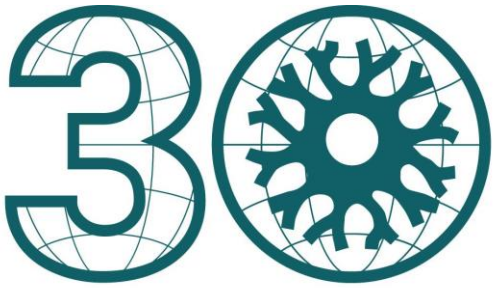


INTERNATIONAL ALLIANCE OF ALS/MND ASSOCIATIONS

Genetics Summit

2022

Table of Contents

Executive Summary

The time is now to further the topic of genetics at a global level!

During the spring and summer of 2022, the Alliance brought together a group of stakeholders who are the foremost experts in the field of genetics, along with the global leadership of ALS/MND Associations. Chairs and representatives from our Advisory Councils, leadership representatives from other Health Charities, Alliance Staff, and c-suite executives from industry partners joined together to determine aspirational goals and action steps in the field of ALS/MND genetics.

This event is a continuation of the Roundtable Series offered by the Alliance to further our vision of *A World Without ALS/MND*.

The Alliance's first roundtable on Genetics in ALS/MND took place in 2021. It welded the ideas of many into a collective call to action to advance genetic understanding at a global level and improve access to genetic counselling and testing for people living with ALS/MND. In addition to identifying areas where innovation and technological advancements can address the evolving and changing needs of people living with ALS/MND, our roundtable on Innovation and Technology, *The Spectrum of Possibilities*, also examined how technology, through artificial intelligence and machine learning, can contribute to a deeper understanding of ALS/MND. These two collective impetuses were the catalyst for the Alliance's 2022 roundtable on Genetics, titled the *Genetics Summit*.

Post COVID-19 in 2022, the Alliance originally planned to conduct this summit in-person in Edinburgh in conjunction with the ENCALS meeting. However, there was such exuberance for the first series of in-person meetings that it became a scheduling nightmare, and there was a recognition that not all participants could join in person, so we reverted to an online environment. We decided on an asynchronous platform to remove the issues of time zones and access, and this program was delivered over ten weeks.

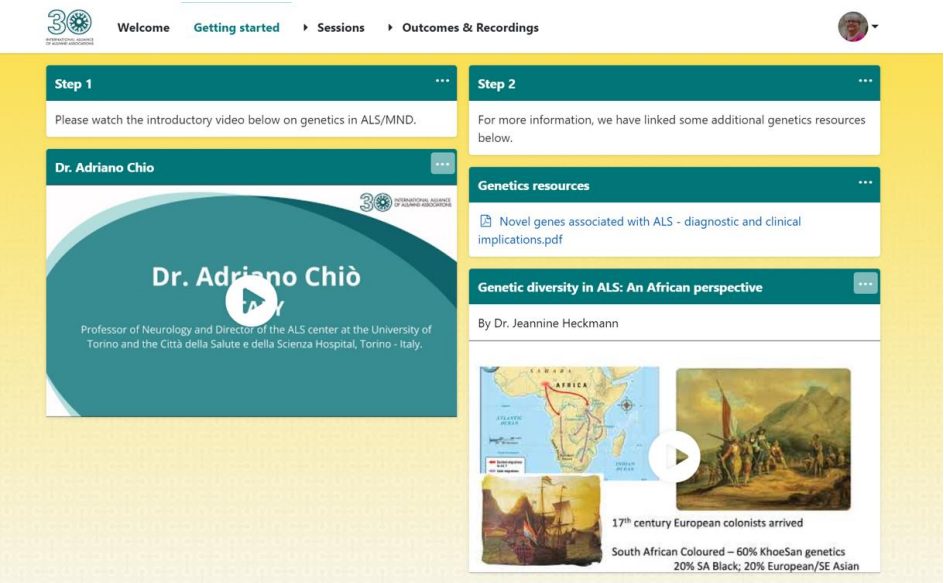


Figure 1: Example of the online platform: HOWSPACE

The overarching goal of the *Genetics Summit* was to serve people living with ALS/MND globally by leveraging worldwide strengths for the benefit of all. The facilitated roundtable discussions on the subtopics of Natural History, Gene Discovery and Clinical Management promoted open communication leading to a common understanding. Each resulted in outcomes of actionable projects to satisfy the principles set at the outset. The principles for each project included:

- uniquely at the global level,
- didn't duplicate work already in progress, and
- included underrepresented communities.

Attendees were challenged to consider how all stakeholders can collaborate in advancing tangible action steps that will improve opportunities for people living with ALS/MND. In addition, we noted that the Alliance had adopted an Open Science statement (See Appendices) and that any proposed project would have to adhere to this statement.

Following the end of the roundtable, project plans were developed, and a survey was sent to participants to help prioritize the outcomes so that the Alliance could develop an action plan.

The Alliance is grateful to all who participated in the Roundtable, especially those with ALS/MND and their caregivers, whose contributions to the entire meeting and its outcomes were instrumental. We are especially grateful to Phil Green and Kristiana Salmon, who took leadership roles in advancing this project throughout 2022.

