MITOCHONDRIAL DISEASE PRIORITY SETTING PARTNERSHIP:

Setting research priorities with patients, carers and clinicians.

ABOUT THE COLLABORATORS

The Lily Foundation is the UK's leading mitochondrial disease charity. Our mission is to improve the lives of people affected by mitochondrial diseases. We are working towards a future where mitochondrial diseases can be effectively treated or cured.

LHON Society is a patient-led support group for a rare condition called Leber's Hereditary Optic Neuropathy (LHON). Our group is comprised of LHON patients and family members. We aim to provide support and information, facilitate research, provide guidance and representation, and promote up to date knowledge and understanding of LHON.

Metabolic Support UK (formerly known as Climb) are the leading patient organisation for Inherited Metabolic Disorders supporting thousands of patients worldwide.

Muscular Dystrophy UK are the UK charity for individuals and families living with muscle-wasting conditions. We support research to drive the development of effective treatments and cures. We ensure access to specialist NHS care and support. We provide services and promote opportunities to enable individuals and their families to live as independently as possible.

The James Lind Alliance (JLA) is a non-profit making initiative established in 2004. It brings patients, carers and clinicians together in a Priority Setting Partnership (PSPs) to identify and prioritise the Top 10 unanswered questions that they agree are the most important. The aim is to make sure that health research funders are aware of the issues that matter most to the people who need to use the research in their everyday lives.

We are the national charity working to improve the lives of patients and families affected by genetic, rare and undiagnosed conditions. We are an alliance of over 200 patient organisations.

Healthcare professionals from the following institutions collaborated in this work:

- Highly Specialised Service for Rare Mitochondrial Disease, Newcastle, Oxford and London
- The University Hospital of Wales, Cardiff
- National Hospital for Neurology and Neurosurgery, London
- UCL Great Ormond Street Institute of Child Health
- Hinchingbrooke and Addenbrooke's Hospitals

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WHY SET PRIORITIES FOR RESEARCH INTO RARE MITOCHONDRIAL DISEASE?

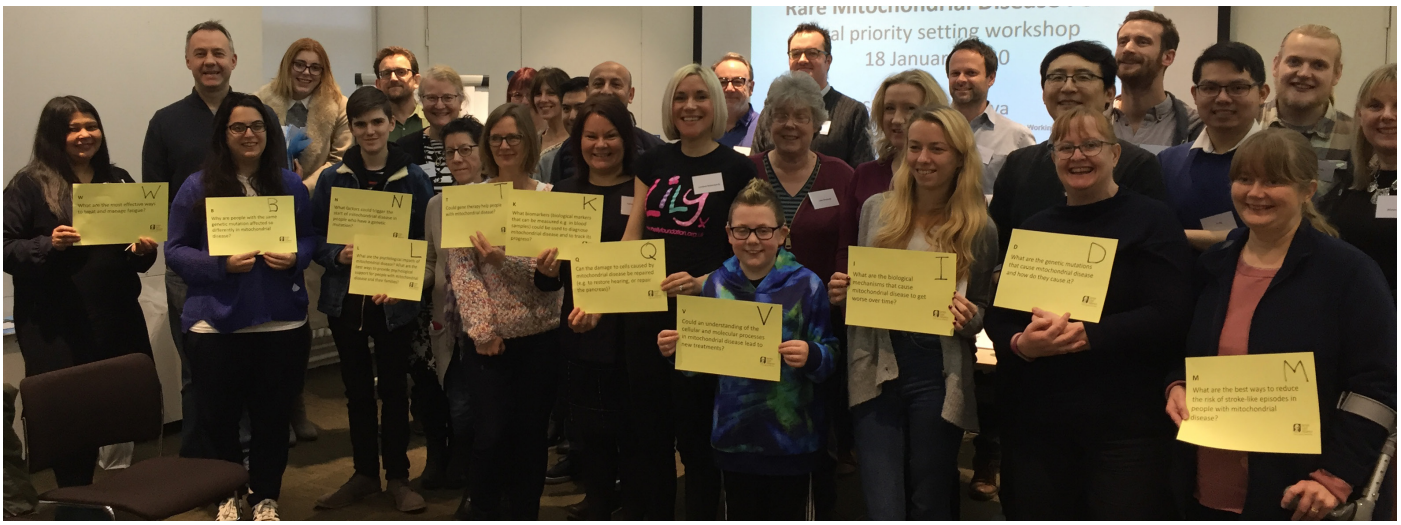
Despite growing research activity in the UK and across the globe, there are still many unanswered questions about mitochondrial disease. Resources for research are limited and consequently it is important for researchers and funding organisations to understand which are the most important questions for research to address from the point of view of patients, carers and healthcare professionals, so that research funding can be targeted accordingly.

