

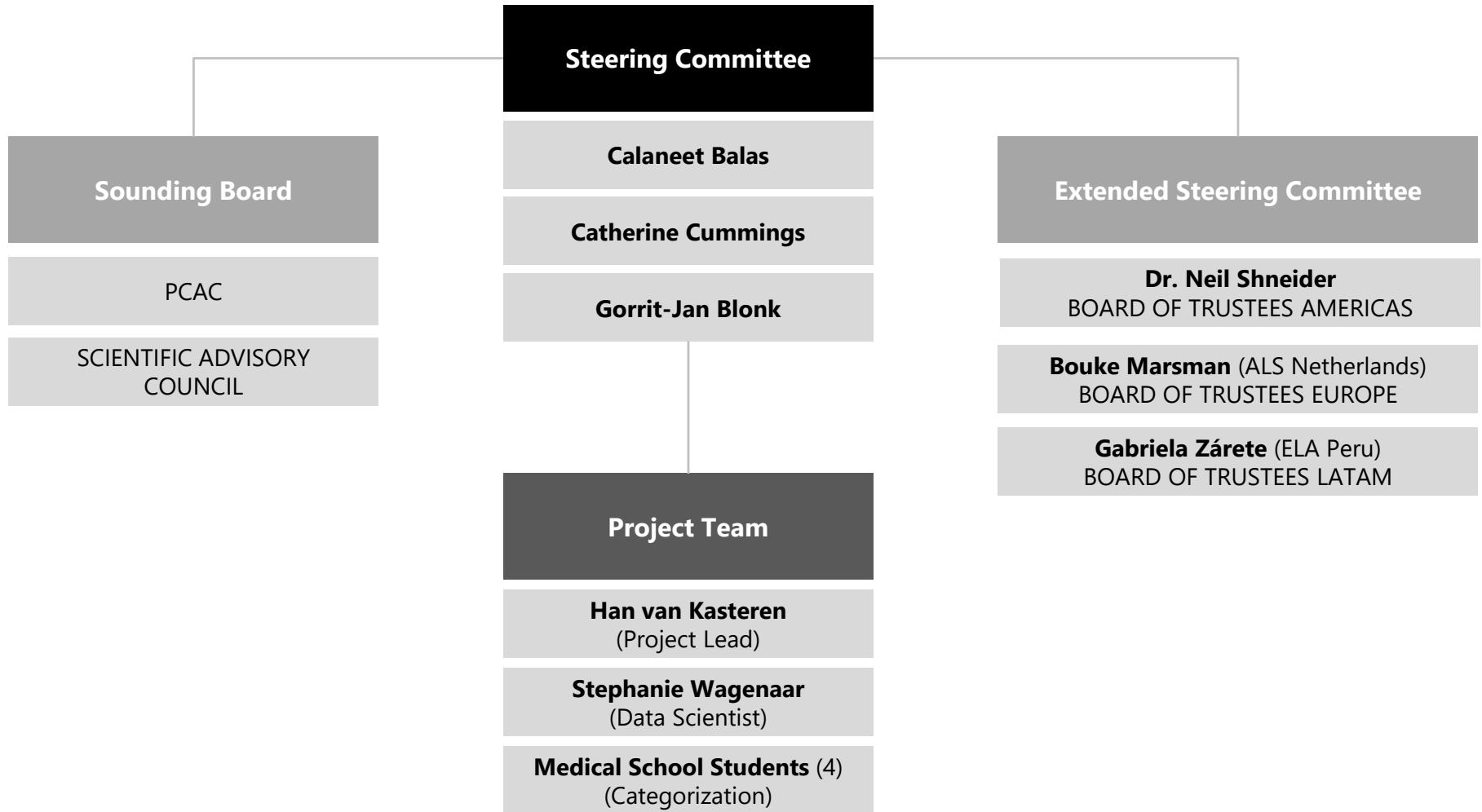


ALS/MND Landscape

Extended Steering Committee Presentation
International Alliance of ALS/MND Associations
4 October 2019

