation.

i Phase 1/2, ClinicalTrials.gov Identifier: NCT03517085. Safety and Dose-Finding Study of DTX401 (AAV8G6PC) in Adults With Glycogen Storage Disease Type Ia (GSDIa)

ii ClinicalTrials.gov Identifier: NCT05139316. A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Adeno-Associated Virus Serotype 8-Mediated Gene Transfer of Glucose-6-Phosphatase in Patients With Glycogen Storage Disease Type Ia also known as Glucogene

Stop press: Ultragenyx have now provided an update on topline results from their ongoing phase 3 study. See **www.tinyurl.com/4fankbw2** for details.

Figure 4

Nutrition

Cornstarch Use	Total Calories	Body Weight
5 of 12 participants reduced cornstarch dose frequency by half or more and received two or fewer doses per day	Total calories from cornstarch decreased, while total calories from diet increased, indicating a shift from cornstarch dependence to a more balanced dietary intake	Body weight decreased for most participants • At Week 52: -4.1% (range: -11.8 to +2.8%) • At last visit: -2.5% (range: -13.2 to +10.8%)

The Journey to Diagnosis

After suffering since I was 16 with a bad back on and off, the doctors had always put it down to slipped discs or static nerve problems.

It wasn't until I dropped just over 10 stone in 18 months, after joining the gym to focus on losing weight and increasing fitness, my legs started becoming weak. Then I started having falls, or my leg would give way. During this time, the doctors referred me to a neurologist. I then became unable to walk up the stairs and I had to crawl on my hands and knees as I couldn't walk up them standing up anymore. On arriving at the appointment with the neurologist, as I walked in, he pointed out my gait. After a few questions he said he believed he may be able to request a biopsy for my muscular tissue in my legs but would need to speak to a specialist in Manchester at Salford to ensure this could be done, as it is not something that is done often.

Within a couple of weeks, I was asked to attend for a muscular tissue test where they inserted needles to test muscular density. When the results came back poor, I was then booked for the biopsy. The biopsy was in August 2022, I remember as it was the week my sister got married. I also had a genetic test. They said everything could take a while to get back as they were going to test me for everything. Just before Christmas 2022, my specialist contacted me at work to explain the results had come back, and it was Pompe disease. He referred me to a specialist in Manchester that dealt with rare diseases.

From there, 2023 was a bit of a blur from lots of hospital trips in a different city, to more tests from physicals to bloods tests etc. I attended my first appointment in Manchester around Feb 2023, where I met my new specialist at that time, and he explained everything to me. I was shocked to know that all the problems I had had from being a child, such as walking on my toes, were signs of the disease. He said I was eligible for enzyme replacement therapy, and he would put me forward. I then waited to hear from them for an assessment to see where I would be on the waiting list.

Aug 2023, I was called in to see my new specialist along with a nurse and a physio. My husband and I went through

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everything with them, and I was assessed by the physio. The specialist believed I needed treatment as soon as possible. I was fortunate to start my treatment in Dec 2023.

During the waiting time of 2023 between appointments, I needed to change jobs due to the physical demand of teaching early years. I moved into management with a private nursery that is still demanding but more office based.

I also had occupational health assessments, which told me I needed lots of aids from walking sticks (which I use), a bed rail to help me in and out of bed, and a raised seat for the toilet. I needed a shower room commode for downstairs as I am unable to get up the stairs and they deemed my house not to be suitable due to having stairs.

Ideally, I needed an extension with a downstairs bedroom and bathroom. Unfortunately, due to working and owning my own home, the government was unable to help me with the adaptations that I needed through the local council. I felt that every opportunity for help kept closing its doors on me.

I found out about *Personal Independence Payment,* which luckily I am eligible for. This is slowly helping us to pay for the changes that we need but it's a long road and still now, in April 2024, I am having to crawl upstairs due to finances and saving for a stair lift. I personally feel for working people who get overlooked as they have an income. I was told to sell my house or stop working but I am a fighter, and I will continue to keep fighting so that I can still work and have my own home. I won't lie, it's hard, but nothing in life comes easy.

