What are the unmet needs and opportunities in the motor neuron disease biomarker field?

Insights from the LifeArc Motor Neuron Disease Biomarker Roundtable

LifeArc

Foreword

> When I started in neurology 30 years ago, motor neuron disease (MND) was seen as a condition with little hope.

What has happened in the years that followed, though, has been transformative. Patients are now seen in specialist clinics, they're listened to, their symptoms are much better managed and treated, and the condition is much more out in public. There's been more investment into research, and we've learned much more about the condition and its genetics. Compared to the frustration of before, there's a sense of hope that we're closer to being able to make a significant impact on MND.

And yet, survival remains unacceptably low. There remains an urgent need for action that's cohesive, logical and focussed.

At LifeArc, we want to drive progress in MND by harnessing the potential of biomarkers, which have helped transform personalised medicine for conditions like cystic fibrosis and cancer. For MND, this still feels largely theoretical – but if we could learn from these more advanced biomarker ecosystems, we may one day achieve the same for people with MND.

The first step is to understand where the gaps are. On 18 September 2024, LifeArc convened a group of experts from the MND biomarker community for a roundtable event, discussing the challenges holding us back and potential solutions. In this report, we're pleased to share with you a summary of the event, which marked an important step towards understanding the current landscape, and opportunities to better harmonise the biomarker ecosystem.

As a neurologist specialising in Parkinson's disease and Huntington's disease, I find the MND biomarker field exciting and full of great opportunity. I hope in reading this report, you share some of the hope we have in this area, and we invite you to engage with our work, to help shape our MND biomarker strategy and make a difference for patients.

Roger Barker
Chair of Neurodegeneration at LifeArc

The LifeArc Motor Neuron Disease Biomarker Roundtable

Our vision is a world where motor neuron disease (MND) becomes preventable and treatable. Although our understanding of this complex condition has vastly improved in recent years, MND remains a rapidly progressing disease for which there is no cure. A third of people die within a year, and more than half within 2 years of their diagnosis[1].

Biomarkers are useful tools that have transformed the way we understand, diagnose and treat other conditions – and have the potential to achieve the same for MND. As described by the FDA, biomarkers are defined characteristics, such as molecular, histologic, imaging, radiographic or physiological features, that can be measured to provide an indicator of normal biological and pathological processes, or response to a therapeutic intervention[2].

Yet we still lack a validated MND biomarker. To capture a picture of the current biomarker ecosystem in MND and the resources needed to drive change, we convened a roundtable with members across the UK MND biomarker community on 18 September 2024, at LifeArc offices in London. Experts from across academia, the clinic, industry, biotech, charity, patient advocacy and investment funds (for full list, see appendix 1) discussed challenges in their respective fields and potential solutions to drive progress.

Discussion was broad, rich and honest – at times revealing the frustrations felt by different parts of the community – and reflected the hope for what could be achieved. Several recurring themes emerged, presented here as questions that remain largely unanswered.

How should we use biomarkers in the context of MND?

"I sometimes feel we should qualify the word 'biomarker' every time we use it," shared one participant. With such broad potential applications comes a question of where limited resources should be prioritised to achieve the greatest impact.

Prompt diagnosis of MND is a major challenge, often involving multiple tests to exclude diseases with overlapping symptoms; by the time diagnosis is confirmed, often significant damage to motor neurons has already occurred and it may be too late for hopeful interventions. Attendees debated the merit of a diagnostic biomarker in general practice, comparing a disease-specific test with a broader marker of neurodegeneration that activates rapid referral to a neurologist. Given the rarity of MND, combining the latter with greater awareness of the condition in primary care may be a more effective option to tackle the challenge of diagnostic delay.

Within scientific research, biomarkers of disease progression, target engagement and treatment efficacy could unlock important information about MND, leading to much-needed new interventions.

[1] MND Association | [2] As defined by FDA Biomarkers, Endpoints and other Tools (BEST) glossary

This could also be invaluable across the translational pipeline, making clinical trials more effective with an objective measure of disease progression and guiding changes to treatment in real time.

Coupled with a deeper understanding of MND, biomarkers could also provide information about individual risk and susceptibility and offer stratification into disease clusters or subtypes. MND is a heterogenous disease and it's likely that different subgroups will benefit from precision treatment.

How can we action results meaningfully for patients and their families?

