Understanding disease age and leveraging this concept in clinical trial design:

Disease progression modeling in familial frontotemporal dementia

Adam Staffaroni, PhD
Associate Professor

University of California, San Francisco (UCSF)
Department of Neurology, Memory and Aging Center
Weill Institute for Neurosciences

FPI
FTD Prevention Initiative

Disclosures

- Research support from NIH, the Association for Frontotemporal Degeneration & ALS Association, the Bluefield Project to Cure FTD, and the Rainwater Charitable Foundation

- Personal compensation for advisory boards or consulting from ADDF, Alector, Aviado Bio, CervoMed, Passage Bio, Prevail Therapeutics/Eli Lilly, Takeda, and Vesper Bio.

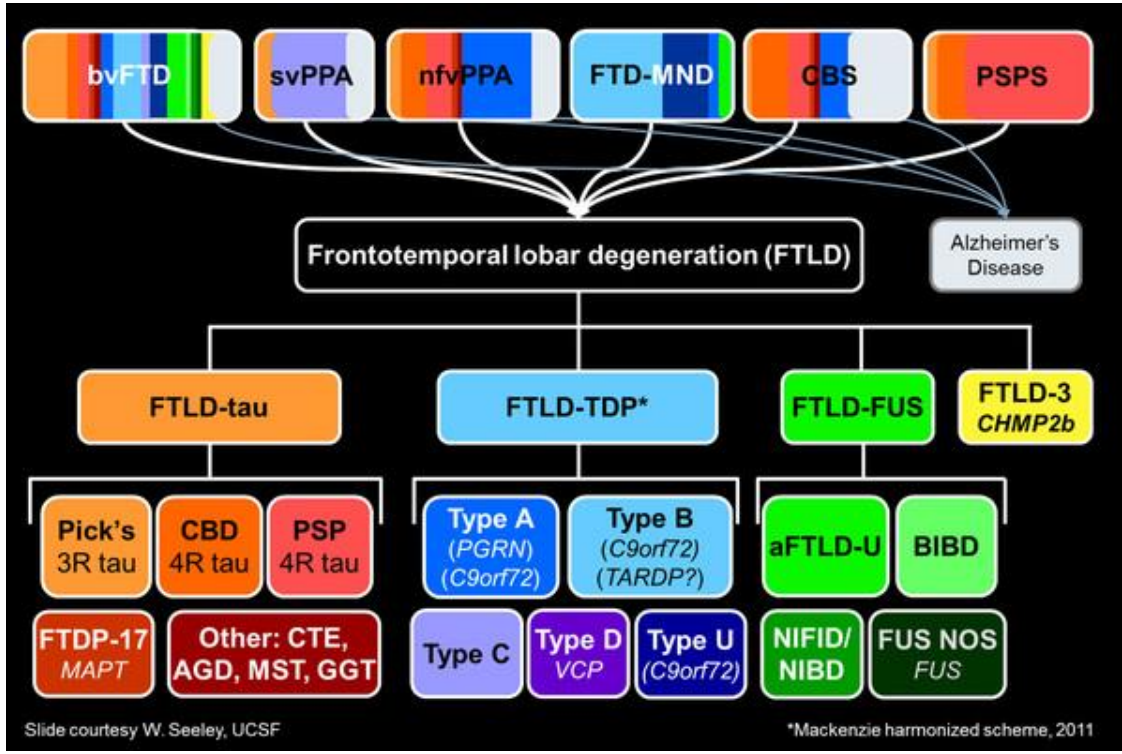
- Licensing fees for smartphone tasks

FPI
FTD Prevention Initiative

What is FTD?

Frontotemporal dementia is a fatal neurodegenerative disease that is as common as AD in those under age 65.

- **Behavior/personality:**
  - Behavioral Variant FTD (bvFTD)
- **Language:**
  - Semantic (svPPA) and Nonfluent Variants (nfvPPA) of Primary Progressive Aphasia
- **Motor:**
  - Progressive Supranuclear Palsy Syndrome (PSP-S) & Corticobasal Syndrome (CBS)
  - FTD-ALS

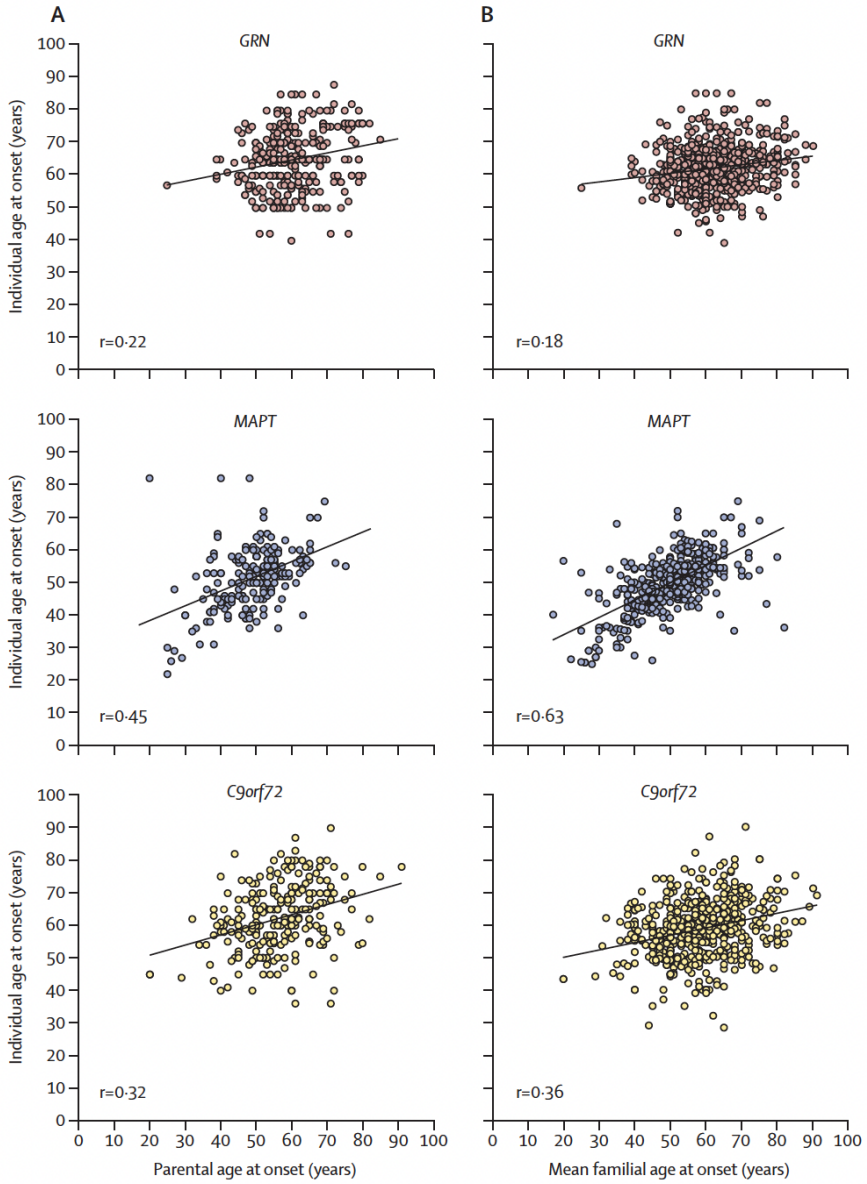


FTLD: several pathological entities that produce varied clinical phenotypes (FTD)