I received two rounds of treatment over Dec 2023 in Salford, but my veins were proving difficult and not working. I started home infusions Jan 2024, but unfortunately, my veins had had enough. Every week they tried and tried again so I ended up going 14 weeks without treatment due to my veins. I was then requested to have an emergency portacath, which was fitted beginning of April 2024, and I have received my first treatment successfully. I am so grateful for all the medical help I have had over the last two years. They have continued to persevere until they got to the bottom of it all.

I think the hardest part other than the physical side of things is the mental drain and learning how to work through emotions. I went from feeling a burden to realising life is too short to be upsetting myself. I have struggled and still struggle with people knowing about my diagnosis as I don't want to let people see I have changed, but I am working through this.

I am very lucky to have an amazing family network and found some amazing support groups online that provide me a safe space to rant when needed. I know my life is changing, but I will not let this disease define me it just makes me fight harder. My advice to anyone is to not lose hope, take each day as it comes and don't be afraid of what people think and don't lock yourself away like I did.

After a lot of research and help from my fellow Pompe friends I have decided to get an electric wheelchair so I can start enjoying family time again and getting out and about. Here's to making new memories!

For more information on financial support, follow this link: **www.gov.uk/disabled-facilities-grants** and for further help contact our specialist care advisor by emailing **info@agsd.org.uk**

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Muscle GSDs Research Round-up

For a group of such rare conditions, it is surprising how much research goes on. Much of it takes many years, or even decades, to come to a conclusion. Here are some reports from recent months, with varying degrees of relevance and interest.

Muscle glycogen unavailability and fat oxidation rate during exercise: insights from McArdle disease.

J Physiol 601.3 (2023) pp 551–566.

This study from Spain showed that McArdle people were significantly better than controls at utilising fat oxidation for energy. The following is a quote from the abstract of the paper. "In summary, patients with McArdle disease show an exceptionally high MFO [maximal fat oxidation] rate, which they attained at near-maximal exercise capacity. Pending more mechanistic explanations, these findings support the influence of glycogen availability on MFO rate and suggest that these patients develop a unique fat oxidation capacity, possibly as an adaptation to compensate for the inherited blockade in glycogen metabolism and point to MFO rate as a potential limiting factor of exercise tolerance in this disease."
https://tinyurl.com/3ceabnn8

Fatigue and associated factors in 172 patients with McArdle disease: An international web-based survey.

Neuromuscular Disorders, Volume 34, January 2024, Pages 19-26.

"We found relatively high fatigue scores in all five domains (general fatigue (12.9 ± 2.2), mental fatigue (10.1 ± 4.1), physical fatigue (13.7 ± 4.1), reduced activity (12.1 ± 4.1), and reduced motivation (10.4 ± 3.4)). Fatigue associated with McArdle symptom severity ($p < 0.005$), lower levels of physical activity (assessed by IPAQ-SF) ($p < 0.05$), and poor sleep (assessed by ISI) ($p < 0.05$). These findings call for clinical focus and future research into fatigue, sleep, and mental health in patients with McArdle disease."
https://tinyurl.com/r998xsaw

Dose–response effect of pre-exercise carbohydrates under muscle glycogen unavailability: insights from McArdle disease.

Journal of Sport and Health Science. Available online 27 November 2023.

This study was led by the team in Spain. The findings included: "CHO [carbohydrate] intake exerts beneficial effects on exercise capacity in McArdle disease, a condition associated with total muscle glycogen unavailability. Some of these benefits were dose dependent."
https://tinyurl.com/4uccy99r

Toward an understanding of GSD5 (McArdle disease): how do individuals learn to live with the metabolic defect in daily life.

Journal of Neuromuscular Diseases, vol. 11, no. 1, pp. 103-116, 2024.