The following document includes the outcomes of the Genetics Roundtable meeting. It is fair to say that the task ahead of us is tremendous. There is a tremendous opportunity for improvement at the global level.

Attendees

Meeting participants included representatives from multiple global ALS/MND organizations, members of the Alliance's staff and PALS and CALS Advisory Council (PCAC), industry officials and invited experts. Louise Pauze, Founder and CEO of Happico, facilitated all sessions. Amylyx, Apellis, Biogen, Cytokinetics, Ionis and Mitsubishi Tanabe Pharma provided sponsorship support for the Roundtable.

Attendee Roster

Family Name	Given Name	Affiliation	Country
Abadia	Karla	Neurologist	Costa Rica
Aguillon	David	Universidad de Antioquia	Colombia
Ali	David	Alliance Board of Directors	Australia
Al-Khleifat	Ahmad	Neurologist	UK
Alonso	Gerardo	FUNDELA	Spain
Andersen	Peter	Umea, Sweden	Sweden
Andrews	Jinsy	Columbia University, USA	USA

Aquino	Irene	Amylyx	USA
Aquino	Pablo	Alliance Board of Directors	Argentina
Asukile	Tunsu	Health Professional	Africa
Atchayaram	Nalini	Health Professional	India
Azlina	Ahmad-Annuar	Health Professional	Malaysia
Baez	Vanessa	PCAC	Colombia
Balas	Calaneet	Alliance Board of Directors	USA
Baver	Scott	Apellis	
Bayerlein	Nancy	MT Pharma	USA
Benatar	Michael	University of Miami	USA
Blonk	Gorrit-Jan	Dutch ALS Foundation	Netherlands
Boyce	Danielle	John Hopkin's University Packard ALS Centre	USA
Carter	Chelsey	Princeton University	USA
Chio	Adriano	Neurologist	Italy
Clark	Rachel	Biogen	
Cochrane	Thos	Biogen	
Cole	Nick	MOTOR NEURONE DISEASE ASSOCIATION (MNDA UK)	UK
Cordova	Vienna	Yale University	USA
Correa	Cristian	Instituto Roosevelt	Colombia
Crook	Ashley	Genetic counsellor - Australia	Australia
Dave	Kuldip	ALSA	USA
De Valck	Dirk	EUPALS	Netherlands
Deepak	Menon	Health Professional	India
Doyle	Anne Marie	Les Turner ALS Foundation	USA
Floudiotis	Niki	Health Professional	Africa
Fradette	Stephanie	Biogen	
Genge	Angela	The Neuro, Canada	Canada
Ghiro,	Ilaria	Technische Universitat Darmstadt	Italy
Green	Phil	PALS	USA
Haley MBE	Jane	MND Scotland	Scotland
Hardiman	Orla	TRICALS	Ireland
Harms	Matthew B.	New York Genome Centre	USA
Harris	Rodney	Australia	Australia
Heckmann	Jeanine	Neurologist	South Africa
Hemangi	Sane	Asha Ek Hope Foundation	India
Henning	Franclo	Motor Neurone Disease Association of South Africa	South Africa
Hughes	Sally	MOTOR NEURONE DISEASE ASSOCIATION (MNDA UK)	UK

Hughes	Ricardo	Neurologist	Chile
Kaya	Alper	ALS/MND Association Turkey	Turkey
Kiernan	Matthew	University of Sydney, Australia	Australia
Kuo	Lung	Alliance Board of Directors	Taiwan
Kvalsund	Michelle	Health Professional	Africa
Landers	John	ALS Compute	USA
Leonard	Fintan	UCB	
Levitsky	Gleb	Nina Levitsky Russian Charity ALS Foundation	Russia
Light	Sally	MOTOR NEURONE DISEASE ASSOCIATION (MNDA UK)	UK
Lillo	Patricia	Neurologist	Chile
Lopera	Francisco	Universidad de Antioquia	Colombia
MacIsaac	Norman	PALS	Canada
Magnussen	Claire	The Neuro, Canada	Canada
Maia	Elizabeth	Apellis	
Manuel	Machelle	Amylyx	USA
Marina	Kennerson	Health Professional	Australia
Melka	Dereje	Ethiopia	Ethiopia
Messmer Uccelli	Michele	Biogen	
Mochan	Andre	Health Professional	Africa
Nel	Melissa	Health Professional	Africa
O´Brien	Daniel	Apellis	
Ocampo	Felipe	PALS	Colombia
Ogunniyi	Adesola	Health Professional	Africa
Pauls Backman	Andrea	Alliance Board of Directors	USA
Pena	Martha	Neurologist	Colombia
Persson	Emmelie	Apellis	
Povedano	Monica	Neurologist	Spain (works with Ethiopia)
Reviers	Evy	Alliance Board of Directors	Belgium
Roggenbuck	Jennifer	Genetic counsellor	Ohio
Rothstein	Jeffrey	AnswerALS	USA
Ruiz	Orlando	ACELA	Colombia
Salmon	Kristiana	The Neuro, Canada	Canada
Sánchez	Diana	Instituto Roosevelt	Colombia
Sara	Feldman,	ALS Hope Foundation	USA
Sethi	Nadia	ALS TDI	USA
Shahrizaila	Nortina	Neurologist	Malaysia

