GLOBAL MND RESEARCH ROUNDTABLE

AFIGHT-MNBEVENT

OUTCOMES FROM THE INAUGURAL EVENT

Contents

1. Introduction

A letter from FightMND

The Global MND Research Roundtable was inspired by the incredible Dr Ian Davis, a talented medical doctor, fierce advocate for vital research to find a cure for MND, and co-founder of FightMND. And every single day we continue to be inspired, motivated, challenged and supported by another of our exceptional co-founders, Neale Daniher.

At FightMND, we raise awareness and fund vital research to find a cure for and improve the lives of those living with MND. In our first 10 years, we have invested close to $100M. We have achieved this by consistently living our values of integrity, efficiency, urgency, community and boldness.

We are bold in the way we approach what we do; FightMND often does things differently and seeks to challenge the status quo where we see opportunity. And we see an opportunity across the global MND research community to bring together the diverse strengths in research, collaboration and partnerships, via the Global MND Research Roundtable.

Each and every Roundtable delegate was personally selected to participate in the event because of their unique superpowers, whether they be wisdom, experience, skills, or approach to MND, to research or to collaboration. Together they have the superpowers and the passion to defeat this beast of a disease.

I would like to personally thank every Roundtable delegate not only for their time and efforts in participating in this inaugural event, but also for their willingness to trust FightMND in leading them through a two day journey of collaboration, problem solving, and bouncing oval shaped footballs. We can't wait to continue this journey together with you to move the dial further and faster, and have the impact we all so desperately seek to achieve.

Thank you.

Bec Sheean, Director Cure Research and Programs at FightMND

Executive summary

The Global MND Research Roundtable ("the Roundtable") was established by FightMND in response to an opportunity it sees: *to accelerate discoveries and find effective treatments and a cure for MND through global alignment and international collaboration*.

From 28th to 30th August 2024, a diverse group of experts from across the globe came together at the inaugural Roundtable event in Melbourne, Australia, to collectively tackle some of the most critical challenges in MND research.

Prior to the Roundtable event, delegates identified the top four global barriers to research translation, which were used as the priority areas for discussion at the event. The following table summarises, at a very high level, the key problems and solutions that were identified throughout the two-day event, for each of the four global barriers.

Global barrier	Key problems	Solutions (in the form of activities)
1. Biomarkers	Lack of disease knowledge Alignment on which biomarker needs more focus Lack of validation/ability to validate Lack of planning	1. Global biobank & AI initiative: harmonise all existing resources with ALS expertise and existing stakeholders 2. Global taskforce initiative: build/integrate guidelines/SOPs
2. Disease fundamentals and drug targets	Primary versus secondary (causes vs consequences) Disease models Reproducibility Variability	3. ProtocALS: a de-centralised Global Core Resource of global best practice recommendations for pre-clinical research 4. Global presymptomatic/asymptomatic discovery study to fund primary/upstream targets and markers
3. Disease heterogeneity	We are treating MND as one disease We don't know which aspects of disease heterogeneity matter We still aren't able to clarify the relationship between the biology and the clinical presentation	5. Working groups: engage key stakeholders and establish a leadership/governance structure 6. SOPs: develop standard operating procedures and publicise 7. Data platform and biorepository
4. Patient stratification and classification	Lack of clear stratification indices: genetics and beyond Lack of availability of very large, comprehensive, standardised and consolidated data sets Unclear how heterogeneity informs clinical trials Lack of clear communication and consensus	8. Global data acquisition and storage: generate a global master protocol to facilitate an MND/ALS global data repository 9. Global metadata protocol

Whilst solutions were developed for each of the four global barriers, there are seemingly two distinct areas in which the delegates' solutions could be categorised:

1. **Global data & biorepository harmonisation**, with the aim to achieve:
    a. Global centralisation of big data, including a current state assessment of the global landscape; and
    b. Global, collaborative biobanking, with a single aggregator search platform. This includes the provision of post-analysis biosamples from industry to the global biobank.
2. **Preclinical recommendations & standardisation**, with the aim to achieve:
    a. Best practice recommendations for the use of preclinical MND/ALS models. This includes the use of models for understanding, therapeutic target identification, and biomarker discovery - a major impetus towards better translational work; and
    b. Human ALS model core. This includes: a preference for decentralised infrastructure; the development of standardised protocols for iPS 2D/3D models; agreeing on master protocols; and consideration of this being a potential source for reproducibility and outsourcing work, instead of laboratories developing their own models.

Delegates also explored ways of working together to create an effective, sustainable and impactful collaboration ongoing. In summary, they recommended for the Roundtable to:

- Establish a relatively small global committee of diverse membership, and including persons with lived experience at every level of governance
- Develop a meaningful global strategy, including:
    - Set a clear mission / purpose
    - Confirm the research areas that would genuinely benefit from global collaboration
    - Undertake a landscape assessment / review of current state for any of the priority areas
    - Set clear aims, and prioritise these aims
    - Determine the principles which the Roundtable would adhere to. For example, delegates' commitment to be courageous

Several commitments were collectively made by the Roundtable delegates in an effort to progress the work started at the Roundtable event. These are to:

1. **Develop a sustainable global collaboration**. Delegates agreed to this in principle.
2. **Share the inputs and outputs from the Roundtable** event. FightMND agreed to take responsibility.
3. **Draft a strategy and quick wins**, seeking feedback from delegates. Bec Sheean, David Taylor and Gethin Thomas agreed to establish a leadership group.
4. **Develop and disseminate communications** that are tailored to key audiences. Although this will be a responsibility of everyone involved in the Rountable ongoing, the leadership group will take a leading role in communications.
5. **Present the strategy at Montreal** in December 2024. This will also be the responsibility of the leadership group.

FightMND is committed to driving the momentum of the Roundtable, to sharing these important outcomes of the event with the global MND community and to progressing these outcomes through strategic and collaborative leadership.

2. Supporting information

Event objectives and design

The objectives of the event were to:

- Establish and build relationships that will grow the global MND research community
- Experience new, innovative ways of working in a fun and memorable event
- Get up to speed with the state of play, progress, challenges and opportunities in the key areas of MND research
- Explore best practice approaches to global research collaboration and understand how this could be applied in our own contexts
- Understand what we can achieve as a collective and align on a Roundtable mission
- Identify, develop and refine initiatives to address the key challenges in our research areas

FightMND designed and developed the Global MND Research Roundtable and the inaugural two-day event with the support of an expert advisory panel and information and recommendations provided by the Roundtable delegates via an electronic survey. The following principles were adopted in the design of and approach to the event:

- This event is not a traditional research symposium. A dynamic, codesign approach is used to design the agenda and format
- This event is focused on research; not on care, access to care, or advocacy
- This is not a stand alone event; rather it is the start of ongoing collaboration
- All information at the event is shared openly, and is not treated confidentially

The design of the two-day workshop agenda was based on the Scan-Focus-Act model; a three-part approach to gathering information on the background and key issues, using that information to decide what's worth exploring more rigorously, and testing whether the areas or ideas of focus can lead to useful results. See Appendix a: Agenda for a copy of the event agenda.

Delegates

The true power of the inaugural Roundtable event was the diversity of experience in the room. The event featured 45 delegates (see Appendix b: Delegates) from around the world, including Australia, Belgium, Canada, France, Malaysia, the Netherlands, New Zealand, Switzerland, the United Kingdom, and the United States. Delegates represented 17 international and 27 national affiliations and have an array of experience across the MND sector and beyond, including:

- pre-clinical and clinical researchers in MND
- global collaborative leaders from other fields
- life science
- strategic investment
- ALS/MND organisations
- people with lived experience of ALS/MND.

Delegates were supported by a number of personnel including advisory panel members, and event hosts, guests and facilitators. See Appendix c: Supporting personnel.

Pre-Roundtable survey

An electronic survey was sent to all delegates prior to the Roundtable event. The objectives of the survey were to:

- Understand the roundtable audience: their strengths and their potential contributions to the Roundtable
- Understand individual perspectives of the most significant barriers to and opportunities for research into effective treatments and a cure for MND
- Build delegates' understanding of the Roundtable event and what to expect
- Gather information from delegates to form the basis for discussions at the event

Survey responses were received from 35 delegates from across the globe: 22 from Australia and New Zealand; six from the United Kingdom and Europe; six from the United States; and one from Asia. Respondents were predominantly researchers with a broad range of experiences, representing a broad range of organisations, and involved in many global research initiatives, as represented in the word map below.

Image: Word map of global research initiatives that survey respondents are involved in.

Collectively, respondents identified the top four global barriers to research translation, as shown in the table below.

Top four major global barriers preventing the translation of research into effective treatments for MND	Average priority rank from 1 (lowest) to 5 (highest)	No. of times listed as top barrier
DISEASE HETEROGENEITY highlighted as a barrier to effective diagnosis, treatment and understanding of the disease across different populations.	4.22	12
BIOMARKERS AND DIAGNOSTIC MARKERS cited as critical areas needing improvement for better diagnostics, treatment and research outcomes.	4.21	11

Top four major global barriers preventing the translation of research into effective treatments for MND	Average priority rank from 1 (lowest) to 5 (highest)	No. of times listed as top barrier
IDENTIFYING DRUG TARGETS AND UNDERSTANDING DISEASE FUNDAMENTALS noted as key priorities for developing effective treatments.	4.23	9
PATIENT STRATIFICATION AND CLASSIFICATION identified as important for achieving more precise and effective research and treatment approaches.	4.28	6

These four global barriers were selected as the priority areas for discussion at the inaugural Roundtable event. See Appendix d: Delegate survey results for additional results from the survey.

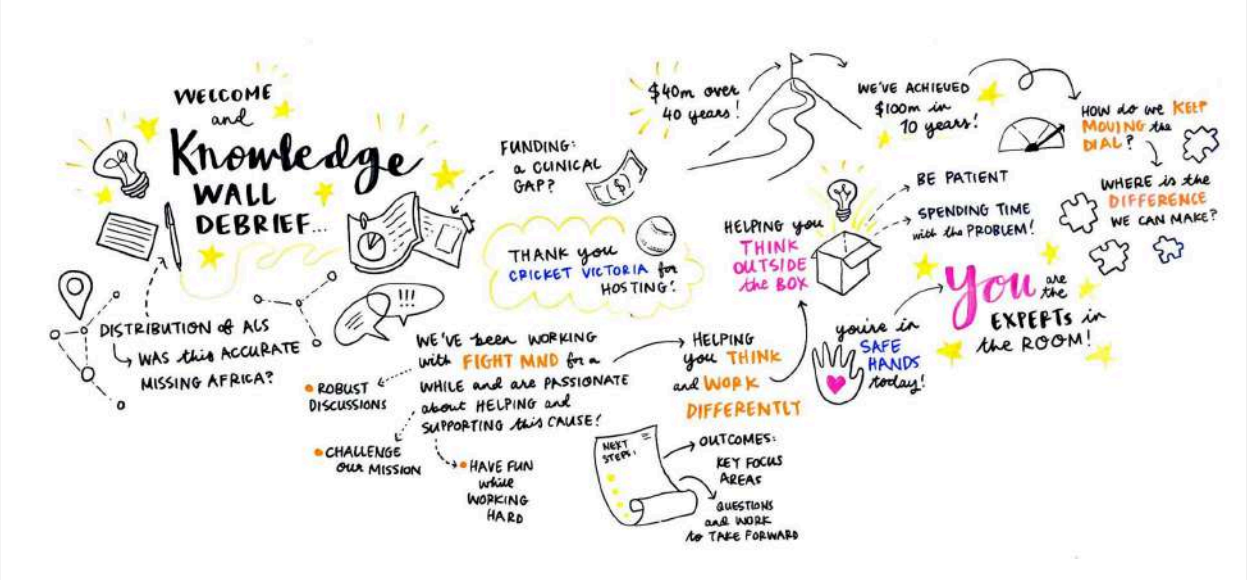
Knowledge wall

At the start of the event delegates were given time to explore a variety of contextual information curated in the form of a 'Knowledge wall'. Information displayed on the Knowledge wall was provided by delegates, across various areas of knowledge and expertise, and by FightMND. See Appendix e: Knowledge wall content for a copy of all of the content that was displayed.

The purpose of the Knowledge wall was to curate a visually engaging gallery of insightful content on global research activities and barriers to research translation. Delegates were asked to provide information from project case studies, interviews, journal articles, infographics etc. The content of the Knowledge wall helped to set the scene for the workshop and ignite delegates' thinking about each of the four global barriers to research translation.

Delegates were encouraged to explore the Knowledge Wall and consider one or two points that surprised or interested them from each of the four global barriers to research translation.

Image: a visual map of the welcome session and discussion about the Knowledge wall



Insights

Some of the insights gained from the Knowledge wall are listed in the table below.

Not all regions are well represented in the global distribution of MND/ALS

Whilst delegates may each be experts in their own right, they have **different experiences and interpretations** of the challenges and opportunities in the MND sector

Delegates commented on the **large number and diversity of MND/ALS initiatives** within the sector

3. The global barriers to research translation

Introducing the four global barriers

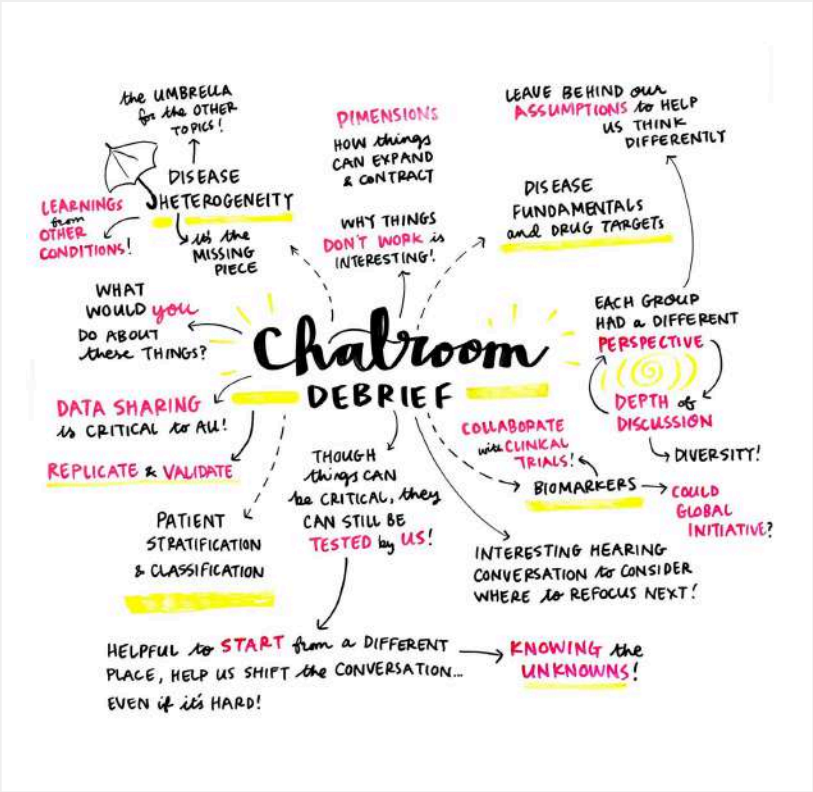
Prior to the event, delegates were each allocated to one of four groups; each group representing one of the top four global barriers. One expert was identified in each group, and asked to prepare and present a brief overview of their allocated global barrier, including the current state of play, key challenges and opportunities. See Appendix f: Introduction to global barriers - presentation materials for a copy of their presentation materials.

The four global barriers, their definitions, and the expert presenters, are shown in the table below.

Global barrier	Definition	Expert presenter
1. BIOMARKERS	Diagnostic, monitoring, predictive, prognostic, target engagement, safety and susceptibility/risk biomarkers relevant to MND.	Lucie Bruijn
2. DISEASE FUNDAMENTALS & DRUG TARGETS	New or well characterised disease mechanisms, causes of MND, disease pathways and pathologies that present as potential targets for therapeutic intervention.	Jeffrey Rothstein
3. DISEASE HETEROGENEITY	The understanding of disease heterogeneity in MND - what does heterogeneity look like in MND, what is driving it and where is it important?	Ammar Al-Chalabi
4. PATIENT STRATIFICATION & CLASSIFICATION	How patient populations should be characterised and classified into sub-groups and how this classification can be used to guide stratification of patients for clinical trials and research.	Angela Genge

At the Roundtable event, delegates formed four clusters, which rotated through each of the 'chat rooms', where the experts presented an overview of their allocated global barrier, then led a Q&A-style discussion. Once the delegates had heard from each of the presenters, a debrief discussion was held with the whole group.

Image: a visual map of the chat room debrief and discussion about the introduction to the four global barriers.



Insights

Some of the insights gained from the introduction to the four global barriers are listed in the table below.

The four global barriers are not mutually exclusive, and present some common challenges and opportunities.

There are **differences in the assumptions made by delegates in their day to day work** in the MND sector.

- These assumptions have significant implications on MND research - the way problems and hypotheses are identified, and how the research is undertaken
- Being transparent about the assumptions we make can help us start our conversations from a different place, think differently and identify the unknowns.

Sharing data is critical and needs to be incentivised.

There are still **many unknowns** and likely unknown unknowns.

Clarifying problems

Delegates were allocated to their groups, by global barriers, and first identified the key problems to be solved.