Familial FTLD

10-40% of cases are familial

- Mostly commonly bvFTD but range of clinical presentations
- Autosomal dominant with high penetrance
- Most caused by 3 genes: *MAPT*, *GRN*, and *C9orf72*
- Early age of onset
  - *GRN*: 61
  - *MAPT*: 50
  - *C9orf72*: 58



FPI
FTD Prevention Initiative

Coyle-Gilchrist, 2016 *Neurology*; Rohrer, 2009 *Neurology*; Moore et al., 2020 *Lancet Neuro*

Importance of FTLD clinical trials

- No approved disease modifying therapies and minimal symptomatic treatments
- Relevant to sporadic diseases of tau and TDP-43
  - Example: Alzheimer's disease, ALS, LATE
- Younger age = less frequent co-pathology
- Rapid progression = shorter duration trials

FPI
FTD Prevention Initiative

Boxer, 2013 *Alz & Dem;* Boxer, 2017 *Lancet Neuro;* Staffaroni, 2019 *Brain*

The interest in FTLD therapeutics has rapidly expanded, **but enrollment challenges remain.**

- Rare disease
- Heterogenous phenotypes
- Short disease duration
- Variable age of onset

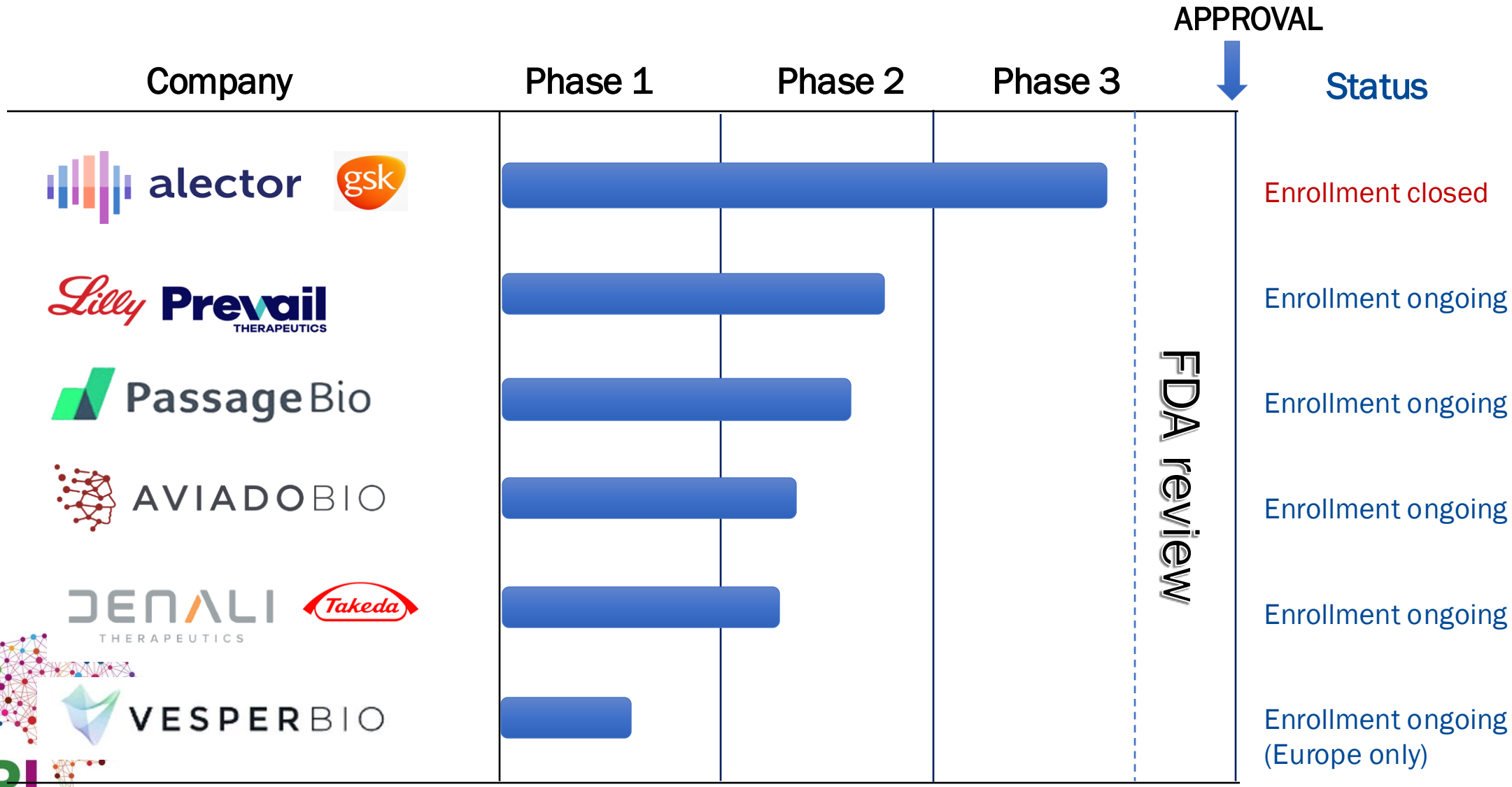
Table 2: Potential Therapeutics in FTLD

	Mechanism	Indication	Phase	ClinicalTrials.gov Identifier	Status
Potential therapies for *C9ORF72* Expansion					
BIIB078	ASO	ALS-*C9ORF72*	1	NCT03626012	ongoing
Potential therapies for *GRN* Haploinsufficiency					
Nimodipine	Calcium channel blocker	FTLD-*GRN*	1	NCT01835665	negative[95]
FRM-0334	HDAC inhibitor	FTLD-*GRN*	2	NCT02149160	negative
AL001	Anti Sortilin Antibody	FTLD-*GRN*	1/2	NCT03987295	ongoing
PR006	AVV9-based gene therapy	FTLD-*GRN*			pending
Potential Therapies for FTLD-tau					
ABBV-8E12 (C2N-8E12)	Anti-tau antibody (N-terminus)	PSP	2	NCT03413319	negative
BIIB092 (BMS-986168)	Anti-tau antibody (N-terminus)	PSP	2	NCT03068468	negative
		CBD, nfvPPA, TES, *MAPT*	1	NCT03658135	terminated
LY3303560	Anti-tau antibody (N-terminus)	AD	2	NCT03518073	active
RO 7105705 (RG 6100)	Anti-tau antibody (N-terminus)	AD	2	NCT03289143	active
UCB0107	Anti-tau antibody (Mid domain)	PSP	1	NCT04185415	active
JNJ-63733657	Anti-tau antibody (Mid domain)	AD	1	NCT03375697	unavailable
BIIB076	Anti-tau antibody (Monomer & filament)	AD	1	NCT03056729	active
AADvac1	Tau vaccine	nfvPPA	1	NCT03174886	active
ACI-35	Tau vaccine	AD	1		unavailable
Davunetide	Microtubule Stabilizations	PSP	2/3	NCT01110720	negative[101]
TPI-287	Microtubule Stabilizations	AD, PSP, CBD	I	NCT01966666, NCT02133846	negative[102]
ASN001	o-GlcNACase inhibitor	-	1	-	-
Salsalate	Tau acetylation inhibition	PSP	1	NCT02422485	negative
TRx0237 (LMTx)	Tau aggregation inhibition	bvFTD	3	NCT03446001	negative
AZP2006	Tau aggregation inhibition	PSP	2	NCT04008355	active
Lithium Carbonate	Glycogen synthase kinase inhibitor	bvFTD	2	NCT02862210	