A major challenge, however, is that we lack a comprehensive understanding of MND, its causes and associated risk factors, hindering our ability to prevent its development. Similarly, we lack robust therapies that could meaningfully impact the patient journey. **"The term MND carries a specific prognosis and perception, compared to conditions with an active route for intervention,"** shared one clinician in attendance.

Identifying and understanding disease clusters and subtypes can be useful – but only if accompanied by tangible action.

What mode of biomarker should be prioritised for MND?

Participants agreed that it's critical we validate the promising biomarkers in development, while also exploring emerging options in discovery research. Similarly, while the ideal scenario would be a simple test to detect and track MND, a multimodal, integrated approach is likely to be more realistic.

The group agreed that all biomarker types – including molecular, imaging, genetic, biofluid and digital – should continue to be explored, both alone and in combination. Importantly, any biomarker approach must consider factors like cost, accessibility, specificity, stability and sensitivity to be practical for real-world use.

Challenges and opportunities in the MND biomarker field

In this report, we'll summarise the main themes of our discussion, presented as opportunities for action, as well as 3 tangible recommendations to help make strides in MND biomarker research and deliver much-needed progress for people with MND.

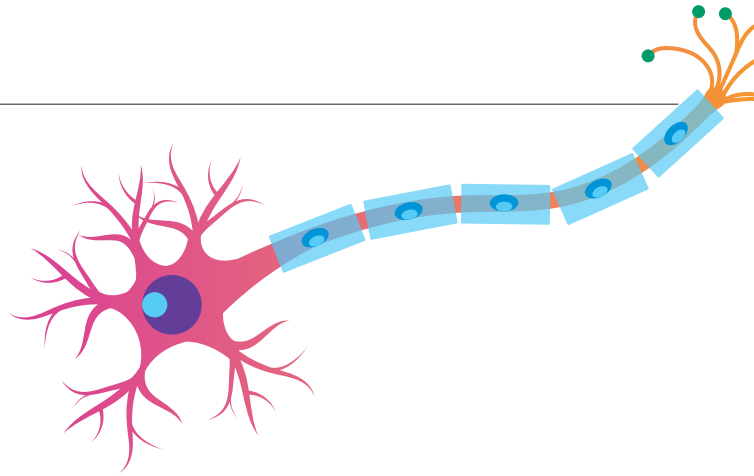
Opportunity 1

Harnessing the potential of NfL and other emerging biomarkers

Neurofilament light (NfL), the frontrunning molecular biomarker for MND, was central to discussion throughout the roundtable. NfL is elevated in biofluids following neuronal damage. In MND patients, levels generally correlate with disease progression and prognosis. It is, however, inherently limited: it is elevated in a range of neurodegenerative conditions and is sensitive to non-disease fluctuations. For example, the injection of certain therapeutics into the spinal fluid can lead to an increase in NfL plasma levels. Additionally, while advances in assays have enabled the detection of ultralow levels of NfL in blood, variability in absolute levels have made it difficult to establish diagnostic thresholds.

But as one participant asked, "should perfect be the enemy of good?" Diagnostically, a marker of neurodegeneration may be a useful tool in general practice to activate the appropriate referrals for more specialist neurological tests. In clinical trials, plasma NfL could provide a measure of disease activity to support clinical outcome measures, as it already has for some MND subtypes, with a reduction in levels signifying a protective effect of a treatment to nerve cells. And in the clinic, NfL has potential to enable more personalised clinical decision making with objective monitoring of disease activity, beyond patient-reported symptoms. Clinical studies, such as EXPERTS-ALS, are already aiming to exploit NfL as an outcome measure of possible disease modification in MND.

Other promising molecular biomarkers have emerged in recent years and may be worth exploring both alone and in combination with NfL, to overcome some of its intrinsic limitations. One of the most advanced candidates is TDP-43, a protein which can form toxic aggregates to cause motor neuron damage and death, and whose



accumulation is a significant factor in MND onset and progression. Nearly all cases of sporadic and some types of familial MND exhibit a degree of TDP-43 pathology, making disease specificity a top characteristic for this protein as a biomarker.

However, since TDP-43 aggregates and different cleaved forms of the protein exist in a spectrum across ageing and neurodegenerative indications, some "healthy" controls may also exhibit TDP-43 pathology. Efforts are underway to understand more about TDP-43, the role of different pathological forms and aggregates in MND and related diseases, and its use as a biomarker. The group discussed the obstacles that need to be overcome in order for TDP-43 to meet its potential, including the need for standardised assays that are specific, sensitive and accurate.