Sherman	Alex		USA
Sigurdsson	Gudjon	Alliance Board of Directors	Iceland
Slatis	Katharina	Apellis	
Sokhi	Dilraj	Health Professional	Africa
Solano	Juan Marcos	Universidad de Antioquia	Colombia
Sproviero	Daisy	IFOM Istituto Fondazione di Oncologia Molecolare	Italy
Sruthi	S. Nair	Health Professional	India
Stevens	John	Apellis	
Taylor	David	ALS Society of Canada	Canada
Thomasat	Priya	Health Professional	India
Timmons	Jamie	Amylyx	USA
Uysal	Hilmi	Alliance Board of Directors	Turkey
Vaibhav	Dr.	Health Professional	India
Van Damme	Philip	UZ Leuven, Belgium	Belgium
Veldink	Jan	MinE	Netherlands
Vengali	Seena	Health Professional	India
virgo	bruce	PALS	Scotland
Vishnu	V. Y.	Health Professional	India
Webb	Lauren	Les Turner ALS Foundation	USA
Werner	Peter	MT Pharma	USA
Williams	Kelly	Macquarie University	Australia
Yersak	Jill	Biogen	USA
You	Bernice	PALS	USA

Agenda

The agenda for the Genetic Summit was unique in that the discussions were spread out over three different time frames and encapsulated in an overall agenda of asynchronous discussion using the platform, HowSpace. Each individual agenda on discussion topic day included a live discussion to set up the format and then small group discussions on the topics of Natural History, Clinical Management and Gene Discovery.

Background

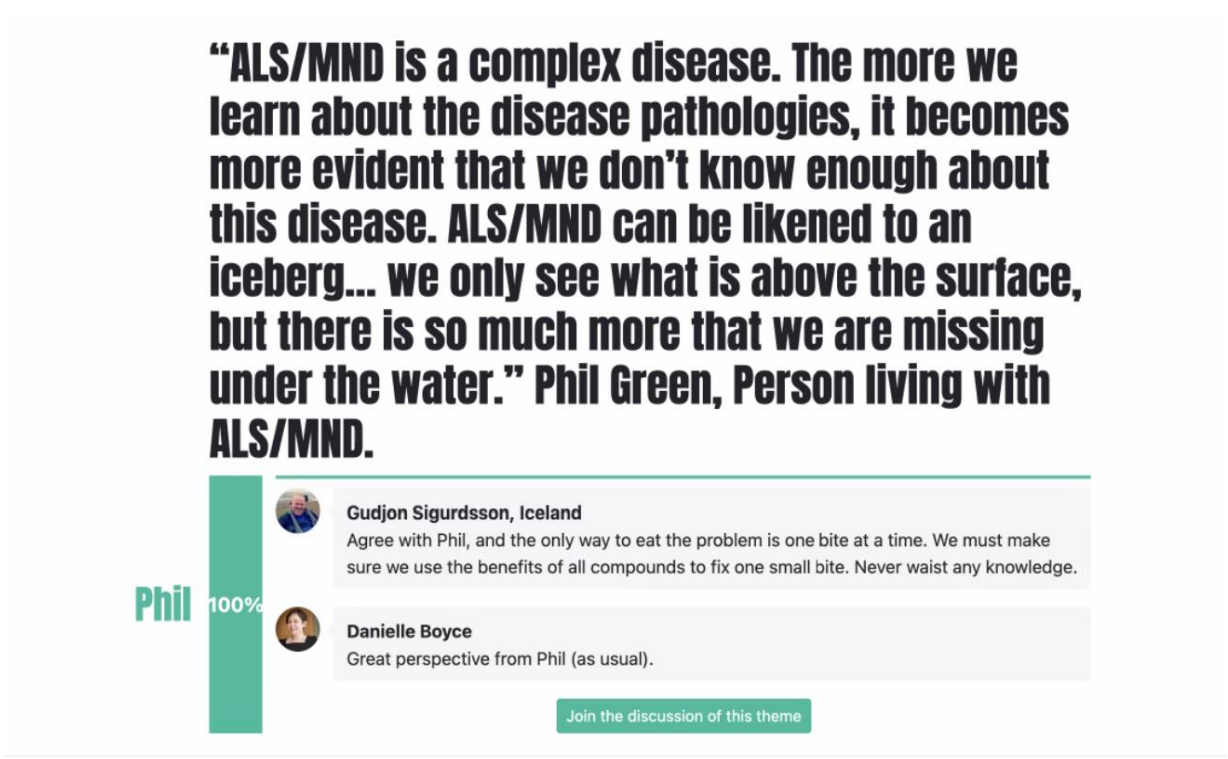
Genetics has largely fueled our understanding of ALS/MND since the discovery of the SOD1 gene in the early 90s. Since then, the community has discovered an exponentially increasing number of genetic variants. According to Dr. Adriano Chio in the opening video for this Summit, “genetics is a major contributor to the understanding of ALS.” Studying genetics in ALS/MND points to biological pathways that are important to motor neuron health, either directly or indirectly. We hope these pathways can yield an understanding that identifies

therapeutic targets that have significant effects for some or all living with ALS/MND. Heterogeneity suggests that several pathways could converge on a final outcome of motor neuron degeneration. Given the above, a better understanding of genetics will lead to a better understanding of the disease spectrum as a whole.