As for many rare diseases, mitochondrial disease has received less research attention than common conditions, so the need to consult with those affected is intensified. The diversity in how mitochondrial disease affects individuals is a further challenge to attracting research. Rarity also means that it can be hard to reach a critical mass in consultations such as this, but by bringing together a motivated team of patient groups and healthcare professionals covering a range of related conditions, we are pleased to have secured the input of over 250 individuals to the process.

This Priority Setting Partnership aimed to stimulate research by finding out what people with these conditions, their carers and healthcare professionals believe to be the most important questions about the **care, treatment, management and the natural history of mitochondrial disease, for adults and children.**

"Given the diverse nature of mitochondrial disease it is often easy to forget that we are part of the same "family." This exercise has been a revelation in showing how much we can benefit from a common approach and a renewed focus on what is really important for patients."
Steering Group member.

"Mitochondrial disorders have multiple causes, can affect people of all ages, and all body systems can be involved. It is therefore remarkable to bring patients and clinicians together to create a shared list of research priorities to set the agenda for research that matters for our community."
Steering Group member.



THE TOP 10 PRIORITIES FOR RESEARCH INTO MITOCHONDRIAL DISEASE

1. Could an understanding of the cellular and molecular processes in mitochondrial disease lead to new treatments?
2. Can the damage to cells caused by mitochondrial disease be repaired (e.g. to restore hearing, vision, or repair the pancreas)?
3. What are the biological mechanisms that cause mitochondrial disease to get worse over time?
4. What biomarkers (biological markers that can be measured e.g. in blood samples) could be used to diagnose mitochondrial disease and to track its progress?
5. Could gene therapy help people with mitochondrial disease?
6. What are the psychological impacts of mitochondrial disease? What are the best ways to provide psychological support for people with mitochondrial disease and their families?
7. What are the best ways to reduce the risk of stroke-like episodes in people with mitochondrial disease?
8. What factors could trigger the start of mitochondrial disease in people who have a genetic mutation?
9. Why are people with the same genetic mutation affected so differently in mitochondrial disease?
10. What are the most effective ways to treat and manage fatigue?

SETTING THE LIMITS OF THIS PRIORITY SETTING EXERCISE

The aim of the PSP was to identify the unanswered questions about care, treatment, management and the natural history of mitochondrial disease, for adults and children, from patient and clinical perspectives. The questions that patients and clinicians agree are the most important are then prioritised. Primary mitochondrial disease, in which the function of the mitochondria is affected by a nuclear or mitochondrial genetic mutation, was the project's core focus. Secondary mitochondrial conditions were excluded because they accompany many non-mitochondrial diseases so would extend the scope too far. Research to improve diagnosis was not included in the scope of the project because this risked broadening the scope too much, and because there is already a strong focus on this area in rare disease policy development.

The PSP steering group actively took the decision to include both adults and children in a single prioritisation process because the questions collected during the first phase were generally not focussed on just one or the other.

Diversity and inclusion

Ethnic diversity

The Breaking Down Barriers project awarded funding to the PSP to support activities aimed at broadening the ethnic diversity of participants. We created a series of videos for use with social media in four languages to encourage people whose first language is not English to take part in the second survey and the workshop. Mitochondrial disease does not appear to affect certain populations more than others, so our choice of languages was a pragmatic decision based on the patient populations known to the clinics involved, and on the availability of speakers during what was a short timeline. Videos were produced in Welsh, Farsi, Arabic and Malay, and were distributed widely including through Facebook using their facility to target specific populations. Too few respondents declared their ethnicity in either survey to confidently assess whether the second survey respondents were more diverse. Of those who did declare, 4% said they have a black and minority ethnic background in the first survey, and 5% in the second (less than the UK population in general). However a greater proportion of workshop attendees had a background other than white British.

More targeted, face-to-face engagement may have helped boost ethnic diversity in the survey respondents, but this would have taken more time and resource than the project had available. It is notable that the mitochondrial patient groups involved report challenges in engaging with BAME families, indicating that careful assessment of the underlying reasons would be required to create a successful plan for improving diversity in future projects.