Cryptic exons and peptides, closely dependent on altered TDP-43 functionality, were also discussed as hallmarks of neurodegeneration that could be harnessed as potential biomarkers, with the acknowledgement that assays need further development. Other promising biomarker candidates include extracellular vesicles and microRNAs which have prognostic potential – miR206, for example, correlates with ongoing muscle degeneration – but lack consensus over which should be focussed on and specificity for MND compared to other neuromuscular diseases.

The "critical thing" with all promising biomarkers, the group agreed, is validation – the confirmation of preliminary findings using large independent sample sets. In this respect, a framework may be helpful to objectively decide when a biomarker is validated and in which context. Other suggestions included clarifying the role NfL, TDP-43 and other candidates play in different disease subtypes, as well as standardising assays and sample collection methods, and developing clear biomarker interpretation guidelines for clinical trials.

Opportunity 2

Improve access to unique collections of MND patient samples

Validating promising biomarkers demands large collections of samples, annotated with clinical data. Participants cited several powerful resources, including the UK MND Collections, AMBRoSIA, the ALS Biomarker Study and the global study Project MinE; and more disease-agnostically, the UK BioBank, Our Future Health and the NHS Research Scotland Biorepository Network.

In the UK, **"we could have a globally unique resource of thousands of tissue samples,"** shared one participant. Yet access remains a major barrier. In accessing samples, a siloed system requires **"jumping through multiple hoops and speaking to too many people"** to be efficient. Meanwhile, those who manage archival samples cited logistical challenges around sharing, adhering to patient consent and making decisions about limited resources, particularly when those requesting access lack clear hypotheses.

The enormous efforts individuals and groups have put into building these resources should not be underestimated. However, bringing harmony to the sampling ecosystem represents a major opportunity. A clear recommendation from the group was a centralised coordinator to enable access – coordinating patient consent, governance and decision-making, and supporting requestors from across academia and industry to develop robust proposals. Other suggestions included standardised governance and access processes, integration of sampling into routine clinical care, and improving sample collection with consistent protocols and operational procedures, as described by the project SOPHIA (Sampling, biomarker OPtimization and Harmonization In ALS).

These actions would require significant investment but may enable us to fully make use of sample collections in the UK and beyond to identify and validate novel biomarkers for MND.

Opportunity 3

Integrate research with existing data efforts to understand MND at the population level

Throughout the roundtable, participants emphasised the need for long-term, well-sampled longitudinal studies, annotated with clinical data.

"Often, what we have available is just a snapshot in time," shared one participant. "That's not enough to understand the progression of a heterogenous disease like MND."

However, we don't necessarily need to invest in new cohorts to make progress in this space. Specific to MND and neurodegeneration, fantastic collections like AMBROsIA, the ALS Biomarkers Study, EXPERTS-ALS and ACORN include a breadth of samples across multiple time points, from patients, first-degree relatives and general population controls.

Beyond neurodegeneration, genetic and health information resources, such as Our Future Health, may provide an opportunity to integrate efforts. Should contributors to these resources develop MND in the future, it may be possible to build new cohorts that can map back to samples provided before the onset of symptoms.

A person's lifetime risk of developing MND is up to 1 in 300, with familial disease affecting up to 1 in 10 people with the condition[3]. Integrating and harmonising longitudinal research efforts could lead to novel biomarkers of risk prediction, potentially providing personalised information about future health and helping to stratify patients into disease subtypes.

[3] MND Association

Opportunity 4

Improve sharing of findings across the community

Participants shared frustrations when promising biomarkers lose momentum, seemingly without reason. When negative results remain unpublished, this leads to unnecessary duplication of efforts, wasting limited resources and funding.

This is not unique to MND. The wider scientific community continues to wrestle with the value of publishing negative findings that don't necessarily progress a career and with ongoing challenges of authorship models. Solutions are complex and, beyond publishing pre-prints,submitting to open access journals and a commitment from journals to publish negative data, demand a shift in the way we assign value to scientific publication.

Within the group, however, there was appetite to encourage wider sharing of all findings across the MND ecosystem – both to avoid pursuit of dead-end avenues and to unlock important information about the disease itself. A full record of clinical trial results, including outcomes of studies that didn't show a response, can provide important information about direct and indirect target engagement and pathways of disease progression. **"Industry should be pressured to publish as much as we can, not keep it as privileged information,"** shared one pharmaceutical participant. **"It's the only way that we as a research community will learn more about the disease."**

Opportunity 5

Harnessing innovation in technology and data

Innovation in data and technology creates a whole host of opportunities in biomarker research. We're now able to use AI to interrogate vast datasets and complex biology, pinpointing nuggets of information that could help to identify a new biomarker.

