PHARMA SUMMIT 24

Exploring Values of Healthcare

18th April 2024

Croke Park conference centre

Speaker Slides:

Prof Orla Hardiman, Beaumont Hospital

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MINDMAP MEDICAL MARKETING

Prof Orla Hardiman

Professor of Neurology, Head of the Academic Unit of Neurology and Academic Director of Trinity Biomedical Sciences Institute, and Consultant Neurologist at Beaumont Hospital.

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Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

"Precision Medicines in Rare Disease"

Bio:

Orla has been HSE Clinical Lead in Neurology from 2019-2023. She is a science and medical graduate from UCD and trained in Neurology in Boston. She is the Director of the National ALS Clinic at the National Neuroscience Centre, Beaumont Hospital Dublin Ireland, where she provides clinical care for over 80% of Irish patients with Amyotrophic Lateral Sclerosis (ALS).

She is the author of over 470 peer reviewed publications and editor of a textbook of Neurodegeneration. Her research group comprises over 5 individuals and her interests include the epidemiology, phenotype, biomarker discovery and genetics of ALS and related neurodegeneration.
She is Co- Chair of the European Network for Cure of ALS (ENCALS) and is editor in chief of the journal Amyotrophic Lateral Sclerosis and the Frontotemporal Degenerations, and a founder of the Neurological Alliance of Ireland and the Irish Brain Council. She is the Lead Investigator of the SFI funded Academic/ Industry Programme PRECISION ALS. She is the recipient of a number of international and national honours and awards including the AAN Sheila Essey Award in ALS Research and the International ALS Alliance Forbes Norris Award, the Tom Connor Distinguished Investigator Award in Neuroscience, The Trinity College Innovation Award, The SFI Researcher of the Year Award, and the HRB Research Impact Award.

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PRECISION MEDICINE in NEURODEGENERATION

PATHWAYS TOWARDS MORE EFFECTIVE THERAPEUTICS

Professor Orla Hardiman BSc, MB,MD,FRCPI, FTCD, MRIA
Head, Academic Unit of Neurology,Trinity College Dublin

COMMON FEATURES OF NEURODEGENERATION

- Progressive & irreversible human diseases
- Advancing age is a risk factor
- Variable in how condition presents
- Associated cognitive & behavioural impairment
- Mendelian inheritance in a percentage of cases

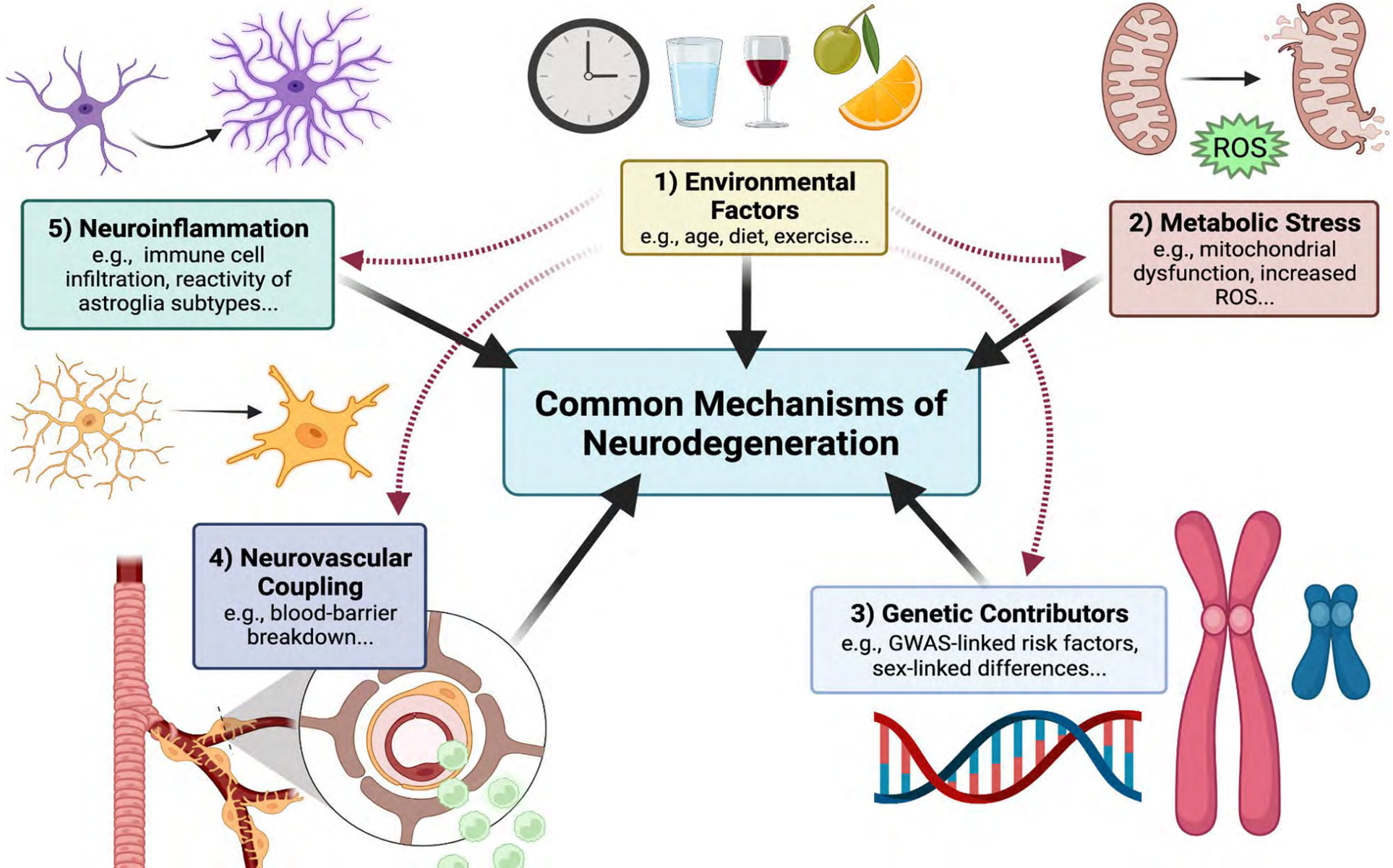
COMMON FEATURES OF NEURODEGENERATION

- Diverse clinical phenotypes may share similar genotypes
- Clinically similar phenotypes may be associated with a wide variety of genotypes
- Different neurodegenerative diseases (and neuropsychiatric disorders) may appear together within a family

CLINICAL OVERLAP OF COMMON NEURODEGENERATIONS

- Frontotemporal dementias with ALS
- Frontotemporal Dementia/Progressive Supranuclear palsy/ corticobasal degeneration
- ALS Parkinsons Dementia complex of Guam
- Dementia in Parkinsons Disease (40%)
- Parkinsonism in Alzheimers Disease (30%)
- Psychosis in FTD , ALS
- Psychosis in Parkinsons Disease
- Chorea in ALS / Fasciculations in Huntingtons Disease
- Spinocerebellar Ataxia 2 and ALS

FACTORS DRIVING PATHOGENESIS



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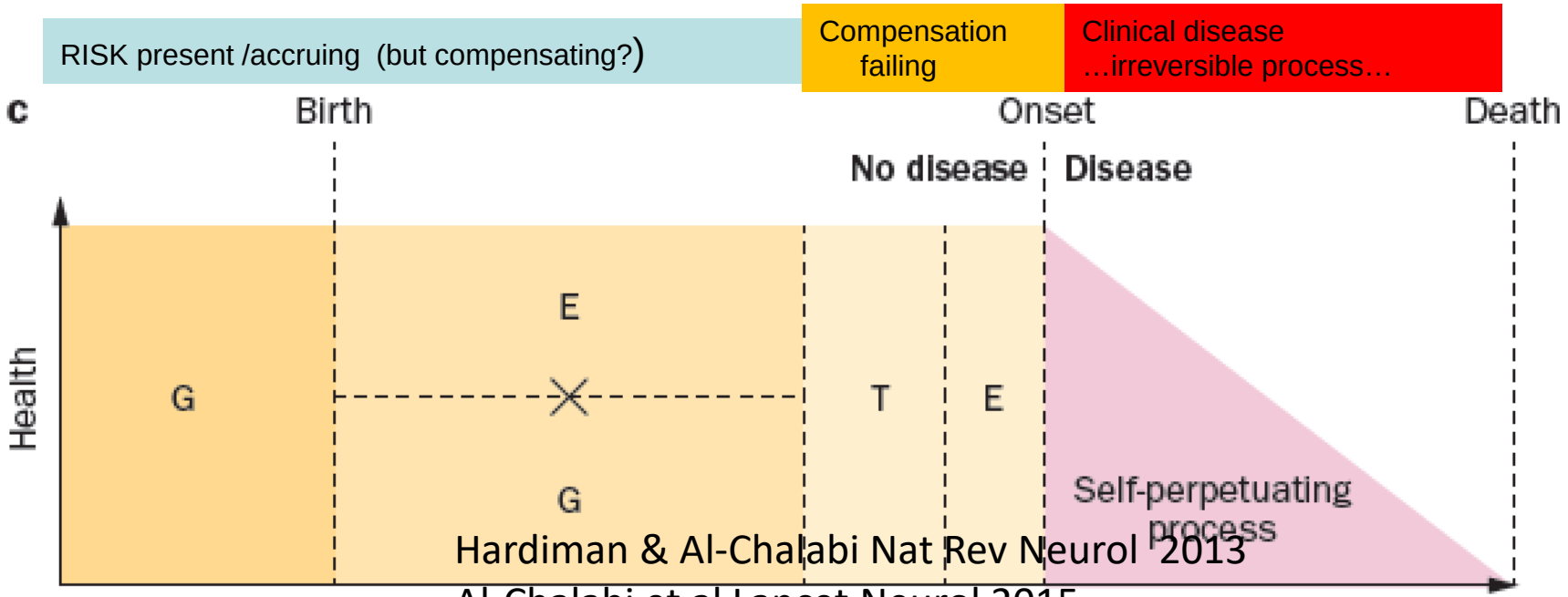
AMYOTROPHIC LATERAL SCLEROSIS AS A MODEL NEURODEGENERATION