Inclusion

Mitochondrial disease can lead to a range of disabilities such as vision loss, hearing loss, and mobility and coordination problems. The way that mitochondrial disease affects an individual can be influenced by their specific genetic change and can vary hugely from person to person. We took several steps to support inclusion for people with a range of disabilities:

- The online surveys were published in large font, and piloted by vision-impaired individuals to ensure readability with screen-reading software across a variety of platforms.
- The surveys were also offered on paper and as PDF attachments for access with screen readers.
- Workshop attendees were asked to advise on their specific access needs, which were then met e.g. meeting an attendee with a visual impairment at the train station, ensuring a T-loop for hearing aids was available, arranging rooms to allow for wheelchair access, and ensuring that all rooms and accessible toilets were on the same floor.
- The materials used in the workshop were printed with large font, and the needs of participants were flagged to the facilitators, who were able to support individuals e.g. through reading the question cards often and describing carefully changes being made to the order of prioritisation.

HOW WERE THE PRIORITIES IDENTIFIED?

Getting started

The project was driven by a steering group of patient organisation representatives and clinicians. The partnership was officially launched in summer 2018.

The first survey

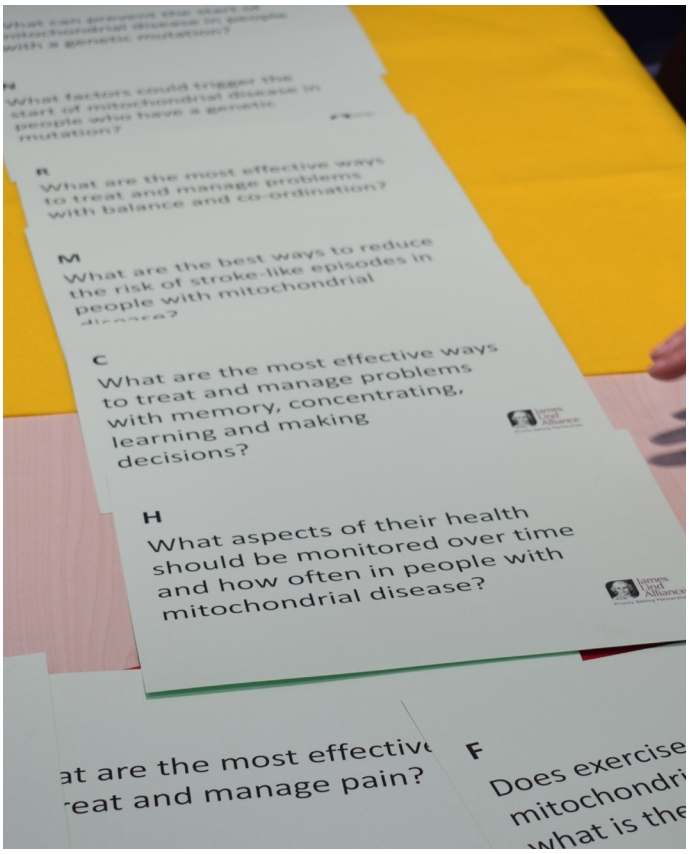
People with a primary mitochondrial disease, their family members and the healthcare professionals who support them, were asked to identify the questions they would like answered by research. They submitted their questions via an online survey in March and April 2019. A paper version of the survey was also made available via a PDF that could be printed locally for distribution.

The steering group members and organisations supporting the project sent the survey out to their networks, via email, newsletters, social media and websites. A total of 147 people submitted a total of 709 questions. The people who responded were people with a mitochondrial disease (34%), carers or relatives (32%), and healthcare professionals (34%). The majority (64%) were female.

Processing the survey results

Among the 709 questions submitted through the first survey were some that were asking for information or advice, that is, questions that do not need research to be answered (85). A further 53 were outside the scope of the project or asking about access to services. Questions about access might need to be addressed through changing policy and practice rather than research. All of these questions were removed.

Of the remaining questions, some were asked by many people, in slightly different ways. Similar questions were grouped together and an overarching question was written which summarised all the questions in the group. A small number of questions were only asked once. These were added to the list of overarching questions. We then checked the published evidence from research that has been carried out in the past and concluded that previous research has not fully answered any of the remaining questions and so no further questions were removed at this stage. At this point, we had 42 unanswered questions – this was our 'longlist' (available on request).