Innovation may eventually offer the opportunity for patients to monitor their disease at home, which would support both discovery research and clinical care. Participants shared that the MND patient community is altruistic, with many people willing to take part in research, but that measurements must be easy and ideally passive to maintain engagement.

For example, bloodspot technology, which supports diabetic patients to monitor their condition remotely, may eventually enable MND patients to track their condition at home, should we identify a blood-based biomarker.

Digital measures were also discussed, such as shoe-based accelerometers to track changes to gait, and speech and facial recognition technology to monitor changes to the voice and face.

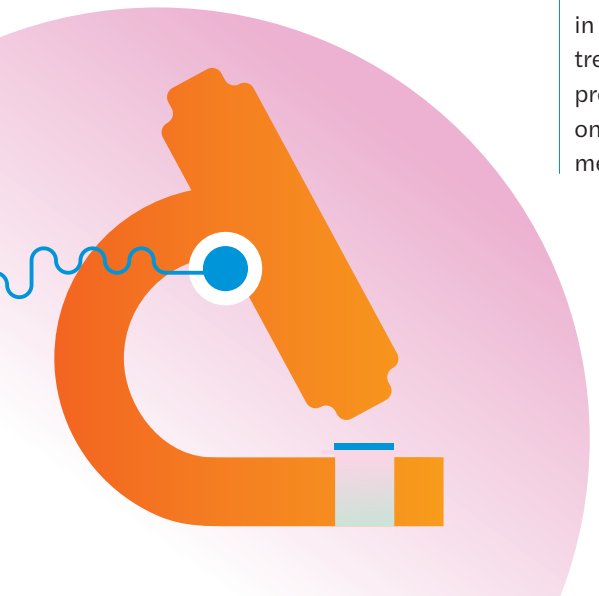
Opportunity 6

Earlier incorporation of biomarkers into clinical trials

Adaptive and flexible trial designs are rapidly improving the way we translate new discoveries to the clinic for a range of disease types. Ineffective drug candidates can be stopped early, new candidates can be introduced, and multiple trial arms enable the grouping of disease clusters, so the effects of promising agents are undiluted by heterogeneity. These innovations have already transformed clinical research for other conditions (the STAMPEDE trial for prostate cancer, for example) and we're hopeful that studies like EXPERTS-ALS and MND-SMART could replicate the same for MND.

There was consensus, however, that biomarkers could be better and earlier integrated into clinical trial design. These should be carefully defined prior to study start, both to enable meaningful analysis and improve MND research.

Pharmaceutical participants highlighted the value of target engagement biomarkers but noted challenges in encouraging the incorporation of multiple measures into trials. A measure of disease progression could support researchers to interpret clinical outcome measures without relying on subjective self-reporting by patients. This would also support rapid decision-making about inclusion, continuation, adjustment or early stopping of experimental therapies. Additionally, a stratification biomarker based on biology, genetics or other disease features could help more people partake in trials, matched to the most promising treatment for their condition; given the fast-progressing nature of MND, most patients only partake in one trial, and many fail to meet inclusion criteria.



Opportunity 7

Learning from other fields

A consultant neurologist specialising in Parkinson's disease and Huntington's disease (HD), our chair Roger Barker shared his perspective on how other fields have overcome similar challenges still faced by the MND community, to develop comparatively advanced, dynamic biomarker ecosystems.

This echoed a key sentiment of the roundtable: well-oiled processes already exist, and we don't necessarily need to "re-invent the wheel" to achieve the same progress for MND. For example, the UK DRI Biomarker Factory, which facilitates the development of fluid biomarkers for dementia, and Enroll-HD, a large observational study and collection of data and samples for HD families, were both cited as potential models for MND to consider.

The group also highlighted the maturity of the cancer research field as an important learning opportunity. For example, if we can develop a risk prediction biomarker, lessons from screening for breast, cervical and bowel cancers may be applicable to targeted population screening for MND.

An ethical question raised across the day was how to meaningfully process risk when limited interventions are available, and when carrying a specific gene imparts high risk but no guarantee of onset. This is a path well-trod by HD, where genetic tests are routine, but nothing can prevent the onset of symptoms. Interestingly, requests for tests grew when media coverage of the AntiSense trial influenced the public's perception that new treatments might be just around the corner. Learning from the HD community, and other heritable conditions, may provide insight on the ethical, legal and social concerns of a predictive biomarker.