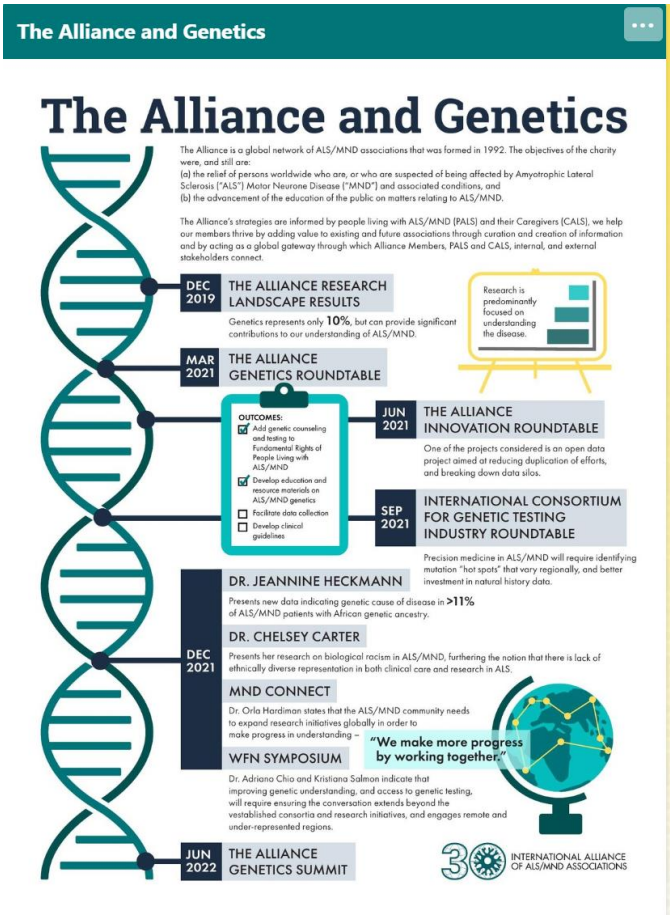
To date, genetic research in ALS/MND has largely been based in and focused on countries and populations of people in privileged positions to conduct such research. Expanding genetic research activities into developing countries could discover new genetic variants in ALS/MND populations not previously studied. These variants could contribute critical pieces to the overall ALS/MND puzzle.

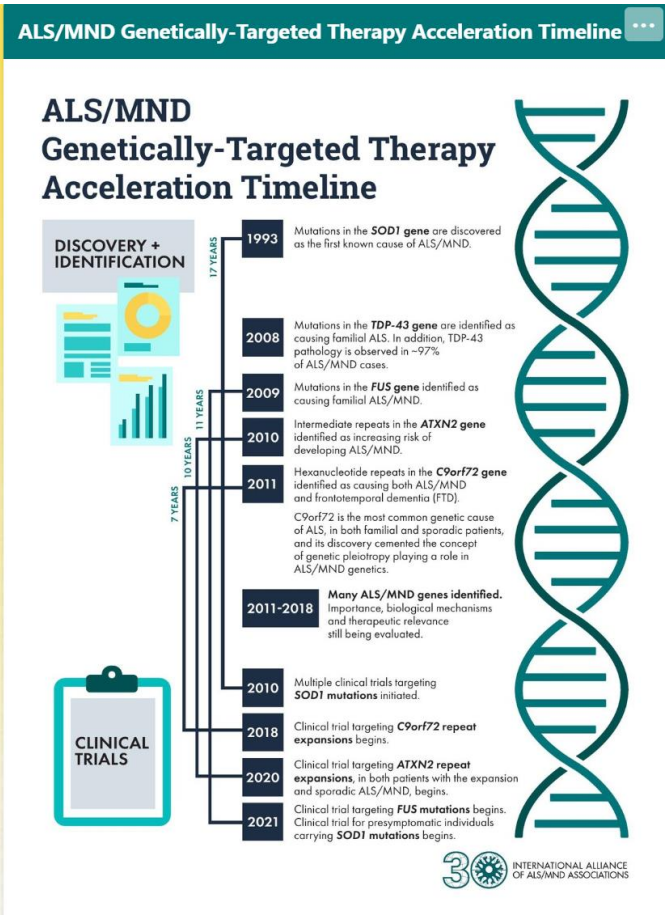
In addition, we are entering the era of personalized medicine. We cannot assume that treatments derived from a small subset of the global ALS/MND population will be applicable and effective to the rest of the world. Furthermore, we should aim to lay the groundwork early that could potentially decrease the number of barriers to accessing therapies for under-represented geographies in the future.