This was followed by a process of interrogative enquiry, called the “5 Whys”, into the nature of each of these problems. Through exploring the chains of cause and effect behind each problem, deeper causes came to light, as well as connection and overlaps between the problems they identified.

Finally, each of the groups had the opportunity to reflect on the problems and causes identified in the other groups, and provide feedback.

#1: Biomarkers

Common problems

The Biomarkers group identified several common problems, as listed in the table below.

Not specific / lack of validation

- For new biomarkers, how much change is needed to be meaningful?
- Target specificity
- Sharing results on biomarkers
- Regulatory agency acceptance of biomarkers
- Identification of meaningful biomarkers
- Lack of validation/understanding and interpretation
- Biomarker that is disease specific: too many (non-specific)
- Challenge of disease heterogeneity

Lack of focus

- Not enough biomarkers
- Ones that reflect disease and response to treatment
- What are they for? Diagnostic, stratification, clinical trials etc

Progression timing

- Need to be progression specific
- Knowing what needs to be measured

Resource limitations

- Ease of assessing biomarker samples

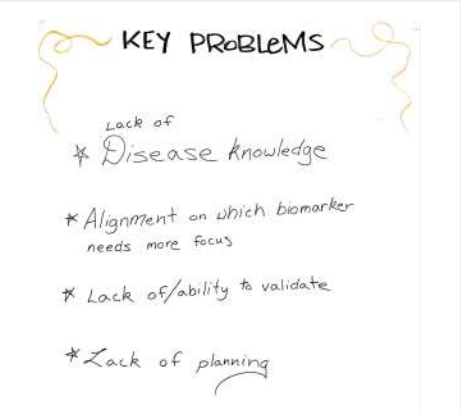
Additional comments

- How do we identify the right biomarkers?
- How can you biomark such a heterogenous and rare disease?
- Lack of understanding of disease mechanisms and timing of disease mechanisms
- Insufficient soluble markers of disease progression
- People have different opinions on what a biomarker is

Key problems

The group consolidated its list into four key problems:

1. Lack of **disease knowledge**
2. Alignment on **which biomarker needs more focus**
3. Lack of/**ability to validate**
4. Lack of **planning**



Causes

All identified causes of key problems in the area of Biomarkers are shown in the table below (note: feedback from other groups is shown in white boxes).

Problem	Why 1	Why 2	Why 3	Why 4	Why 5
DISEASE KNOWLEDGE	Complex disease	Heterogeneity	Multiple causes		
Diseases Knowing the right biomarker Need well defined starting material/ samples for your biomarker studies	Lack of education Priorities Source of biomarker, serum might not reflect CNS events	Temporal and spatial changes Different pathways at different disease stages Classified as one disease Genetic vs sporadic non-genetic	Drug mechanism biomarkers vs disease mechanisms		
WHICH BIOMARKER/ ALIGNMENT	Different needs	Multiple stakeholders	Different opinions	Heterogeneity	

Problem	Why 1	Why 2	Why 3	Why 4	Why 5
Pre-analytical variables of the samples Evaluation of existing candidates (for variety of purposes)	Different types of biomarkers need to be independently & strategically addressed Diagnostic, prognostic, disease stage, treatment response, target engagement		Need for an evidenced based approach Economic and other disincentives	Multimodal biomarkers required – how to define these & combine them	
VALIDATION	Methodology -Variation -Limitations	Lack of standards	Lack of collaboration	Silos	Resources
Lack of samples	No defined pathway/process for new biomarkers Limited engagement of regulatory bodies	More data from prospective cohorts Database for the real world needs a sponsor and identification of variables (might be possible) Identifying preclinical translatable biomarkers	Novelty is valued and prioritised over validation	Fear of transparency Lack of communication No definitive way to diagnose Geographical distances Communication	Academic goals vs solving disease Career competition, researcher retention Not enough people & resources focussed on combining & eliminating silos For academics – what is the reward for this work (who will be incentivised?)
LACK OF PLANNING	Limited pre-clinical biomarker work	Translation gap	Relationships: Industry – academia (pre-clinical), Clinical - industry	Knowledge and expertise	Pathways

Problem	Why 1	Why 2	Why 3	Why 4	Why 5
	Lack of collaboration Deep review of current knowledge Access to longitudinal samples Model fitting/Associations Over simplification Need to target engagement biomarkers One size fits all approach	No consensus on strategy Biomarker development isn't approached strategically Targeted funding calls	Different motivations of industry & academia Don't know where the precompetitive-competitive level is Some countries have limited industry, pharma, biotech	Data analytics – need for more people in this area in MND	

#2: Disease fundamentals & drug targets

Common problems

The Disease fundamentals & drug targets group identified several common problems, as listed in the table below.

Heterogeneity

- MND is heterogenous
- Which patients do you include/exclude?

Models

- What's the right model?
- Can't examine early mechanisms in humans
- Lack of reliable disease models
- Models that don't predict human disease
- Lack of human tissue validation

Reproducibility

- Lack of consistent testing, diagnostics
- Reproducibility
- Lack or replication including of key work
- Lack of human validation

Funding

- Need funding of fundamental discovery research
- Funding biases

Drug targets and development

- Drug Screening methodologies & harmonisation
- Too many potential drug targets – need prioritisation
- Drug development is difficult
- Targeting cause vs secondary effects
- We continue to run trials on targets that many scientists do not believe in or are not excited about
- Need target engagement biomarkers especially for trials
- Many people do work with no ability to clinically develop

Unknowns about disease

- Unknown disease mechanisms
- Too many disease mechanisms implicated (too many drug targets)
- Actual target is not known
- We don't know what causes MND
- Not every genetic mutation leads to disease

Collaboration

- We don't try to disprove hypothesis
- People who work on certain things want their hypothesis to be true
- Lots of silos
- We don't adapt learnings in clinic/people back to lab research (and vice versa)
- Disconnect between fundamental research and pharma

Key problems

The group consolidated their list to four key problems:

1. **Primary versus secondary** (causes vs consequences)
2. Disease **models**
3. **Reproducibility**
4. **Variability**

Causes

Identified causes of key problems in the area of Disease fundamentals & drug targets are shown in the table below (note: feedback from other groups is shown in white boxes).

Problem	Why 1	Why 2	Why 3	Why 4	Why 5	Unknowns
PRIMARY VS SECONDARY (CAUSE vs CONSEQUENCE)	We don't know when ALS/MND starts	We see people with ALS well after disease mechanisms have started	The disease cannot be detected early enough	No reliable tests	We don't have any disease specific biomarkers We don't have a diagnostic test	
	We don't know why ALS/MND starts		Lack of awareness	Rare disease		
			Doctors delay		Terminal disease	
	Bias/personal research areas of interest Different causes at different times		Psycho-social determinants of access Even if we can diagnose early, still not quick Age			We don't understand the disease Lack of clear understanding of environmental and lifestyle factors It's not one disease
DISEASE MODELS	Many don't recapitulate human disease They don't translate		Genetic disease Mice are not human	Ethics		
Wrong starting point! Models are not the disease but a tool for answering defined questions	Many have no phenotype but multiple nature papers Lack of training		We are not asking the right question of the right model Not multiplexing	Not predictive of what happens in humans We can experiment on humans (gene carriers)	We can't model sporadic disease Yes we can! Can model sporadic using reprogrammed cells	Genome wide integration might not be high resolution enough
REPRODUCIBILITY	Different methods	Lack of collaboration	Novelty/ competition	Career pressure		
			Funding			
			Time	Admin burden		

Problem	Why 1	Why 2	Why 3	Why 4	Why 5	Unknowns
			Methods poorly articulated			
	Use established platforms rather than boutique to increased reproducibility & utility	Need some differences between models for robustness Different animal house environments	Grant based research vs problem solving/hypothesis testing We must reproduce the TDP-43 aptamer data quickly	Selfish Poor communication Complexity in methods/ models		
VARIABILITY						
Haven't answered Need more discovery research Pre-conceived ideas on 'causes' e.g. TDP-43	Pre-clinical research is not perfect	Not yet establishing (and using) guidelines to decide whether a clinical model is useful				

#3: Disease heterogeneity

Common problems

The Disease heterogeneity group identified several common problems, as listed in the table below.

We don't understand the disease complexity

- We do not understand why onset of loss of function is focal
- Why some people can live to old age with mutation
- Differing disease mechanisms not accounted for in clinical measurements
- Understanding which aspects if disease differences are most important
- We can't define disease mechanisms fully so can't reduce heterogeneity
- Complex mechanisms of disease causation
- Don't know the cause/s

Heterogeneity

- Why young or old? Why slow or fast? Why UMN or LMN?
- We do not understand why it is different in males and females
- Why is it less common in people of African origin?
- Why some anatomical regions are spared

- We don't always state why we care about heterogeneity
- What does heterogeneity mean for treatment? What are we looking for?
- Animal ? human ? drug ? – Differences in heterogeneity

Classification

- Diagnostic criteria not harmonised
- We don't know how to classify – we don't have the correct tools to classify
- Data sharing – lack of?

Genetics

- Lack of genetic testing
- Lack of diversity in existing databases
- Genetic variation – what else? Other variations

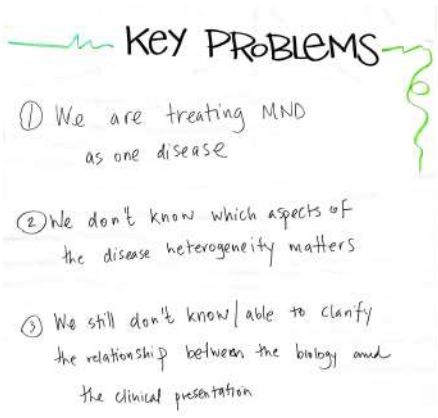
Progression and treatment

- Can't detect drug efficacy
- Disease course prediction
- Diagnostic delay
- Clinical trial eligibility
- Biomarkers NFL – what do they mean?

Key problems

The group consolidated their list to three key problems:

1. We are **treating MND as one disease**
2. We don't know **which aspects of the disease heterogeneity matter**
3. We still don't know / aren't able to clarify the **relationship between the biology and the clinical presentation**



Causes

Identified causes of key problems in the area of Disease heterogeneity are shown in the table below (note: feedback from other groups is shown in white boxes).

Problem	WHY 1	WHY 2	WHY 3	WHY 4	WHY 5
We don't understand what differences	*Lack of depth of breadth of data*	*Lack of systematic*	*Unsure of which data matters*	*We don't understand the disease*	*Its complex*

Problem	WHY 1	WHY 2	WHY 3	WHY 4	WHY 5
between patients matter		*collection of data*	*Lack of resources*		
	We don't know if clinical vs biological matters	*Lack of biomarkers*			
Balance between amount of evidence needed to determine subtype vs benefit of subtyping Genetic vs biological pathways	Matters to who?	Communication No incentives to share data or methods PLEx introduced to value of data early – data as important as trials Lack of data sharing No longitudinal collections being shared Sharing data in complex data sets is complex Not lack of biomarkers but lack of consensus building, validation & collective approach Clear biomarkers for stratification in clinical trials	Reliance on clinics not PwMND See where other diseases are going e.g. PD Model of disease involvement Some data types have proven signal – Fund to collect e.g. genomics (GWS) Stuck on same approaches Data repository with clinical + omics data Incentivise integrative analyses and iterative research	Different disease mechanisms, what role do they play in heterogeneity ? Not enough numbers/data to sub-group Multiple causes We don't integrate people with MND voice Different scientists see different "truths" Lack of pre-clinical research	We can't model it or "see" it developing Cop out!! We don't tackle the problem strategically
For treatment	*We don't understand the relationship between the biology and clinical presentation*				

Problem	WHY 1	WHY 2	WHY 3	WHY 4	WHY 5
How to treat early	Unsure which category matters clinical/ biological	Better communication between research and clinical sectors See AD field!	The perceived incentive for industry to address this is low		
For diagnostics **We are treating it like one disease**	*We don't have a way of subtyping it based on biology*	*Personalised treatment is expensive and lack specific targets*			
Not enough patients for clinical trials Are there final effectors for multiple causes?	Ammar's evidence – distinct progression subtypes. Why not classify on this? Spectrum between FUS/SOD1/etc – sporadic, sport injuries	No clinical algorithm Not enough molecular characterisation pre-clinically			

#4: Patient stratification & classification

Common problems

The Patient stratification & classification group identified several common problems, as listed in the table below.

Problems to solve

- Clinical Trials
  - Adaptive trial need
  - Need for additional biomarkers of therapeutic efficacy
  - Need for disease progression biomarkers for clinical trial stratification
  - Identification of responder sub-groups in clinical trials
  - Establishment of a minimum data set for any MND clinical trials and other studies
  - Unsure clinical trial effectiveness
- Data
  - Data (lack of) sharing – natural history studies
  - Data repository for all data for all patients
  - Limited data repositories to enable classification
  - Comparable data
  - Variable data collection across patients
  - Funding for basic unified data production

    - Lack of diversity from lower/middle income countries
- Access to genetic screening
    - Clear genetics e.g. FUS = ASO vs complex genetics vs sporadic
    - Lack of offering of genetic screening to all MND patients
    - Not all MND patients receive a genetic workup (WGS)

Heterogeneity

- We don't understand the drivers of heterogeneity
- Clinical pictures heterogenous – lump or split?
- People/Patients are different
- Define how/how far stratification should be to unravel treatment
- Why does the same cause present in a different way?

Replication

- Replication & Application of pathway identification via 'omics
- Replication –
    - variables into a database & analyse and compare
    - Big "n" vs little "n" studies = credibility
- Different pathways involved at different times
- Small #'s patient in some sub-groups

How to stratify

- Is there a universal marker or are we condemned to multimodality
- Classify by rate of progression but don't understand drivers
- Biomarkers to detect MND
- Biomarkers to classify subtypes
- Need for biomarkers for relevant biological pathways contributing to motor neuron injury
- Can we have an AI based ALSFRS-omic composite marker?

Classification

- Consensus on classification
    - Do we have the right stratification factors?
    - Criteria for classification are unclear
    - What criteria to use to stratify
    - Agreement of criteria/classification across countries
    - Pre-defined "classification"
    - No define standards for patient classification & clustering
    - Once classified, can it change?
    - How to classify – site of onset vs biomarker?
- Lack of definitive markers to group patients
- Resources required to apply stratification tools

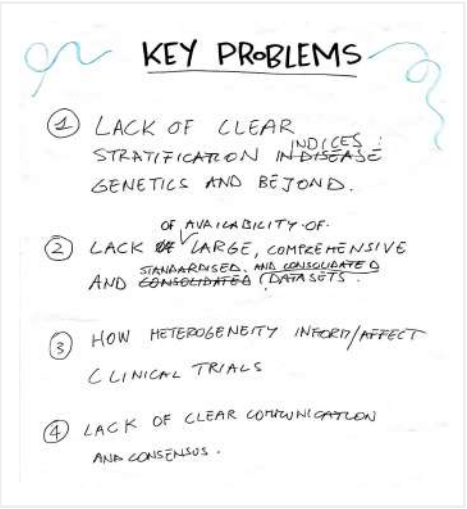
Miscellaneous

- Diagnosis delays
- Availability and skill levels of neurologists

Key problems

The group consolidated their list into four key problems:

1. Lack of clear **stratification indices**: genetics and beyond
2. Lack of availability of very large, comprehensive, standardised and consolidated **data sets**
3. How **heterogeneity informs clinical trials**
4. Lack of clear **communication and consensus**



Causes

Identified causes of key problems in the area of Patient stratification and classification are shown in the table below (note: feedback provided by other groups is shown in white boxes).

Problem	WHY 1	WHY 2	WHY 3	WHY 4	WHY 5
Lack of clear stratification	Not everyone gets genetic testing	Cost and access to genetic counselling	Unclear of value	Lack of consensus on impact	Lack of communication of value
All means of stratification More than just genetics required to stratify Other stratification – late vs early	Lack of understanding of underlying disease mechanisms	Better awareness and training for genetic counsellors	Not since Tofersen		Why? Do we understand what matters?
Not enough data	Need standards/ Consensus on what and how and why we collect data	Different motivations	Difference in funding streams	Different understanding of value of data silos	Lack of communication and joined funding priorities

Data – cost and time issue Lack of transparency by companies Data collecting – sporadic/ random Data collection not easily understood Data ownership – data is currency	Pharma do not make trial data publicly available No resources/ honest broker to pull data sets together Need to agree why we want to know Need funding for maintaining databases	Barriers to data sharing: national laws Lack of clear goal Lack of rewards /incentive for collaborating		Publication of data, open access	
How does heterogeneity inform/affect clinical trials	Confounds its	Signal to noise	Lack of ability to identify responders	Lack of knowledge of relevant biomarkers	Lack of data sharing and merging
Personalised medicine (e.g. cancer) Replication + validation We have to group people (with differences) to treat/ study	We don't push industry to embrace current best practices in design Trial size too small Differences of opinions amongst key people on how to address heterogeneity in trials Trial duration too short + no long-term follow up Inclusion criteria excludes many patients and groups		Lack of prognosticatio n that informs sub groups		Lack of education Lack of sample sharing Lack of understanding mechanisms that contribute to heterogeneity

Insights

The insights gained from clarifying the problems and identifying their causes are, most notably, the commonalities across each of the global barriers. Some of these are listed in the table below.