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

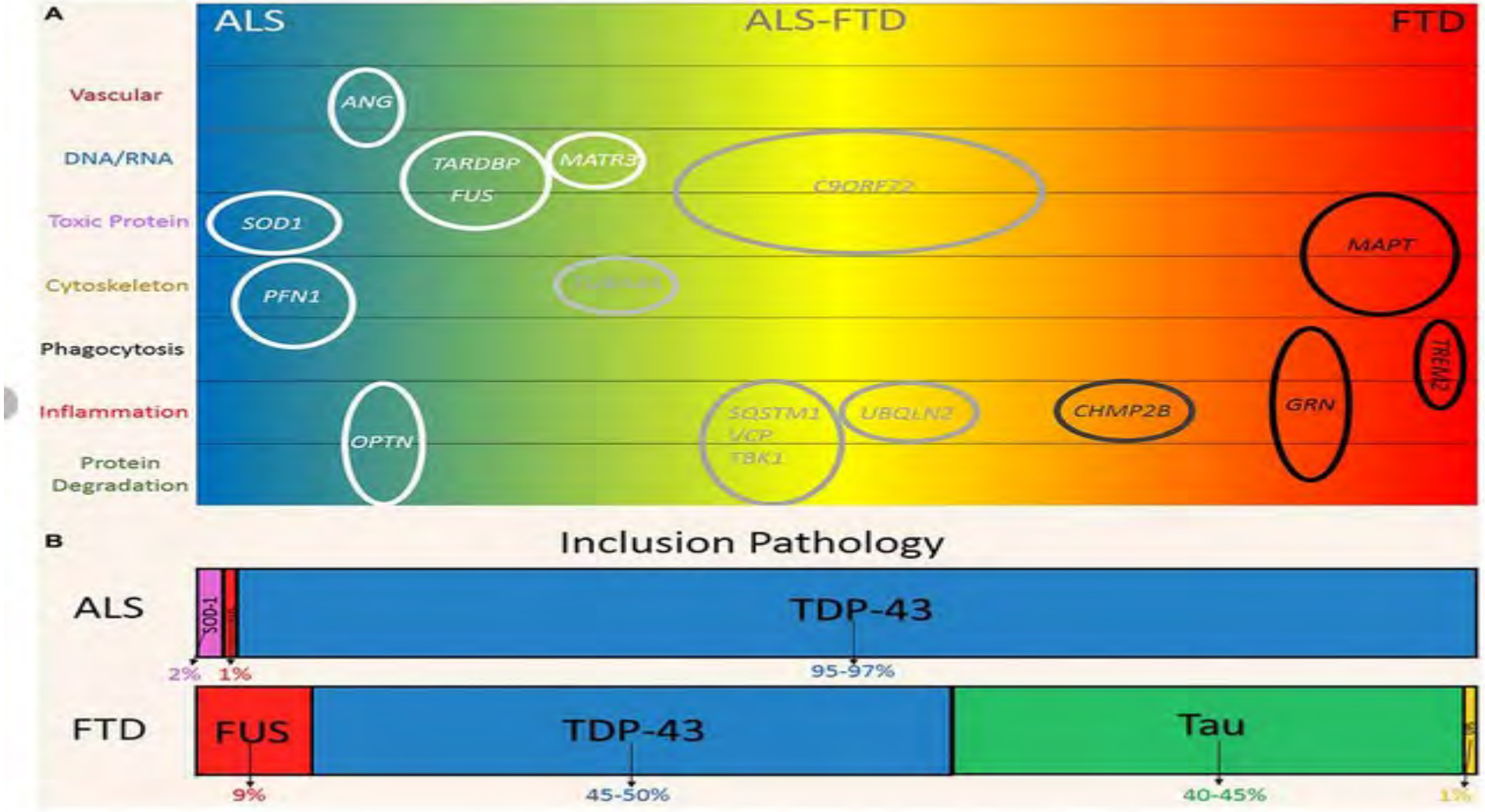
- Upper and lower motor neuron degeneration, cognitive & behavioural change
- Incidence of 3.1 per 100,000: Lifetime risk is 1:350
- Progressive, incurable and terminal
- Overlaps with Frontotemporal dementia (FTD – “Picks” disease)
- 50% fatality within 30 months of symptom onset

DISEASE PATHOGENESIS:
GENE /ENVIRONMENT INTERACTION + TIME
6 Step Hypothesis in ALS



Hardiman & Al-Chalabi Nat Rev Neurol 2013
Al-Chalabi et al Lancet Neurol 2015
Chio et al Neurology 2018

OVERLAP BETWEEN ALS and FTD



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CLINICAL OUTCOME MEASUREMENT

ALSFRS-R

48 point scale in 4 domains
Bulbar
Gross Motor
Fine Motor
Respiratory

ALS Functional Rating Scale

1. Speech
- Normal speech processes
- Detectable speech disturbance
- Intelligible with repeating
- Speech combined with nonvocal communication
- Loss of useful speech

2. Salivation
- Normal
- Slight but definite excess of saliva in mouth; may have nighttime drooling
- Moderately excessive saliva; may have minimal drooling
- Marked excess of saliva with some drooling
- Marked drooling; requires constant tissue or handkerchief

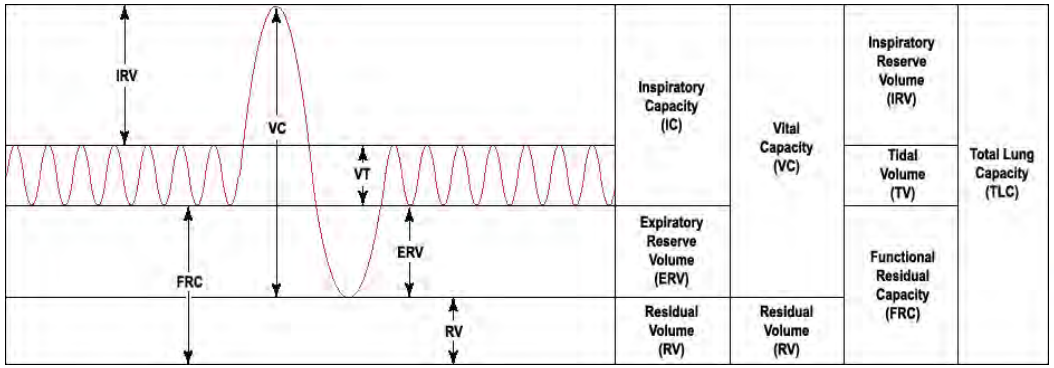
3. Swallowing
- Normal eating habits
- Early eating problems-occasional choking
- Dietary consistency changes
- Needs supplemental tube feeding
- NPO (exclusively parenteral or enteral feeding)

4. Handwriting
- Normal
- Slow or sloppy; all words are legible
- Not all words are legible
- Able to grip pen but unable to write
- Unable to grip pen

5. Cutting food ☐ with gastrostomy
- Normal
- Somewhat slow and clumsy, but no help needed
- Can cut most foods, although clumsy and slow; some help needed
- Food must be cut by someone, but can still feed slowly
- Needs to be fed

RESPIRATORY

Vital Capacity



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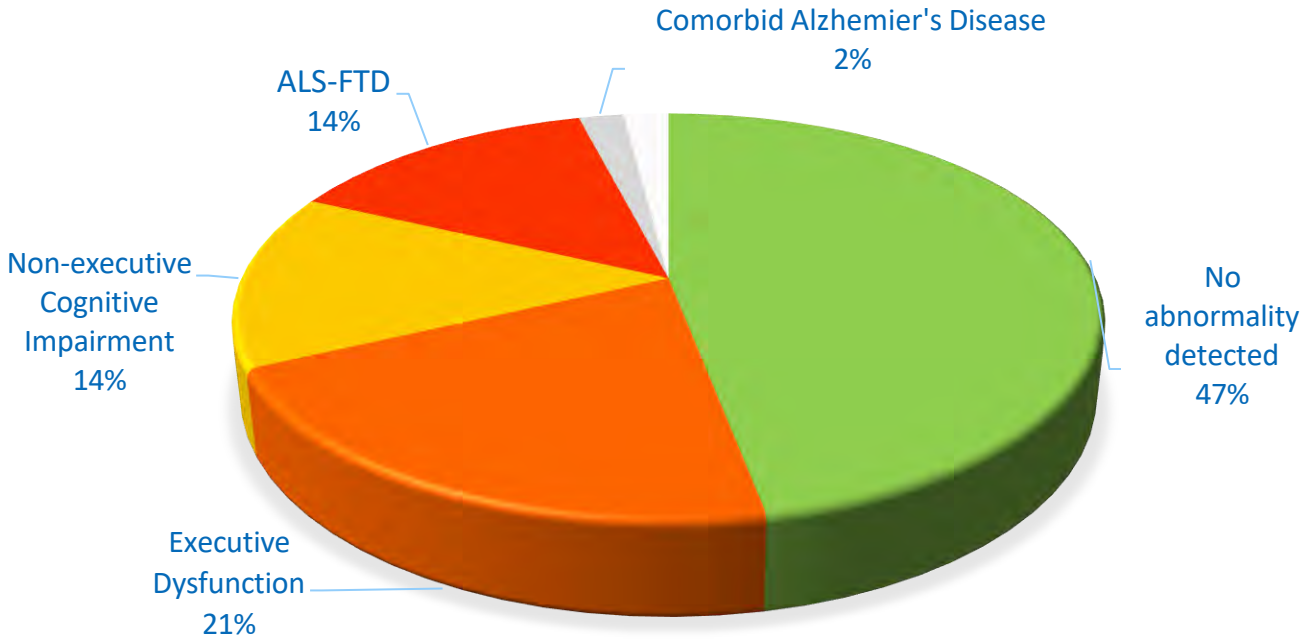
RESEARCH PAPER

The syndrome of cognitive impairment in amyotrophic lateral sclerosis: a population-based study

Julie Phukan,[1] Marwa Elamin,[1] Peter Bede,[1] Norah Jordan,[2] Laura Gallagher,[2]
Susan Byrne,[1] Catherine Lynch,[1] Niall Pender,[2] Orla [illegible][1,3]

J Neurol Neurosurg Psychiatry 2012;**83**:102—108. doi:10.1136/jnnp-2011-300188



BEHAVIOURAL CHANGES

Factor Loading	Superordinate Classification of Dysfunction	Cognitive/ Behavioural Dysfunction
1	Initiation (Apathy)	Loss of interest; inability to plan; impulsiveness; decreased sex drive; lack of appropriate embarrassment.
2	Adherence to social norms	Emotional changes; social disinhibition; social seeking.
3	Social Engagement	Social withdrawal; distractibility; cognitive rigidity.
4	Interpersonal Engagement	Aggressiveness; irritability; Increased lability; hypersensitivity to stimuli.
5	Self-regulation	Reduced concern for hygiene; change in food preferences; new onset repetitious/obsessive behaviour.