- One of the strategic goals of the International Alliance of ALS/MND Associations (IAAA) is to promote and support scientific research for the cause, avoidance, cure and treatment of ALS
- In doing so, associations within the IAAA would benefit from [improved alignment and commitment on the focus areas for allocation of funds](#)
- In addition, the associations would benefit from an [improved and relieved decision making process](#) for new funding requests
- Therefore, the initiative was taken to execute an independent study to draw a global [Landscape for Strategic Fund Allocation](#) for cure-related funding,
 - to avoid research gaps or unintended overlaps,
 - and to realize optimal application of funds
- The outcome of this project will be [shared with all associations](#) within the IAAA
- The Landscape could assist each Association in determining their future roadmap
- This initiative is sponsored by Stichting ALS Nederland

Project Team Set-up





Objectives and Process

The project had 5 objectives:

- Create **insight** on current ALS/MND research activities in terms of type of research, researchers, research institution, to map who is doing what and where
- Create **overview** of trends in academic focus areas, breakthrough findings and impact, Key Opinion Leader opinions, recent publications
- Clarify **expectations** of key stakeholders on the focus and impact of the ALS/MND allocated funds
- Create **alignment** on the focus areas where to and where not to allocate funds in the coming 5 years within the ALS leadership teams
- Create a **decision making template** which makes the funding process more efficient, objective and traceable



Initial focus on analysis of ALS research

Within the available time for this project, the main focus has been:

- Insight on current ALS/MND research activities to build the Landscape picture
 - ▶ Collect ALS/MND related PubMed studies
 - ▶ Identify type of research (based on title, abstract and keywords)
 - ▶ Log author, institution, geography
 - ▶ Categorize all studies to map who is doing what and where
 - ▶ Create several cross sections and find correlations to build the Landscape

Key finding during the project

- Decided to focus on creating insights in recent research, before other objectives
- Analysis of type of research best done based on PubMed publications
- PubMed categorization and analysis would consume majority of available time



Fund allocation and research trends postponed to stage two

Currently out of scope but recommended for the future:

- Distribution of allocated funds per ALS association
 - ▶ Per institution
 - ▶ Per purpose, e.g. patient care vs research
 - ▶ Per geography
 - ▶ Per type of (clinical) research, biomarker, treatment or therapy (drugs, stem-cell or gene therapy, antibodies)
- Outlook of research trends
 - ▶ Per type of (clinical) research
 - ▶ Per technique/methodology
 - ▶ Key institutions, researchers, (international) trials
 - ▶ Level of cooperation and knowledge sharing between research entities
- Decision making template
 - ▶ To make funding process more efficient, objective and traceable

Initial scope

New possible stage two opportunity:

- Machine Learning model
 - ▶ Build basis for Machine Learning model for future automated PubMed research categorization to continuously update the Landscape

Addition

First step was an interview round

- Goal: Test, refine and confirm the objectives and the approach, and establish the categorization
- Spoken to:
 - Dr. David Taylor – Chair Scientific Advisory Board Of International Alliance of ALS/MND Associations
 - Dr. Leonard van den Berg – ALS Centre at UMC Utrecht
 - Jaap Kerstjens – Board of Trustees Stichting ALS Netherlands
 - Dr. Neil Shneider – Columbia University, New York
 - Dr. Wouter Jansen – External consultant to TRICALS
 - Vincent Cornelissen – Chairman PAC Netherlands
 - Gudjon Sigurdsson – PALS/CALS advisory council; MND Association Iceland

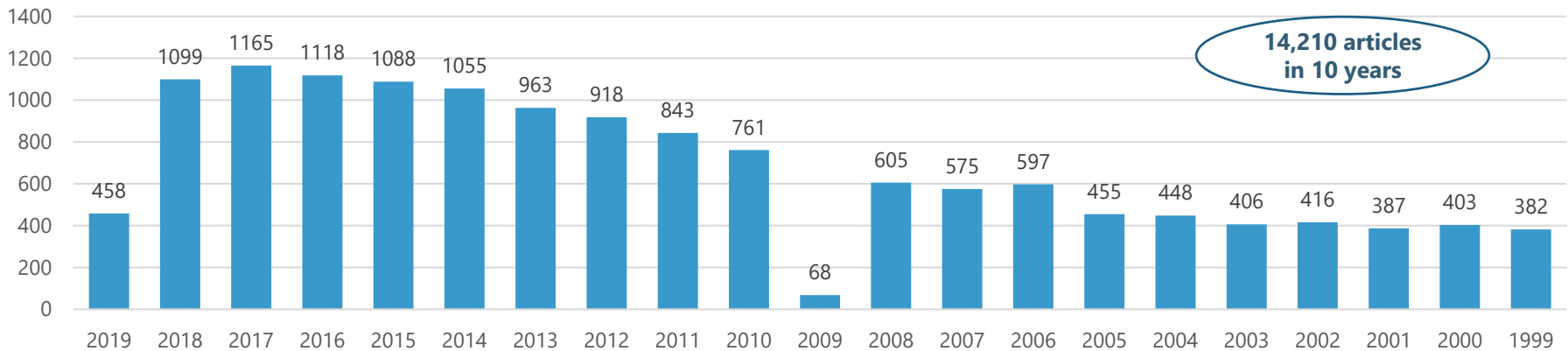
Key finding → Since research article analysis was key focus, further interviews to collect trends and opinions were postponed