Ljubenkov & Boxer, 2021 *Adv Exp Med Biol*

FPI
FTD Prevention Initiative

Six companies are currently testing experimental drugs for FTD-*GRN*



FPI
FTD Prevention Initiative

Slide courtesy of Laura Mitic, Bluefield Project

FTD Prevention Initiative (FPI)

Effort spearheaded by Drs. Adam Boxer and Jonathan Rohrer to uniform clinical trial standards in f-FTLD and develop a harmonized MDS (PIs: Hesse & Staffaroni)

FPI
FTD Prevention Initiative

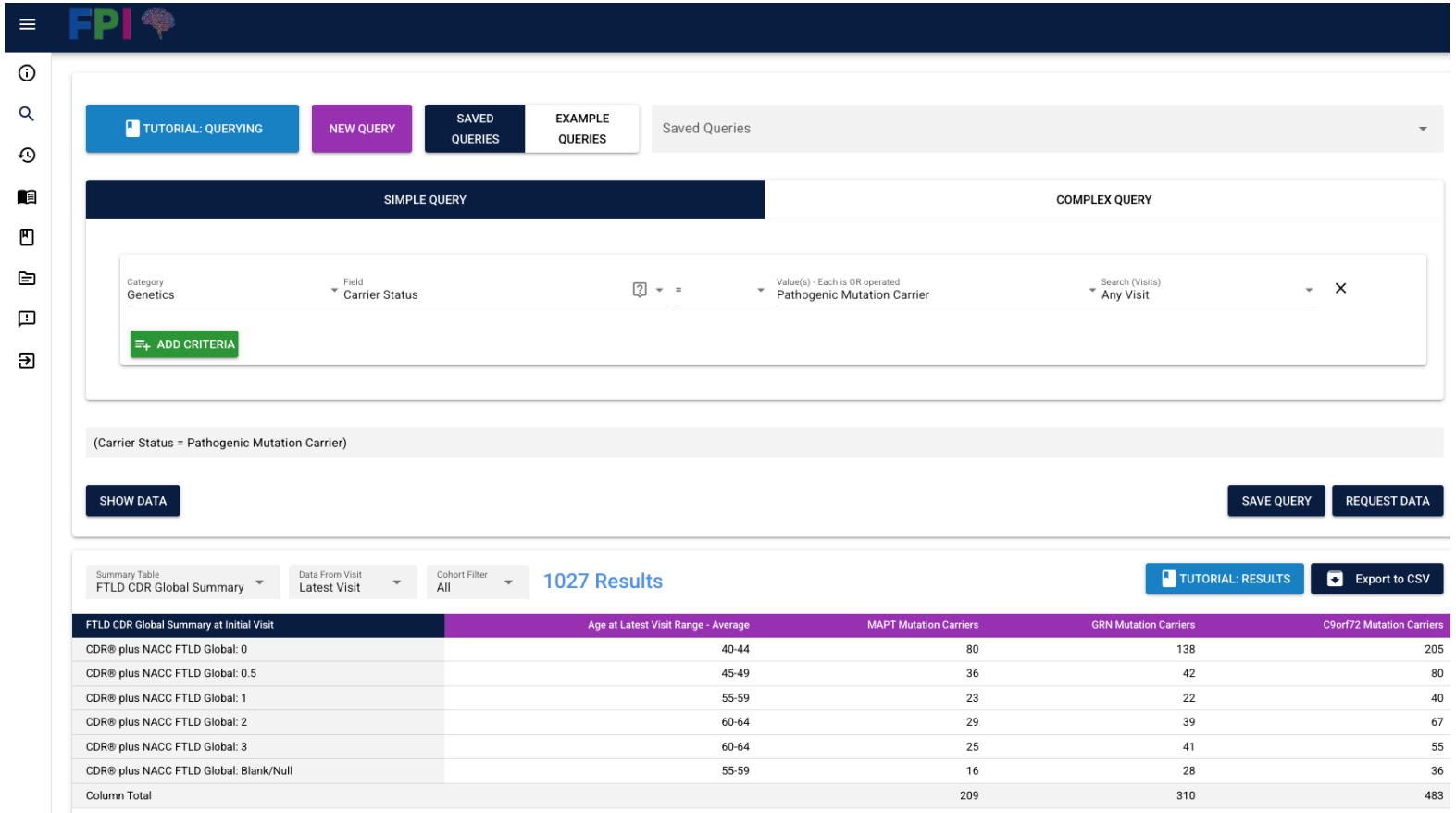
https://thefpi.org

8

Online FPI Cohort Tool & Harmonized Minimum Dataset (MDS)

FPI-MDS includes:

- > 250 clinical variables
- Records from 1649 participants with 4641 visits.
- info@thefpi.org