Recommendations to advance the MND biomarker field

Meeting the opportunities outlined above could unlock important insights about MND, potentially leading to much-needed biomarkers for patients and a world in which MND becomes preventable and treatable.

We asked participants to rank the following opportunities to explore where limited resources should be focused to achieve the greatest impact, with 1 representing the highest priority:

1. Establish the context of use and type of biomarkers that would be most useful to focus on

2. Share positive and negative results from trials to increase the efficiency of research funding and minimise duplication and siloed working

3. Discover new, disease-specific biomarkers that correlate with biology of targeted pathway

4. Explore combinations of different biofluid biomarkers

5. Improve access to existing samples and data

6. Identify the optimal biofluid to collect and use for real-world applicability of biomarkers

7. Improve our ability to perform reliable replication and/or confirmation studies

8. Explore combinations of different biofluid biomarkers that incorporate novel digital biomarkers

9. Make use of existing and develop new best practice recommendations and guidelines for identifying and validating biomarkers

This set of recommendations developed by the roundtable group serves as a foundation and would benefit from further refinement in collaboration with the wider community.

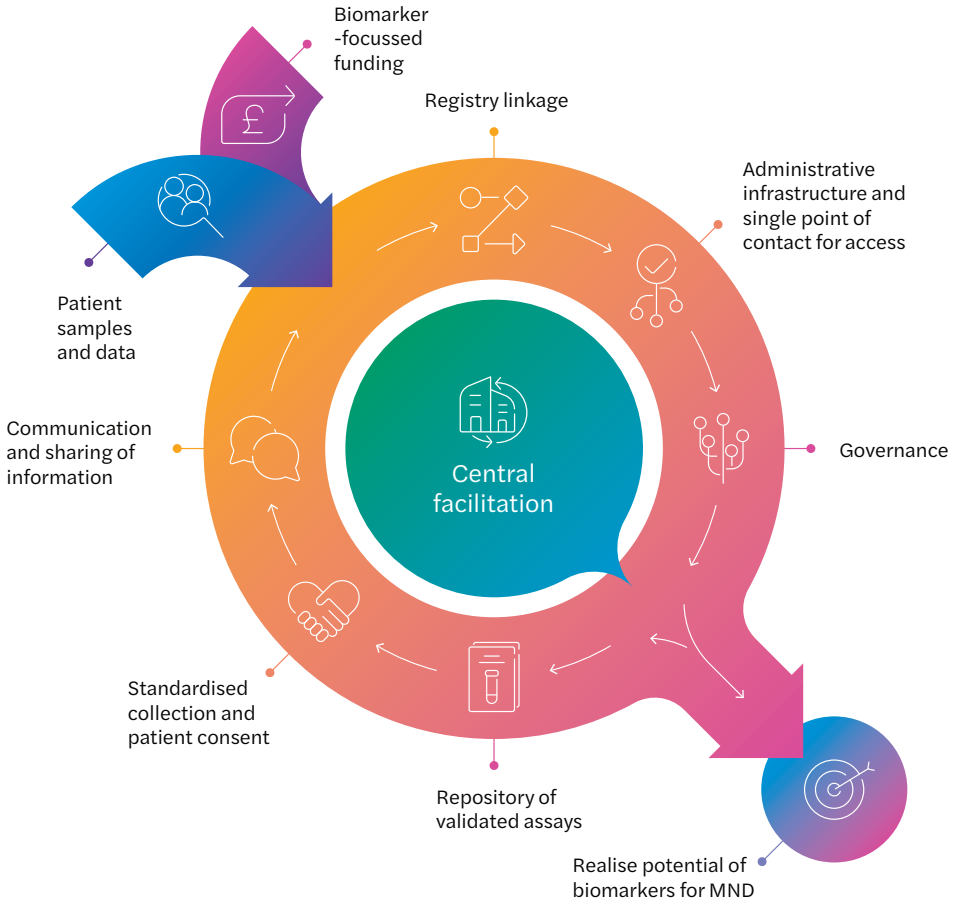
Tell us what you think!
Scan the QR code to give your feedback.

Tangible recommendations to drive progress

The event ended with an open discussion, focused on tangible actions that could help to overcome some of the challenges associated with biomarkers in MND research.

What's clear is that great initiatives already exist – and there are fantastic, disease-agnostic resources that the MND community can harmonise with. Equally, MND is still a specific disorder with bespoke needs; focused efforts like the UK MND Research Institute (MNDRI) remain critical to drive progress.