Subsequent focus was analyzing the PubMed articles

- PubMed lists in total (regardless of timeline):
 - 31,700 articles with the keyword Motor Neuron Disease
 - 25,968 articles with the keyword Amyotrophic Lateral Sclerosis
 - 19,571 articles with keyword Motor Neuron Disease *and* Amyotrophic Lateral Sclerosis

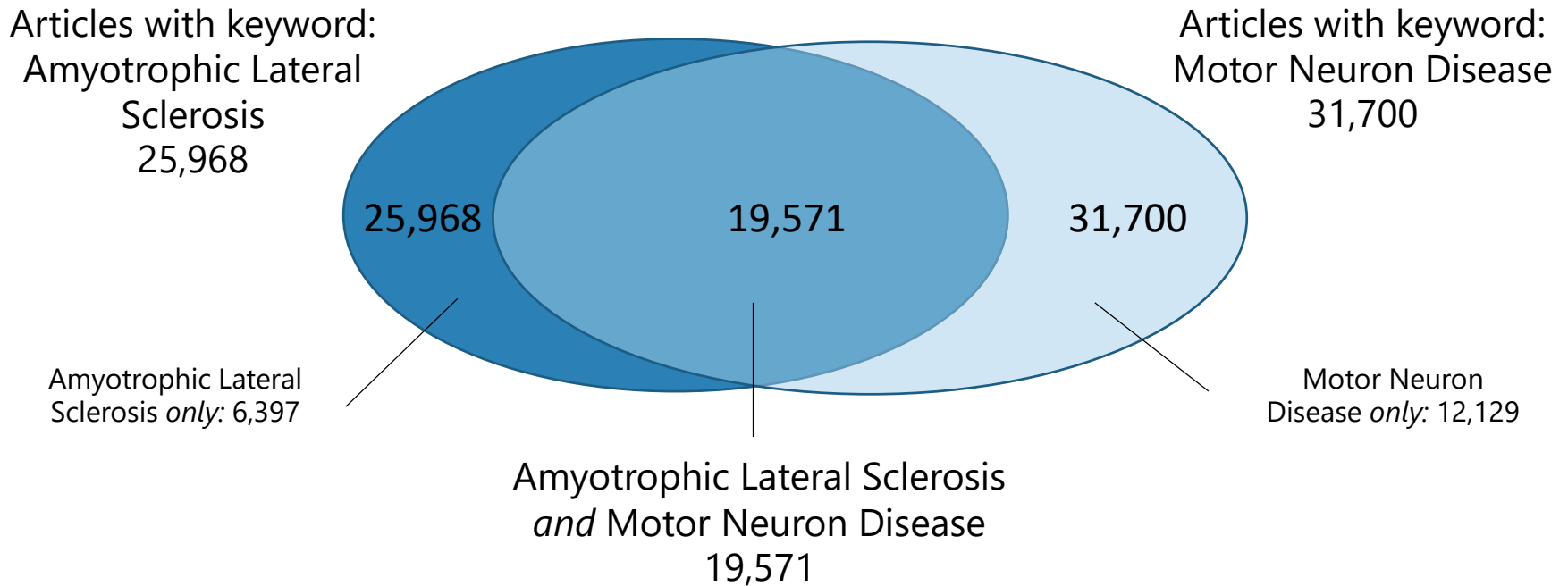
Publications on ALS and MND



Key finding → A steady growth in publications on ALS and MND



Subsequent focus was analyzing the PubMed articles



Of the 25,968 articles with Amyotrophic Lateral Sclerosis, we selected **2,100 *cure related* articles** for categorization, which covers c. **1.5 years of publications (2018 – mid 2019)**