Communication and collaboration across the sector globally isn't yet good enough. Causes include: misalignment of incentives; lack of and/or misaligned funding; ownership of data; and regulation barriers

Global, **big data** does not yet exist in useful forms. The causes are similar to those listed above for Communication and collaboration not yet being good enough. An additional cause is the significant differences that exist between data sets across geographic and institutional boundaries

We aren't able to **aggregate and search biomedical data** globally, such as from a global MND biobank. There are many causes, including most of those already listed above.

There is significant variation in the development and use of **preclinical MND models** globally, limiting reproducibility. The most significant causes are variations in protocols and lack of validation.

The **number of participants in clinical trials** is small. Causes include: MND is an uncommon condition; restricted inclusion criteria.

The **impact of heterogeneity on clinical trials** is not yet well understood, caused by a lack of understanding of MND heterogeneity, resulting in significant differences in opinions across the sector

Across many aspects of research **consensus and validation** is lacking. Causes include: bias and misalignment of priorities, lack of incentives/funding for validation studies, preference for novel research.

Identifying solutions

Delegates were first tasked with identifying initiatives that would address the key problems. Subsequently they prioritised the initiatives, and broke down the highest priority initiatives into discrete activities, using the activity template provided.

#1: Biomarkers

The Biomarkers group first brainstormed a list of initiatives to address two key problems, as shown in the table below.

Problem 1: Lack of biomarkers and disease understanding

Solutions:

- Need to align brain function with anatomy
- Pooling of existing data
- Lessons from genetic carriers SOD1/C9
- Transcriptomics, genomics, sample analytics
- National screening platform
- Focus on the pre-diagnosis stage
- Transcriptomic screening

Problem 2: Lack of preclinical biomarker development that translates to the clinic

Solutions:

- Preclinical biomarker strategy plan
- Multidisciplinary preclinical program
- Industry and academia partners
- Involve collection of biomarkers in all projects
- ALLS ALS SOPs
- Core screening program of compounds
- Drug development
- Preclinical biomarker plan
- Clinical trial
- Drug and biomarker for SOD1
- Funders require biomarker components for all studies
- Funding agencies broker
- Campus Plus PhDs (commercial and academic)

Initiatives

The Biomarkers group then developed two priority initiatives, as shown in the tables below.

Problem	Initiative	Details	Activities
Lack of biomarkers and disease understanding	Global biobank & AI initiative	Biomarker focus – digital, imaging, others Build on existing expertise/precedence Focus on genetic carriers & sporadic Spatial understanding of disease Alignment of brain function and anatomy Sample sharing Stratification and heterogeneity	1. Perform inventory of what is out there and access 2. Data scientists/AI specialists to inform integration 3. Identify task force members: ○ Funding agencies ○ Biomarker experts ○ Other biomarker initiatives – ALL ALS, TRICALS/ENCALS ○ PLEX (leadership role) 4. Define the projects ○ Unbiased/biased analysis ○ Technologies to generate new data ○ Handling of new samples ○ Access and storage to samples ○ Combining old data ○ Inclusivity – combine natural history data for C9/SOD1 ○ Identify the best model 5. Data ownership (ALLFTD, GENFI)
		ICMJE ALS consortium	

Lack of preclinical biomarker development that translates to the clinic	Establish task force to build global guidelines for preclinical studies to inform clinical trials and disease heterogeneity	Stakeholders: ● Regulators ● Funding agencies ● Academic ● Industry ● PLEx ● Clinicians ● C-Path	1. Industry think tank ○ Sharing of biomarker data from clinical trials 2. Manuscript ○ Refresh ○ Life Arc – build on ○ Rotating committee – consult ○ Caution – don't stifle innovation ○ Terms of engagement

Activities

The Biomarkers group broke the priority initiatives down to focus on two key activities: the Global biobank and AI initiative, and the Global taskforce initiative.

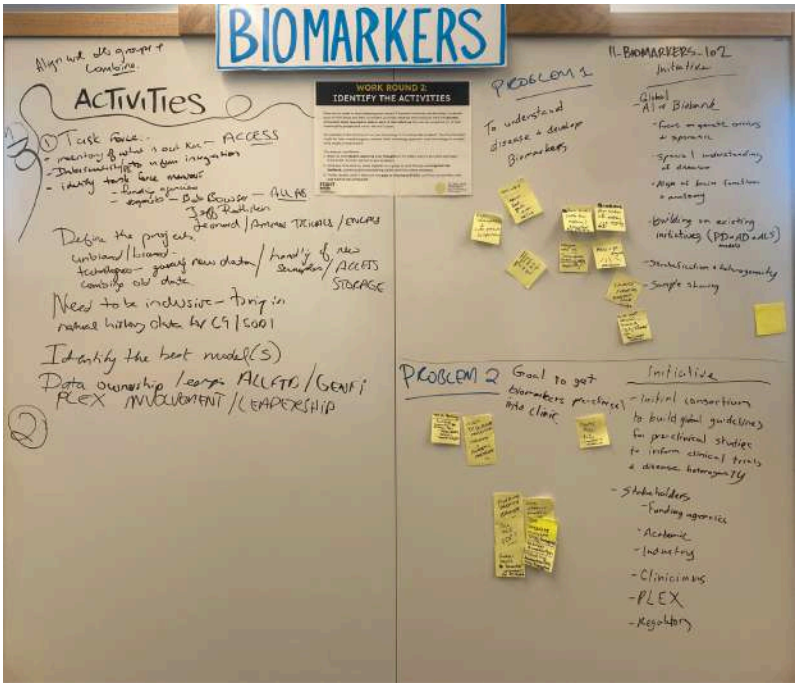
Activity 1

Activity: Global biobank & AI initiative	**Priority initiative:** SWOT analysis (inventory of what is out there and access)
Description: Harmonising all existing resources with ALS expertise and existing stakeholders	
Resources and infrastructure required: ● Project management/governance ● Recruitment of task force	**Information and expertise required:** ● Leadership ● Data management ● IT ● Legal ● Data analytics
Risks: ● Lack of focus ● Silos ● Privacy and security ● Lack of engagement ● Financial support ● Lack of momentum	**Interdependencies:** Stakeholders buy in
Key outcome(s) and milestone(s): Focused project identifying and validating biomarkers	
Starting time: Immediately	**Time to complete:** ~2 years

Activity 2

Activity: **Establish a global taskforce**	**Priority:** Translating biomarkers to clinic
Description: Build/integrate guidelines/SOPs	
Resources & infrastructure required: • Funding/admin for task force meeting • Assess landscape for existing guidelines/SOPs	**Information & expertise required:** Stakeholders: • Regulators • Funding agencies • Academic • Industry • PLEx • Clinicians • C-Path
Risks: • Remain status quo	**Interdependencies:** • Understanding other initiatives scope/progress
Key outcome(s) & milestone(s): Acceptance and implementation of work/recommendations	
Starting time: 2024	**Time to complete:** 2025

Image: the work of the Biomarkers group.



#2: Disease fundamentals & drug targets

Initiatives

The Disease fundamentals & drug targets group developed five priority initiatives to address the two highest priority problems to solve, as shown in the tables below.

Problem	Initiative(s)	Details/feedback	Activities
Lack of appropriate/translatable disease models Lack of reproducibility	Knowledge summit	Best practice recommendations for pre-clinical research	Build name and logo (ProtocALS) Guidelines: • Working group • Global Survey • Define global leaders to include in summit, identify key targets and funding • Meeting to plan overall program • Knowledge summit at ALS meeting • Paper
	Validation and drug targets core from external resource (Global network)		Scoping exercise for research core Funding engagement
Lack of understanding of disease mechanisms (primary vs secondary)	Human: Gene carriers	Pre-symptomatic research Expand genetic testing Global approach	
	Aus/Global Biobank (UK biobank)	Genetic data Healthy motor system ageing Environmental data	Rethink brain computer interface to learn about the disease (blue sky idea)
	Preclinical: Develop new cortical-spinal-motor model with increased complexity to understand the healthy system	Organoid/ assembloid models of sporadic ALS	

Activities

The Disease fundamentals & drug targets then broke the priority initiatives down to focus on two key activities, named 'ProtocALS' and 'ASAP: the MND clock'.

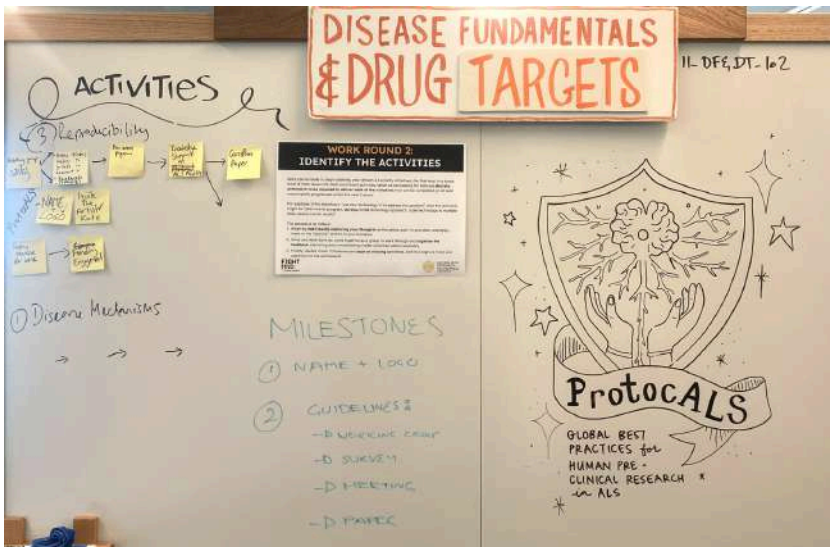
Activity 1

Activity: ProtocALS		
Resources & infrastructure required: De-centralised Global Core Resource		**Information & expertise required:** • Global Protocols Group • Program Managers Team and Leader • Survey
Risks of doing: • Funding • Time • Resources • Stifle innovation	**Risks of not doing:** • Lack of reproducibility • Waste of resources • Lack of translation	**Interdependencies:** • Funding for core • Public-private partnerships
Starting time: ASAP (MND Clock)		**Time to complete:** 24 months

Activity 2

Description: Global presymptomatic/asymptomatic discovery study to fund primary/upstream targets and markers	
Resources & infrastructure required: Global biobank	**Information & expertise required:** • ACORN, ALL-ALS, PREFALS • Any other existing resources? • PLEX
Starting time: ASAP (MND Clock)	**Time to complete:** 24 months

Image: the work of the Disease fundamentals & drug targets group.



#3: Disease heterogeneity

Initiatives

The Disease heterogeneity group focused on one key initiative to address the problem, 'we are treating MND as one disease' (note: feedback provided by other groups is shown in white boxes).

Problem(s)	Initiative	Details	Activities
We are treating MND as one disease We still don't know how to clarify the relationship between biology and the clinical presentation	TIDALS (Trial Initiative for Data in ALS)	Define layers of heterogeneity • Clinical • Biological/omics • Pathology • Epidemiology Harmonise and integrate SOPs for data collections • Public (website) • Assess SOPs Incorporate above into all trials for analysis (collaborations cross-disciplines e.g. biotech vs academia All trials are required to collect data longitudinally and share for analysis and include under-represented groups	1. Working groups 2. SOPs 3. Data & Biorepository 4. Stratification 5. Definitions 6. Omics 7. Iteration process
		See initiatives in other countries Resources/infrastructure Consider funding/legal challenges Don't set barrier to participation too high What if it appears to be one disease?	
We don't know which aspects of the disease heterogeneity matters			

Activities

The Disease heterogeneity group then planned out the steps to address the problem, before detailing three activities in the activity templates

Step 1: Develop working groups

- Diverse – industry, regulatory bodies, stakeholders, funding bodies, patient advocates, data scientists
- Engage trial leaders to incorporate at the start
- Include international legal experts
- Bring in regulatory for buy in early
- Overarching body to accredit or validate data collection

- Group leaders working on the different layers of heterogeneity
- Build PLEX group to produce position statement on need for open data access
- Employ coordinators to oversee regions
- Identify funding opportunities
- Industry workshop to scope out terms for making biomarker data

Step 2: Harmonisation and development of SOPs

- Scan horizon and harmonisation of existing SOPs
- Develop new standards that
    - are publicly available
    - that have data/sample ownership rules

Step 3: Data and biorepository

- Remote collection - not just from clinical trials and in other global regions
- Retrospective inclusion into global initiatives
- Clinical sites onboard for accessing/generating the requisite data to the right standard
- Common data sharing platform/repository
- QMS (Quality and management system)
- Identify and integrate existing data sets

Step 4: Patient stratification

- Stratify all biomarker studies and iteratively remove clinical descriptors according to those that do not inform
- Group disorders based on predominant features (e.g. genetics, disease progressions)
- Test subgrouping sizes – what is the optimal cluster size for clinical similarity vs drug effects.

Step 5: Definitions

- Better define or harmonise key measures
- Define what is important and what we mean by “disease”
- Direct focus on environmental and lifestyle factors

Step 6: Omics: understand biology through omics data

- Longitudinal collection and analysis at depth with clinical/biological data
- Gather omics data on people before and after Tofersen to capture treatment response
- Follow other initiatives as examples (e.g. project MinE)
- Analysis and integration of existing data into a centralised database – can inform new data collection
- Large dataset – each subgroup has meaningful numbers to study and map disease subtypes

Step 7: Iteration

- Between drugs and biomarkers in clinical trials to resolve subtypes (e.g. Lithium/UNC13A)
- For efficiency – can’t collect optimal dataset from outset

Activity 1

Activity: Working Groups	**Priority initiative:** #1
Description: • Engage key stakeholders – PLEX, industry, funders, regulators • Establish a leadership/governance structure	
Resources & infrastructure required: • Workshops – teams of use for , standards for trials • People – project management, digital resources	**Information & expertise required:** Expert stakeholders (as above)
Risks: • Too many meetings • Not inclusive • Competing agendas • Not sustainable	**Interdependencies:** • Industry buy in • Funding cooperation
Key outcome(s) & milestone(s): 1. Standards document/publications 2. Framework for data sharing	
Starting time: Jan 2025	**Time to complete:** 2027

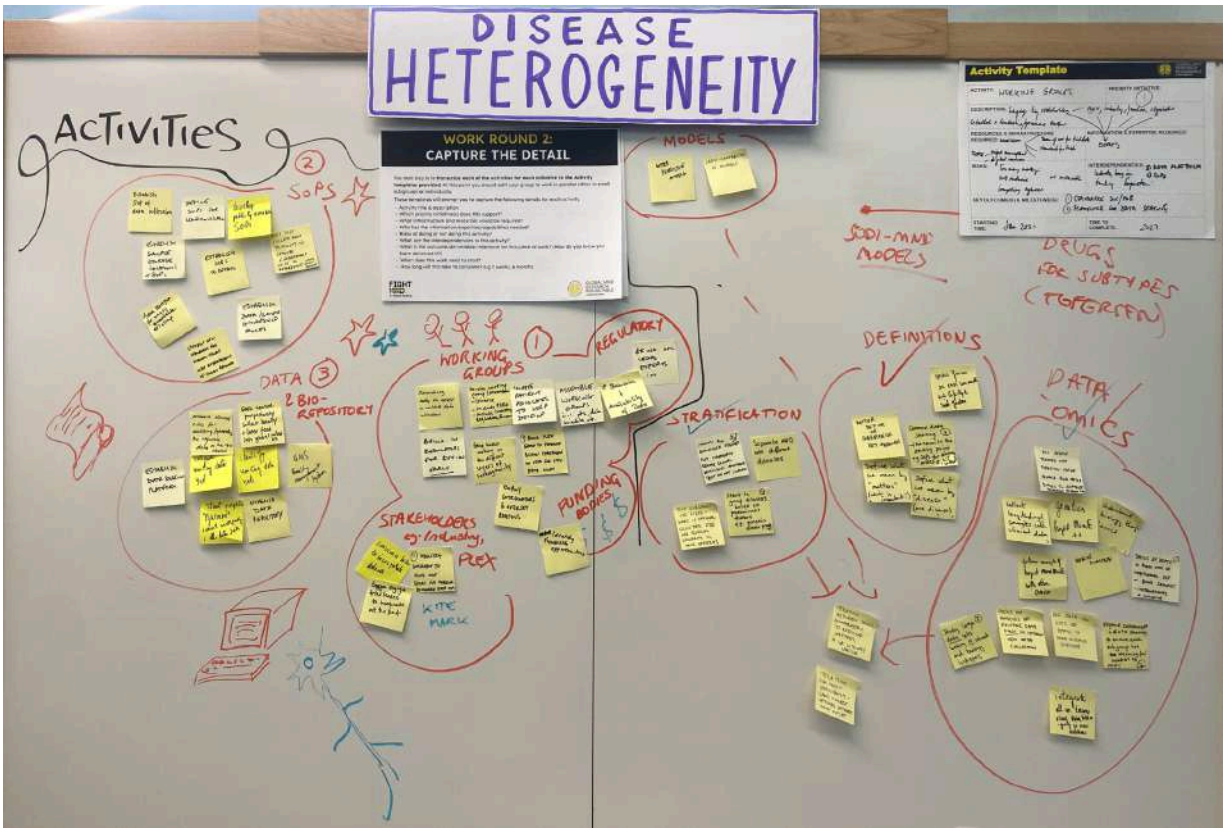
Activity 2

Activity: SOPs	**Priority initiative:** #2
Description: Develop standard operating procedures and publicise	
Resources & infrastructure required: • Central global website • Data scientists • IT specialists	**Information & expertise required:** • Legal • Funding • Data scientist • Domain name
Risks: • Poor quality management • Inadequate SOPs • No buy in • Inequity	**Interdependencies:** • Expertise • Buy-in
Key outcome(s) & milestone(s): 1. Establish working group 2. Formalise harmonised SOPs 3. Establish website	
Starting time: January 2025	**Time to complete:** January 2027

Activity 3

Activity: Data platform + biorepository	**Priority initiative:** #3
Description: Establish data repository	
Resources & infrastructure required: • Working group • Website • Neuropathologist	**Information & expertise required:** • Legal/IP (for data sharing) • IT experts (to build infrastructure • Clinical/omics • Samples
Risks: No buy-in	**Interdependencies:** Working group
Key outcome(s) & milestone(s): Website available	
Starting time: Jan 2025	**Time to complete:**

Image: the work of the Disease fundamentals & drug targets group.