The International Alliance of ALS/MND Associations represents all persons living with ALS/MND globally but has not yet taken an operational role in ALS research. Establishing complex research initiatives in developing countries, such as clinical trials, can be challenging. Research focusing on ALS/MND genetics provides a solid, approachable, static, and impactful entry point to exploring and understanding ALS/MND and people living with the disease outside the developed world. With its global reach and perspective, the Alliance can leverage other ongoing initiatives (e.g., Project MinE, ALS Compute, etc.) to bring in other areas of the world. Three decades of foundational groundwork in studying ALS/MND genetics will allow this first foray into having an operational arm of research to be well-established from the onset. The time is now for the Alliance to pave the way for a better understanding of ALS/MND at a global level.



Multiple meetings at the local and regional levels, as well as discussions among various stakeholder groups on the subject, have led to an opportunity for the International Alliance to convene a collective conversation in its role as an “information gateway” among all the relevant parts of the ALS/MND global community. The infographics below illustrate the genetic timeline and the need for Alliance intervention.





Background on the three subject areas discussed, Natural History, Gene Discovery and Clinical Management, is provided in the following.

Natural History

The issues we were trying to solve with the Natural History discussion related to our understanding of the disease and how natural histories are collected. Much of our knowledge of ALS/MND, both genetically and in disease presentation and progression, consists of data collected from privileged countries and white people. Natural history data, combined with genetic data (not necessarily disease-causing genes, but especially modifier genes), can provide valuable insight into our understanding of the disease, how patients progress, and optimal times for treatment/clinical trials. Dr. Adriano Chio said during our meetings leading up to the Summit, **"we will never understand ALS if we continue to collect small snapshots in time. We must watch the whole movie."**

Numerous regional natural history data collection projects are ongoing – it is unclear how other platforms/projects/countries share data. Previously, many natural history projects have been initiated and have failed. How can we harmonize data collected from natural history projects? What is the minimum viable data set that could be collected longitudinally on an ALS/MND patient that is simple enough to introduce into a new, previously under-represented geography/ethnicity that would provide impact in terms of natural history data?

Gene Discovery

The issues the Alliance is trying to address within the Gene Discovery area are inclusion and access, sharing of information, and coordination.

There are a number of ongoing, large-scale gene discovery initiatives in ALS/MND that are underway currently. However, our general understanding of genetics in ALS/MND is limited primarily to geographies of European descent and white ethnicities. How do we initiate an ALS/MND gene discovery initiative in previously under-represented geographies?

How do we ensure that ongoing initiatives are sharing data? How harmonized is data sharing across the ongoing gene discovery initiatives currently?

Clinical Management

Clinical Management discussions focus on the best practices for managing ALS/MND globally, emphasizing genetic counselling and testing. What is available locally versus what could be available globally that is universal and accessible even in areas where infrastructure and resources do not exist? We were cautioned about this and other areas to steer clear of research and clinical management colonialism, whereby more developed nations were telling underrepresented communities what to do in their jurisdictions, which may not be culturally appropriate or welcomed.

Outcomes and Alliance Action Plan

As stated at the beginning of this report, the Alliance's overarching goal was to serve people living with ALS/MND globally by leveraging worldwide strengths for the benefit of all. We wanted outcomes of actionable projects that could be taken forward in a short to medium time frame in tangible ways to best serve people living with ALS/MND. To say the discussions were robust would be an understatement. It is abundantly evident that everyone participating in this summit wants the same thing – a world free of ALS/MND – to be solved one step at a time as urgently as possible. There were 14 projects suggested, and they are each outlined below. The Word Cloud for the Clinical Management portion of the hybrid e-learning platform is a great illustration of how that discussion unfolded.

Project Suggestions

Natural History

Expanding ALS research in global populations: Partner with local clinical, research, and patient communities to increase genetic diversification in databases. Disseminate findings in a culturally-appropriate manner.

Landscape Assessment: Create an inventory of available data sets and associated metadata, including clinical trials, natural history studies, and other longitudinal data or bio-samples.

Single ALS Sandbox: Identify and share best practices, barriers, incentives, and data-sharing strategies. In addition, identify and share best practices for acknowledgement of the patient contribution and explain the data collection results to patients and other stakeholders.

Universal Inclusive data collection: Collaborate with and empower decision-making in individual countries to create a common data infrastructure that results in increased participation in global natural history studies and clinical trials.

Clinical Management

Best practice consensus guideline development: Review, update, align, and harmonize existing guidelines resulting in the publication of global consensus guidelines on the management and care of ALS. Guidelines should include genetic counseling and testing, focusing on variant interpretation.

Infrastructure: Provide organization and infrastructure on a global scale for virtual genetic testing, bioinformatics pipelines, standardized NGS gene panels, and variant interpretation resources.

Education/Dissemination: Develop and disseminate visual aids, other tools and resources on genetic education and counseling appropriate for multiple audiences, including specialists. These materials can help to lessen the impact of the genetic counselor shortage.