Key finding → A large overlap between ALS and MND

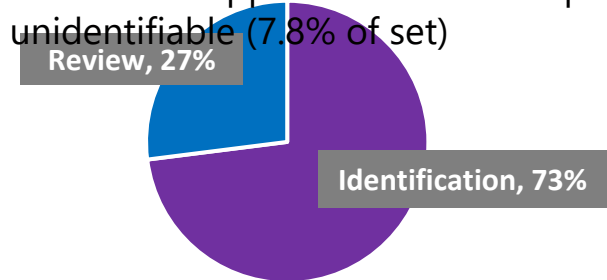


Nine categories were defined to allocate 2,100 articles to

- The below categorization¹ was used to allocate the articles:
 1. Clinical Management of ALS/MND
 2. Clinical Understanding of ALS/MND
 3. Assisted Technology
 4. Epidemiology
 5. Clinical Trials
 6. Biomarkers
 7. Genetics
 8. Laboratory – therapeutic targeting of ALS/MND
 9. Laboratory – pathogenic understanding of ALS/MND
- Two categories to allocate non-related publications:
 10. Case reports
 11. Other topic or unidentifiable
- The categorization for the types of research was created in cooperation with Dr. Shneider, Dr. Van den Berg, Dr. Jansen

The chosen set of 2,100 articles contained mainly new identifications

- Articles with search criteria Amyotrophic Lateral Sclerosis
- In period of June 2019 to Jan 2018
- 73% of studied articles were a new identification,
- Whilst 27% were reviews on earlier studies
- 27 articles were case reports (1.3% of set)
- 157 articles appeared to be off-topic or unidentifiable (7.8% of set)

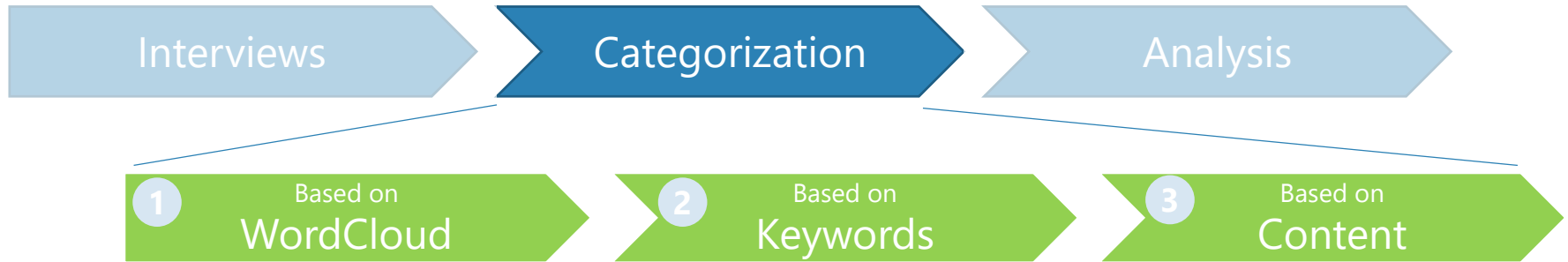


(1) Detailed description in the appendix

Key finding → An ideal categorization is difficult to determine



Iteratively discovered best way to categorize



Method: **Automated ranking on frequency of keywords in titles**

Finding: Obviously, words like ALS, motor, mouse, disease, drug found most frequently

Result: Low value add, but helped in first step to explore the data rather than actually classifying the data

Method: **Manual categorization on keywords in abstract**

Finding: Categorization was driven by keywords rather than reflection of real subject in scope

Result: Low value add, but helped in building the desired categorization

Method: **Manual categorization by experts based on content**

Finding: Allocation to defined categories based on deep interpretation of content of the article¹

Result: Categorization now reflects true subject of study, but categories might differ in size (breadth)

(1) Also taking into account concepts, entities and relationships which are often not explicitly mentioned in a text but can only be inferred/deduced