#4: Patient stratification & classification

Initiatives

The Patient stratification & classification group focused on one key initiative for each of the two highest priority problems (note: feedback provided by other groups is shown in white boxes).

Problem(s)	Initiative(s)	Details	Activities
Lack of stratification plan	Develop a stratificatio n plan	Set up committee (co-chair scientist + PLEX) Define protocols Set up funding to facilitate Horizon scan of what is available and what is being done for other diseases	Standardisation of protocols • Universal access to genetic subclassification for MND patients • Clinical data (Examples: longitudinal, site of onset, age, gender, baseline etc, therapies, cognitive, MRI) • NFL • Omics (transcriptomics, metabolomics, lipidomics, methylation, proteomics) • Inclusion of the right and robust controls Feasibility & Implementation of protocol • Scoping exercise • Consultation at regional level • Global consensus
		Offer a standardised genetic analysis for all patients enrolled in research and clinical trials Sustainability of funding – who is going to pay for it Implementation science trial Regulators Burden of patient Scoping exercise – companies running trials storing data Clinical data, transcriptomics	
Lack of availability of large, comprehensive standardised and	Generate a global master protocol	Data repository with low barriers to access to facilitate AI and more	Research how feasible to identify patient subtypes

Problem(s)	Initiative(s)	Details	Activities
consolidated datasets			
		Centralised infrastructure and clinical biological data collection Access by industry Link with UK biobank for controls & MND Collaborate with other disease groups/funders	Validation of biomarkers and new biomarkers

Activities

The Patient stratification & classification group then detailed two key activities, as shown in the activity templates below.

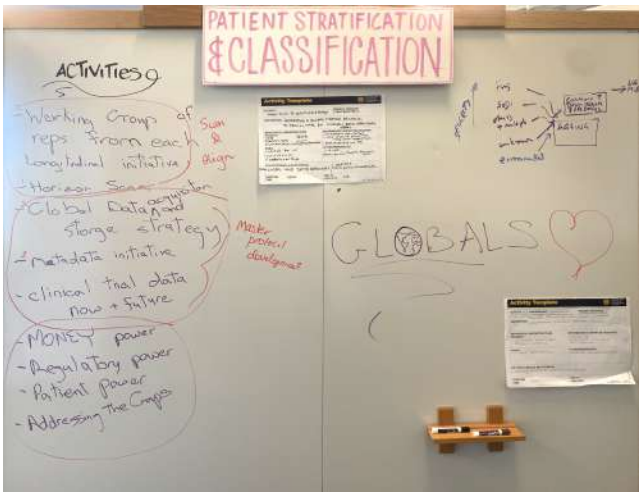
Activity 1

Activity: Global data acquisition and storage	**Priority initiative:** Stratification
Description: Generating a global master protocol to facilitate an MND/ALS global data repository	
Resources & infrastructure required: • $$$ • Horizon scan • Leadership/working group committee • Data	**Information & expertise required:** • IT experts (data storage) • Lead research group with large data repositories • Data analysts including AI
Risks: • Lack of buy in • Lack of funding • Lack of leadership	**Interdependencies:** • Funding agencies • Pharma • Research groups
Key outcome(s) & milestone(s): 1. Global MND Data Repository 2. Milestone 1 = New patient stratification	
Starting time: Now	**Time to complete:** n/a

Activity 2

Activity: GLOBALS Stratification plan/Disease classification	**Priority initiative:** Generate a global metadata protocol
Description: • Global data acquisition, metadata • Working groups of rep longitudinal data • Funding, regulatory, advocacy	
Resources & infrastructure required: • Consortia of funders • Existing initiatives	**Information & expertise required:** A panel of established clinicians and scientists
Risks: Poor participation	**Interdependencies:** • Biomarkers • Heterogeneity groups
Key outcome(s) & milestone(s):	
Starting time: Now	**Time to complete:**

Image: the work of the Disease fundamentals & drug targets group.



Insights

Observations

The following observations were made during the detailed problem solving process:

Delegates found it **difficult to explore the chains of cause and effect behind each problem**, and relatively easier to identify solutions to these problems.

Some **common activities and principles were proposed across the groups**, including:

- Horizon scanning: understanding current activity and context prior to commencing new activities
- Industry and regulatory engagement
- Consensus and validation
- Data sharing and consolidation
- Understanding key unknowns: a top down approach to research and data

Outcomes

Whilst solutions were developed within each of the four groups, there are seemingly two distinct areas in which the solutions could be categorised:

1. **Global data & biorepository harmonisation**, and
2. **Preclinical recommendations & standardisation**

The primary goals for Global data & biorepository harmonisation, are:

- **Global centralisation of big data**, including a current state assessment of the global landscape
- **Global, collaborative biobanking**, with a single aggregator search platform. This includes the provision of post-analysis biosamples from industry to the global biobank

The primary goals for Preclinical recommendations & standardisation, are:

- Best practice **recommendations for the use of preclinical MND/ALS models**. This includes the use of models for understanding, therapeutic target identification, and biomarker discovery. This should be communicated as a major impetus towards better translational work
- **Human ALS model core**. This includes: a preference for decentralised infrastructure; the development of standardised protocols for iPS 2D/3D models, agreeing on master protocols; and consideration of this being a potential source for reproducibility and outsourcing work, instead of laboratories developing their own models.

4. Effective research collaborations

Reflections from an expert panel

The purpose of the discussion was to shed some light on how the Roundtable delegates might set themselves up for success beyond this inaugural Roundtable event. The panel comprised of four delegates with expertise and experience in effective research collaborations:

- David Pearce, Leader of the International Rare Disease Research Consortium
- Leonard van den Berg, Leader of European ALS research initiative (TRICALS)
- Melanie Bahlo, Bioinformatician
- Paula Trefiak, International alliance committee member, and lives with MND

Panellists shared their perspectives on what has and has not worked well in their experiences of global research collaboration. Specifically, the discussion explored the following four domains of collaborative research initiatives:

1. Mission & goals
2. Governance
3. Ways of working
4. Partnerships & funding

Image: The expert panel on Effective research collaborations, in action

Insights

The following insights were gained from the panellists and their discussions with delegates.

Vision, mission and goals

- **Start with the vision**, the why
- It is critical to establish a clear and concise mission from the outset, in order to set the scope and boundaries of the collaboration
- Goals or **aims must be clear**, tangible and achievable
- First yield to the expertise you have, and evolve from there
- Ensure there is **strong communication** and **consensus on the approach**
- It's helpful to have a memorable name for the initiative

Clinical trials

- We need a higher number of clinical trials globally
- **Harmonisation of trial design** is needed
- Improvement of clinical trial design would expedite knowledge and help to better measure impact
- **Training platforms** are really important

Current gaps in the MND sector that might benefit from global collaboration

- A **top-down approach to data**
- Addressing consent, which is currently very broad and out of date
- Application of governance models from other diseases; we don't yet understand what is working well and why

- **Courage** to work with people with different opinions across the sector, and a willingness to **be open minded**

Working together and building partnerships

- We all share the same struggles; collaboration is hard. It is challenging to be across multiple initiatives, to focus, and to successfully deliver
- **Representation must be diverse**; it takes a multidisciplinary team, but it does need to be harmonised
- Harnessing **patient advocates** is crucial
- Learning from experts, trusting each other, and seeking out lessons from others' wins are all important
- Involvement in research forums is important for sharing of information and gathering contextual information
- We need to determine how to better share data in order to leverage work in a competitive landscape
- National and international collaboration needs to be well coordinated
- Creating collaboration between funders is challenging, but key to progress

Image: A visual map of the panel discussion about effective research collaboration.

Global MND Roundtable - proposed ways of working

Following the panel discussion, delegates were asked to self-organise into groups of interest and to respond to key questions around the mission, governance, ways of working and partnerships and funding.

Outputs

Outputs from this session are listed below.

Mission & goals

What should be the purpose of this roundtable, ongoing?

Effective collaboration & alignment

- Harmonisation and alignment
- Roundtable needs to produce a report with key goals and actions
- Create honest and trusting processes that break down silos, establish meaningful collaborations and build matrix of data sharing
- Funding opportunities that will develop a drug that will slow disease progression

Define key questions and goals

- First define a mission statement
- Formulate action points
- Idea and collaboration accelerator
- Align initiatives, trends consortia
- Brainstorming solutions to barriers
- Identify and prioritise the questions to answer
- what are the fundamental blockages to progress
- logistical challenges

How to tackle the key questions

- Tackling key questions or problems with achievable acceleration in the field
- Be the drivers of change

What specifically can this group achieve that will help the world to find an effective treatment or cure for MND?

Define focus & alignment

- Define the fundamental questions – priority and tractability
- Strategic prioritisation of issues to tackle and work towards a common goal
- Identify 1 or 2 clear action items to operationalise and use roundtable to refine
- Take courageous leadership in designated central coordinator
- ID and provide list of worldwide resources and data for MND research
- Prepare the next generation of ALS researchers
- Tackle core questions head on even if difficult
- Establish global priorities and ways of working

Prioritise funding

- Don't fund all research; fund the right research that has best chance to get to market
- Improve funding to pull through translation of discoveries to clinical trials

- Data access coordinated funding of projects

Through collaboration

- Multi-disciplinary approaches
- Identify global partnerships opportunities, applications and launching projects
- Openness to new and different ideas
- Harmonise and improve clinical trial design
- Facilitate convergence harmonisation
- Choose to collaborate globally
- Update on the industry/state of research

Achieve outcomes

- Define both ways of doing trials
- Define a few critical questions to solve FAST! (TDP-43)
- Speeding up the development of more effective neuroprotective therapies
- Bridge the gaps to develop treatments

The top ideas for Mission and goals were identified:

1. Define the key questions/**focus areas that are priorities and tractable**
2. Facilitate **collaboration where a global effort would be valuable**

Governance

How should we organise ourselves/set ourselves up for success?

Define clear goals

- Defined strategy
- clear scope and timeline
- clear objectives, purpose and goals (short, mid and long-term)
- develop SMART goals that are achievable and measurable
- focused on the important problems to solve
- Create committees to tackle goals
- Advocate to large MND collaborators
- Clarity of mind, vision, resilience
- A specific resource dedicated to driving an issue forward
- Regular review of strategy and goals
- Action for next meeting (virtual)

Identify barriers

- Institutional barriers need to be streamlined to facilitate collaborations
- Do we need global logistics and project management?

Work together with all partners & stakeholders

- International broker to bring together
- Inclusion of all stakeholders and globally: Patient reps; Multidisciplinary teams/representatives

How do we hold ourselves accountable?

Openness

- Strive for consensus
- Agree to disagree

PLEx leadership

- Involvement of people living with MND at every level
- PLEx as committee chairs not reps
- Put solutions through stakeholder engagement and then disseminate widely

Transparency

- Transparent governance
- Can't start without good governance

Auditable outcomes

- Need deliverables on items (goals) that can be achieved with timetables
- Do what you say you will do
- Observable measurable outcomes
- Need a challenge e.g. $40 mil in 4 yrs from FightMND

Meetings

- Regular meetings with defined agenda

The top ideas for Governance were identified:

1. Define **clear goals**
2. **Work together with all** partners & stakeholders
3. **Identify barriers**
4. **PLEX leadership**
5. **Regular meetings**
6. **Auditable outcomes**

Ways of working

In what ways can we work collaboratively for success? E.g. Information sharing, staff exchange, use of technology

Awareness

- Listen to all stakeholders
- A key person accountable to harness everyone together for a key problem
- Identify skills and priorities in MND researcher community
- Patient advocacy key to success

Data sharing & IT systems

- Democratise data access (e.g. open access)
- Centralised data source with information exchange technology and funding support
- Trainee exchange
- Tech for federation of data from identified to de-identified
- Totality of data

Ideas/collaboration exchange

- Dismantle publication incentives – need to collaborate on the real problems
- Utilise organisation/connector components of the group, that will naturally join people
- Host staff and students from collaborators
- Encourage more junior scientists to gain experience in other groups
- Pair up people with ALS with researchers – each learn from each other
- Staff participation in other teams – reducing duplication

Urgency

- Start at Montreal December meeting

How can we use our differences to our advantage?

Create the right team (expertise & personality)

- Thoughtfully curated
- Informed and open-minded personalities
- Non expert "neutral" as chair to avoid COI/vested interest
- Inclusivity and diversity (regional/geographical)
- Map out and capitalise on the differences in expertise/knowledge
- Harmonise on an agreed way forward
- Identify what role others outside of MND can play
- Identify missing pieces and avoid duplication

Other

- Scope the unknown vs known
- Commercial vs industry
- Natural experiments comparative effectiveness

The top ideas for Ways of working were identified:

1. Creating the **right team** (equals: right expertise & a 'champion')
2. Better **data sharing** & IT systems
3. Encouraging **collaboration in science, early**

Partnerships & funding

What partnerships should be formed to make this roundtable successful?

Define goals and problems

- Prioritise that problems that will benefit from a global approach – not all problems need a global approach
- Aligned to the Roundtable objectives
- Only partner when there is a clear need/benefit (consider cost of coordination – time and resources)
- Research for sake of research does not work, it needs to meet clinically relevant needs

Biomarker and data

- Biomarker consortium (orchestrated by Novartis)
- Define process website
- Steering group: Data, biomarkers, therapeutics, clinical trials

Define stakeholders and funding across types of interests

- Key stakeholders: Global industry, academics/researchers, funders, government, payers, patients, regulators, insurance companies
- Disconnect between academic and commercial research needs to work together
- To commercialise a drug, need to fund clinically, regulatory and relevant research
- Partnerships and problems (not 'usual partners')
- Incentivise collaboration by funding streams for priority areas
- Bring known collaborative groups together to come up with sharing projects
- Create skillful divergent teams
- Merge efforts of individual consortia that is accessible to all
- Core funding for some initiatives

Partnerships between funders globally

- Partnerships with other research funders
- Partnerships of major disease focused funding agencies to fund large projects
- Bring in other rare disease groups for comparison of approaches

What initiatives can we advance without the need for additional funding?

People exchange

- Collaborative support of trainees (grad/post-doc)
- Sabbaticals for research in other countries/labs

Communication

- Inform the outside world about the results
- Roundtable opinion piece publication
- Consensus statements

Agree on roundtable priorities

- Global committee focused on 1 or 2 action items
- Bring partners in to operationalise

Research priorities

- Committee to prioritise biomarkers to advance path forward
- Standardising approach to diagnosis & functional evaluation
- Step by step harmonisation of clinical trial design

Information sharing

- Global data sharing – incl. rare MND disease subtypes
- Sharing ideas about successful approaches and failures

Equity

- Access for all
- Engage with lower economical and represented countries (e.g. China, India): Focus on those with less access to MND clinical trials

The top ideas for Ways of working were identified:

1. **Biomarker & Data Consortium**
2. Partnerships between different stakeholders & equity

Insights

The delegates' responses indicate an exciting, contemporary and purposeful way forward for the Global MND Research Roundtable. This includes:

Establish a relatively small global committee of diverse membership; diverse in sector roles and geography. Include persons with lived experience at every level of governance

Develop a meaningful global strategy

- Set a clear mission / purpose
- Confirm the research areas that would genuinely benefit from global collaboration
- Undertake a landscape assessment / review of current state for any of the priority areas
- Set clear aims, and prioritise these aims. Be clear about the outcomes you expect to achieve
- Determine the principles which the Roundtable would adhere to, such as:
    - be courageous
    - work with urgency
    - value meaningful partnerships
    - foster collaboration and sharing, particularly early in science
    - be inclusive and respectful
    - work efficiently

Consider actions to:

- **Establish a biomarker and data consortium**, or working group
- **Harmonise the design of clinical trials**

5. Progress and commitments

All the delegates came together to discuss what commitments are required to ensure the work of the Roundtable progresses. The following reflections were made by delegates throughout the discussion:

Momentum and progress

- It is persistence that will win this disease
- The people in this room are time poor, next steps must be sustainable. Could we obtain funding or support from FightMND to establish a project management team?
- Today is the start! So let's synthesise together the things we want to take forward, including presenting and delivering the strategy in December

Communication

- We need to find new ways of working and thinking
- Lets share this with our peers – keep it simple e.g. 1 pager
- We should start with a small team then grow
- What is the role of the international alliance?