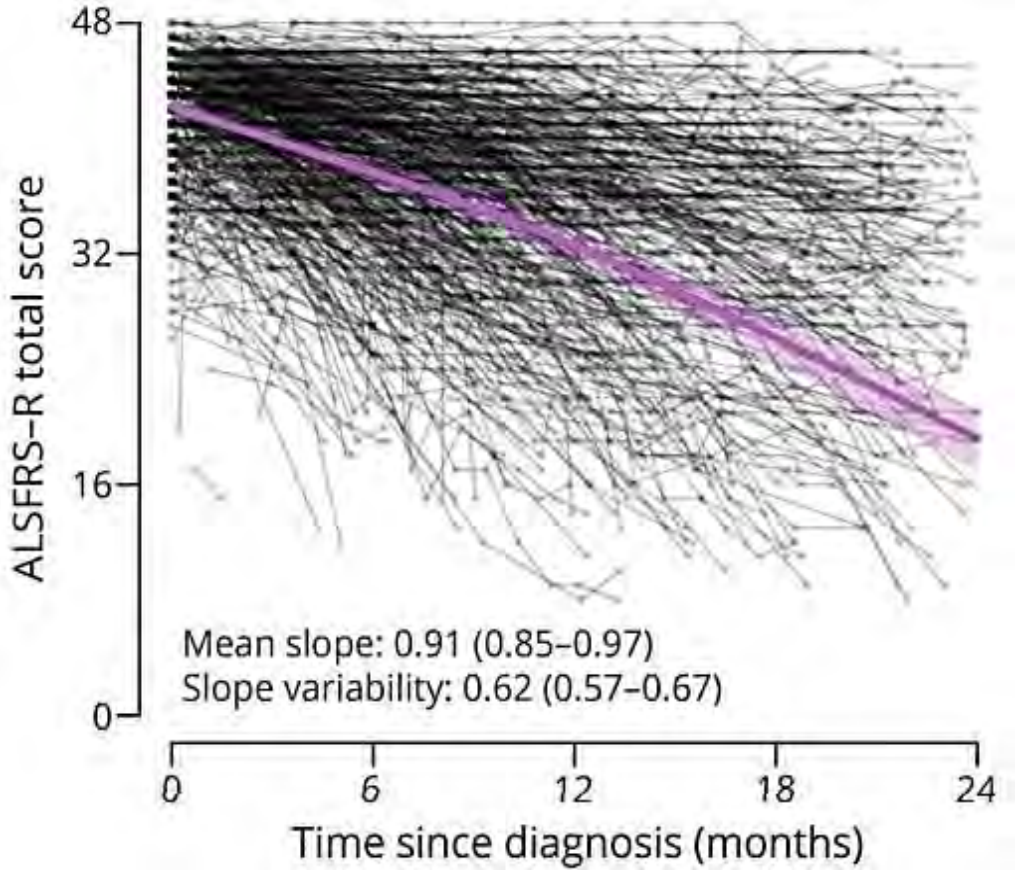
Elamin M et al; Identifying behavioural changes in ALS: Validation of the **Beaumont Behavioural Inventory** (**BBI**). Amyotroph Lateral Scler Frontotemporal Degener. 2017 Feb;18(1-2):68-73

ALS PROGRESSION IS NOT UNIFORM IN HUMANS

Variable symptoms and severity

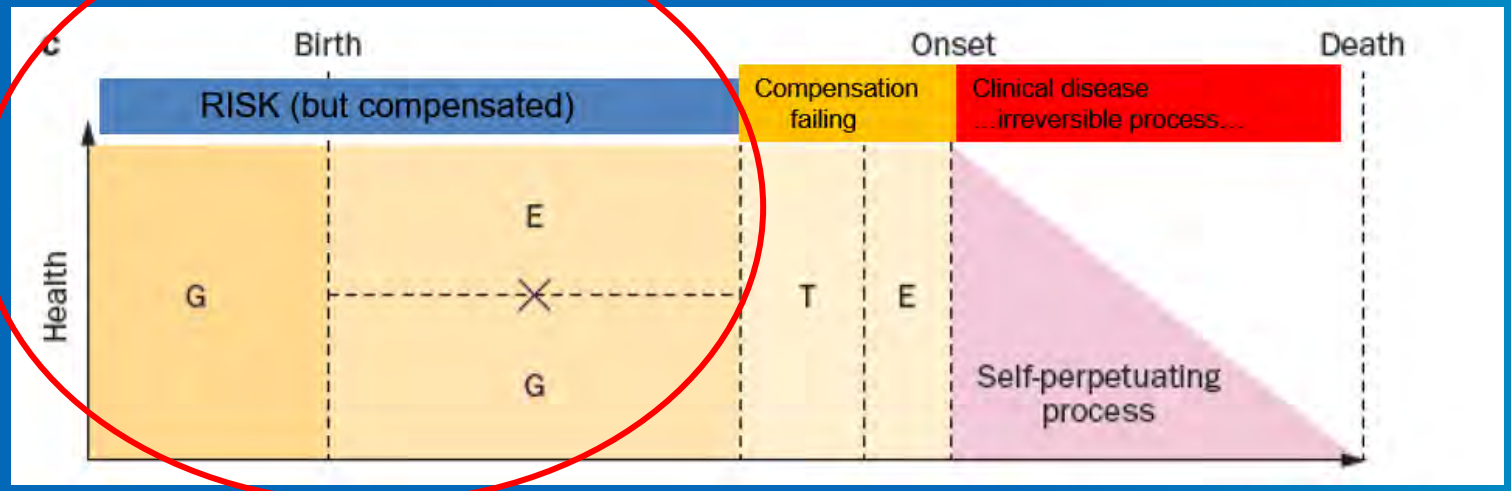
PROGNOSTIC FACTORS:

- Cognitive change (ignored by ALSFRS!)
- Site of onset
- Rate of decline (as measured by the ALS Functional Rating Scale (ALSFRSR)

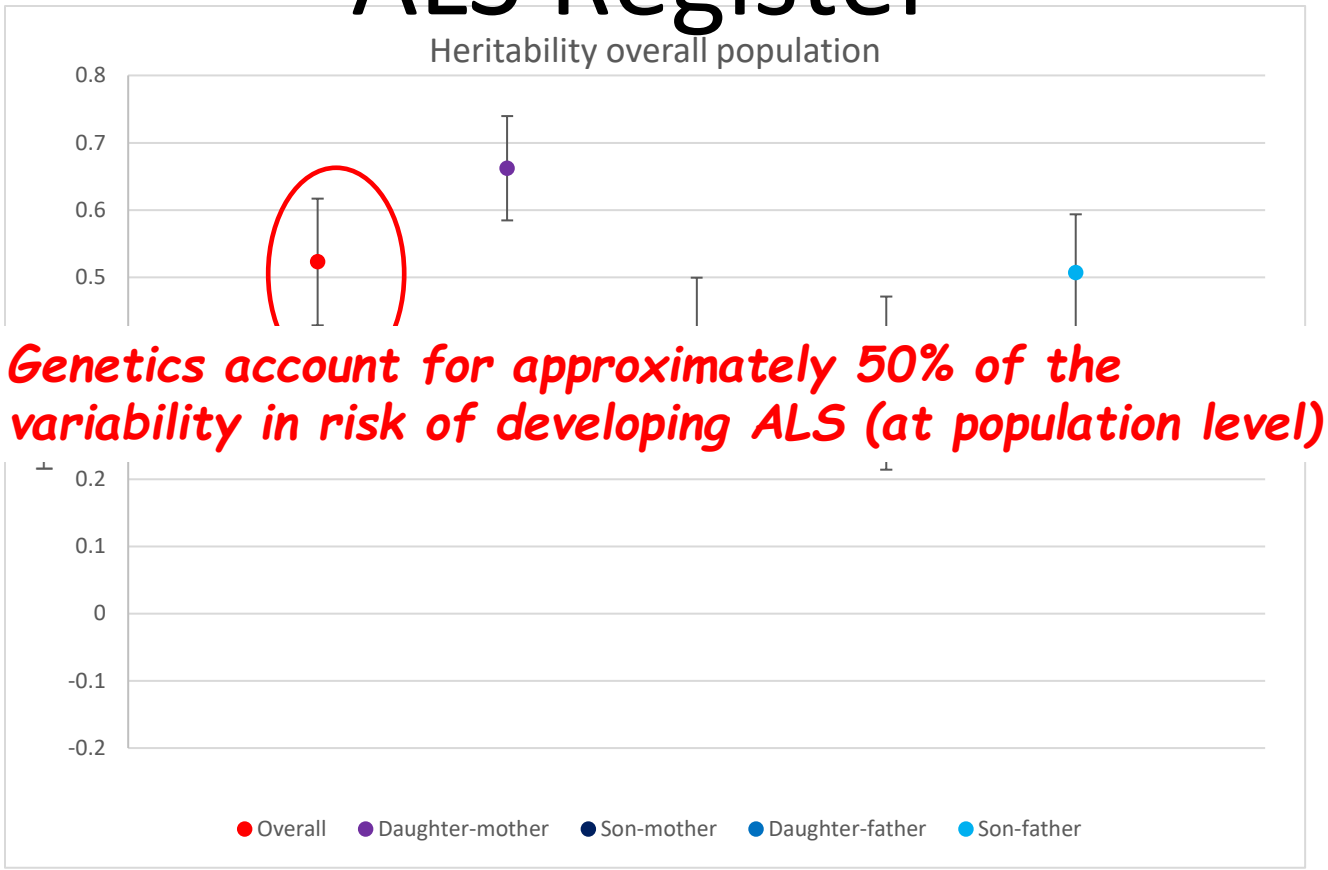


van Eijk et al., 2019

FINDING THE "CAUSE(S)" of ALS



Heritability Estimates using the Irish ALS Register



Genetics account for approximately 50% of the variability in risk of developing ALS (at population level)