Key finding → Profound understanding required to categorize

2 Based on
Keywords

Manual categorization by interpretation of keywords in abstract

Scoring on Keywords	
Category	Count
Genes	384
Cells	167
Genetics	161
Cognition (incl. Neuroimaging)	159
Relation to other diseases	147
Proteins	94
Muscles (incl. lungs/speech/heart)	86
Chemicals (not being medicine)	83
Medicine	81
Biomarker	71
External Factors (incl. BMI/weight*)	60
Statistics (incl. databases, nearest neighbour; K-means)	54
Motor neuron	41
Neuroinflammation	25
Diagnositic (incl. trial design)	25
Spinal Cord	24
Metabolism	16
Tools (incl. procedures)	12
Nerves	9
Microbiota	8
Virus	6
Heratibility	4
Nutrition	3

n = 924 PubMed
articles
from 2018-2019



Profound understanding required to categorize

3

Based on
Content

- Allocation of publications to the categories required profound understanding of the publication and the capacity to understand its context
- Even when the title contains clear keywords, the article could belong to various categories
- Example: Three articles on the SOD1 gene

Article title:	Categorized into:
<i>SOD1 deficiency: a novel syndrome distinct from ALS</i>	Genetics
<i>Mechanisms of SOD1 regulation by post-translational modifications</i>	Laboratory – pathogenic understanding of ALS
<i>Neuroprotective Effects of Genistein in a SOD1-G93A Transgenic Mouse Model of ALS</i>	Laboratory – therapeutic targeting of ALS

Key finding → Profound understanding required to categorize

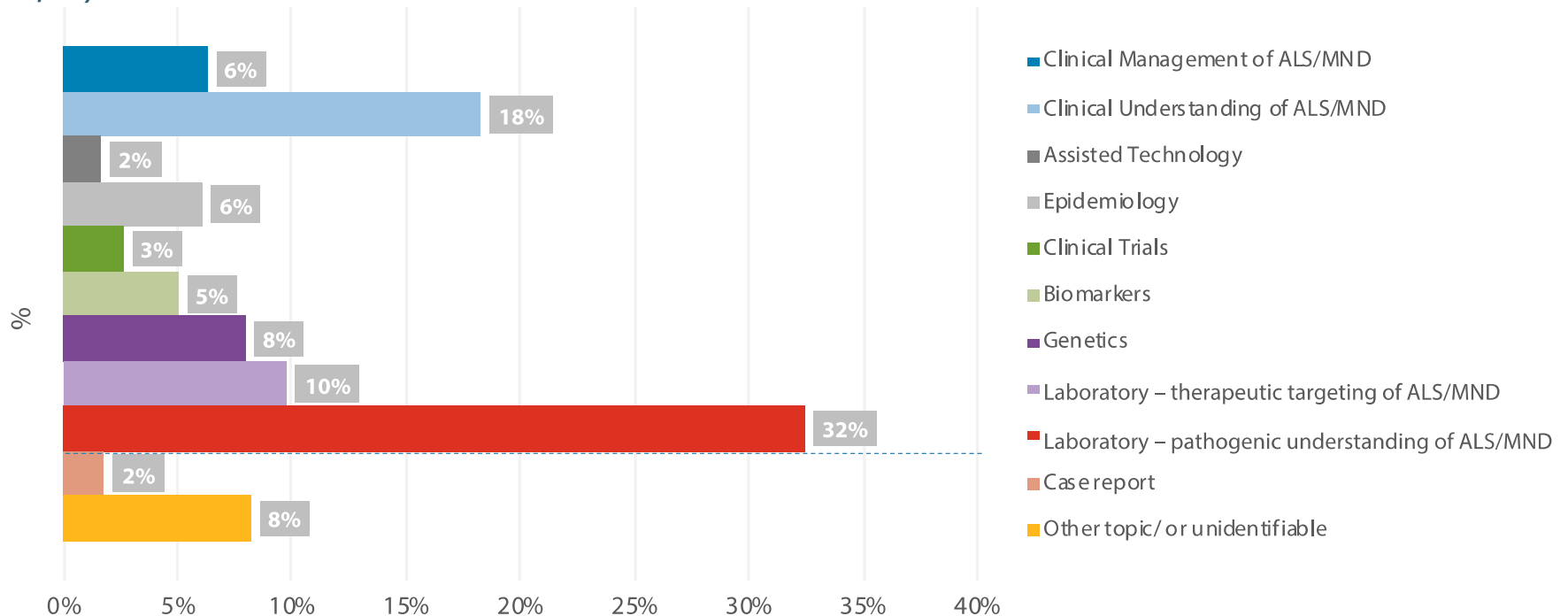


Results



Outcome: Research predominantly focused on cause of the disease (pathogenic understanding)