- Horizon scanning
    - Where do we need help?
    - Make these regular points of check in
    - Keep iterating
    - Are these converging realities?

Create impact together

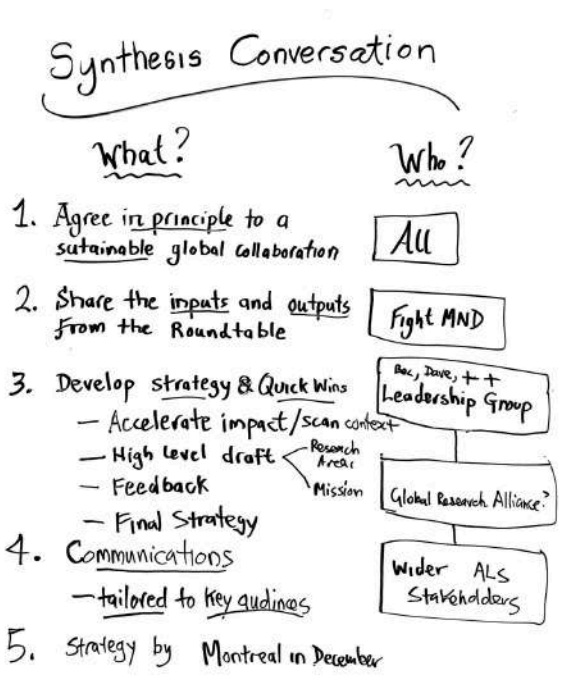
- Remember that we are a subset of those with vested interest?
- How do we create impact together? Start with small actionable steps, focus, then expand
- The Scientific Directors are leaders – can we meet before we come together in Montreal?
- Build on what has already been done. For example, La Sagrada Familia, Barcelona - It took 9 generations

Image: A visual map of the 'synthesis' conversation about progress made during the Roundtable event and commitments to next steps.

The commitment

Commitment was made by the delegates to the following five actions:

1. **Develop a sustainable global collaboration**. Delegates agreed to this in principle.
2. **Share the inputs and outputs** from the Roundtable event. FightMND agreed to take responsibility.
3. **Draft a strategy and quick wins**, seeking feedback from delegates. Bec Sheean, David Taylor and Gethin Thomas agreed to establish a leadership group.
4. **Develop and disseminate communications that are tailored to key audiences**. Although this will be a responsibility of everyone involved in the Rountable ongoing, the leadership group will take a leading role in communications.
5. **Present the strategy at Montreal in December 2024**. Again, this will be the responsibility of the leadership group.



6. Events & activities

Welcome event

On the first evening of the Roundtable event, FightMND hosted a welcome event, sponsored by Perron Institute. Participants had the opportunity to meet with fellow delegates and hear from Bec Sheean - Director Cure Research and Programs, FightMND; Matt Tilley - CEO, FightMND; A/Prof Trevor Chong - Board member, FightMND and Josh West from the Bunurong Land Council Aboriginal Corporation who gave the Welcome to Country and a didgeridoo performance.

Image: Global MND Research Roundtable Welcome Event delegates wearing Big Freeze beanies

Australian Football League (AFL) activity

During the first day of the Roundtable event, a session was held on Australian Rules Football. This included a brief introduction to the sport for the benefit of the international audience in the form of a short explainer video, followed by a series of fun and participative activities on Junction Oval lead by Rohan Obst from FightMND.

Event dinner

Delegates were transported in the FightMND bus (provided by Bayside Coaches) from their hotels to Captain Baxter, St Kilda, for an entertaining evening of delicious food and relaxed socialising in the heart of Melbourne's nightlife with panoramic views of the iconic St Kilda Beach. The event was sponsored by TEVA Pharmaceuticals.

Images: 1. Matt Tilley, FightMND; Bec Sheean, FightMND; and Bernd Merkel, TEVA Pharmaceuticals. 2. Captain Baxter networking dinner.

Helium sticks activity

To commence the second morning of the Roundtable event, delegates participated in a light physical activity designed to test collaboration and teamwork. The seemingly simple task of lowering a stick to the ground was more challenging, and entertaining, than delegates anticipated.

Image: A team of delegates attempting to lower the stick during the Helium sticks activity.

Pitching ideas

In the final session of the Roundtable event, each of the four research groups developed and presented a pitch to an expert panel of judges: Kerri Lee Sinclair, Helena Fern and Judith Slocombe.

In preparation, Kerri Lee Sinclair - entrepreneur, executive and investor - presented “How to Sell Your Story”. Her presentation included topics such as: hooking the heart, and why emotions matter; story structure; and what a good pitch canvas template looks like.

Image: Kerri Lee Sinclair presenting How to sell your story.

Image: a visual map of Kerri Lee Sinclair's presentation and discussion on How to sell your story.

Whilst delegates had already discussed their proposed solutions in previous sessions, the pitches challenged delegates to effectively communicate complicated research initiatives to people outside of the research community.

Each of the four pitches were entertaining and of high calibre, particularly given the limited preparation time, and the Biomarkers group were awarded the "Best pitch" due to their compelling story and clear ask of investors.

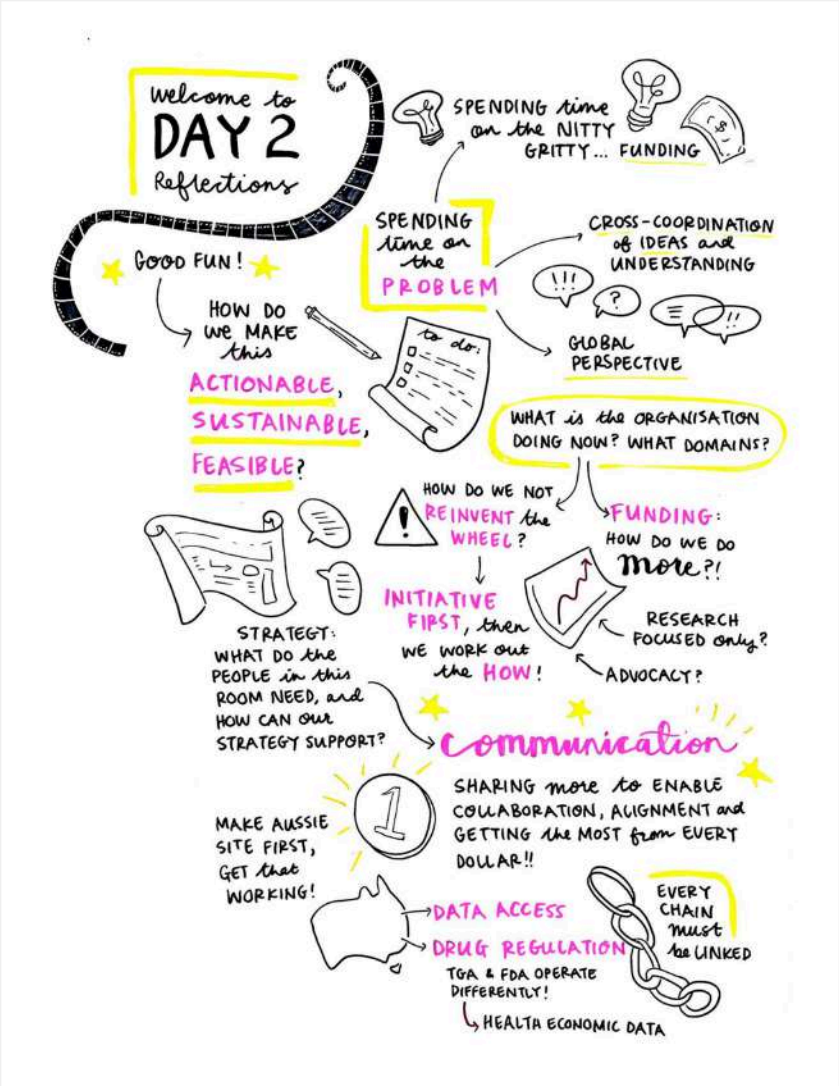
Image: The winning Biomarkers team accepting their trophy.

7. Reflections & feedback

Day 1 reflections

At the start of the second day, delegates were asked to reflect on the first day's work and activities, where they invested considerable time understanding the problems (the Scan and Focus phases) within the different research areas, in addition to considering key domains to global research collaboration.

Image: A visual map of the delegates' reflections about day one.



Day 2 closing comments

At the end of the second day, delegates were asked to reflect on the two days of work and activities. Their responses are depicted in the image below.

Image: A visual map of the delegates' comments about the Roundtable event.

Post event feedback

Participants were emailed a feedback survey a week after the inaugural Roundtable event. Below is a summary of feedback responses.

Overall

- 97% of delegates reported that they would attend another Roundtable meeting
- Responses from delegates about the event were mostly positive; i.e. good to excellent ratings

Highlights

Participants reported the following as highlights of the event:

- The testimony from Paula Trefiak; it had an incredible impactful on the room
- Networking and collaboration with global leaders
- New knowledge and understanding
- The Australian Football League (AFL) session

Areas of strength

Participants reported the following as areas of strength throughout the event:

- Scan, focus, act exercises united delegates in determining common ground and a common goal to work towards
- Getting scientists and clinicians to get out of the weeds and think about gaps and blue sky thinking
- Everyone came at the problem in different ways and yet all came to a similar plan/goal and the barriers that were identified during the process were different
- Provided time for important relationship building, deep thinking, respectful challenging and development of tangible outcomes that will (hopefully) make a real difference in the research landscape
- Innovative approach to developing solutions to challenges in the field
- Strong engagement and buy-in from the room and drive to keep things moving
- Everyone had a voice, all perspectives and opinions heard, respected and appreciated
- Dynamic format and facilitation
- Unique approach to solving problems versus standard approaches of regular symposia or meeting
- Helped researchers bring back new understanding for where to put our research efforts.

Areas for improvement

Participants reported the following areas as opportunities for improvement:

- Given the limited focus on basic science we may need to establish a separate roundtable for challenges in basic research
- We need further discussion to:
    - identify the really critical problems in ALS research
    - consolidate ideas and
    - develop actionable outcomes
- We need to consider delegate fatigue. The program was intense at the end of an already busy week. It was consistently reported that it was beneficial to schedule the conference in the same week, however a day in between the two events would have helped
- The use of AI-powered meeting analytics could be considered for transcribing conversations and providing feedback or summaries based on the dialogue
- Continue to improve inclusivity and representation of stakeholders, including: preclinical researchers; basic scientists; early-mid career researchers; PLEx; industry; local key neurologists from around Australia; underrepresented geographical regions such as Asia, Latin America, Africa; ALS organisations, such as ALSA and Target ALS; investors; government; regulatory agencies, such as TGA; and experts in global logistics
- The communication masterclass session needed to be tailored specifically to the research world and would benefit from having real investors to invest

Next steps for success

Participants identified several next steps that are important for ongoing success of the Rountable:

- Keeping the group engaged
- Framework for development and implementation
- Need workgroups to meet in Montreal already having done some research/progress
- Future roundtable meetings
    - Could be built from the strategy to build momentum, or have a completely different MND focus
    - Consider a mix of new and old delegates

Appendices

Appendix a: Agenda

Day 1 - Wednesday 28 August

Time	Title	Description
5:30pm	Welcome meet and greet *Sponsored by Perron Institute*	CitiPower Centre, Lakeside Dr, St Kilda.
6:05pm	Welcome from FightMND	
6:15pm	Welcome to Country and didgeridoo performance	
6:25pm	Introduction to FightMND	
8:00pm	End of day 1	

Day 2 - Thursday 29 August

Time	Title	Description
8:30am	Arrival and registration	CitiPower Centre, Lakeside Dr, St Kilda.
9:00am	Explore knowledge wall	Explore and discuss a curated gallery of information on the various challenges we'll be focusing on throughout the session.
9:25am	Welcome and acknowledgement	
9:30am	Introduction to Roundtable	Clarify the purpose, vision and objectives of the Roundtable.
9:50am	Survey results summary	Explore and discuss insights and key takeaways from the participant survey.
10:15am	Morning tea	
10:25am	Research chatrooms	Get up to speed with the state of play, key challenges and opportunities in four key areas of MND research.
12:10pm	Lunch *Sponsored by Alithia Life Sciences*	
12:35pm	Clarify the challenges	Develop a deeper understanding of the challenges in each global barrier through an iterative process of interrogative enquiry.
2:20pm	AFL Activity	Learn about this uniquely Australian sport and the league's partnership with FightMND.
3:00pm	Afternoon tea	

Time	Title	Description
3:10pm	Panel discussion – Global collaboration in research	Hear from experts on best practice approaches to global collaboration in research.
3:55pm	Roundtable mission	Understand what we can achieve as a collective and align on a mission.
5:15pm	Closing reflections and wrap-up	
6:00pm	Transport to networking dinner	Pick up at Pullman Melbourne & Mercure Melbourne Hotels.
6:30pm	Networking dinner *Sponsored by Teva Pharmaceuticals*	Captain Baxter, St Kilda 3 course dinner and drinks.
10:00pm	End of day 2	

Day 3 - Friday 30 August

Time	Title	Description
8:30am	Arrival and registration	CitiPower Centre, Lakeside Dr, St Kilda.
9:00am	Collaboration activity	Explore how we can collaborate and problem solve together.
9:25am	Acknowledgement of Country & Reflections	Reflect on the outcomes of day 1 and recap the plan for day 2.
9:35am	Identify the solutions	Identify and prioritise initiatives to address the key challenges.
10:40am	Morning tea	
10:50am	Develop the solutions	Continue iteratively refining the initiatives and develop an initial roadmap.
12:45pm	Lunch	
1:10pm	Synthesis Conversation – Mission	Check in to ensure each group's work aligns with our Roundtable Mission, and identify any additional work required to achieve this.
1:55pm	Communication Masterclass	Learn from an expert on how best to communicate the value and impact of the initiatives.
2:15pm	Final work round	Select one initiative to apply these learnings to.
3:30pm	Showcase	Showcase our work.
4:50pm	Closing reflections and wrap-up	Reflect on the process and outcomes, agree on the next steps.
5:00pm	End of day 3	

Appendix b: Delegates

Name	Affiliation
Prof. Allan McRae	University of Queensland, Australia
Prof. Ammar Al-Chalabi	King's College, United Kingdom
Prof. Andrea Malaspina	University College London, United Kingdom
Andrew Corbett	Biogen, Australia
Prof. Angela Genge	McGill University, Canada
Prof. Anthony Akkari	Perron Institute, Australia
Dr. Anthony Filippis	Percheron Therapeutics Ltd, Australia
Bec Daniher	FightMND, Australia
Dr Bec Sheean	FightMND, Australia
Dr Bernd Merkel	Teva Pharmaceuticals
Prof. Bob Bowser	Barrow Neurological Institute, United States
Prof. Bradley Turner	Florey Institute, Australia
Prof. Cathy Blizzard	University of Tasmania, Australia
Chantelle Chakour	Teva Pharmaceuticals
Prof. Dame Pamela Shaw	University of Sheffield, United Kingdom
Prof. David Berlowitz	University of Melbourne, Australia
Prof. David Pearce	Sanford Health, United States
Prof. David Taylor	ALS Society of Canada, Canada
Eleanor Ramsey	Allstar Clinical Trials, Australia
Dr. Emma Scotter	Centre for Brain Research, New Zealand
Gary Nugent	FightMND, Australia
Dr. Gethin Thomas	MND Australia, Australia
Prof. Jeffrey Rothstein	John Hopkins University, United States
Dr. Jennifer Hollands	Cell Therapies, Australia
Dr. Judith Slocombe	FightMND, Australia
Prof. Julie Atkin	Macquarie University, Australia
Prof. Kevin Talbot	Oxford University, United Kingdom
Prof. Leonard van den Berg	UMC Utrecht, Netherlands

Name	Affiliation
Dr. Lucie Bruijn	Novartis, Switzerland
Prof. Ludo Van Den Bosch	KU Leueven, Belgium
Prof. Mary-Louise Rogers	Flinders University, Australia
Prof. Matthew Kiernan	Neuroscience Research Australia, Australia
Matthew Webb	Canada
Prof. Melanie Bahlo	Walter and Eliza Hall Institute, Australia
Prof. Michael Spedding	Spedding Research Solutions, France
Dr. Nicky Wallis	PharmAust, Australia
Prof. Nortina Shahrizaila	Malaya University, Malaysia
Prof. Paul Talman	Barwon Health, Australia
Paula Trefiak	International Alliance, Canada
Phil Camden	Australia
Prof. Shyuan Ngo	University of Queensland, Australia
Steve Jensen	Australia
Dr. Thanuja Dharmadasa	Florey Institute, Australia
Prof. Tina Soulis	Alithia Life Sciences, Australia
Prof. Trevor Chong	Monash University, Australia