The second survey

In the second survey we asked people to rank each of the 42 questions in the longlist to indicate the degree of its importance to them. The second survey went out to the same networks as the first survey in order to gather as much input as possible, with additional promotion through four videos in different languages. The survey was live in October and November 2019 resulting in 166 responses: 63% were patients, 21% were carers or relatives, and 16% were healthcare professionals. A majority of respondents were female (66%).

The questions in the second survey were presented in random order and were randomised each time an individual accessed the survey. Participants were asked to consider each of the 42 questions, choose 10 and then rank them in order of priority (1 being top priority). Equal weighting was given to responses from patients, carers and healthcare professionals.

This exercise resulted in all the questions being given a score and placed in order separately for each type of respondent. The lists were then combined, resulting in a final list of shared priorities, from 1 to 42. The top 24 questions – the 'shortlist' – were taken to the next step of the process.

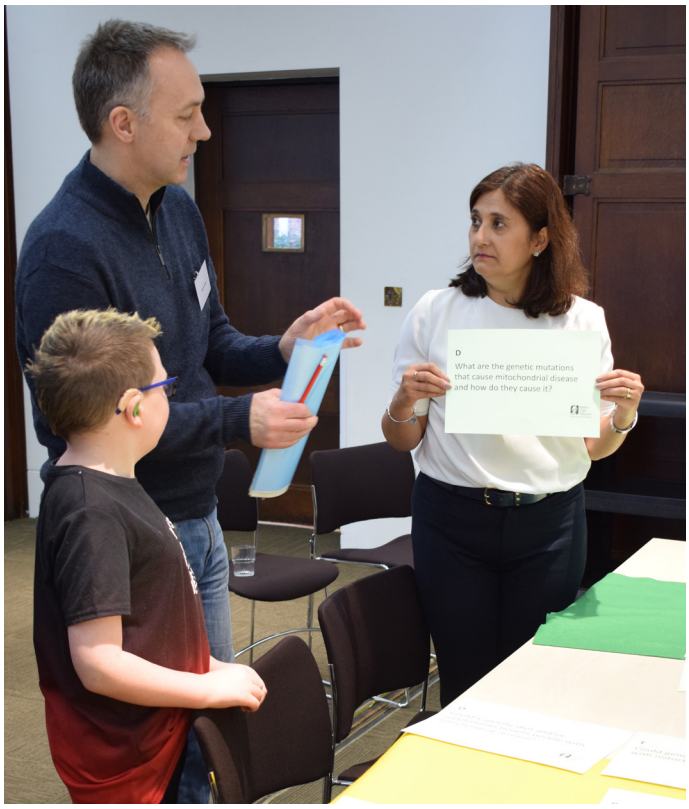
THE PRIORITY SETTING WORKSHOP

The 24 shortlisted questions were discussed at a workshop held in London in January 2020. Invitations to the workshop were sent out through the steering group: 32 people participated, comprising 8 people with a mitochondrial disease, whose conditions affected vision, control of movement and epilepsy; 9 carers/family members; 2 patient organisation representatives; 13 healthcare professionals from 9 different disciplines. Given the complex health needs of many individuals with mitochondrial disease, it was important to include a wide range of professionals.

Of the 32 participants, 7 were members of the steering group.

The participants were asked to look at the 24 shortlisted questions before they came and to think about how they would rank them in order of importance. By attending the workshop, and taking part in a number of small group discussions, everyone was able to hear one another's views on which questions were most and least important and why. This helped the group as a whole to reach an agreement about which questions should be a priority.

The top 10 questions are listed in full on page 4 of this report. The full list of 24 questions in order of importance as agreed by the people at the workshop is given in the appendix.



"Really wonderful to meet so many people who are involved in managing, researching and supporting mitochondrial disease. Hearing from patients and families has been enlightening and raised awareness of the challenges they face."
Workshop attendee.

"Excellent [workshop]. Real privilege to be part of the process."
Workshop attendee.

NEXT STEPS

The JLA Mitochondrial Disease Priority Setting Partnership, by identifying these priority questions for research, seeks to ensure that future research is focused on the issues that matter most to people with mitochondrial disease, their carers and relatives and the healthcare professionals who support them. The steering group will disseminate the questions through their patient and professional networks, by presentation at academic and patient conferences, publication in a peer-reviewed journal, and by liaising directly with research funders.

"The energy and passion in the room at the final prioritisation meeting was palpable and this highlighted in a very real and personal way just how important these questions are to the patients and their families and carers" Steering Group member.