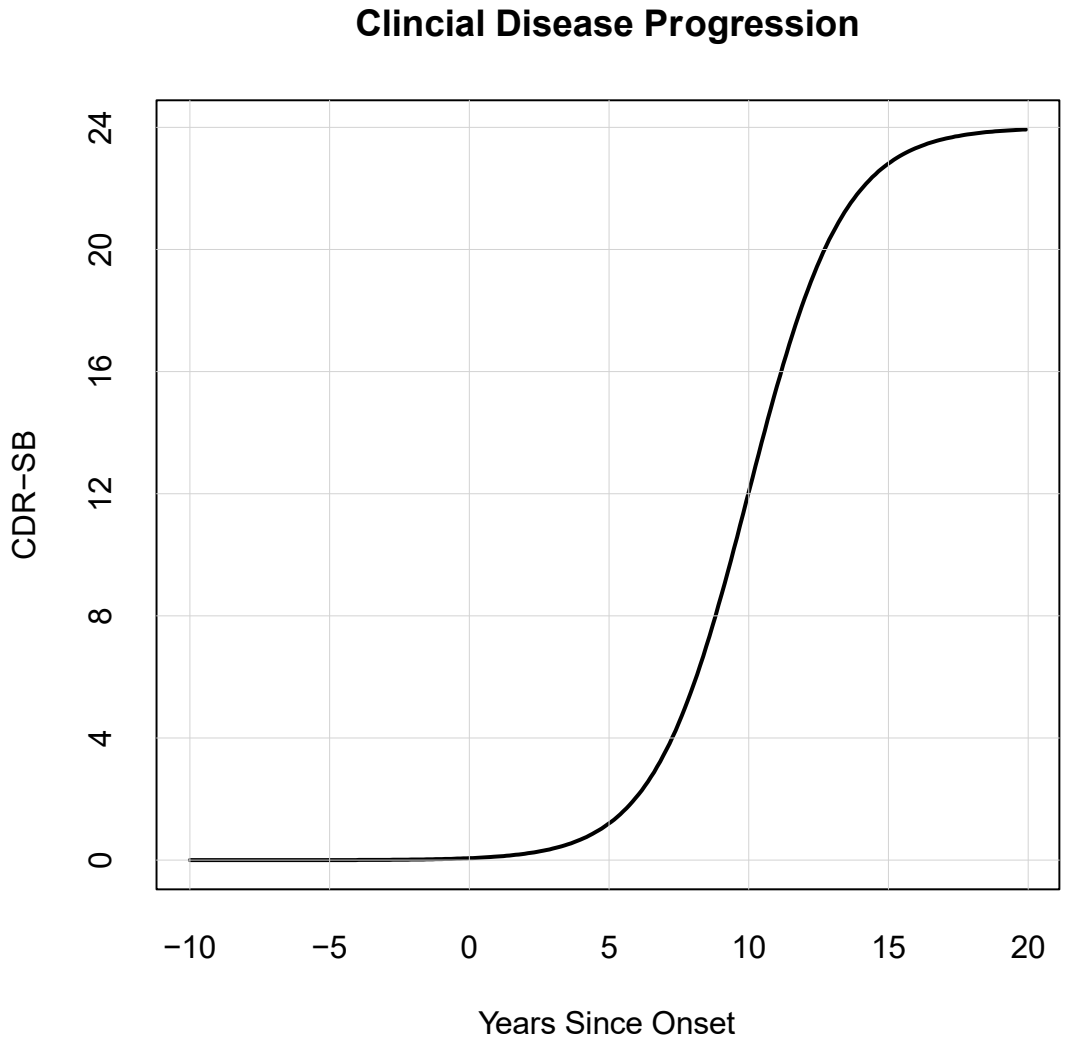


FTLD CDR Global Summary at Initial Visit	Age at Latest Visit Range - Average	MAPT Mutation Carriers	GRN Mutation Carriers	C9orf72 Mutation Carriers
CDR® plus NACC FTLD Global: 0	40-44	80	138	205
CDR® plus NACC FTLD Global: 0.5	45-49	36	42	80
CDR® plus NACC FTLD Global: 1	55-59	23	22	40
CDR® plus NACC FTLD Global: 2	60-64	29	39	67
CDR® plus NACC FTLD Global: 3	60-64	25	41	55
CDR® plus NACC FTLD Global: Blank/Null	55-59	16	28	36
Column Total		209	310	483

FPI
FTD Prevention Initiative

Disease Progression Model (DPM)

- Mathematical function that captures individual disease evolution in terms of biomarkers and/or clinical measures
  - Used to plan efficient trials in rare diseases
  - Tool for analyzing the effects of interventions causing deviations from expected disease progression

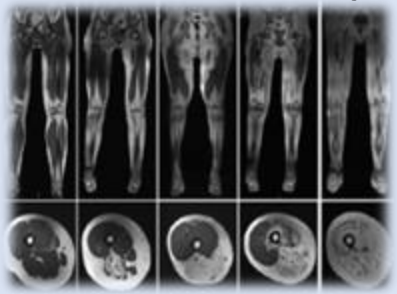


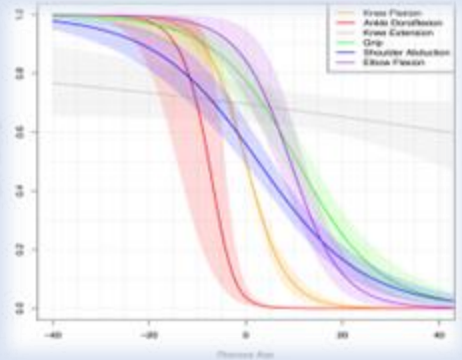
FPI
FTD Prevention Initiative

Examples of DPMs in Rare Genetic Disease

GNE Myopathy

Rare genetic muscle disease w/ slowly progressive muscle weakness & atrophy

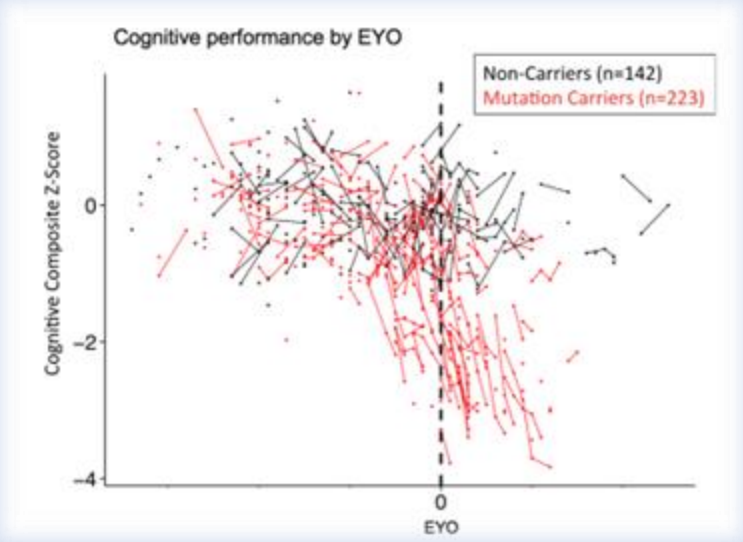




Quintana et al., 2019

Dom. Inherited Alzheimer's

Rare genetic form of Alzheimer's

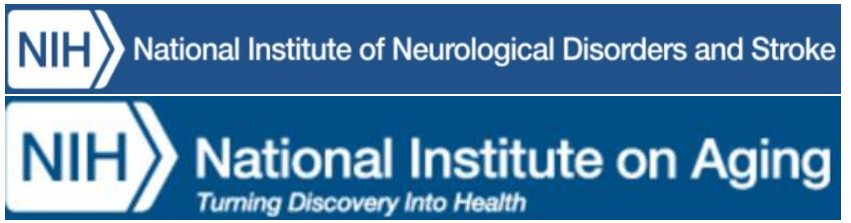


Wang et al., 2018

FTD

Special thanks to:

ALLFTD & GENFI research participants



FPI DPM Team
Adam Boxer
Jonathan Rohrer
Howard Rosen
Bradley Boeve
Hilary Heuer
Lucy Russell

Berry Consultants
Melanie Quintana
Barbara Wendelberger

Fluid Biomarkers
Tania Gendron
Len Petrucelli
Carolin Heller

Genetics
Dan Geschwind
Marisa Ramos
Rosa Rademakers
Mario Masellis
Saira Mirza
Ekaterina Rogaeva
Andrew Paterson

UCSF Imaging Core
Amy Wolf
Yann Cobigo
Howard Rosen

FPI
FTD Prevention Initiative

Uses of DPM in clinical trial design

fFTD DPM: Estimate progression as a function of disease age (DA)

DA Based Targeted enrollment

- Enroll pre-symptomatic participants likely to progress

DA Based Analysis Tool

- Account for DA to reduce unexplained variability in progression rates
- Estimate slowing in disease progression due to a treatment across multiple endpoints

FPI
FTD Prevention Initiative

FPI DPM Methods

- Harmonized clinical endpoints & biomarkers in ALLFTD & GENFI
  - Disease severity (CDR® + NACC FTLD SB)
  - Cognitive testing (UDS)
  - Neurofilament Light Chain (NfL)
  - Brain MRI

- Jointly modeled all endpoints to estimate latent “disease age”
  - Bayesian latent mixed effects model
  - Prior: clinicial estimates age of onset or chronological age
  - Years since clinical onset

nature medicine ARTICLES
https://doi.org/10.1038/s41591-022-01942-9
Check for updates

Temporal order of clinical and biomarker changes in familial frontotemporal dementia