Genetic mutation carriers: Develop a research agenda for identifying risk mitigation, treatment, and environmental or lifestyle modification strategies for gene mutation carriers.

Empower members to influence their local stakeholders: Create a broader movement to make genetic counseling and testing part of clinical management.

Gene Discovery

Advocacy Project to promote consented data sharing worldwide: Advocate to the UN to include in the Convention Rights of People with Disabilities act an open science article for orphan and incurable diseases.

ALS Infrastructure Network Mentoring Model For Under-Resourced Areas: Partner with well-organized and well-resourced organizations to develop a network and resources to facilitate collaboration between clinicians, students, and researchers. Document lessons learned into a toolkit or roadmap for other stakeholders for the development of national registers and DNA banks in lower- and middle-income countries.

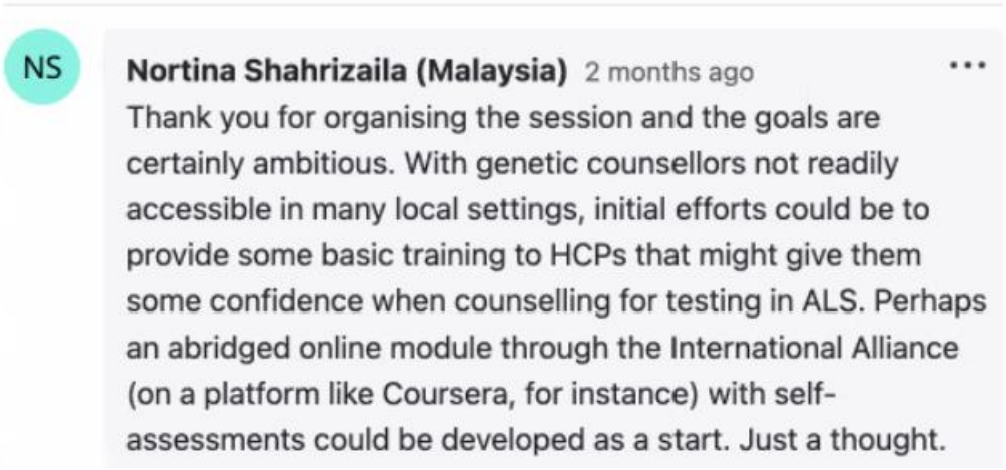
Develop registers and biobanks in countries globally regardless of income or infrastructure: This will improve diversity in genetic and clinical studies by providing an open platform to share an inventory of global datasets. This program includes mentoring, training, and protocols for testing.

Expand Genetic Diversity in Existing Large ALS Data Sets Set up a standardized template for collection and sharing of data: Partner with researchers in other countries not represented in existing large ALS data programs to expand genetic collection through existing free methods. In addition, partner with existing collection efforts in Africa, Asia and South America.

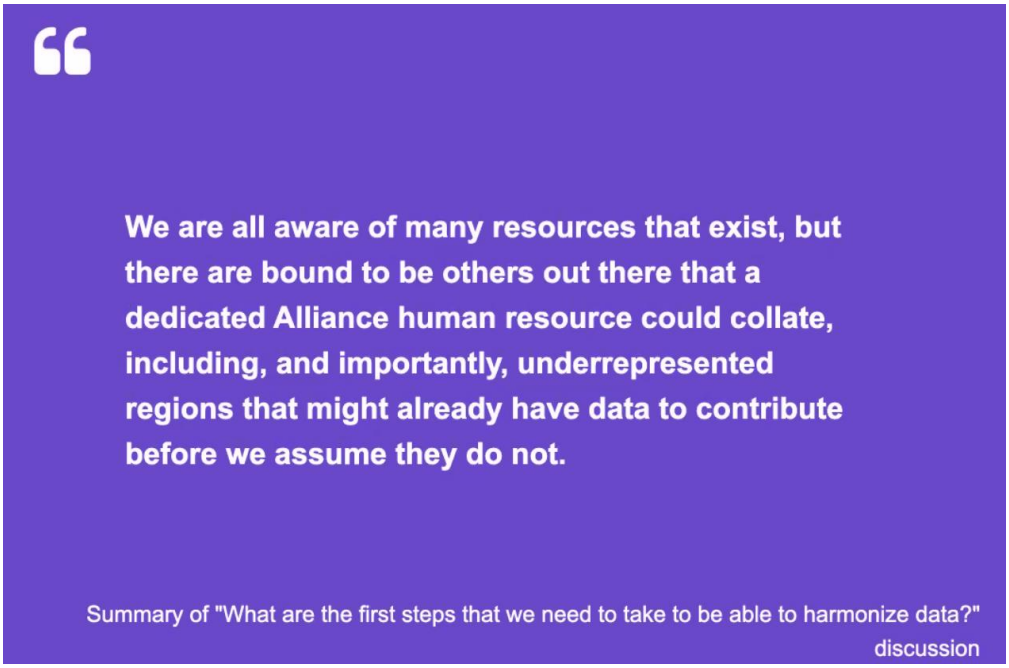
Global genetic discovery infrastructure pilot competition: Solicit applications to be the region or country for piloting Alliance support in building better internal infrastructure, filling gaps, and contributing to the global pool of sequence data.