Research

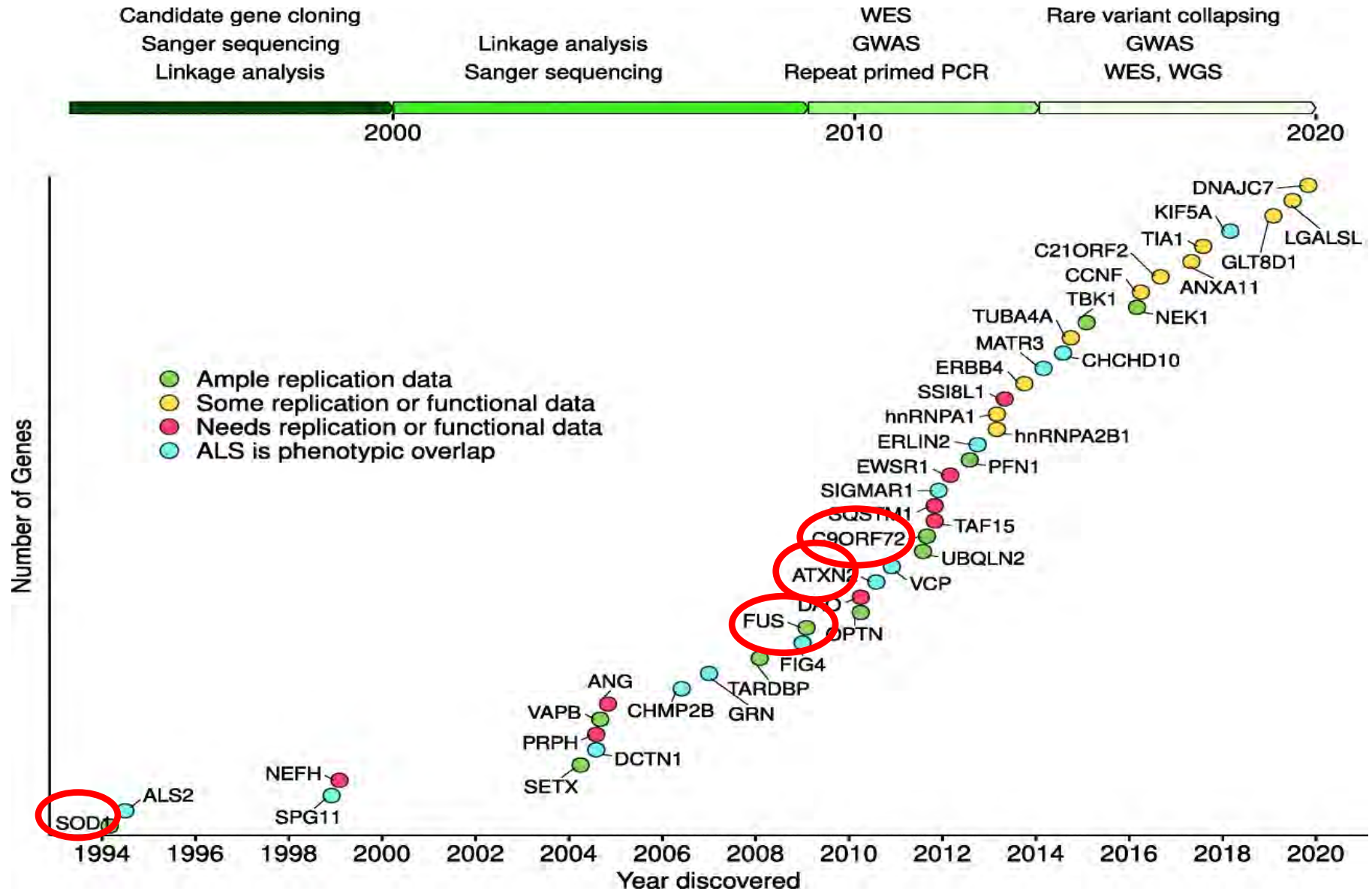
JAMA Neurology | Original Investigation

JAMA Neurol. 2019 Nov 1;76(11):1367-1374.

Lifetime Risk and Heritability of Amyotrophic Lateral Sclerosis

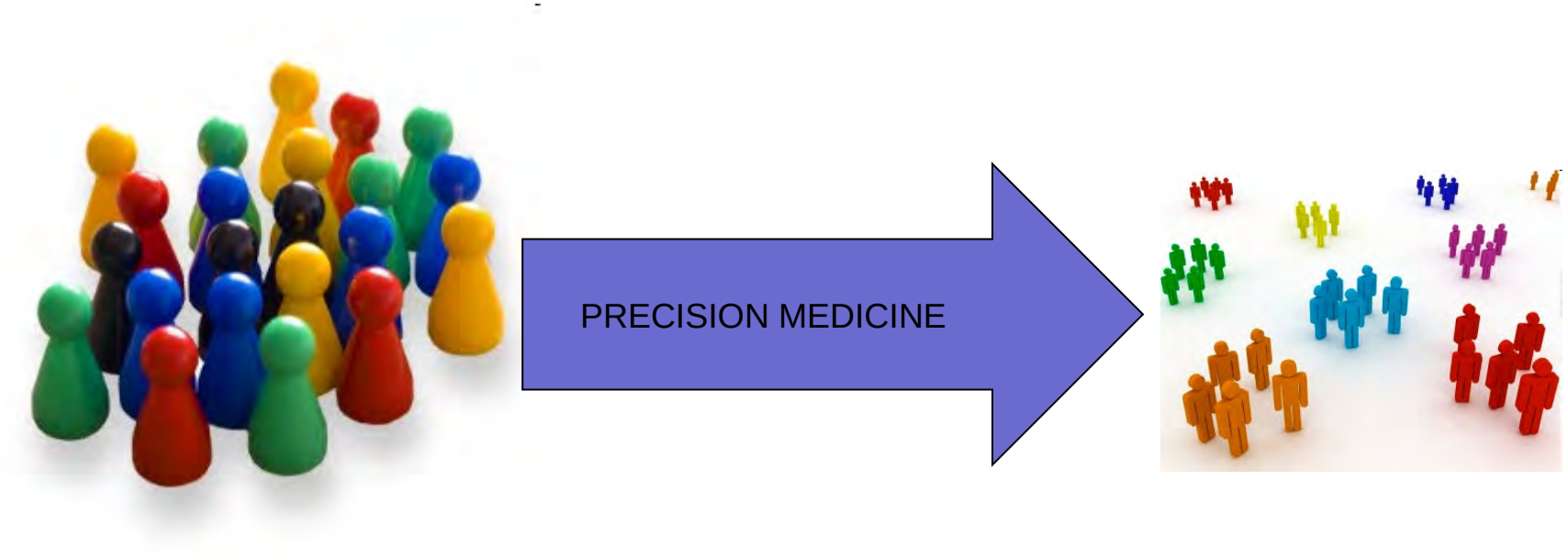
Marie Ryan, MRCPI; Mark Heverin, MSc; Russell L. McLaughlin, BSc, HDip, PhD; Orla Hardiman, BSc, MD, FRCPI

MAJOR GENES ASSOCIATED WITH ALS



Gregory, J.M et al . *Curr Genet Med Rep* **8,** 121–131 (2020)

ALS IS MORE THAN ONE CONDITION



..A FEW CONSIDERATIONS in ALS...

- Disease pathobiology indicates that ALS **is a syndrome rather than a singular condition**
- Not all Familial ALS is the same- different pathogenesis & different phenotypes
- Risks for developing ALS may differ from factors that drive disease progression – this should determine how we target treatments (but often does not)
- Disease "onset" is best viewed as an arbitrary definition bounded by clinical phenomenology
- **We do not fully understand the underlying biological processes leading to disease onset, clinical presentation or progression**

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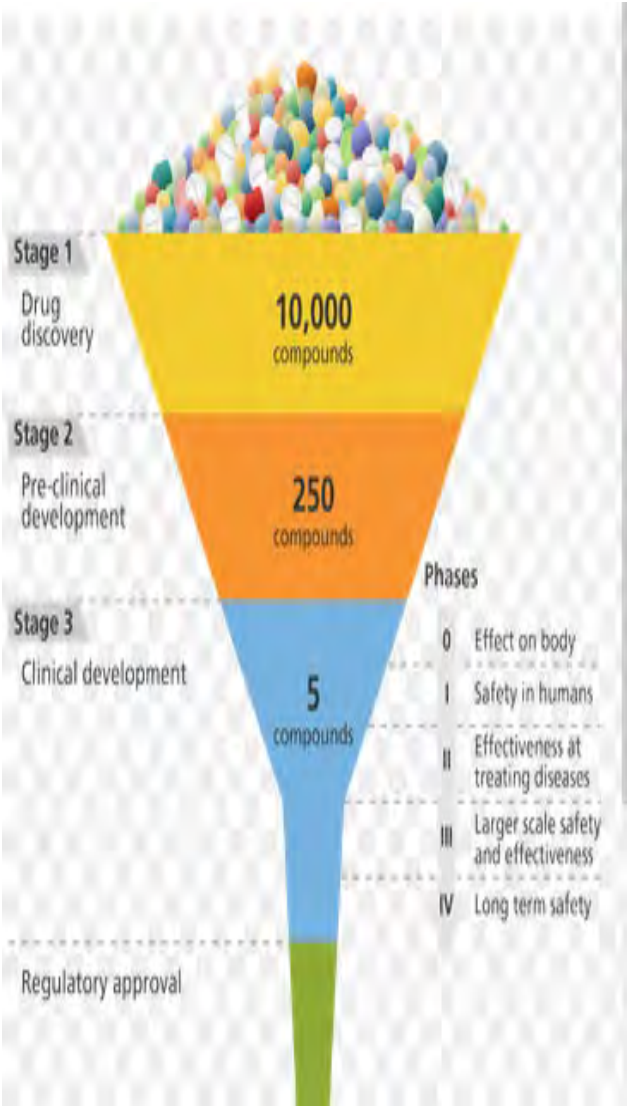
FINDING EFFECTIVE TREATMENTS