Appendix c: Supporting personnel

Advisory Panel to the Global MND Research Roundtable

Name	Affiliation
Prof. Anthony Akkari	Perron Institute, Australia
Prof. Bradley Turner	Florey Institute, Australia
Prof. Matthew Kiernan	Neuroscience Research Australia, Australia
Prof. Shyuan Ngo	University of Queensland, Australia
Dr. Thanuja Dharmadasa	Florey Institute, Australia

Event hosts

Name	Affiliation
Dr Bec Sheean	FightMND
Dr Isabelle De Luzy	FightMND
Matt Tilley	FightMND

Presenters

Name	Affiliation
Helena Fern	Fern Creative
Dr Judith Slocombe	FightMND
Kerri Lee Sinclair	Co:Act Capital; Springboard Enterprises

Facilitators

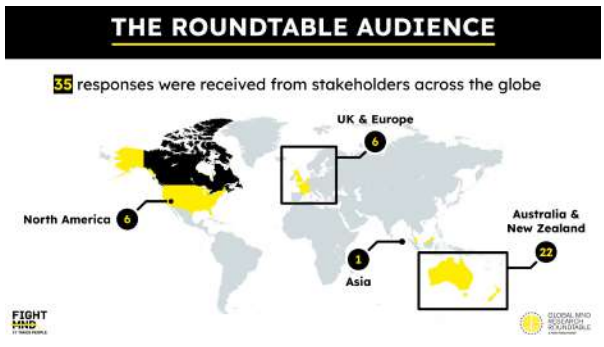
Name	Affiliation
Amanda Nolan	Nolan Consulting Co
James van Smeerdijk	Atticus Now
Rohan Obst	FightMND

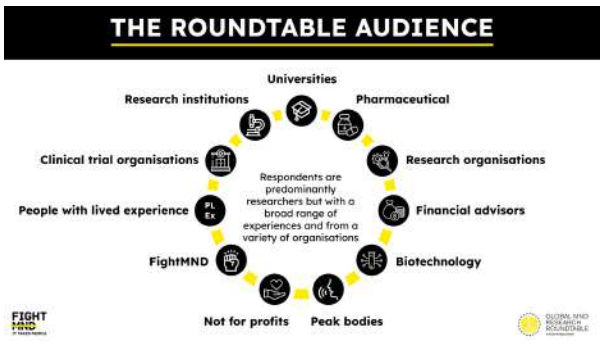
Guests

Name	Affiliation
Dr Fiona McIntosh	Heidrick & Struggles
Neale Daniher	FightMND

Appendix d: Delegate survey results

Delegate survey results presented at the Roundtable event





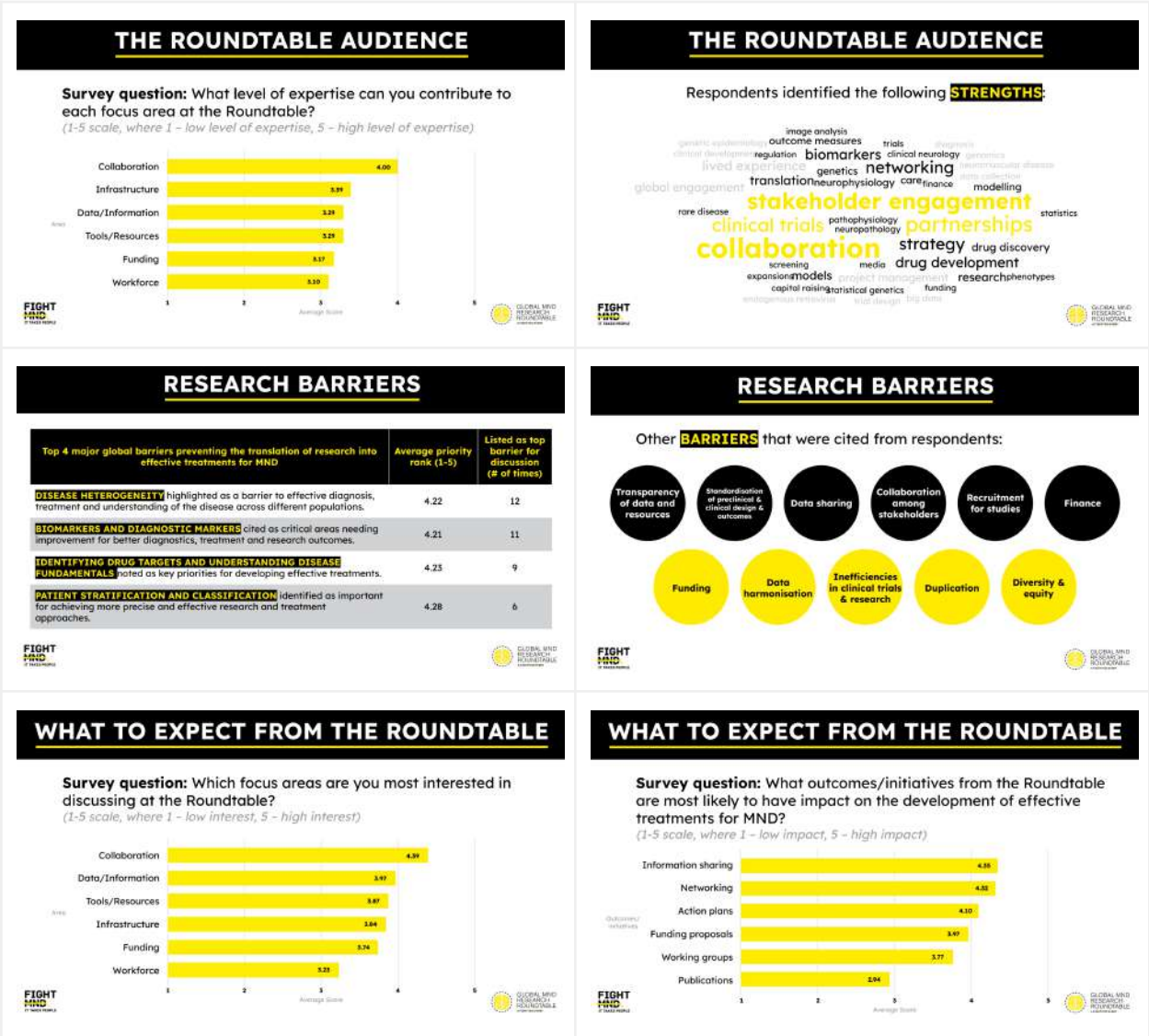
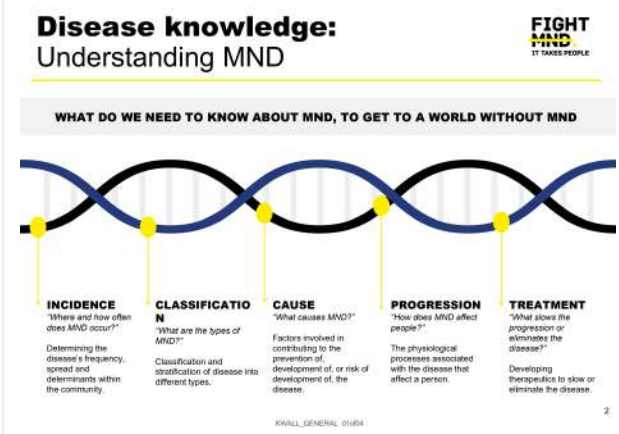
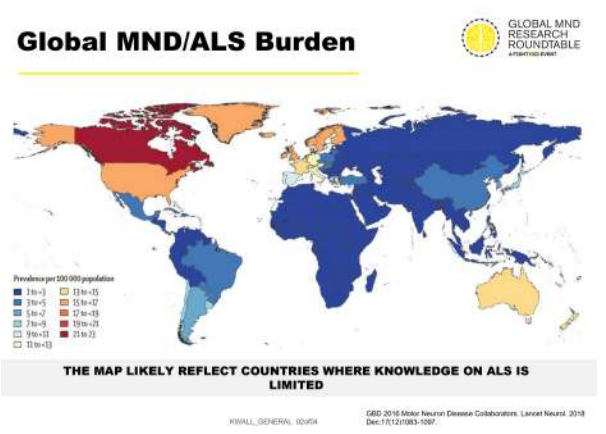


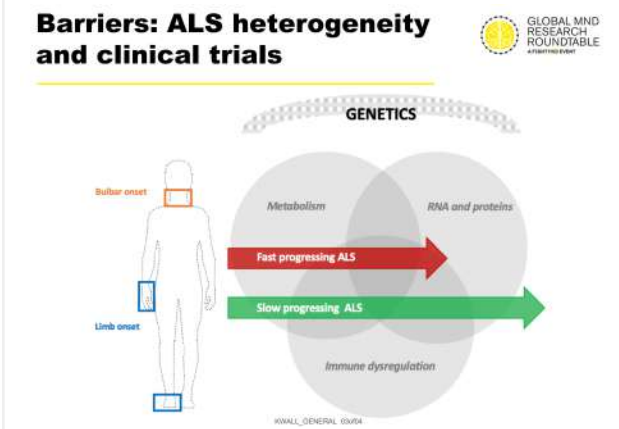
Image: a visual map of the presentation and discussion about the survey results.

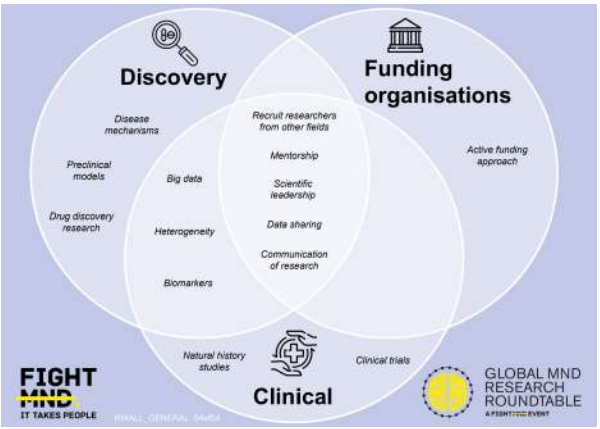
Appendix e: Knowledge wall content

General information

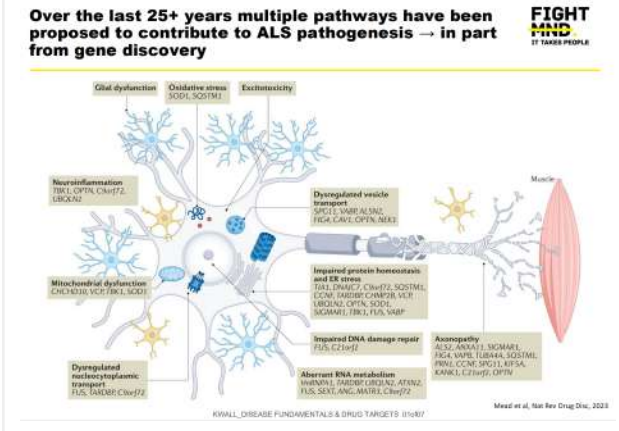


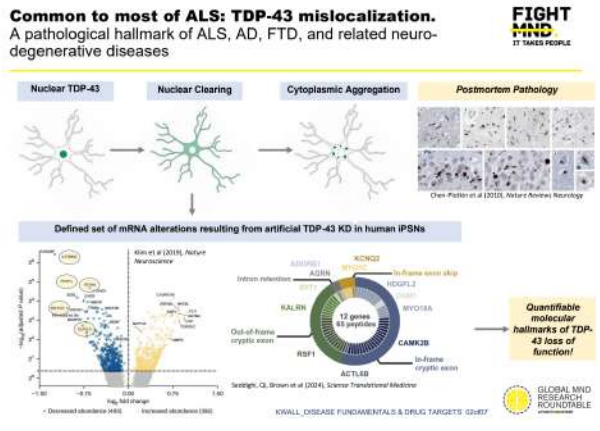




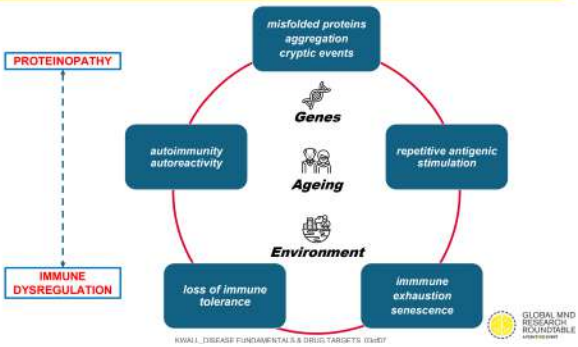


Disease fundamentals, drug targets and biomarkers

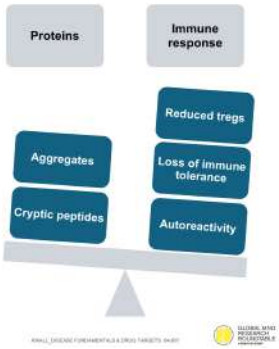




Barriers: modelling ALS pathobiology



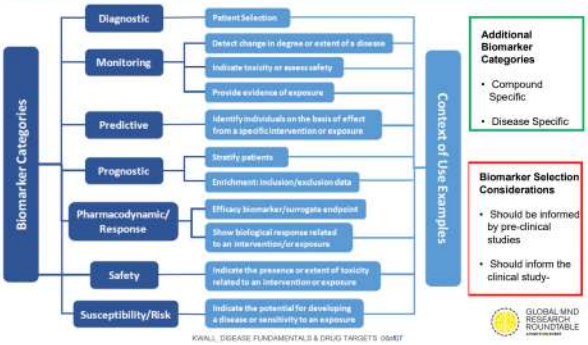
Losing the balance



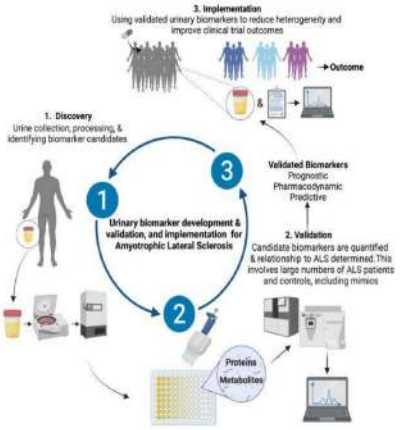
Disease Fundamentals

- High quality, evidence based symptomatic management to improve QoL and life expectancy
- Contribution of environmental factors: gene -environment interactions
  - Focus on strenuous physical activity as a risk factor for MND in the presence of genetic predisposition

Biomarker Considerations

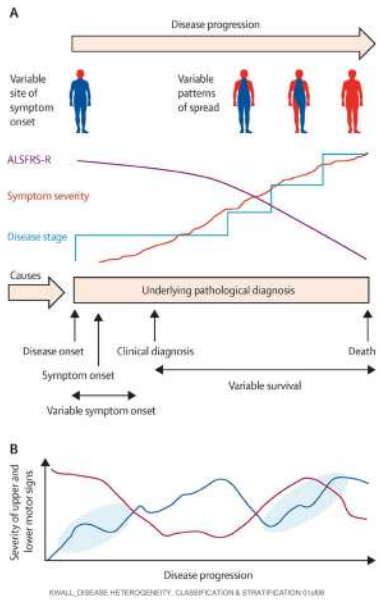


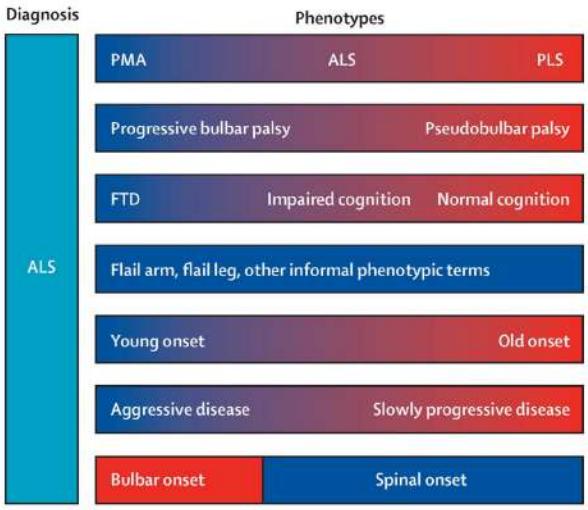
Urinary biomarkers

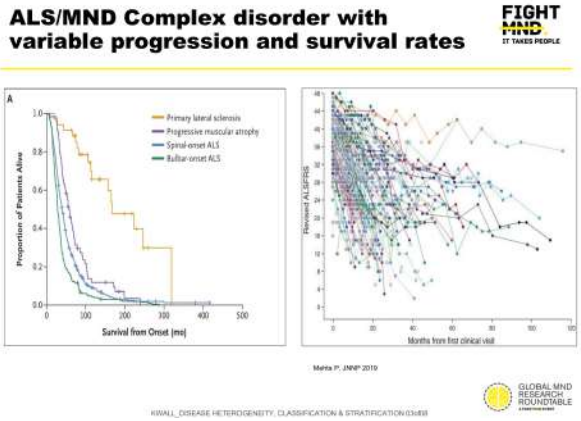


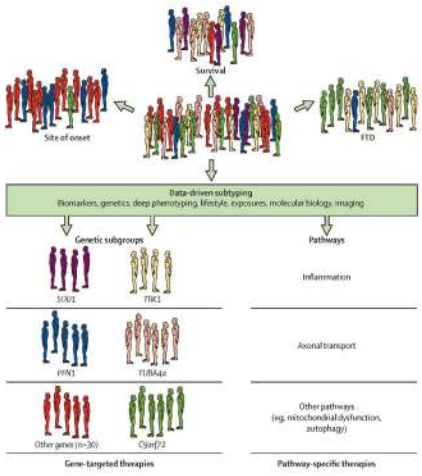
Rogers, M. L., Schultz, et L. (2023). *Brain Communications*, 5(6)