Share of articles based on current dataset (cumulative scoring, n=8,400)

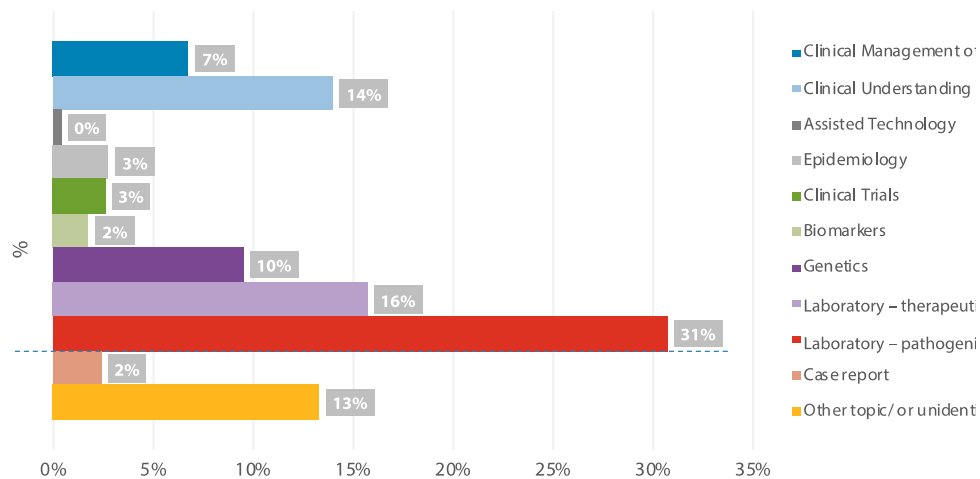


Key finding → Pathogenic understanding is largest; This is in line with expert expectations and earlier surveys: many research still focused on cause of the disease

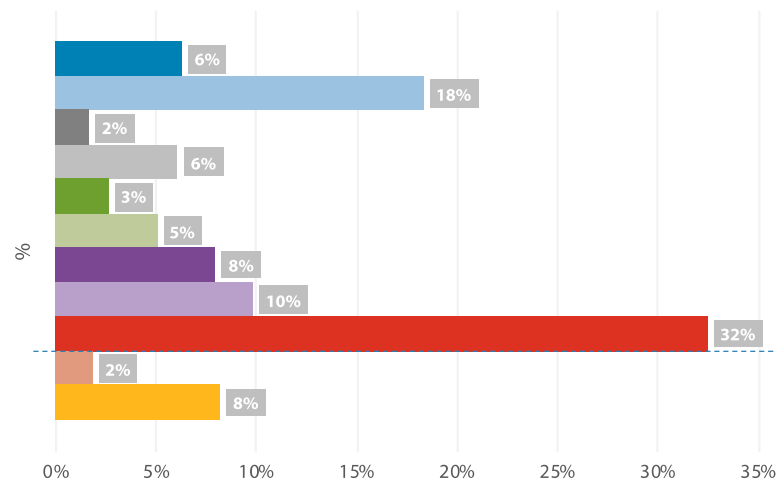


MND research is focusing on the same topics as ALS research

Distribution of MND-only articles (n=1,000)



Distribution of ALS articles (n=2,100)



Key finding → Comparable distribution of articles – and hence studies – per main focus area

Some categories are strongly correlated

Heatmap primary focus and secondary focus – Excluding articles that had no secondary focus area