Action Plan

The International Alliance of ALS/MND Associations has its work cut out for it. In addition to the projects listed above, there were many suggestions in the online comments, such as developing specific online resources as indicated below.



We would be unable to undertake each of these projects with our current human resources. The summary for the discussion on the question “What are the first steps we need to take to be able to harmonize data“ in the Natural History discussion is illustrated below and mentions a dedicated Alliance human resource.



Therefore, one of the first action items that the Alliance will be undertaking is to hire a Scientific Director. This individual will be responsible for building and implementing the Alliance's research strategy and supporting the advocacy and education efforts related to research, including genetics. The Scientific Director will play a key leadership role in facilitating global collaboration in ALS/MND research to deliver value to the Alliance's members and the global ALS/MND community.

As mentioned, all participants were sent a survey to help prioritize the 14 projects that developed from the Genetics Summit. That data, along with other inputs, will set the strategy that the Alliance will pursue in this area in 2023 and beyond. The results of the survey are included in the appendices. The other inputs we will use are the financial resources required; whether our role is creation or coordination; and, last but not least, what human resources are required from both a staff and volunteer perspective.

We would also like to note that the Education/Dissemination project is already underway at the Alliance. Genetics is a key focus of our webinar series, roundtables and a stream at our conferences. In addition, we perform outreach through other organizations, such as the NSGC.

Sponsors

Thank you to our sponsors for this event; Biogen, Ionis, Amylyx, Apellis, Mitsubishi Tanabe Pharma, and Cytokinetics. We could not have done it without their support!

Appendices

Appendix 1 – Open Science Statement

The Open Science Statement of the International Alliance of ALS/MND Associations consists of Values, Principles and Practices as shown in the chart below. The practices are outlined in more detail following the chart. Our expectation is that any Alliance research collaborators must commit to making their outputs (materials and knowledge) publicly available without restriction on use and adhere to the following values, principles and practices, which support the values of the International Alliance of ALS MND Associations with respect to Open Science.

VALUES, PRINCIPLES AND PRACTICES

Values	Principles	Practices
Human-centric	• Fairness	• Representative • Respectful
	• Inclusive	• Communications • Behaviours • PALS/CALS driven
	• Accountability	• IP • Auditable
Knowledge-sharing	• Urgency	• Timely
	• Transparency	• Article access
	• Interoperable	• Data & code access
	• Replicable & reproducible	• Protocols
Trustworthy	• Reliability	• Accessible documentation
	• Private & secure	• Compliance processes & guidelines