A call to arms

Many people gave their time and effort to submit their questions and to work through the JLA process to identify the final top 10 questions for future research. We want to ensure that these efforts are respected and recognised and therefore:

- We encourage research funders to include these priorities in their research strategy and to target these topics for future research funding.
- We encourage researchers to focus their efforts on answering the highest priority questions and to mention the JLA Mitochondrial PSP in their applications for funding. If a researcher receives funding to address any of the listed priorities, we ask that they please inform the JLA.
- We encourage funders, researchers and all interested parties to share this report with others and to raise awareness of the need for more research on mitochondrial disease in the UK.

If you have any queries or comments about this work, please contact Amy Hunter: amy.hunter@geneticalliance.org.uk.

Further information about the project can be found at: jla.nihr.ac.uk/priority-setting-partnerships/mitochondrial-disease.

If you would like more information and advice about mitochondrial disease or LHON, please contact:

- The Lily Foundation thelilyfoundation.org.uk
- LHON Society lhonsociety.org
- Further information can also be found at mitochondrialdisease.nhs.uk

ACKNOWLEDGEMENTS

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Russell Wheeler, Patient Advocate & Trustee, Leber's Hereditary Optic Neuropathy Society

James Lind Alliance Adviser and Chair of the Steering Group: **Sheela Upadhyaya, JLA**

"At the Lily Foundation, our mission is the improve the lives of people with mitochondrial disease. We believe that identifying the top ten research priorities for mitochondrial disease will ensure that future research can help us achieve our ultimate goal and we are very proud to have been involved in the PSP process." Steering Group member

APPENDIX: THE SHORTLIST OF RESEARCH QUESTIONS

1. Could an understanding of the cellular and molecular processes in mitochondrial disease lead to new treatments?
2. Can the damage to cells caused by mitochondrial disease be repaired (e.g. to restore hearing, vision, or repair the pancreas)?
3. What are the biological mechanisms that cause mitochondrial disease to get worse over time?
4. What biomarkers (biological markers that can be measured e.g. in blood samples) could be used to diagnose mitochondrial disease and to track its progress?
5. Could gene therapy help people with mitochondrial disease?
6. What are the psychological impacts of mitochondrial disease? What are the best ways to provide psychological support for people with mitochondrial disease and their families?
7. What are the best ways to reduce the risk of stroke-like episodes in people with mitochondrial disease?
8. What factors could trigger the start of mitochondrial disease in people who have a genetic mutation?
9. Why are people with the same genetic mutation affected so differently in mitochondrial disease?
10. What are the most effective ways to treat and manage fatigue?
11. What are the genetic mutations that cause mitochondrial disease and how do they cause it?
12. Could a specific diet and/or supplements benefit people with mitochondrial disease?
13. What can prevent mitochondrial disease from getting worse over time?
14. How do the different genetic mutations cause the symptoms people experience with mitochondrial disease?
15. Is there a way to predict who will become ill with mitochondrial disease, and whose symptoms will be worse?
16. What can prevent the start of mitochondrial disease in people with a genetic mutation?
17. What are the most effective ways to treat and manage problems with muscle weakness?
18. What aspects of their health should be monitored over time and how often in people with mitochondrial disease?
19. What are the most effective ways to treat and manage problems with memory, concentrating, learning and making decisions?

20. What are the most effective ways to treat and manage pain?
21. What are the most effective ways to treat and manage problems with balance and co-ordination?
22. How does mitochondrial disease change over time as people get older?
23. Does exercise benefit people with mitochondrial disease? If yes, what is the best form of exercise?
24. What causes the genetic mutation in people with mitochondrial disease whose parents don't have the mutation?

The PSP and its findings are endorsed by the following European Reference Networks: EpiCARE, ERN-EYE, Euro-NMD and MetabERN.

Fighting Mitochondrial Disease
WWW.thelilyfoundation.org.uk

LHON SOCIETY

METABOLIC SUPPORT UK
Your rare condition. Our common fight.

Muscular Dystrophy UK
Fighting muscle-wasting conditions

James Lind Alliance
Priority Setting Partnerships

GENETIC ALLIANCE UK

European Reference Network
for rare or low prevalence complex diseases
Network
Epilepsies (ERN EpiCARE)

European Reference Network
for rare or low prevalence complex diseases
Network
Neuromuscular Diseases (ERN EURO-NMD)

European Reference Network
for rare or low prevalence complex diseases
Network
Eye Diseases (ERN-EYE)

European Reference Network
for rare or low prevalence complex diseases
Network
Hereditary Metabolic Disorders (MetabERN)