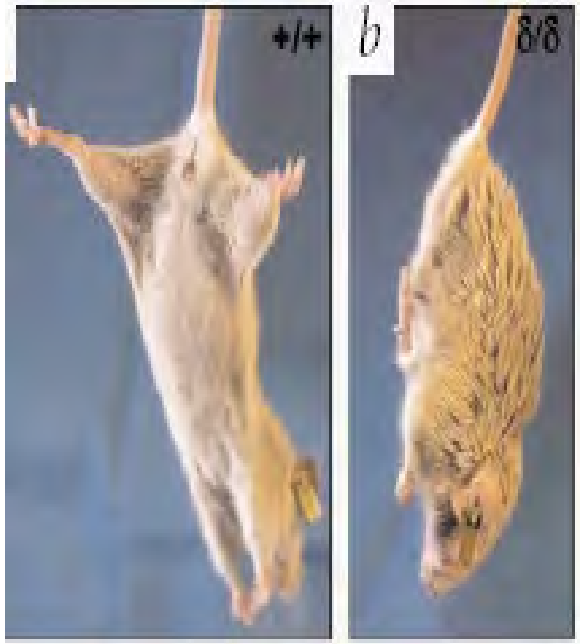
…(NOTWITHSTANDING)….

CLINICAL TRIALS

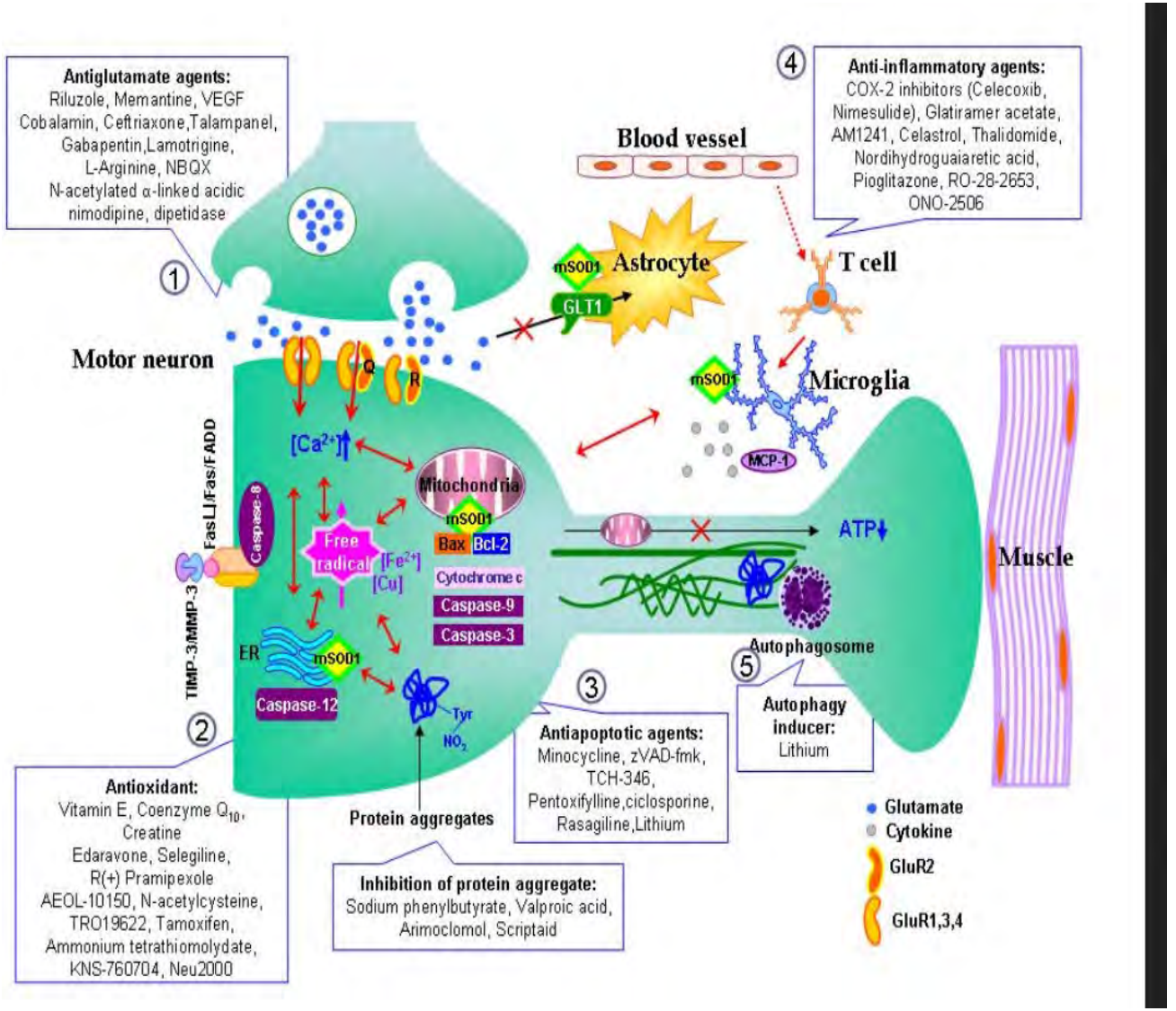
- PRE-CLINICAL Drug screening, efficacy, safety, toxicity
- PHASE 1 : Safety
  Healthy controls and /or patients with disease
- PHASE 2: Safety & Tolerability
  Patients with disease, toxicity & dose finding
- PHASE 3: Pivotal
  Submission to regulatory authorities
- PHASE 4: Post marketing



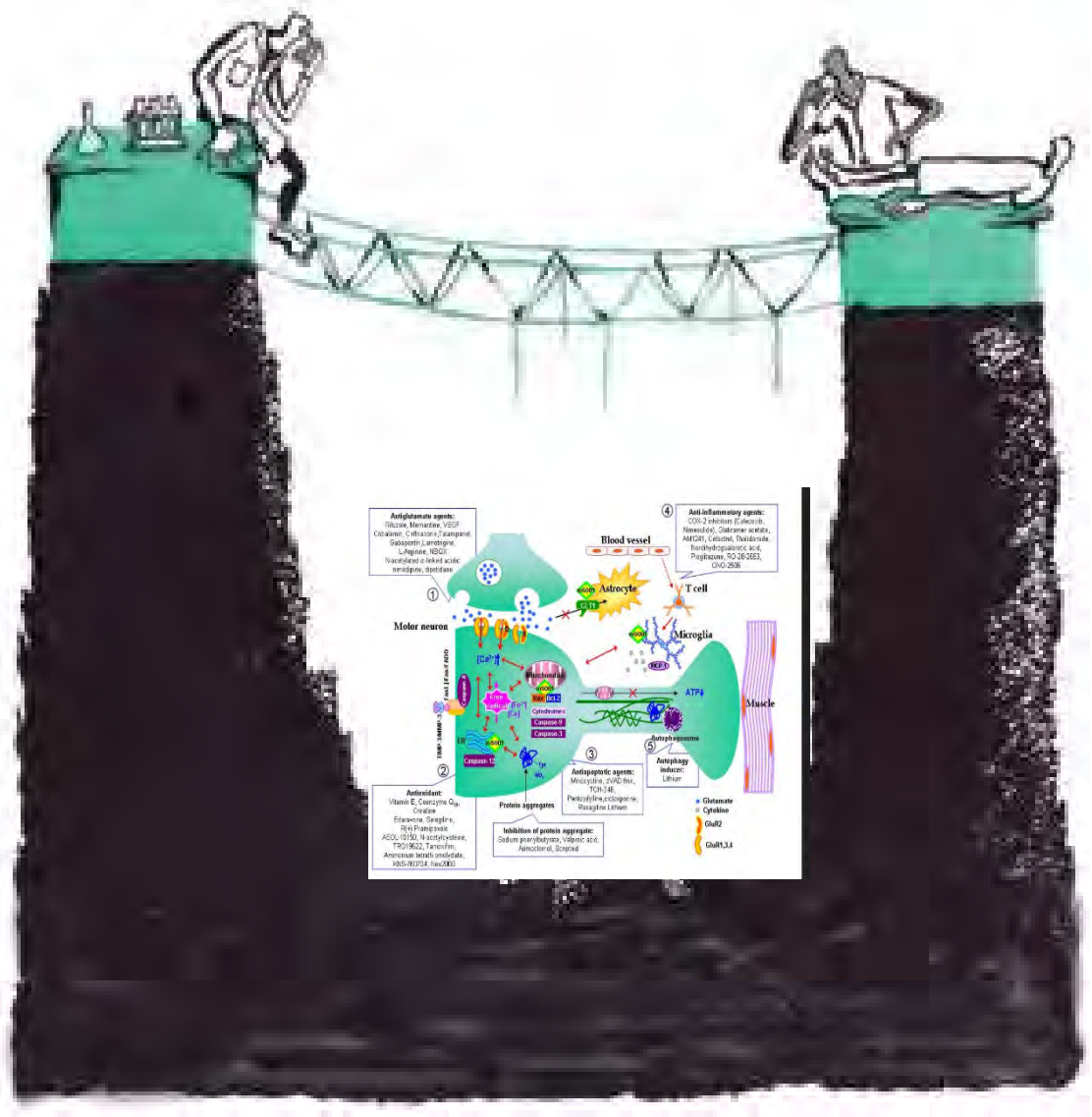
LESSONS FROM ANIMAL MODELS



SOD1 mouse



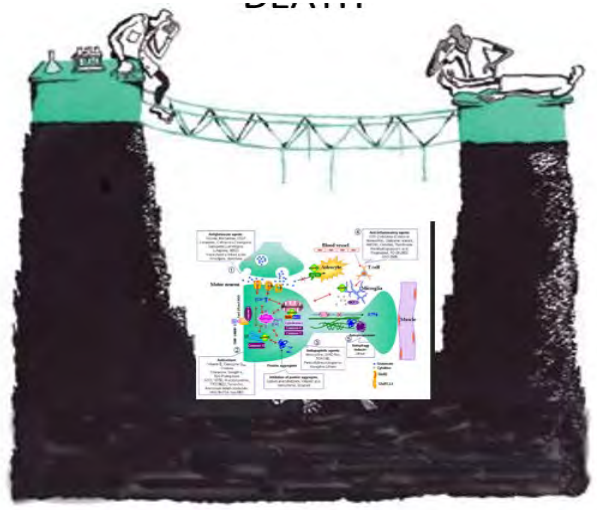
MANY DRUGS FAIL IN THE “VALLEY OF DEATH”



PRE-CLINICAL PROBLEMS

- Animal models useful but limited…
  - Anatomy differs
  - Genetic background important: “strain effect”
  - Gender Differences
  - Copy number effects
  - Small studies, Poor replication

HUMAN PROBLEMS



..>100 negative human trials…..