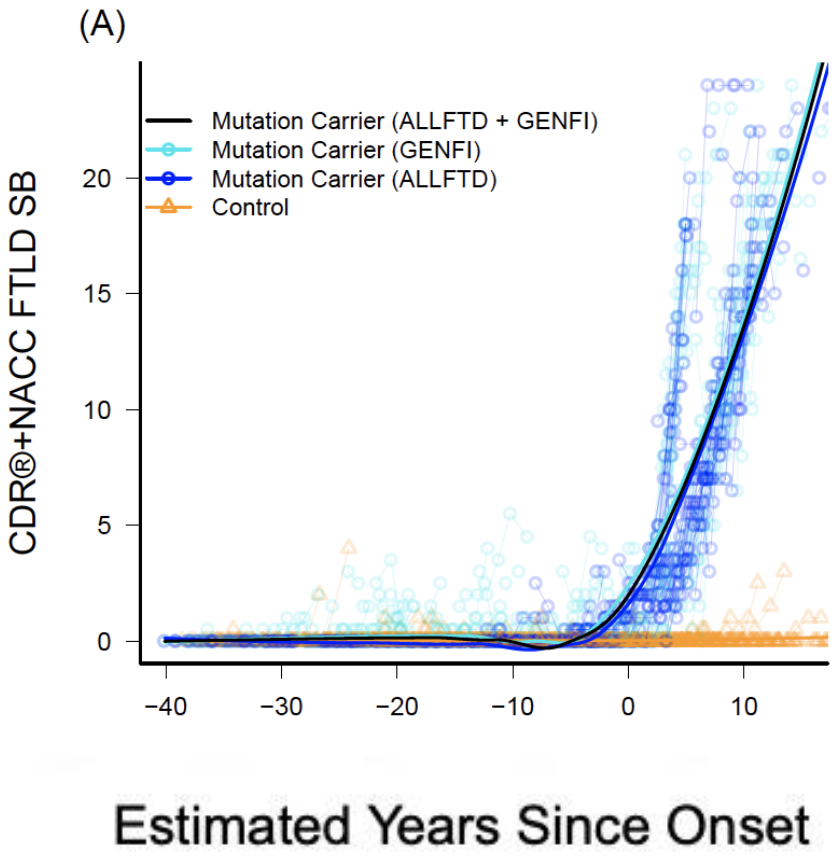
Adam M. Staffaroni[1✉], Melanie Quintana[2], Barbara Wendelberger[2], Hilary W. Heuer[1], Lucy L. Russell[3], Yann Cobigo[1], Amy Wolf[1], Sheng-Yang Matt Goh[1], Leonard Petrucelli[4], Tania F. Gendron[4], Carolin Heller[3], Annie L. Clark[1], Jack Carson Taylor[1], Amy Wise[1], Elise Ong[1], Leah Forsberg[5], Danielle Brushaber[6], Julio C. Rojas[1], Lawren VandeVrede[1], Peter Ljubenkov[1], Joel Kramer[1], Kaitlin B. Casaletto[1], Brian Appleby[7], Yvette Bordelon[8], Hugo Botha[5], Bradford C. Dickerson[9], Kimiko Domoto-Reilly[10], Julie A. Fields[11], Tatiana Foroud[12], Ralitza Gavrilova[5], Daniel Geschwind[8,13], Nupur Ghoshal[14], Jill Goldman[15], Jonathon Graff-Radford[5], Neill Graff-Radford[16], Murray Grossman[17], Matthew G. H. Hall[1], Ging-Yuek Hsiung[18], Edward D. Huey[15], David Irwin[17], David T. Jones[5], Kejal Kantarci[5], Daniel Kaufer[19], David Knopman[5], Walter Kremers[6], Argentina Lario Lago[1], Maria I. Lapid[11], Irene Litvan[20], Diane Lucente[9], Ian R. Mackenzie[21], Mario F. Mendez[8], Carly Mester[6], Bruce L. Miller[1], Chiadi U. Onyike[22], Rosa Rademakers[4,23,24], Vijay K. Ramanan[5], Eliana Marisa Ramos[8], Meghana Rao[5], Katya Rascovsky[17], Katherine P. Rankin[1], Erik D. Roberson[25], Rodolfo Savica[5], M. Carmela Tartaglia[26], Sandra Weintraub[27], Bonnie Wong[9], David M. Cash[3], Arabella Bouzigues[3], Imogen J. Swift[3], Georgia Peakman[3], Martina Bocchetta[3], Emily G. Todd[3], Rhian S. Convery[3], James B. Rowe[28], Barbara Borroni[29], Daniela Galimberti[30,31], Pietro Tiraboschi[32], Mario Masellis[33], Elizabeth Finger[34], John C. van Swieten[35], Harro Seelaar[35], Lize C. Jiskoot[35], Sandro Sorbi[36,37], Chris R. Butler[38,39], Caroline Graff[40,41], Alexander Gerhard[42,43], Tobias Langheinrich[42,44], Robert Laforce[45], Raquel Sanchez-Valle[46], Alexandre de Mendonça[47], Fermin Moreno[48,49], Matthis Synofzik[50,51], Rik Vandenberghe[52,53,54], Simon Ducharme[55,56], Isabelle Le Ber[57,58,59], Johannes Levin[60,61,62], Adrian Danek[60], Markus Otto[63], Florence Pasquier[64,65,66], Isabel Santana[67,68], John Kornak[69], Bradley F. Boeve[5], Howard J. Rosen[1], Jonathan D. Rohrer[3], Adam. L. Boxer[1✉] and Frontotemporal Dementia Prevention Initiative (FPI) Investigators*

FPI
FTD Prevention Initiative

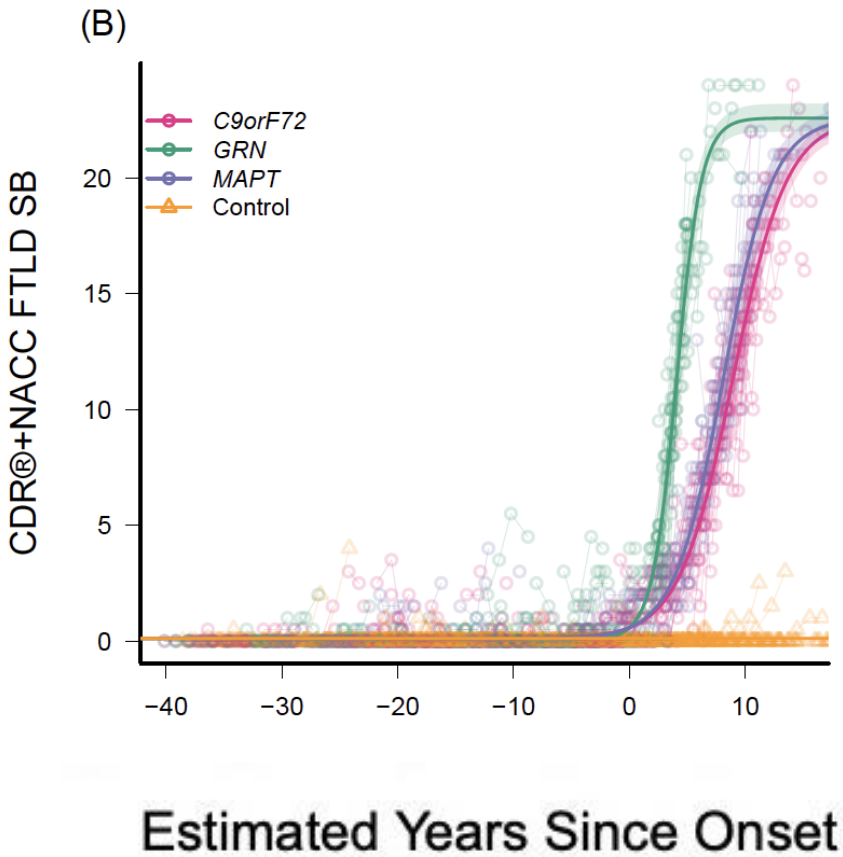
Publication sample

Characteristic	All Carriers	*C9orf72+*	*GRN+*	*MAPT+*	Non-Carriers
Sample Size	796	347	281	168	412
Visits (total number)	2.1	2.0	2.1	2.5	2.2
Total number of observations	1,695	690	592	413	910