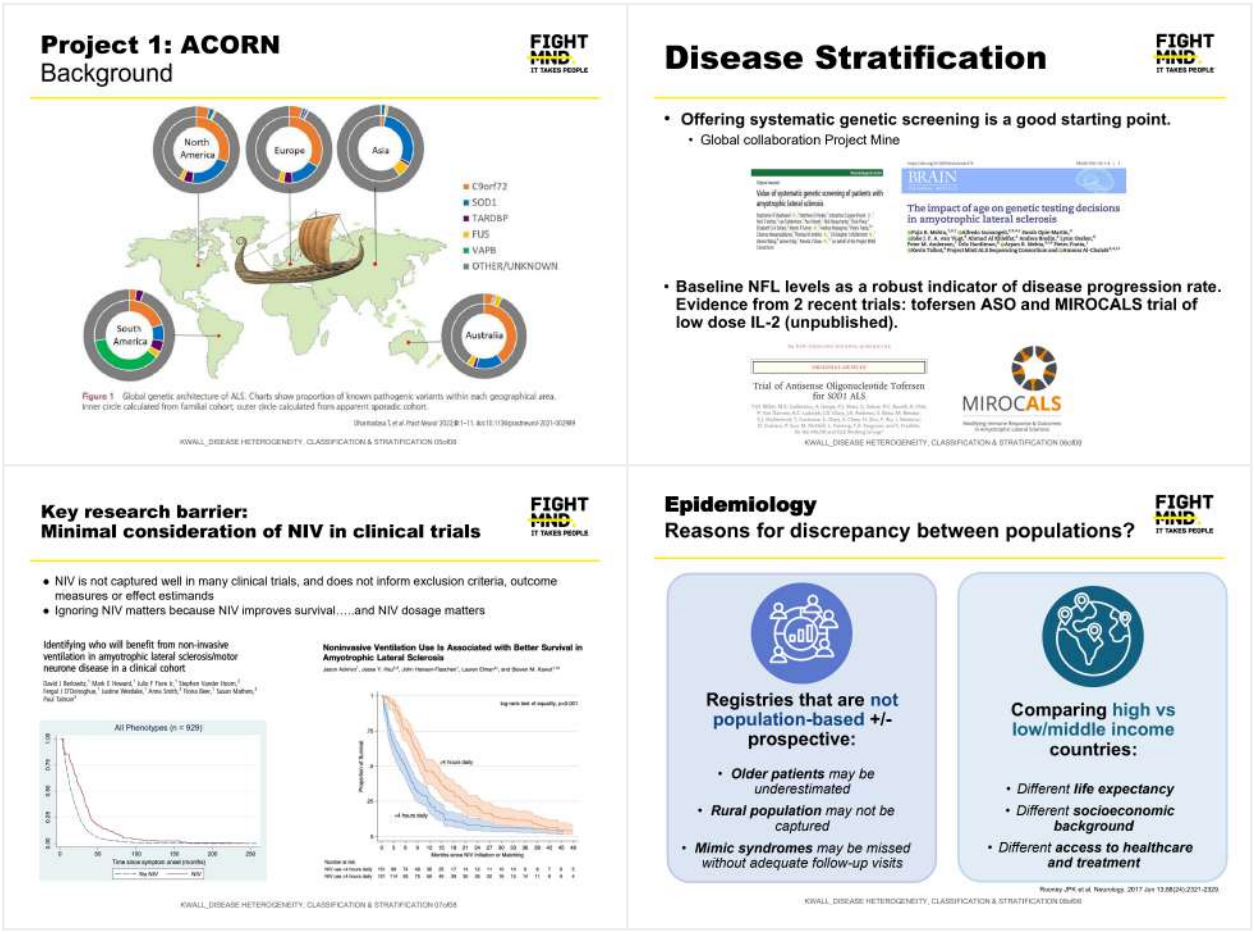
Disease heterogeneity, classification and stratification











Appendix f: Introduction to global barriers - presentation materials

Biomarkers, presented by Lucie Bruijn

BIOMARKERS

Development of Novel Therapies for ALS – A focus on biomarker development

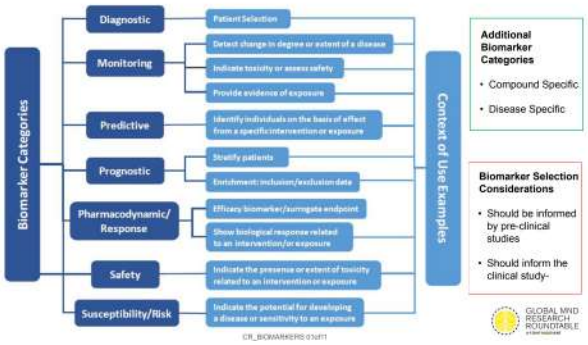
Lucie I Bruijn, Ph.D. MBA
Therapeutic Area Biomarker Lead, Novartis

Disclosure – Lucie is a full time employee of Novartis

FIGHT MND IT TAKES PEOPLE

GLOBAL MND RESEARCH ROUNDTABLE

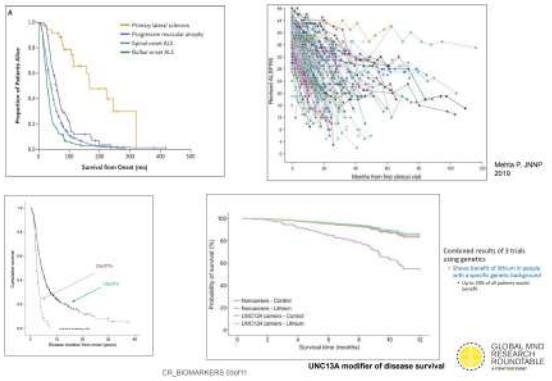
Biomarker Considerations



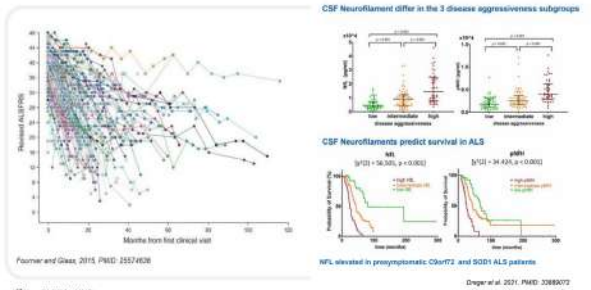
Essential Biomarkers for Successful Clinical trials for ALS

- Target Engagement
- PD/PK – sufficient levels reaching target cells
- Biomarkers to define the population included in the trial
- Treatment response biomarkers-direct or indirect marker to ensure that the treatment approach is affecting the pathway of interest
- Does the biomarker correlate with a clinical benefit
- CSF, Plasma, soluble, imaging, functional outcome measures

ALS/MND Complex disorder with variable progression and survival rates

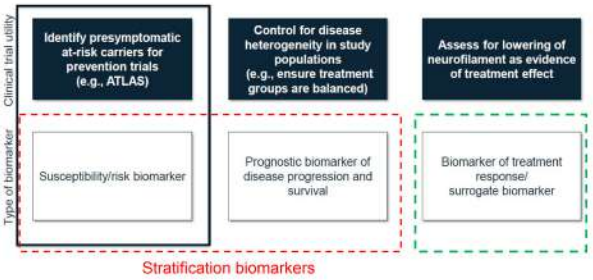


Heterogeneous Disease and Need for Fluid Biomarkers in ALS



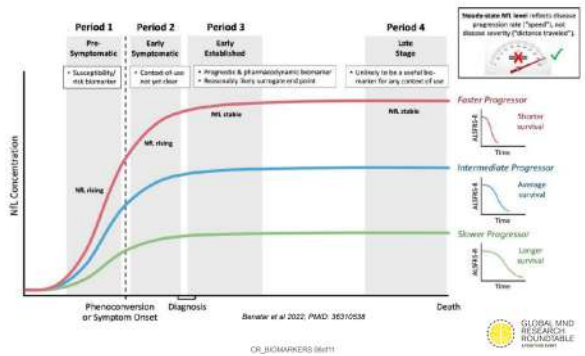
GLOBAL MND RESEARCH ROUNDTABLE

Utility of neurofilament in ALS trials

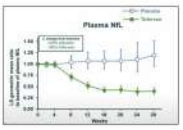


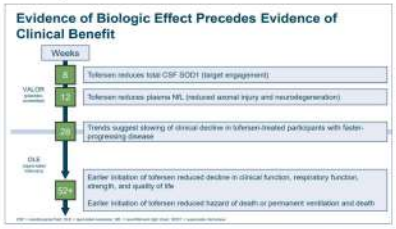
GLOBAL MND RESEARCH ROUNDTABLE

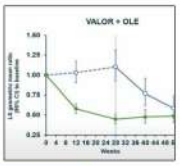
NFL in disease progression and BM use



FDA Grants Accelerated Approval for QALSODY™ (tofersen) for SOD1-ALS, a Major Scientific Advancement as the First Treatment to Target a Genetic Cause of ALS





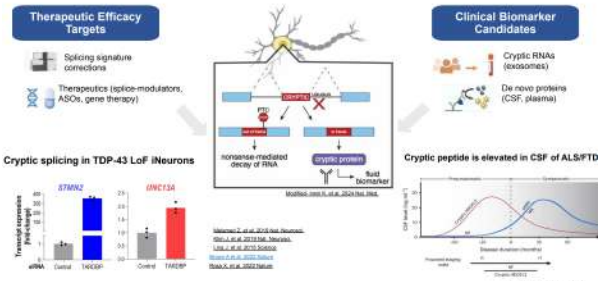


N.B. - NFL reduction correlated with clinical benefit in SMA, MS, and HIV

Development of TDP43 Biomarkers: Key biological and technical challenges

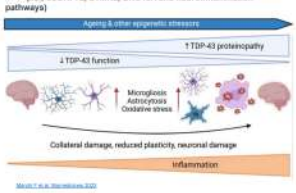
- ***Limited/no knowledge of the expression patterns of TDP-43 and species over longitudinal disease course and in different patient sub-populations***
- ***Detection and quantification of total and (p)TDP-43 and species is highly challenging and variable in CSF & plasma of ALS/FTD patients***
- ***Contradictory findings in the literature – is the level of circulating TDP-43 or pTDP-43 (disease-conformer) elevated in ALS patient biofluids?***
- ***Need for robust and assays to reliably measure TDP-43 species and RNA targets as surrogate biomarkers in different matrixes***
- ***These assay(s) should ideally be translatable from pre-clinical models to clinical samples***

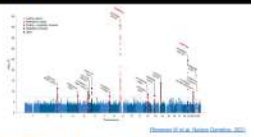
TDP-43 measures for therapeutic efficacy & novel biomarkers



Summary

- **Utilize phenotypic approaches using relevant cell culture models mimicking aspects of TDP-43 pathobiology**
  - Expedite the discovery, validation of potential drug targets to ameliorate TDP-43 pathobiology for development of new therapeutics (i.e., TDP-43 biomolecular condensates, kinases, restore chaperone activity)
  - Consider the multifactoriality of the disease. It is likely that drugs targeting different causal or modifying factors will be most effective (i.e., C9ORF72, STMN2, UNC13A and neuroinflammation pathways)





- **Integrate efforts to characterize translatable TDP-43 pharmacodynamic measures and specific biomarkers early-on in drug discovery**
  - Build assays with high sensitivity for detection of TDP-43 cryptic RNAs and peptides in ALS/FTLD. AD patient biofluids for prodromal biomarkers
  - Understand impact of TDP-43 targeted therapeutic strategies on cryptic splicing and investigate biomarker correlates (phosphoTDP-43, neurofilaments, chitinases and cytokines)

Profiling of human ALS CSF and plasma samples

Inflammatory and neurodegeneration markers targeted analysis

NOVARTIS | Reimagining Medicine

Disease fundamentals and drug targets, presented by Jeffrey Rothstein

DISEASE FUNDAMENTALS & DRUG TARGETS

Upstream pathways

Jeffrey D. Rothstein MD, PhD
Department of Neurology, Brain Science Institute
Johns Hopkins University School of Medicine

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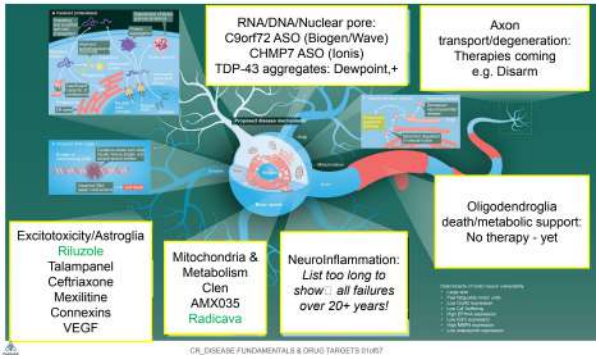
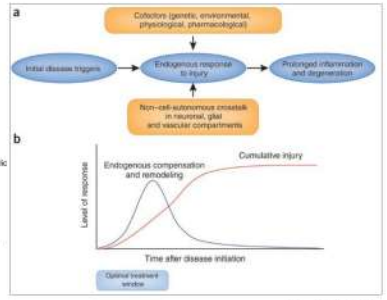
ALS Pathways:
Preclinical Research Leading to candidate drugs



Variability in pathogenic pathway activation: Temporal relationships to disease progression

- **Disease initiators/early disease therapies**
  - tALS Gene mutations
    - SOD, C9orf72, FUS, TDP-43
  - Protein coding variants (sALS)
  - TDP-43 LOF
  - Nuclear Pore/Transport
- **Disease propagators**
  - Stress granule biology?
  - Protein aggregation
  - Cellular networks
    - Chronic excitability
    - Glial connectivity (e.g. connexins)
    - Glial dysfunction - Oligodendroglial metabolic support
  - DNA damage?
  - ?Risk Genes (e.g. Ataxin, TMEM106b, UNC13)
- **Late disease Therapies**
  - Neuroinflammation
    - Complement inhibition, microglial inhibition
    - Exosomes (?)
  - Glutamate toxicity
    - Riluzole
  - Oxidative stress:
    - Tedaravone



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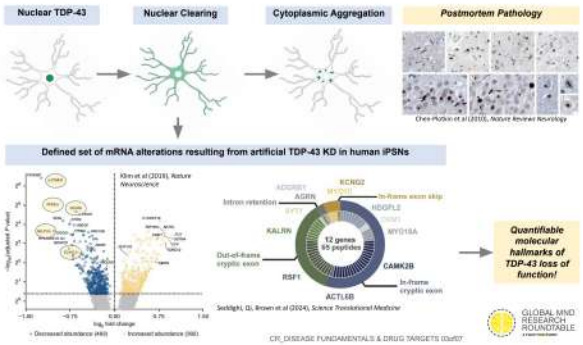
CR_DISEASE FUNDAMENTALS & DRUG TARGETS 02of07

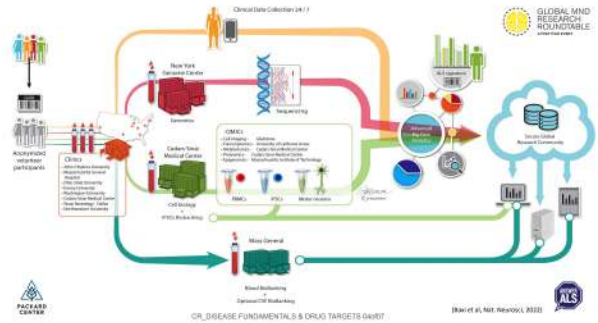
Common to most of ALS: TDP-43 mislocalization.