Heatmap		Secondary focus									Total
Cat #	Primary focus	Clinical Management	Clinical Understanding	Assisted Technology	Epidemiology	Clinical Trials	Biomarkers	Genetics	Laboratory – therapeutic targeting	Laboratory – pathogenic understanding	
1	Clinical Management of ALS/MND		29,6%	12,3%	12,3%	30,9%	1,2%	-	9,9%	3,7%	100%
2	Clinical Understanding of ALS/MND	24,3%		1,5%	12,9%	6,6%	26,5%	11,0%	2,6%	14,7%	100%
3	Assisted Technology	61,5%	38,5%		-	-	-	-	-	-	100%
4	Epidemiology	7,4%	32,8%	-		7,4%	3,3%	21,3%	-	27,9%	100%
5	Clinical Trials	59,4%	15,6%	1,6%	3,1%		7,8%	1,6%	7,8%	3,1%	100%
6	Biomarkers	1,4%	40,1%	-	6,3%	4,2%		9,9%	9,2%	28,9%	100%
7	Genetics	1,2%	8,6%	-	10,3%	-	6,2%		11,1%	62,6%	100%
8	Laboratory – therapeutic targeting of ALS/MND	6,6%	2,6%	-	-	14,6%	7,3%	13,2%		55,6%	100%
9	Laboratory – pathogenic understanding of ALS/MND	0,3%	6,4%	-	2,5%	0,3%	9,3%	29,3%	52,0%		100%
		8,2%	11,7%	0,8%	5,5%	4,6%	9,6%	16,3%	23,3%	19,9%	

Key finding → Strong correlation between:

- Genetics & Pathogenic understanding of ALS/MND
- Clinical trials & Clinical management of ALS/MND
- Biomarkers & Clinical understanding of ALS/MND
- Therapeutic targeting & Pathogenic understanding of ALS/MND

An interesting first study, providing insight in research focus landscape. Strong conclusions hard to derive

- many research still focused on cause of the disease
 - Pathogenic Understanding (laboratory) is largest category (33%); This is in line with expert expectations and earlier surveys
- Runners up are Therapeutic Targeting (laboratory) (18%) and Clinical Understanding (10%)
- Most articles have clear single focus; Largest correlation with secondary focus for
 - Genetics & Pathogenic Understanding of ALS/MND
 - Clinical Trials & Clinical Management of ALS/MND
 - Biomarkers & Clinical Understanding of ALS/MND
 - Therapeutic Targeting & pathogenic understanding of ALS/MND



Next step: A recurring model

- Study the possibility and process of creating an algorithm
 - This analysis would gain value when updated regularly
 - Manual allocation to categories is labor intensive
 - An algorithm would greatly assist in future automated categorization
 - The established set of 8,400 scores can serve as training set for a to-be-built

Other next steps:

- Study possibility to collect metadata (authors, dates, institutes) automatically from PubMed
- Collect funding data to connect research categories to past funding decisions
- Decide whether analysis on trends is valuable



Appendix

1. **Clinical Management of ALS** – anything related to providing better care/QOL for people with ALS. Could include clinical trials of treatments aimed at symptom management and clinical care research
 - Medicine / chemicals if aimed at reducing salivation due to dysphagia
2. **Clinical Understanding of ALS** – anything related to a clinical understanding of human ALS.
 - Includes imaging and neurophysiological
 - as well as other things like cognitive testing and understanding other symptoms/clinical manifestations at a clinical exam level
 - Motor Neuron (MUNE) in clinic
3. **Assisted Technology** – Literature on devices and technology that will enhance QOL outside of the clinic setting, e.g. Brain Computer Interface work
4. **Epidemiology** – Epidemiologic research including risk factors, environmental correlations, measures of ALS incidence, prevalence, global impact etc.
5. **Clinical Trials** (disease modifying) – trials/design, etc. – anything related to trials that aim to affect the disease progression/target disease mechanisms
 - Testing of drug to slow disease progression
6. **Biomarkers** – detectable biological readouts of disease
 - Proteins, depending on the context
7. **Genetics** – anything related to an understanding of human ALS genetics
8. **Laboratory – therapeutic targeting of ALS**
 - Pre-clinical work attempting to modify disease leaving #9 to be.
 - Proteins, depending on the context
 - Medicine / chemicals if being tested on a mouse, or neuron in culture, or zebrafish
 - Motor neuron in culture being treated with a potential drug
9. **Laboratory – pathogenic understanding of ALS**
 - Including all omics, mechanistic and pre-clinical.
 - Proteins, depending on the context
 - Studying the proteomics of IPS (Induced Pluripotent Stemcells) derived motor neurons
 - Pre-clinical work aimed at understanding the disease pathogenesis at the cellular and molecular level
10. **Case reports** (only if a case report could not be classified in a distinct category)
11. **Other topic or unidentifiable**