- Drug didn’t work (poor translation from mouse to human)
- Many treatment paradigms are designed based on biological factors that confer risk… disease progression is likely a different pathogenic process
- Bad clinical trial design
- Not clear that the drug did what it was supposed to do
- Effect may be confined to subgroups of patients

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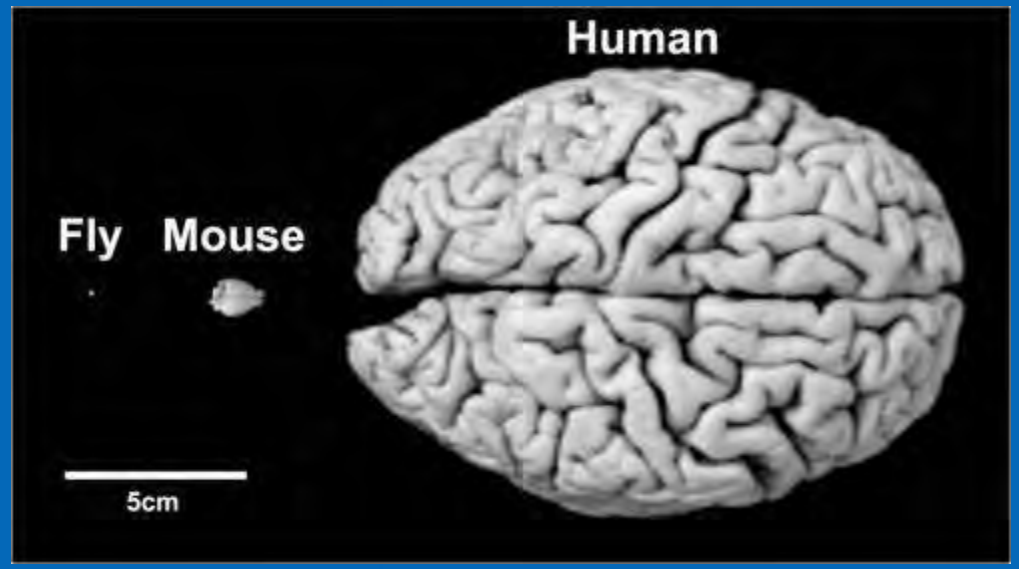
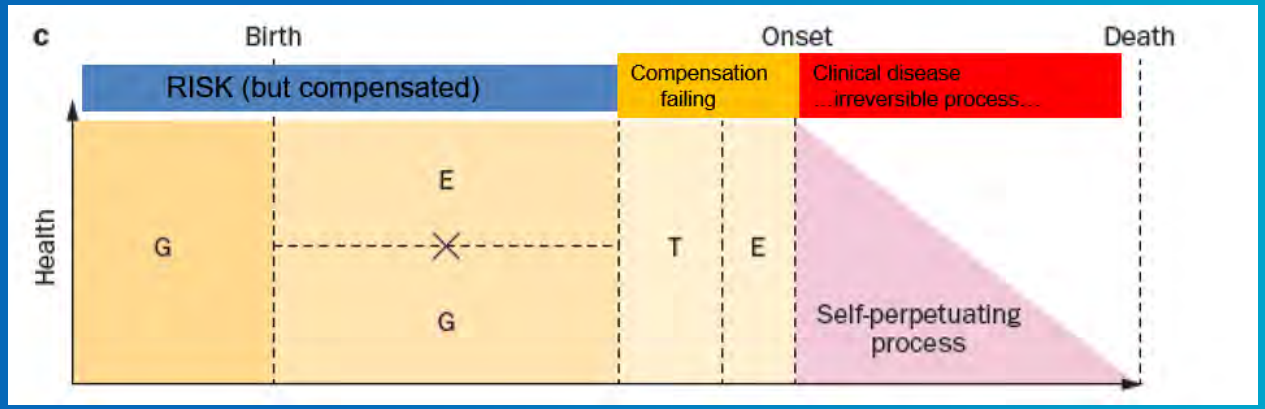
WHY HAVE TREATMENTS FAILED?





LESSONS LEARNED ..We need…

- EARLIER DIAGNOSIS and EXPERT MANAGEMENT IN SPECIALIST CLINICS
- BETTER DRUGS : Discriminate between Risk and Progression
- BETTER TRIAL DESIGN
- BETTER PATIENT SELECTION –(PRECISION MEDICINE)
  - Not all patients are the same
- BETTER OUTCOME MEASURES
- BETTER BIOMARKERS

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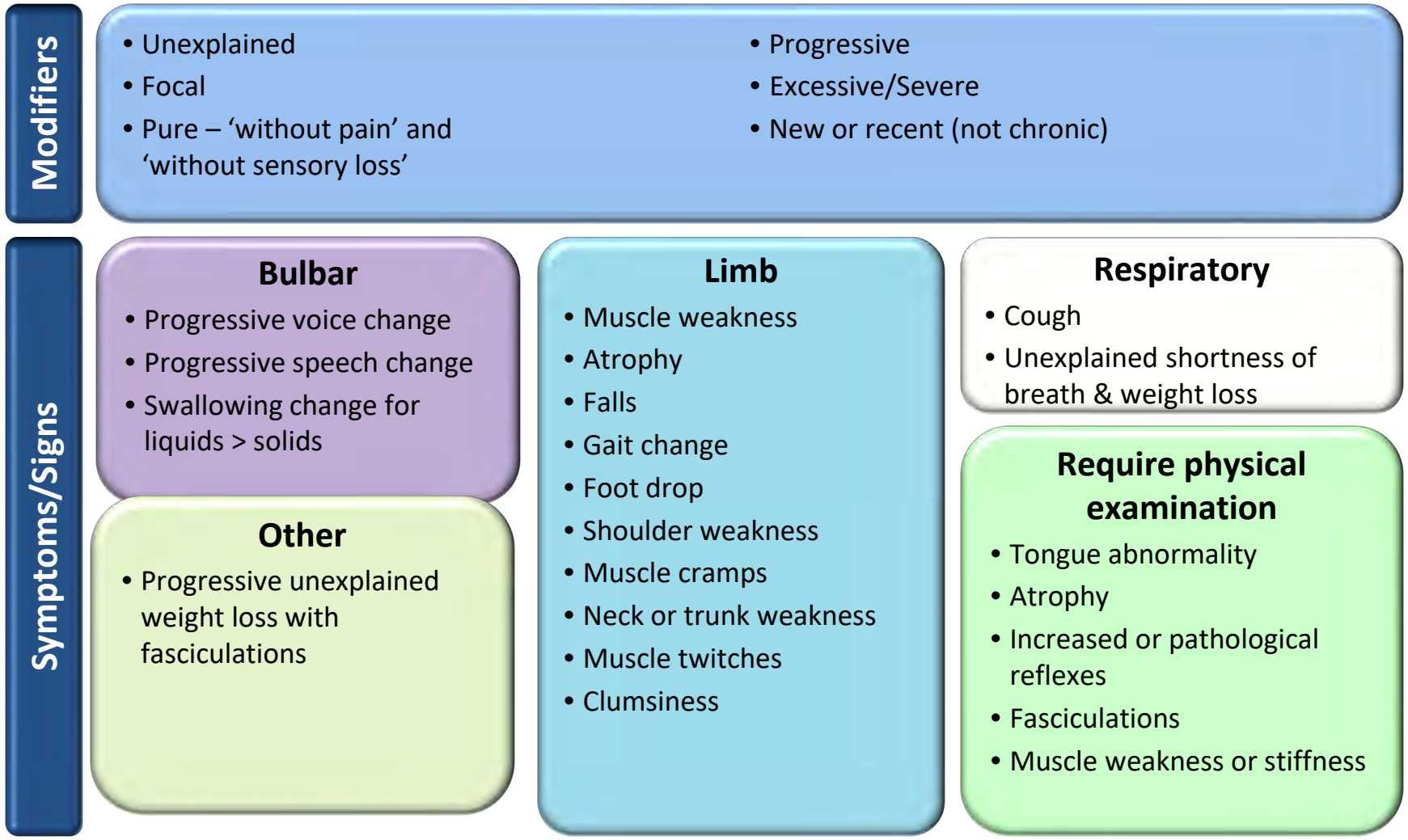
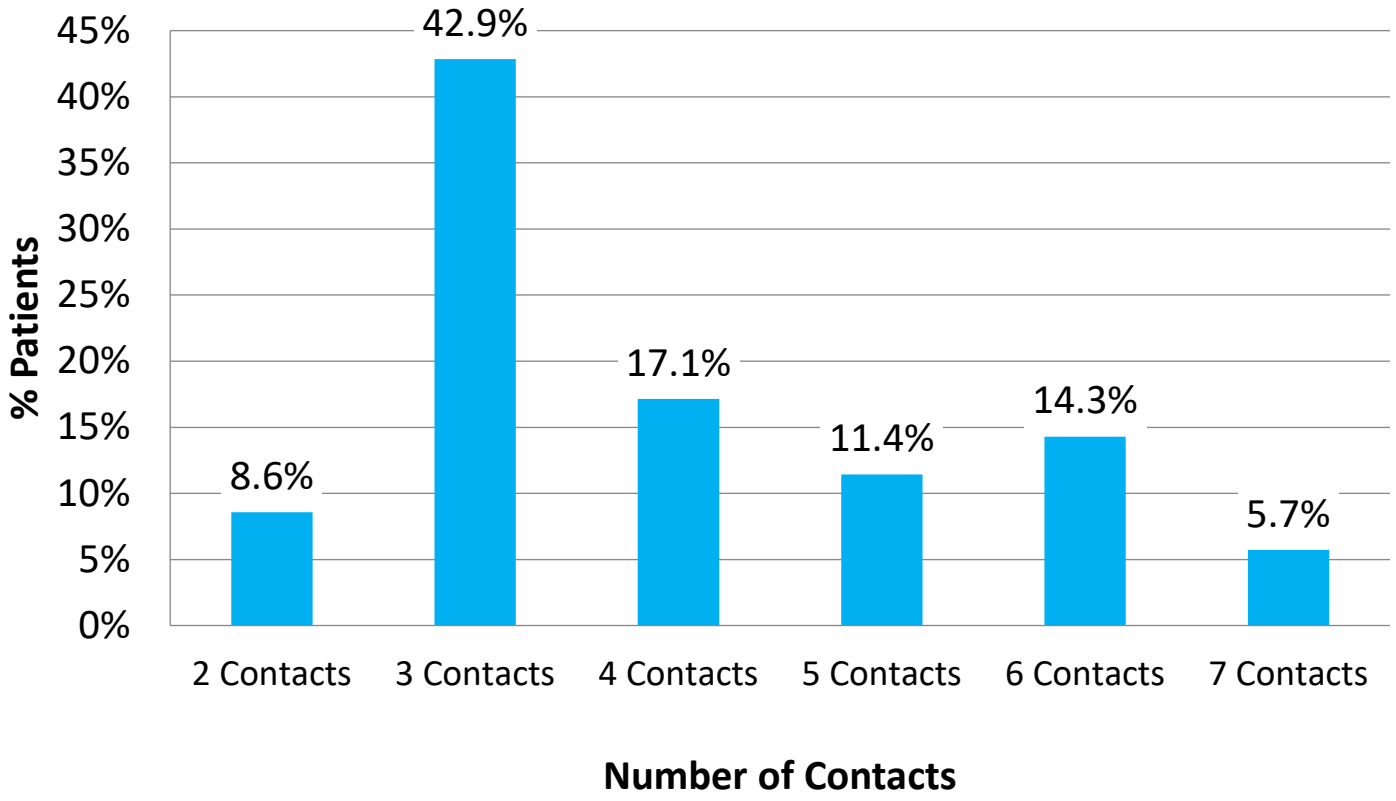
RED FLAGS: IS THIS ALS??