A pathological hallmark of ALS, AD, FTD, and related neurodegenerative diseases



CR_DISEASE FUNDAMENTALS & DRUG TARGETS 03of07

Stratifying ALS Patients Can Lead to Personalized Medicines: Authentic Human Platform: Patient-Derived iPS cells



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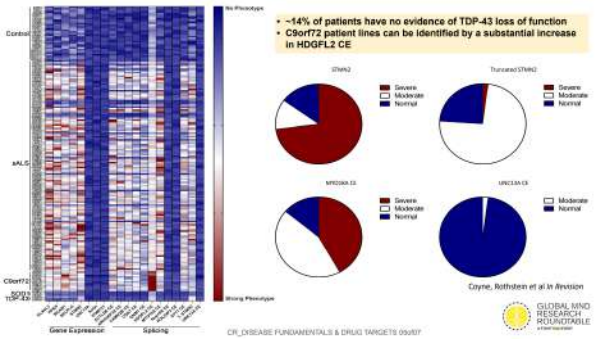
(Baker et al, Nat. Neurosci., 2022)

CR_DISEASE FUNDAMENTALS & DRUG TARGETS 04of07

Molecular signatures of TDP-43 loss of function are variable but can define molecular "subgroups" of sALS patients



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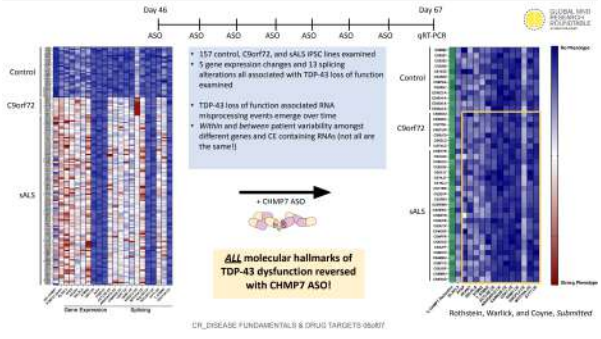
CR_DISEASE FUNDAMENTALS & DRUG TARGETS 05of07

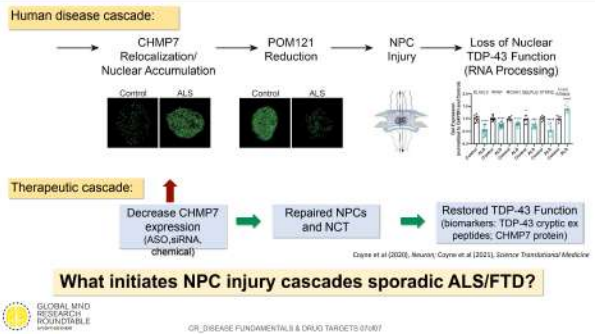
Variable molecular signature TDP-43 LOF in authentic sALS and C9orf72 iPSNs but....ALL repaired with CHMP7 ASO treatment in CHMP7+ patients



Rothstein, Warlick, and Coyne, Submitted

CR_DISEASE FUNDAMENTALS & DRUG TARGETS 06of07

Summary: ALS injury cascade: 1)initiated by CHMP7 nuclear enrichment, 2) followed by NPC dysfunction and 3) later TDP-43 loss of function



What initiates NPC injury cascades sporadic ALS/FTD?

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CR_DISEASE FUNDAMENTALS & DRUG TARGETS 07of07

Disease heterogeneity, presented by Ammar Al-Chalabi

DISEASE HETEROGENEITY

Ammar Al-Chalabi MB, ChB, PhD
Professor of Neurology and Complex Disease Genetics
King's College London

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Problem

- **What is heterogeneity?**
  - Different presentations, trajectories and causes of disease

Relevance

- **Why does it matter?**
  - The why affects the how, the how affects the what

Context is crucial here.

Familial/sporadic, genetic/non-genetic, young/old, bulbar/spinal, EE definite/EE other, male/female, gene1/gene2, ALS/PMA/PLS, pathological basis 1, 2, etc.

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Heterogeneity affects management

1. Diagnostic Classification
2. Information given to patients
3. Information given to family
4. Prognosis
5. Pathological basis
6. Drug choice
7. Drug delivery

These effects are linked in a hierarchical chain with some dominant subchains:

1 – 2 – 3 – 4 in clinic responding to common patient questions
1 – 5 – (4*) – 6 – 7 for therapy and trials
**pathological basis has a complex relationship with prognosis*

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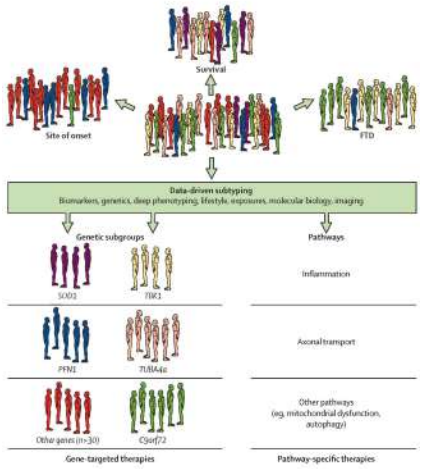

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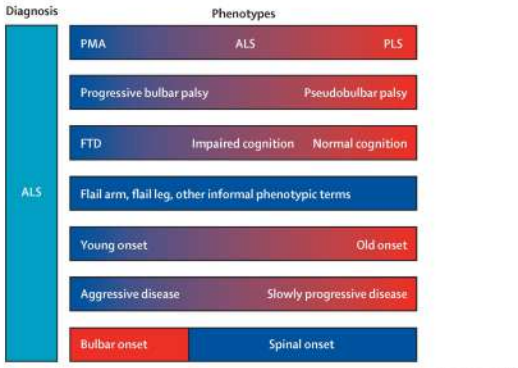
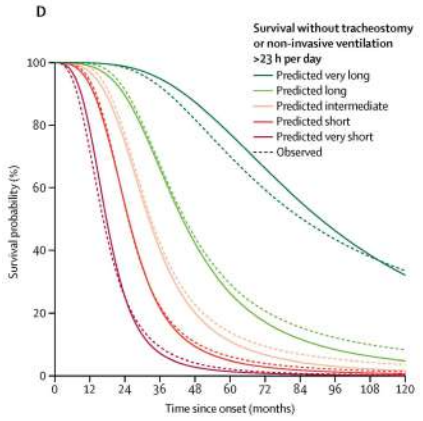
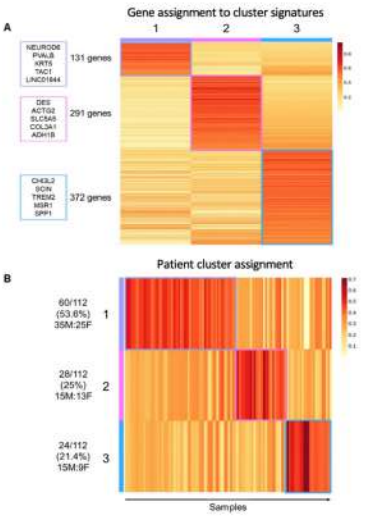
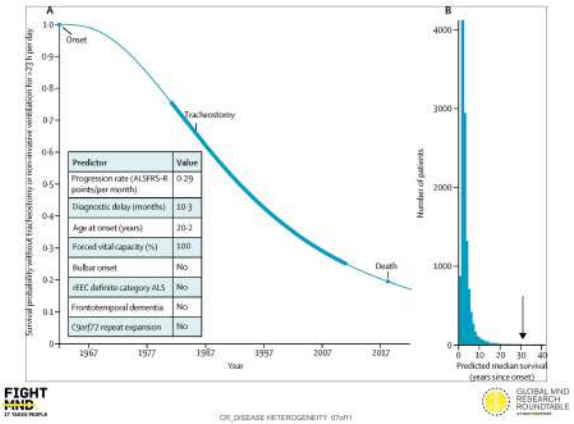
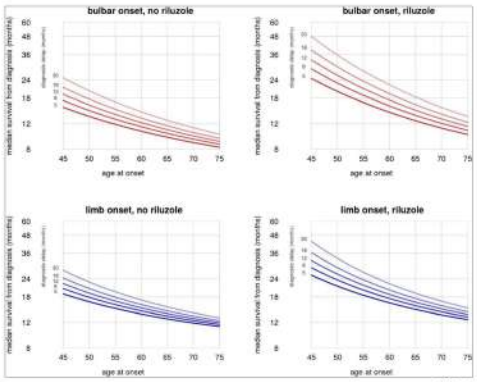
GLOBAL MND RESEARCH ROUNDTABLE

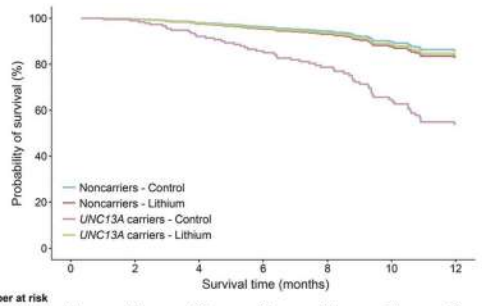

Diagnosis
Phenotypes
ALS
PMA
ALS
PLS
Progressive bulbar palsy
Pseudobulbar palsy
FTD
Impaired cognition
Normal cognition
Flail arm, flail leg, other informal phenotypic terms
Young onset
Old onset
Aggressive disease
Slowly progressive disease
Bulbar onset
Spinal onset


D
Survival without tracheostomy or non-invasive ventilation >23 h per day
Predicted very long
Predicted long
Predicted intermediate
Predicted short
Predicted very short
Observed
Survival probability (%)
Time since onset (months)

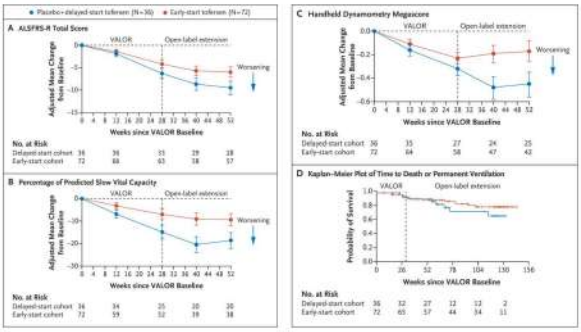

A
Gene assignment to cluster signatures
1
2
3
131 genes
291 genes
372 genes
B
Patient cluster assignment
60/112 (53.6%) 35M:25F 1
28/112 (25%) 15M:13F 2
24/112 (21.4%) 15M:9F 3
Samples

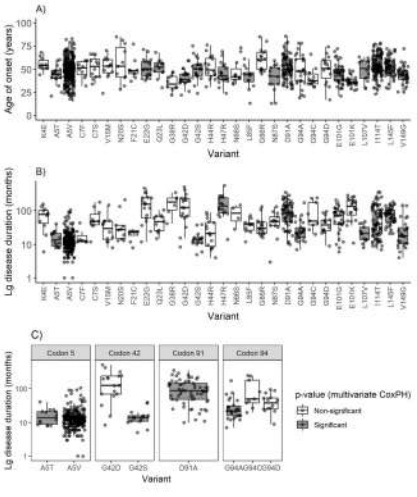

A
B
Onset
Tracheostomy
Death
Predictor
Value
Progression rate (ALSFRS-R points/per month)
0·29
Diagnostic delay (months)
10·3
Age at onset (years)
20·2
Forced vital capacity (%)
100
Bulbar onset
No
revised El Escorial criteria definite category ALS
No
Frontotemporal dementia
No
C9orf72 repeat expansion
No
Year
Number of patients
Predicted median survival (years since onset)





Number at risk							
Noncarriers - Control	114	112	105	96	89	76	69
Noncarriers - Lithium	109	106	94	84	76	68	65
UNC13A carriers - Control	26	25	20	15	13	10	7
UNC13A carriers - Lithium	20	20	19	16	14	12	10





Patient stratification and classification, presented by Angela Genge

PATIENT STRATIFICATION & CLASSIFICATION

Angela Genge, MD, FRCP(C)
Director, ALS Centre of Excellence for Research and Patient Care

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ALSFRS R Summit and initiatives

- Harmonize the ALSFRS R training across Europe and Asia Pacific
- Develop and promote self reported ALSFRS R as an independent outcome measure
- Consider and recommend statistical options for analysis of ALSFRS
- Develop one approved translation in every language for ALSFRS R

CR_PATIENT STRATIFICATION 01of10

Trial design dilemmas

Narrow more homogenous patient population using stricter inclusion criteria.
Examples Amylyx, Mitsubishi, Biogen SOD1
Vs
Broad "all comers" inclusion criteria Ferrer, Amylyx Phoenix

Use of Algorithms for inclusion into trial (ENCALS prediction model)

Use of algorithms for stratification in statistical analysis plans

Use of biomarkers as an inclusion criteria eg Neurofilament levels at screening, presence of specific mutations, presence of UNC13A SNIPs, Pet imaging

Best primary outcome measure in pivotal trials

CR_PATIENT STRATIFICATION 02of10

Outcome Measures in ALS Clincal Trials

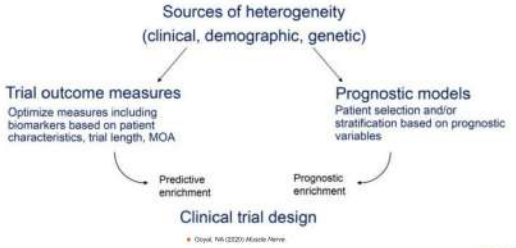
Dr. Angela Genge
Director – ALS Center of Excellence
Montreal Neurological Institute and Hospital

ALSFRS R Summit and initiatives:
- harmonize the ALSFRS R training across Europe and Asia Pacific
- develop and promote self reported ALSFRS R as an independent outcome measure
- Consider and recommend statistical options for analysis of ALSFRS
- Develop one approved translation in every language for ALSFRS R

CR_PATIENT STRATIFICATION 03of10

ALSFRS-R
Current state challenges

Trial design dilemmas:
Sources of heterogeneity



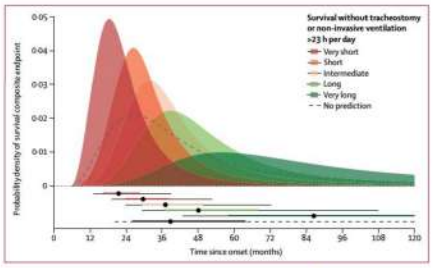
Trial design dilemmas

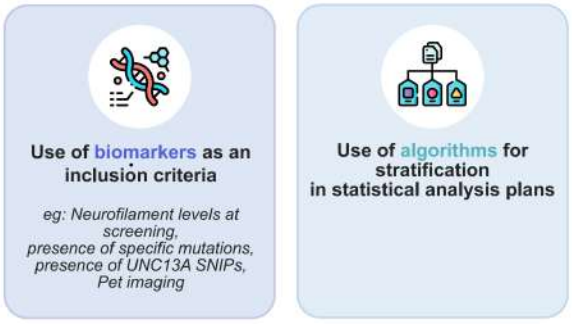
-narrow more homogenous patient population using stricter inclusion criteria. Examples Amylyx, Mitsubishi, Biogen SOD1

vs

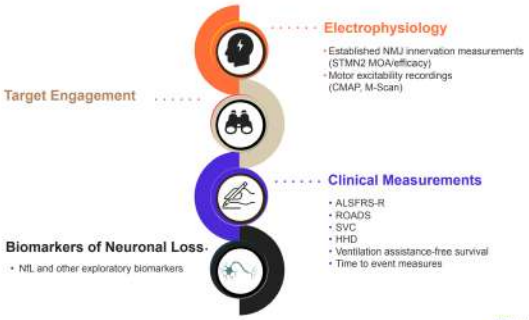
-broad "all comers" inclusion criteria Ferrer, Amylyx Pheonix

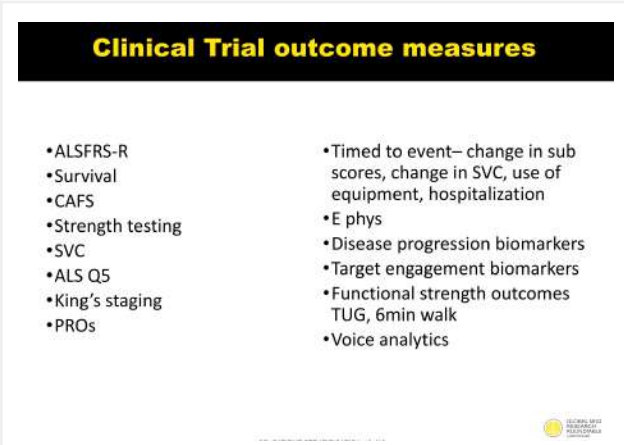
-Use of Algorithms for inclusion into trial
(ENCALS prediction model)





Clinical Trial outcome measures





Appendix g: Event photo gallery


GLOBAL MND
RESEARCH
ROUNDTABLE
MISSION


Disease
Heterogeneity


GLOBAL MND
RESEARCH
ROUNDTABLE
A FIGHT MND EVENT


ROUNDTABLE MISSION:
PRIORITISE
GOAL!!!
DEFINE CLEAR GOALS
WORK TOGETHER WITH ALL PARTNERS & STAKEHOLDERS


GLOBAL MND
RESEARCH

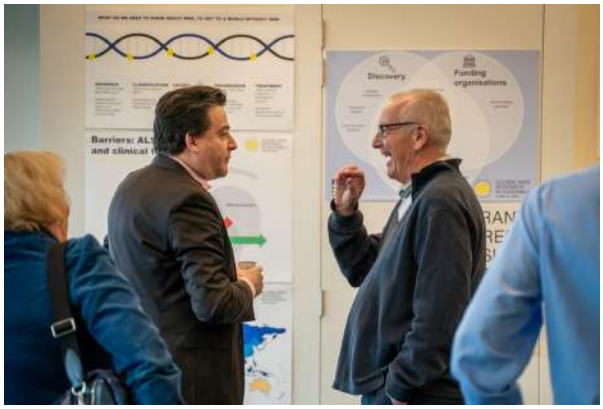

GLOBAL MND
RESEARCH
ROUNDTABLE


RESEARCH
ROUNDTABLE


DAY 2


PATIENT STRATIFICATION
&CLASSIFICATION


GLOBALS
GLOBALS


Discovery
Funding organisations


WHY 1
WHY 2
WHY 3
WHY 4
WHY 5


Knowledge
WALL
DEBRIE


Knowledge
WALL
DEBRIEF
BE PATIENT
SPENDING TIME
WHERE in the
DIFFERENCE
WE CAN MAKE?
You
EXPERTS in
the ROOM!
IS RESPONSES GLOBALLY