The group made three main suggestions, outlined below and overleaf.



1. A central facilitator to unite the ecosystem

Several themes throughout the roundtable are underpinned by siloed efforts and disparate needs of key players across the MND biomarker ecosystem.

A central body could begin to overcome these challenges by coordinating research efforts, brokering collaborations and identifying opportunities to build on existing infrastructure. A deep understanding of stakeholders and their respective needs could identify where efforts should be channelled to advance the field. Similar models for other conditions include the ASAP (Aligning Science Against Parkinson's) initiative, which fosters collaboration, research-enabling resources and data-sharing to advance research into Parkinson's disease, while CHDI Foundation's Enroll-HD is a clinical research platform for Huntington's disease.

Importantly, this centralised body should work with existing initiatives to harmonise efforts and develop new models of collaboration and funding to help drive progress in the most effective way.

2. A centralised resource to harness unique collections of samples and data in the UK and beyond

Easy access to rich and annotated samples and data would be transformative in biomarker research, but major hurdles include access, administration and linkage between registries. Participants also raised considerations around the ethical handling of genetic information and the need for protocols that maintain anonymity.

The group agreed that connecting infrastructure that unites existing cohorts, registries and biorepositories could be a hugely helpful resource. This would require significant capital to establish but offers potential for cost recovery and lower onward investment once up and running.

Proposed solutions included:

- scoping to understand the current repository landscape in the UK and beyond
- linkage of data between registries
- a single point of contact to understand available resources and request access
- standardised sample collection and patient consent
- administrative infrastructure, such as dedicated personnel to manage sample collection and preparation, and research professionals to help interested parties develop impactful research proposals
- governance to make decisions around use of limited samples
- a repository of validated assays

3. A biomarker-focussed initiative

Finally, the group shared the need for long-term investment in MND biomarker research if we are to validate existing biomarkers and identify promising new ones. A holistic initiative that includes funding, networking, accessibility and expertise on biomarker identification and validation could enable a rapid response to new, emerging ideas, while aligning with the priorities of the wider research community.

Longer term, such an initiative could influence the clinic with the translation of validated findings, assays and biomarker detection kits into practical solutions for patient care.

Conclusion

The MND Biomarker Roundtable concluded with clear direction: to develop pragmatic, real-world appropriate biomarkers, we must both seek new opportunities and validate the promising biomarkers already in development.

Addressing the challenges associated with slow progress is complex, requiring multifaceted solutions. But what's clear is that any new activity should focus on integration and harmonisation, rather than duplication of existing efforts. There's a great deal of promising activity already underway within the field – which should be appropriately recognised, and the efforts of which shouldn't be underestimated. The unmet need is for alignment.

This represents a major opportunity for a central coordinating body to develop infrastructure that facilitates efficient collaboration within the community. Given its small size and connected health system, the UK is in a unique position to drive this change.

We invite members of the MND community to share their thoughts on this document. Let us know your priorities for resource investment and your ideas on shaping a biomarker strategy. Your feedback will help guide our next steps

Scan the QR code to give your feedback.

We cannot change the current ecosystem alone, and we look forward to connecting and working with you.

Importantly, the field is ripe, and the ecosystem is eager. The time to act is now, to drive progress so that one day, MND becomes preventable and treatable.

Appendix

Attendees at the LifeArc Biomarker Roundtable, 18 September 2024

Roger Barker
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Professor of Clinical Neuroscience, the University of Cambridge Consultant Neurologist, Addenbrooke's Hospital

Lucie Brujin
Therapeutic Area Biomarker Lead for ALS, Novartis UK

Manuela Cerina
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Ben Cryer
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Brian Dickie
Director of Research Development, Motor Neurone Disease Association

Anna Ettorre
Director of Translational Science, Bioassays, and Biomarkers, AviadoBio

Jenna Gregory
Senior Clinical Lecturer, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen

Majid Hafezparast
Professor of Molecular Neuroscience, School of Life Sciences, University of Sussex

Shubhangi Lal
Project Manager, Translational Science, Neuroscience, Foundation for the National Institutes of Health (FNIH)

Jessica Lee
Director of Research, My Name'5 Doddy

Richard Ribchester
Trustee, MND Scotland

Ruth McKernan
Venture Partner, Dementia Discovery Fund (DDF), SV Health

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Martin Turner
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Paul Wright
Head of Motor Neuron Disease Translational Challenge, LifeArc