ALS DIAGNOSIS: CONTACTS WITH HCPs PRIOR TO DIAGNOSIS



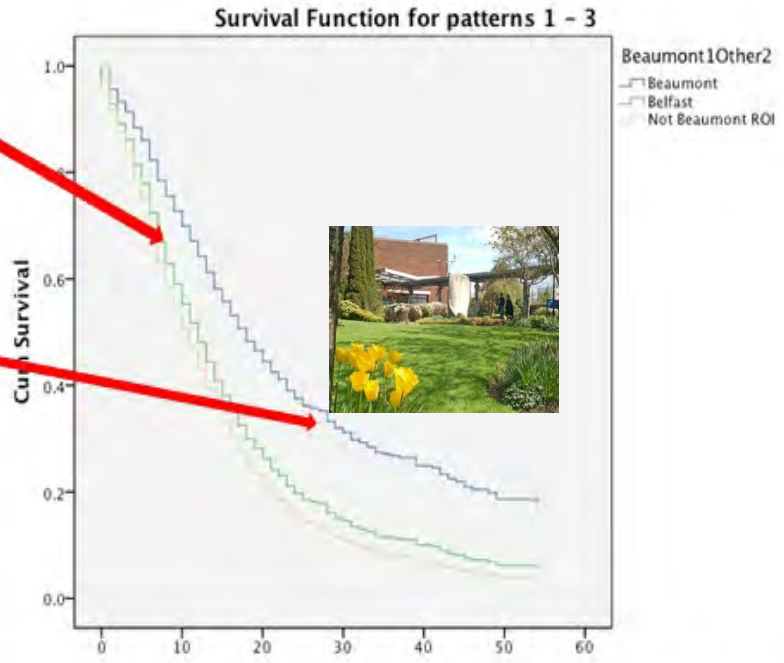
Galvin el al BMC Health Serv Res 2015

TIMELINES

Figure 2 Timeline –First Symptom Timeline

	A. First Symptom to GP Visit	B. First Symptom to First Neuro	C. First Symptom to Diagnosis	4. First Symptom to MDC
	● ----- 5.5 mths----->			
	● ---------- 11.2 mths---------->			
	● ---------- 16.0 mths ---------->			
Months	● ---------- 19.1 mths ---------->			
Mean	5.5	11.2	16.0	19.1
Median	3.0	8.0	13.0	14.6
SD	6.8	8.4	9.5	11.6
Range	0 - 25	0 - 35	4 - 48	8 - 54
N	31	33	35	35

COMPARISON BETWEEN MDC, DEVOLVED CARE & GENERAL CARE



Rooney et al JNNP 2015

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GENOME BASED THERAPIES FOR KNOWN MUTATIONS (True “Precision Medicine”)

ANTI SENSE OLIGONUCLEOTIDES

Drug / Company	Target	Phase	Mechanism of Action and Comments	Clinical Trial Number
Tofersen Biogen	SOD1	3 (completed)	• Antisense oligonucleotide against SOD1 • The trial did not meet its primary endpoint in 2021, but several positive biomarker results emerged • Open-label extension trial on-going.	NCT02623699
ION-363 IONIS	FUS	3	• Antisense oligonucleotide against FUS • Safety, efficacy, pharmacokinetics and pharmacodynamics trial • Estimated completion in 2024.	NCT04768972
ION-541 IONIS	ATXN2	2	• Antisense oligonucleotide against ataxin 2 • Safety and pharmacokinetics trial • Estimated completion in 2023.	NCT04494256
BIIB-078 Biogen	C9ORF72	1/2	• Antisense oligonucleotide against C9orf72 • Safety and pharmacokinetics trial • Completion in 2021 - results awaited.	NCT03626012
WVE-004 WAVE LIFE SCIENCES	C9ORF72	1/2	• Antisense oligonucleotide against C9orf72 • Safety, pharmacokinetics and pharmacodynamics trial • Estimated completion in 2023.	NCT04931862

RJ Mead ——— PJ Shaw *Nature Reviews Drug Discovery 2022 (Invited Review)*

ALS TRIALS IN IRELAND(2023-24)

TRICALS Towards a cure

- PHASE 1: Genomic (PRECISION MEDICINE APPROACH)
- WAVE ASO – C9orf72 FAILED
- ANQUR Stathmin2 In progress
- FUSION ASO – FUS In progress
- PHASE 2
- DAZALS Dazucorilant- corticoid receptor antagonist: In progress
- CARDINALS Utreloxastat – oxidative stress: In progress
- MERIDIAN Complement inhibition FAILED
- PHASE 3
- ADORE Oral edaravone FAILED
- PHOENIX Phenylbutazone & TUDCA FAILED
- TUDCA (Horizon funded investigator led study) FAILED
- LIGHTHOUSE Triumeq- anti HERV2 In progress
- MAGNET Lithium in carriers of U13A at risk alleles In progress