This patient-led study aimed to capture the daily life experiences of GSD5, with a focus on adapting to and coping with their physical activity intolerance. It was conducted by the team in the Netherlands. The conclusion stated: "Participants have provided guidance for newly diagnosed people, including the advice to accept one's limited abilities and maintain an active lifestyle. We conclude that adequate counselling on ways of adapting and coping is expected to increase both health-related quality of life and physical activity."
https://tinyurl.com/2ub28x5h

Creation of an iPSC-based skeletal muscle model of McArdle disease harbouring the mutation c.2392T>C (p.Trp798Arg) in the PYGM Gene.

Biomedicines 2023, 11(9), 2434.

This study presents "the generation of the first human iPSC-based skeletal muscle model harbouring the second most frequent mutation in PYGM in the Spanish population: NM_005609.4: c.2392T>C (p.Trp798Arg)."

"The created McArdle skeletal muscle model was validated by confirming distinctive biochemical aspects of the disease such as the absence of myophosphorylase, the most typical biochemical feature of these patients. This model will be very valuable for use in future high-throughput pharmacological screenings."
https://tinyurl.com/yyzfm9e4

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Muscle GSDs Research Round-up continued...

Syndromic PRD: case report of McArdle retinopathy and review of literature.

Published online: February 28, 2024. ©2024 Canadian Ophthalmological Society. Published by Elsevier Inc.

"Ophthalmologists need to be aware of the existence of syndromic PRD [pattern retinal dystrophy]. We recommend systems review, a detailed family history, and consideration of genetic testing to aid in the diagnosis of underlying syndromes and to rule out phenotypically similar macular dystrophies (e.g., due to PRPH1, BEST1, IMPG1, and IMPG2). Because PYGM is not included in typical IRD [inherited retinal disease] panels, whole-exome and mitochondrial testing is probably the best option. Ongoing ophthalmic monitoring is recommended due to the risk of vision-threatening complications, even though this risk is low."

https://tinyurl.com/yc2bwbyc

Acute ketone supplementation in the absence of muscle glycogen utilization: insights from McArdle disease.

Clinical Nutrition, Volume 43, Issue 3, March 2024, Pages 692-700.

"In individuals who cannot utilize muscle glycogen but have a preserved ability to oxidize blood-borne glucose and fat (McArdle disease), acute ketone supplementation impairs exercise capacity, whereas carbohydrate ingestion exerts the opposite, beneficial effect."

https://tinyurl.com/57p8afza

Glycogen storage disease type V: a still under-recognized condition lacking definitive genotype-phenotype correlates.

Pediatr Res (2024).

Nothing very useful from this paper is publicly available, but it poses the possibility that there are very many more cases undiagnosed.

https://tinyurl.com/zufeccrw

Patient-reported experiences with a low-carbohydrate ketogenic diet: an international survey in patients with McArdle disease.

Nutrients 2023, 15(4), 843.

"We found that one-third of the cohort had tried a LCKD, and almost 90% experienced some degree of positive effect, with the most prominent effects on McArdle disease-related core symptoms (e.g., activity intolerance, muscle pain, and muscle fatigue). Adverse effects were rare and generally rated as mild to moderate. These patient-reported findings underline the need for randomized clinical trials to decisively determine if a LCKD is a suitable nutritional strategy for patients with McArdle disease. The results from this study can prompt and contribute to the design of such a clinical trial."

https://tinyurl.com/yc4jm7tt

Gene therapy for glycogen storage diseases. Special Issue: Mission possible: gene therapy for inherited metabolic diseases.

January 2024, Pages 93-118.