Loess Fit by Carrier Status and Cohort

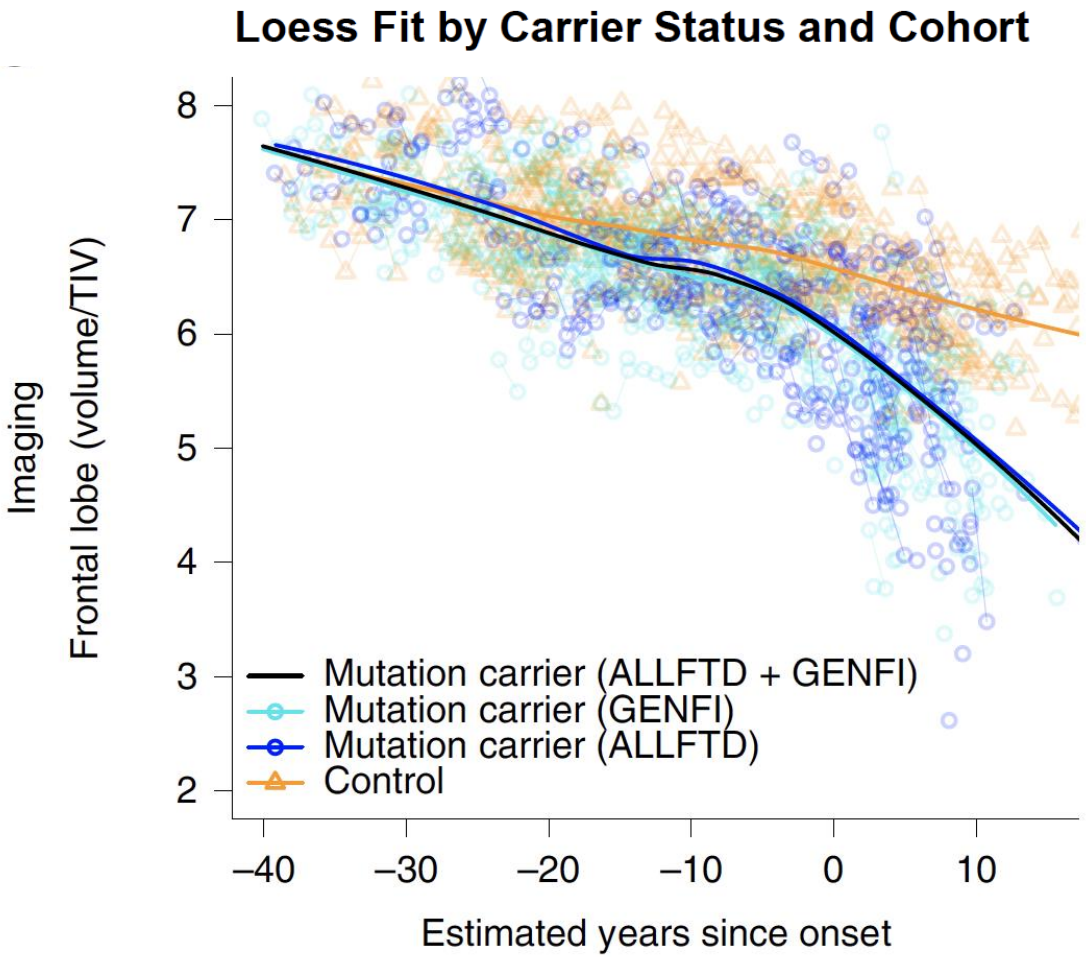


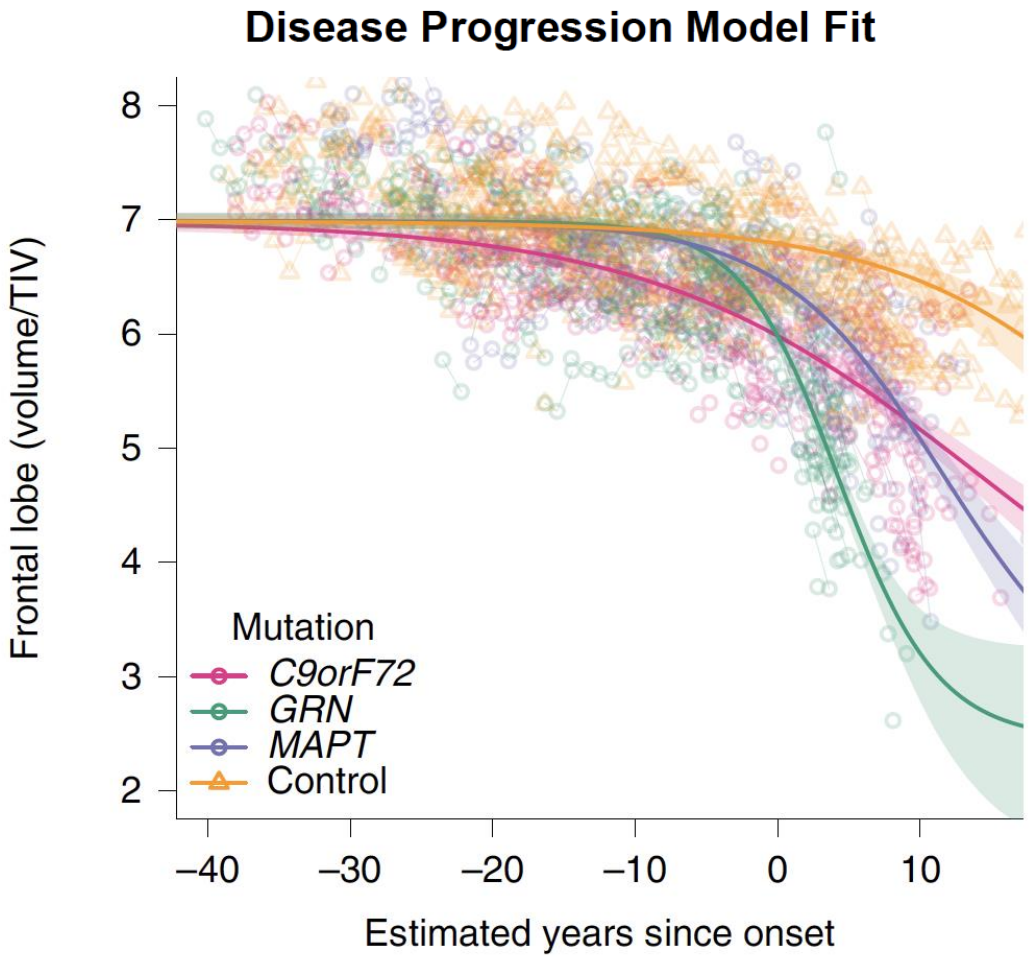
Disease Progression Model Fit



FTD Prevention Initiative

Staffaroni et al., 2022 *Nature Medicine*

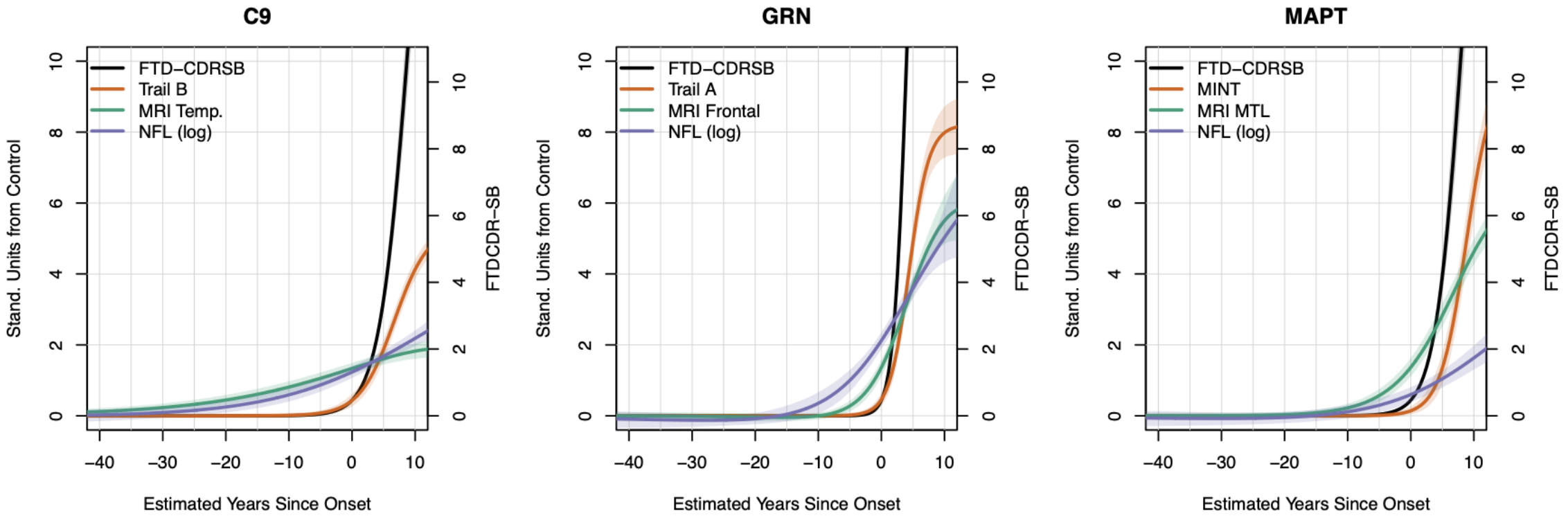




Staffaroni et al., 2022 *Nature Medicine*

FTD Prevention Initiative

Temporal dynamics differ by genetic group



Staffaroni et al., 2022 *Nature Medicine*

FPI
FTD Prevention Initiative

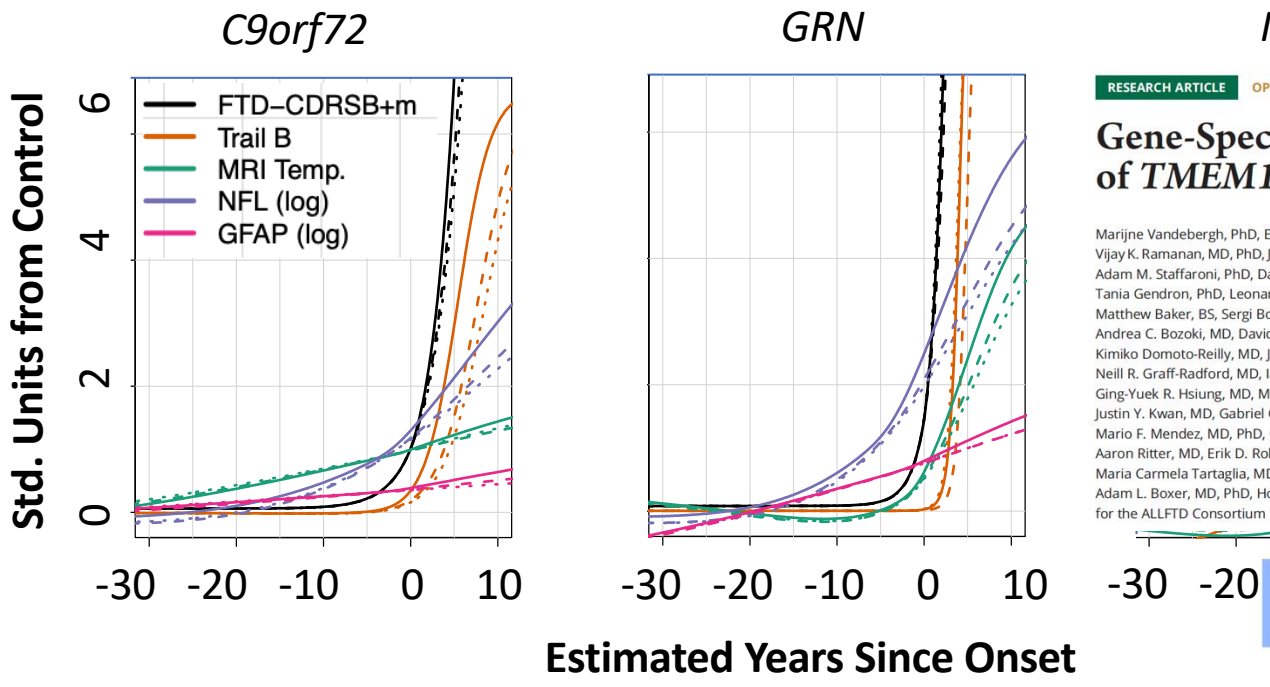
Updated Methods & Sample

- Fit a change point model instead of decay function
- Retained neuropsychological tests, volumetric MRI, and plasma NfL
- Harmonized quantified neurological exam to create FTLD-CDR + Motor
- Added plasma GFAP
- Built capacity to test modifiers of progression: e.g., *TMEM106B*

Characteristic	All Carriers	*C9orf72*+	*GRN*+	*MAPT*+	Non-Carriers
Sample Size	1,018	486	322	210	505
Visits (total number)	2.4	2.2	2.4	2.8	2.5
Total number of observations	2,417	1,060	763	594	1290

FPI
FTD Prevention Initiative

TMEM106B modifies disease progression



RESEARCH ARTICLE OPEN ACCESS

Gene-Specific Effects on Brain Volume and Cognition of *TMEM106B* in Frontotemporal Lobar Degeneration