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  ..Enrolment criteria, stratification parameters, biomarkers, duration, endpoints…
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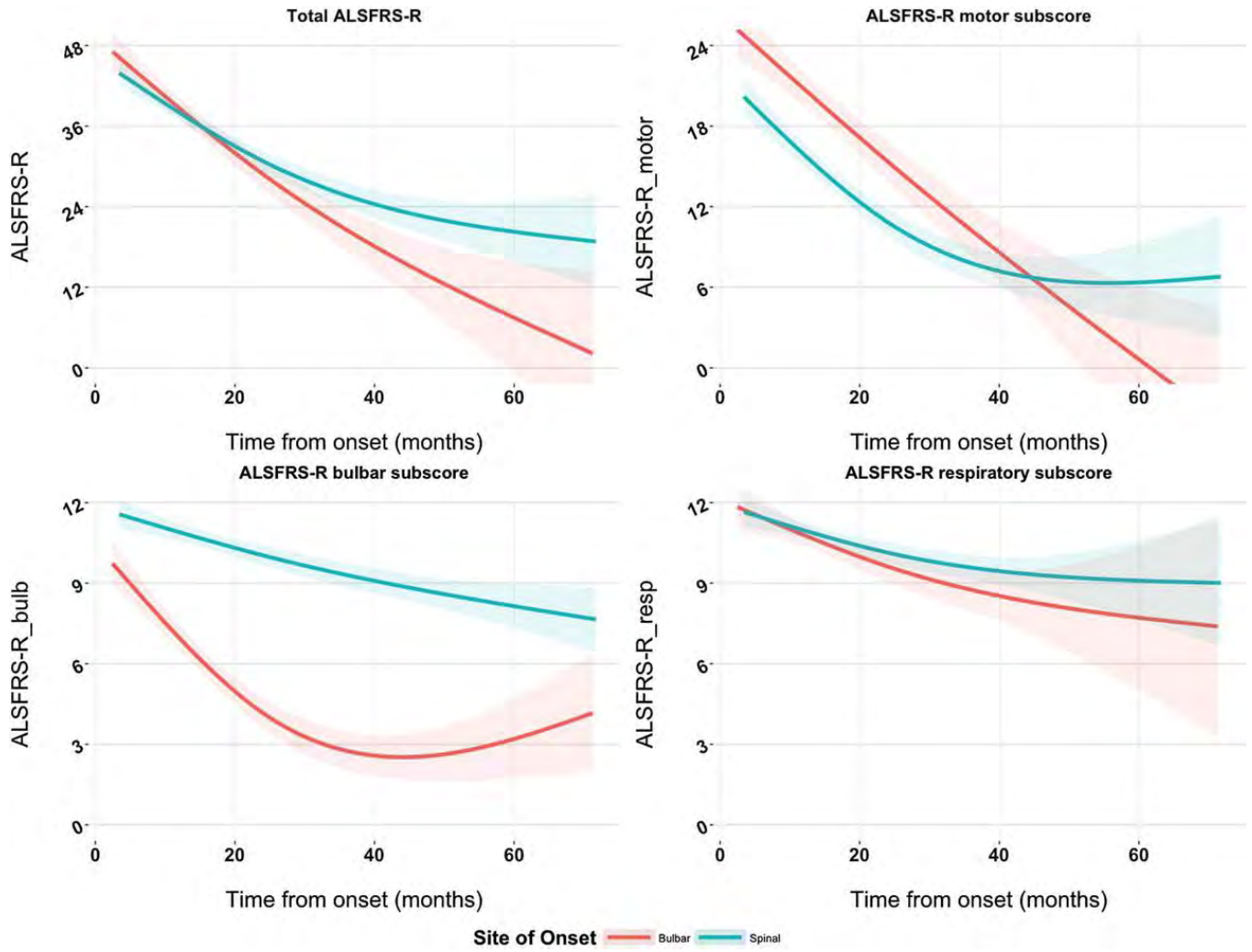
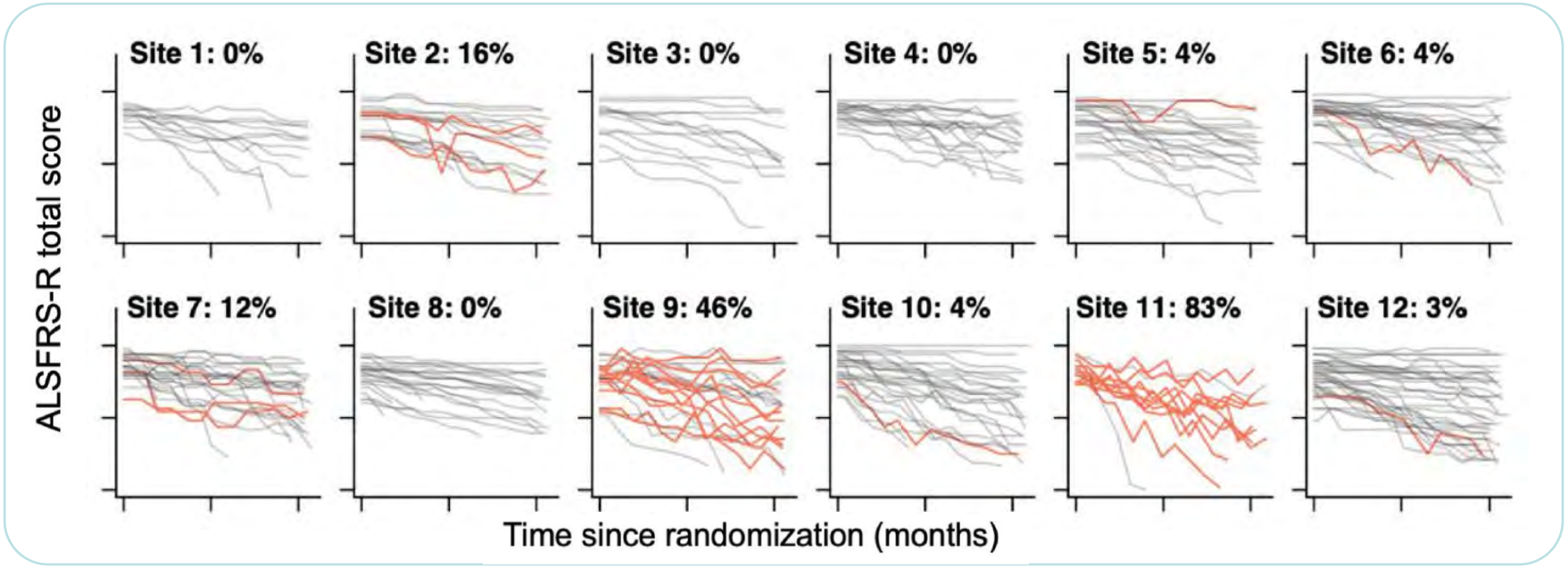
PROBLEMS WITH CLINICAL SCALES : ALS FRSR IS NOT LINEAR!

Graph of longitudinal total ALSFRS-R and ALSFRS-R subscores.



James Rooney et al. J Neurol Neurosurg Psychiatry 2017;88:381-385

RELIBABILITY OF ALSFRSR ACROSS SITES ENGAGED IN CLINICAL TRIALS



Per centre, the number of patients with **a 5-point or more increase in ALSFRS-R** total score are highlighted in red. ALSFRS-R, Bakers JNE, et al. *Amyotroph Lateral Scler Frontotemporal Degener.* 2021; doi:

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POSSIBLE QUANTITATIVE OUTCOME MEASURES

Advance neurophysiology

Quantitative EEG, EMG

Digital technologies

Home monitoring devices

REGULATORY ISSUES

Over the years, a number of suggestions have been made to innovate the design of clinical trials

Clinical trials have remained relatively conservative, especially when initiated by industry

Deviating from trial guidelines could affect regulatory acceptability

Amendments of the current regulatory guidelines are required to successfully adopt innovation

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nature reviews neurology

https://doi.org/10.1038/s41582-023-00891-2

Review article

Check for updates

Biomarkers in amyotrophic lateral sclerosis: current status and future prospects

Roisin McMackin[1,2], Peter Bede[2,3,4], Caroline Ingre[5,6], Andrea Malaspina[7] & Orla Hardiman[2,8]

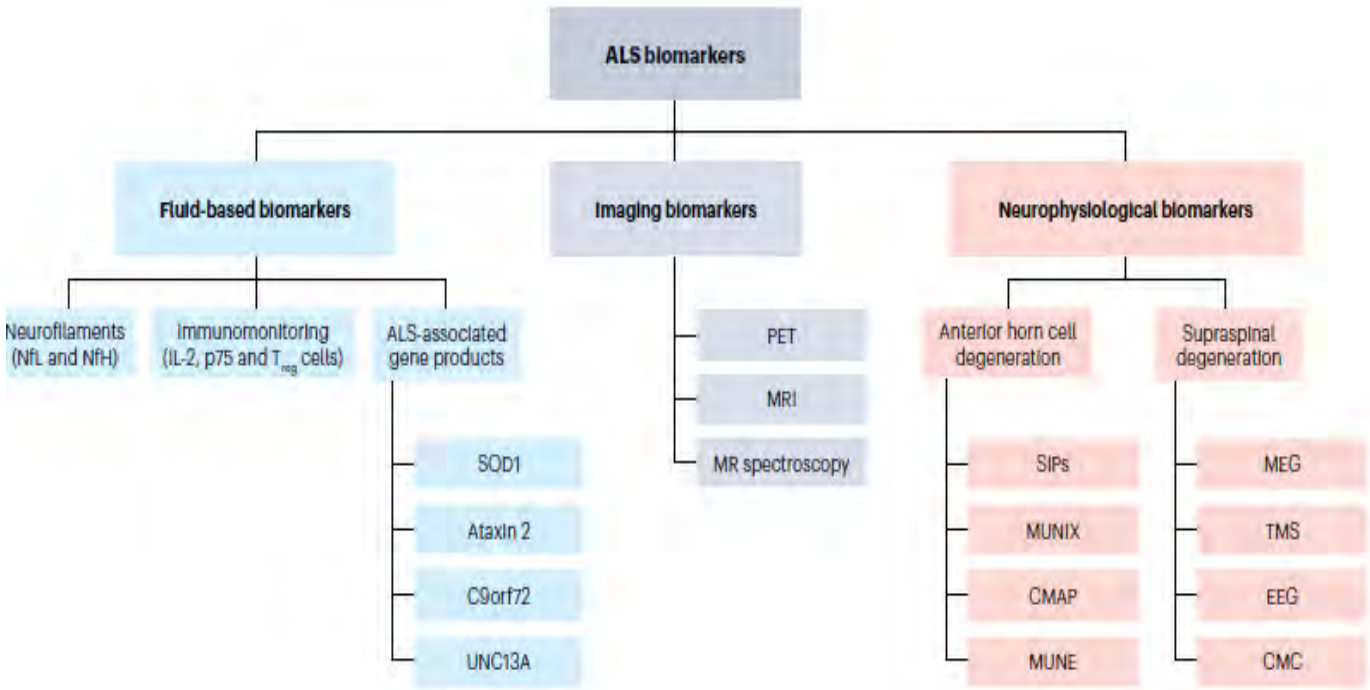
Biomarkers: general principles

Requirements

- Sensitive: can identify a disease or process.
- Specific: can discriminate between diseases and/or processes.
- Reproducible: repeated assessments of the same target produce the same result.
- Practical: cost-effective, ethical and applicable in the clinic.

Categories

- Diagnostic: can discriminate the disease of interest (in this case, amyotrophic lateral sclerosis) from other conditions and enable early diagnosis.
- Categorical: defines disease subgroups with different characteristics and can be used to select individual patient cohorts.
- Prognostic and predictive: defines what will happen during the disease course and can be used for patient stratification in clinical trials.
- Pharmacodynamic: demonstrates target engagement.



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NEXT STEPS..

PRECISION ALS

An International Academic Industry Partnership built on Scientific Collaboration and Mutual Trust

www.precisionals.ie

OBJECTIVES

Enable electron integration of prospective multimodal and multi-sourced clinical, imaging, neuro-electric-signalling, genomic, and biomarker datasets: 6000 cases over 3 years

Develop novel ICT solutions towards data integration, interoperability, and analytics

Generate new knowledge to drive translational and clinical research in neurodegeneration

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CONCLUSIONS

Eponymous classification of disease is an over-simplification

Multiple subcohorts exist with differing pathogenic processes and disease trajectories

In ALS, early success with SOD1 anti-sense oligonucleotides point to future genomic therapies , but there are many caveats

Data driven approaches will help to tailor future treatments to patient subcohorts

ACKNOWLEDGEMENTS

Current Team (PIs)
MIRIAM GALVIN
BAHMAN NASSEROLESLAMI
RUSSELL MCLAUGHLIN
DARA MELDRUM
DEIRDRE MURRAY
PETER BEDE
LARA MCMANUS
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