- Follow-on research
- Re-use
- Attribution & acknowledgement

PRACTICES

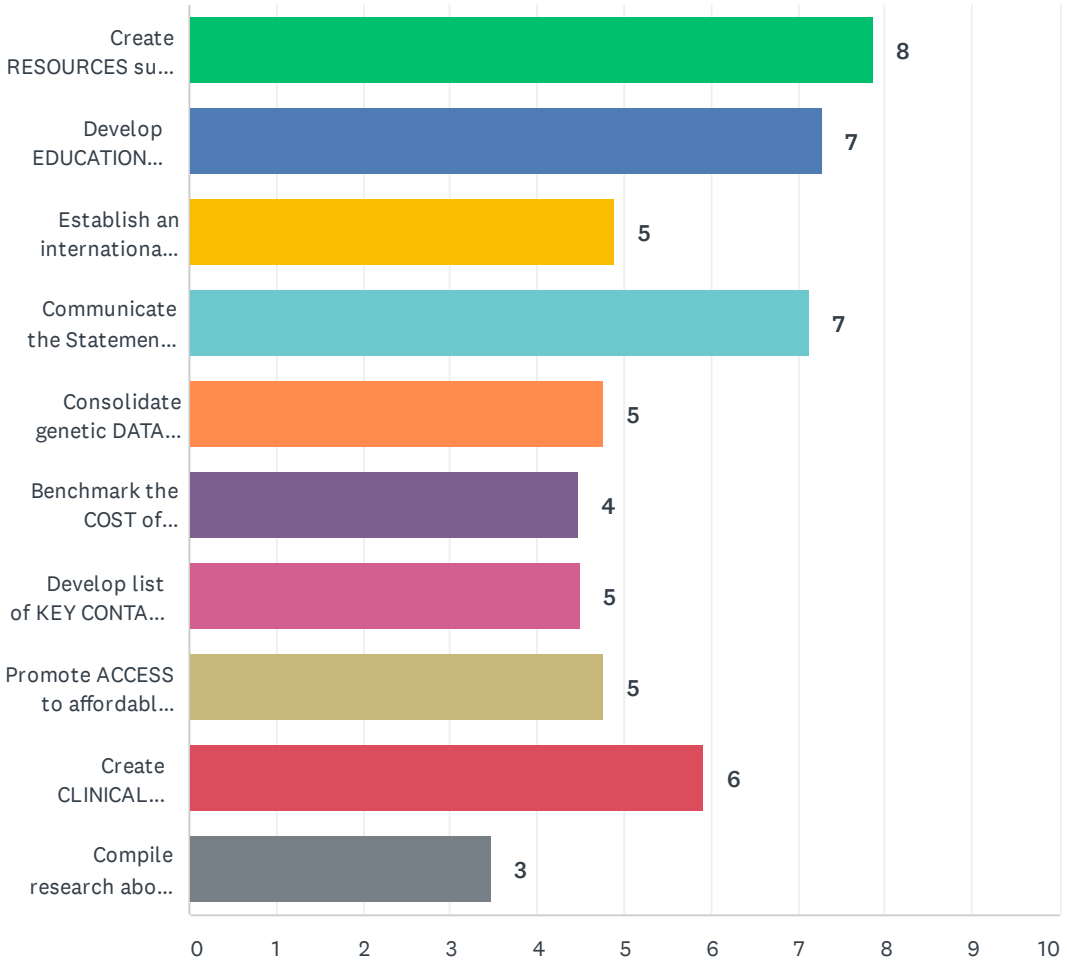
1. Each researcher or project will have a plan for how the principles of Open Science will be adhered to from inception to the end of the project. That plan will include how the values of human-centric, knowledge sharing and trustworthiness will be met.
2. Where possible, existing human data will be used, so PALS and CALS do not have to undergo repeat testing if they have made informed consent to make their data available under open science principles.
3. Post experimental protocols to a protocol-sharing service, such as protocols.io
4. All articles resulting from funding must be published in a fully open-access journal or posted in an open repository with free, immediate readership rights
5. Researchers will seek to place open-access results arising from research projects (internal or collaborative) in the public domain. Researchers will not, under any Alliance Project they undertake (internal or collaborative), file any form of the patent application, or allow a collaborator to restrict the research use of Open Access Project Outputs.
6. Data will be shared according to FAIR principles [Findability, Accessibility, Interoperability, and Reuse of digital assets]
7. Researchers will promptly release the associated output data through free and publicly accessible digital repositories while still maintaining compliance with any privacy and confidentiality regulations.
8. Any data, code, and software needed for independent verification of research results must be curated and made free and publicly available in an established, open repository no later than the publication of the first paper based on the data or no later than the expiration of the grant, whichever comes first.
9. Research outputs (articles, data, code, and software) resulting from funding must be made available with generous reuse & remixing rights (e.g. CC BY.CCO licences)
10. Applicants will be encouraged to include the anticipated costs for making their work open in their grant applications.
11. All researchers and projects will include a data-sharing plan as part of the application process and there will be compliance checkpoints throughout the term of engagement which proactively compiles proof of policy compliance as a component of interim and final reports

Appendix 2 – Results from a survey on priorities

Genetics Roundtable - Project Prioritization

Q1 Please rank the following project ideas from highest priority (1) to lowest priority.

Answered: 30 Skipped: 0



Q2 Was there anything discussed at the roundtable not mentioned in the project list that you think should be included?

Answered: 11 Skipped: 19

#	RESPONSES	DATE
1	None	4/23/2021 4:30 PM
2	Physician education/mentorship is critical to changing practice.	4/23/2021 1:08 PM
3	Promotion of invitro fertilisation and pre implantation genetic testing for identified causal genes to stop familial ALS/MND in its tracks. Start with PLS (Kennedy's Disease)	4/22/2021 12:01 AM
4	Should tofersen prove effective, I think the Alliance should consider some form of SOD1 targeted program akin to the EDUCATION piece above to ensure everyone in the world at risk is aware of the treatment and has an opportunity to look for ways to obtain it.	4/21/2021 11:53 PM
5	All includes	4/21/2021 3:38 PM
6	No	4/21/2021 2:14 PM
7	Importance of whole genome sequencing for the entire community as opposed to testing for known ALS variants. We need this data to identify possible polygenic factors in ALS.	4/20/2021 6:24 PM
8	Nothing to add.	4/19/2021 5:11 PM
9	because legislation and access take the longest, suggest prioritize starting those first	4/19/2021 12:29 PM
10	not really	4/12/2021 2:32 PM
11	Not mentioned above (and probably for a good reason) is the aspiration around DNA Banking. DNA banking for research purposes can be expensive and potentially time consuming in busy clinics, so the rationale and benefits need to be clearly thought through.	4/9/2021 6:46 AM

Resources:

Webinars

Alliance Genetics Webinars

Infographics

Ethical Considerations in ALS/MND Genetics
Introduction to Genetics: What is genetic variation?
Introduction to Genetics: What is your genome?
ALS/MND Genetics: Why is genetics relevant to ALS/MND?
ALS/MND Genetics: Can genes affect the type of ALS/MND?
ALS/MND Genetics: What can we do about genetic ALS/MND?

Videos

Genetic diversity in ALS: An African perspective

Papers

Genetics Roundtable Resrouces