"Clinical research to understand the natural history and progression of the GSDs provides invaluable outcome measures that serve as endpoints to evaluate benefits in clinical trials. While promising, gene therapy and genome editing face challenges with regard to clinical implementation, including immune responses and toxicities that have been revealed during clinical trials of gene therapy that are underway. Gene therapy for the glycogen storage diseases is under development, addressing an unmet need for specific, stable therapy for these conditions."

https://tinyurl.com/3whvcjdr

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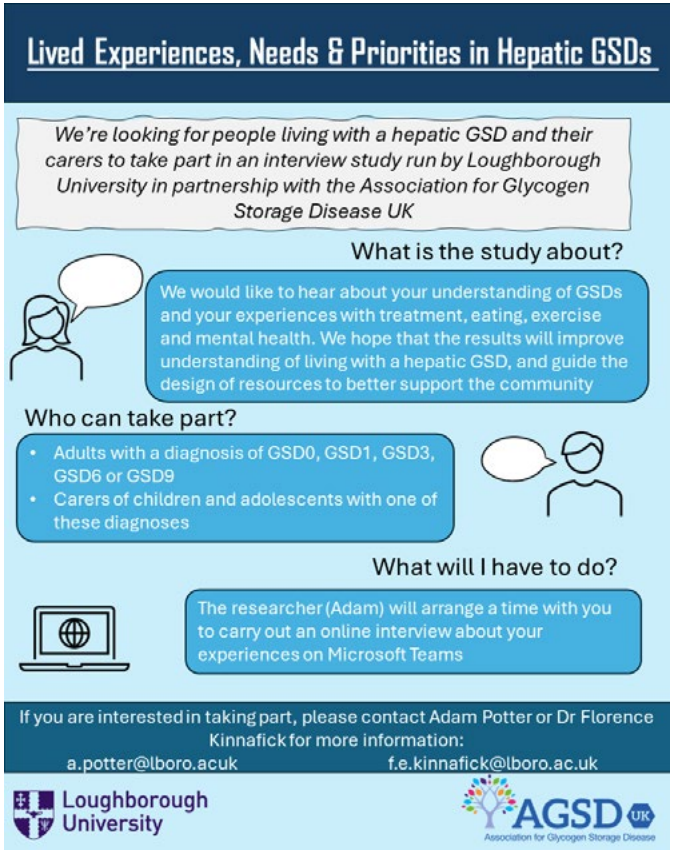
Chance to take part in Hepatic GSD study

A team from *Loughborough University* are looking to interview adults with hepatic GSDs, and carers of children and adolescents with hepatic GSDs.

We are keen to hear about your lived experiences of GSD and treatment, and the impact it has on eating, physical activity and mental health. The study, which is part of a PhD project by ***Adam Potter*** supervised by ***Dr Flo Kinnafick***, will be used to promote greater understanding of living with a hepatic GSD and guide the design of resources to better support the community.

If you are interested in taking part, or would like to know more about the study, please contact Adam at a.potter@lboro.ac.uk or Flo at f.e.kinnafick@lboro.ac.uk



Take aways from this edition

- Use the election as a chance to engage your candidate about rare conditions
- Contact **info@agsd.org.uk** if you're interested in joining our friendly online socials or forthcoming parenting and men's groups
- Email **info@agsd.org.uk** for details of upcoming local Pompe and hepatic get togethers
- Visit **agsd.org.uk** to find out more about this year's Main Event
- Email **type5@agsd.org.uk** if you're interested in the under 21 or adult McArdle walking courses
- Contact Adam at **a.potter@lboro.ac.uk** or Flo at **f.e.kinnafick@lboro.ac.uk** to take part in research exploring lived experience, needs and priorities in hepatic GSDs

Thank you for continued support from the Industry, Foundations and Trusts that help AGSD-UK. These grants allow us to work on projects and ensure our members at AGSD-UK have access to a high level of support and so we are able to run events and contribute to research in GSD. Thank you for the continued support from Amicus, Astellas Audentes, Beam, The Mosawi Foundation, Sanofi, Spark Therapeutics, Ultragenyx and Vitaflo.

AGSD UK
Association for Glycogen Storage Disease

Jen Dickson, Rachel Walker and Taylor Adam

UPCOMING EVENTS

Local Pompe get together: Newcastle, 29th June

Living Well social: on-line,18th July

McArdle walking courses: Bannau Brycheiniog, 29th July (under 21) / 5th August (adult)

Local hepatic get together: Reading, 7th September

The Main Event: Loughborough, 9th-10th November

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Spring 2024

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