Marijne Vandebergh, PhD, Eliana Marisa Ramos, PhD, Nick Corriveau-Lecavalier, PhD, Vijay K. Ramanan, MD, PhD, John Kornak, PhD, Carly Mester, BA, Tyler Kolander, BA, Danielle E. Brushaber, BS, Adam M. Staffaroni, PhD, Daniel H. Geschwind, MD, PhD, Amy A. Wolf, BS, Kejal Kantarci, MD, Tania Gendron, PhD, Leonard Petrucelli, PhD, Marleen Van den Broeck, BS, Sarah Wynants, BS, Matthew Baker, BS, Sergi Borrego-Écija, MD, PhD, Brian Appleby, MD, Sami Barmada, MD, PhD, Andrea C. Bozoki, MD, David Clark, MD, R. Ryan Darby, MD, Bradford C. Dickerson, MD, Kimiko Domoto-Reilly, MD, Julie A. Fields, PhD, Douglas Galasko, MD, Nupur Ghoshal, MD, PhD, Neill R. Graff-Radford, MD, Ian M. Grant, MD, MA, Lawrence S. Honig, MD, PhD, Ging-Yuek R. Hsiung, MD, MHSc, Edward D. Huey, MD, David J. Irwin, MD, David S. Knopman, MD, Justin Y. Kwan, MD, Gabriel C. Léger, MD, Irene Litvan, MD, Joseph C. Masdeu, MD, PhD, Mario F. Mendez, MD, PhD, Chiadi U. Onyike, MD, MHS, Belen Pascual, PhD, Peter S. Pressman, MD, Aaron Ritter, MD, Erik D. Roberson, MD, PhD, Allison Snyder, MD, Anna Campbell Sullivan, PsyD, Maria Carmela Tartaglia, MD, Dylan Wint, MD, Hilary W. Heuer, PhD, Leah K. Forsberg, PhD, Adam L. Boxer, MD, PhD, Howard J. Rosen, MD, Bradley F. Boeve, MD, and Rosa Rademakers, PhD, for the ALLFTD Consortium

Correspondence
Dr. Rademakers
rosa.rademakers@uantwerpen.vib.be

BRAIN
ORIGINAL ARTICLE

Disease-modifying effects of *TMEM106B* in genetic frontotemporal dementia: a longitudinal GENFI study

Saira S. Mirza,[1,2,†] Maurice Pasternak,[1,†] Andrew D. Paterson,[3] Ekaterina Rogaeva,[4] Maria C. Tartaglia,[4,5,6] Sara B. Mitchell,[6] Sandra E. Black,[1,2,6,7] Morris Freedman,[6,7] David Tang-Wai,[6,7,8] Arabella Bouzigues,[9] Lucy L. Russell,[9] Phoebe H. Foster,[9] Eve Ferry-Bolder,[9] Martina Bocchetta,[9] David M. Cash,[9] Henrik Zetterberg,[9,10,11,12] Aitana Sogorb-Esteve,[9,13] John van Swieten,[14] Lize C. Jiskoot,[14] Harro Seelaar,[14] Raquel Sanchez-Valle,[15] Robert Laforce Jr,[16] Caroline Graff,[17,18] Daniela Galimberti,[19,20] Rik Vandenberghe,[21,22] Alexandre de Mendonça,[23] Pietro Tiraboschi,[24] Isabel Santana,[25,26] Alexander Gerhard,[27,28] Johannes Levin,[29,30,31] Sandro Sorbi,[32,33] Markus Otto,[34] Florence Pasquier,[35,36] Simon Ducharme,[37,38] Chris Butler,[39,40] Isabelle Le Ber,[41,42] Elizabeth Finger,[43] James B. Rowe,[44] Matthis Synofzik,[45,46] Fermin Moreno,[47,48,49] Barbara Borroni,[50] Jonathan D. Rohrer[9] and Mario Masellis[1,2,6] on behalf of the GENetic Frontotemporal dementia Initiative (GENFI)

FPI
FTD Prevention Initiative

Uses of DPM in clinical trial design

fFTD DPM: Estimate progression as a function of disease age (DA)

DA Based Targeted enrollment

- **Enroll pre-symptomatic participants likely to progress**

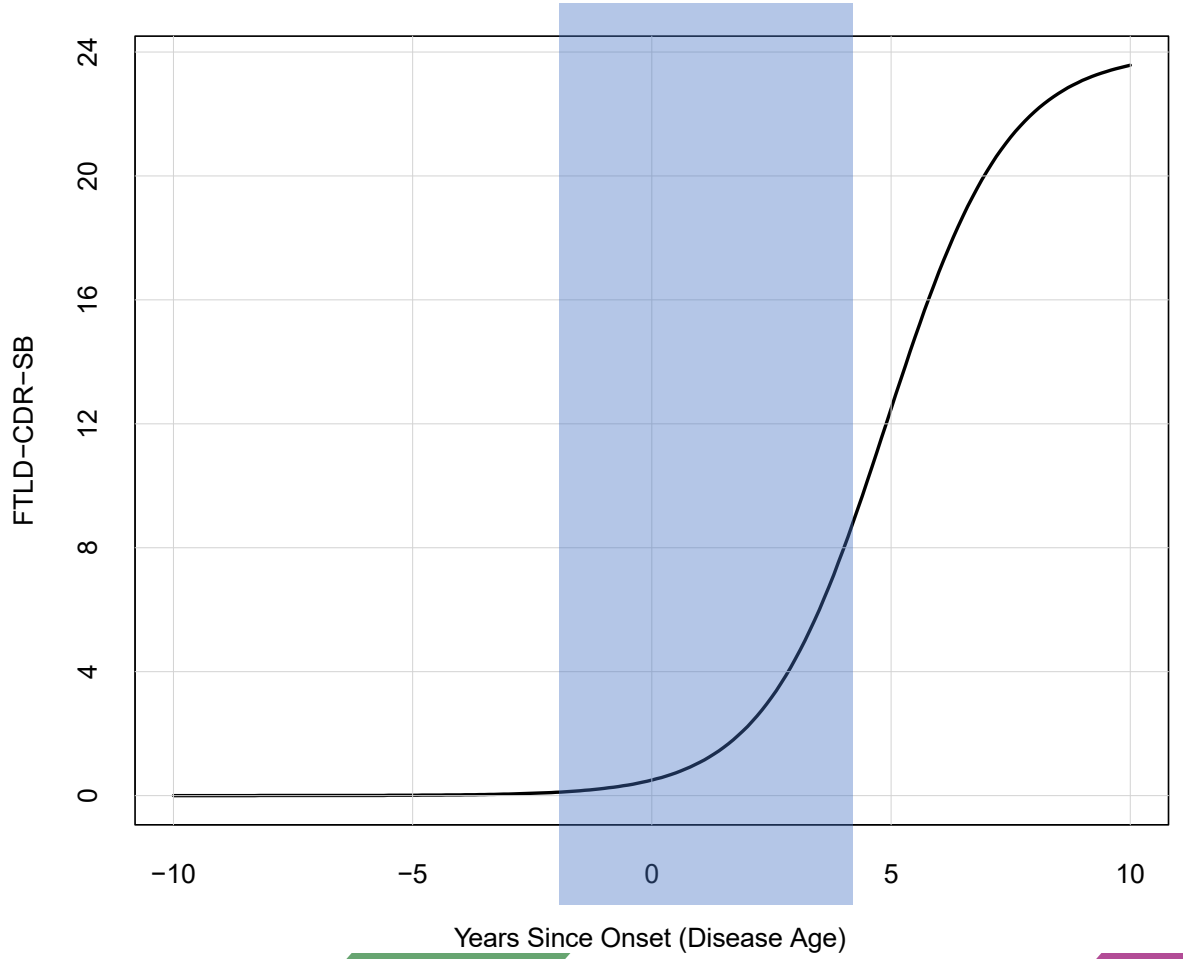
DA Based Analysis Tool

- Estimate slowing in disease progression due to a treatment across multiple endpoints
- Account for DA to reduce unexplained variability in progression rates

FPI
FTD Prevention Initiative

Disease Age based enrollment for f-FTLD trials

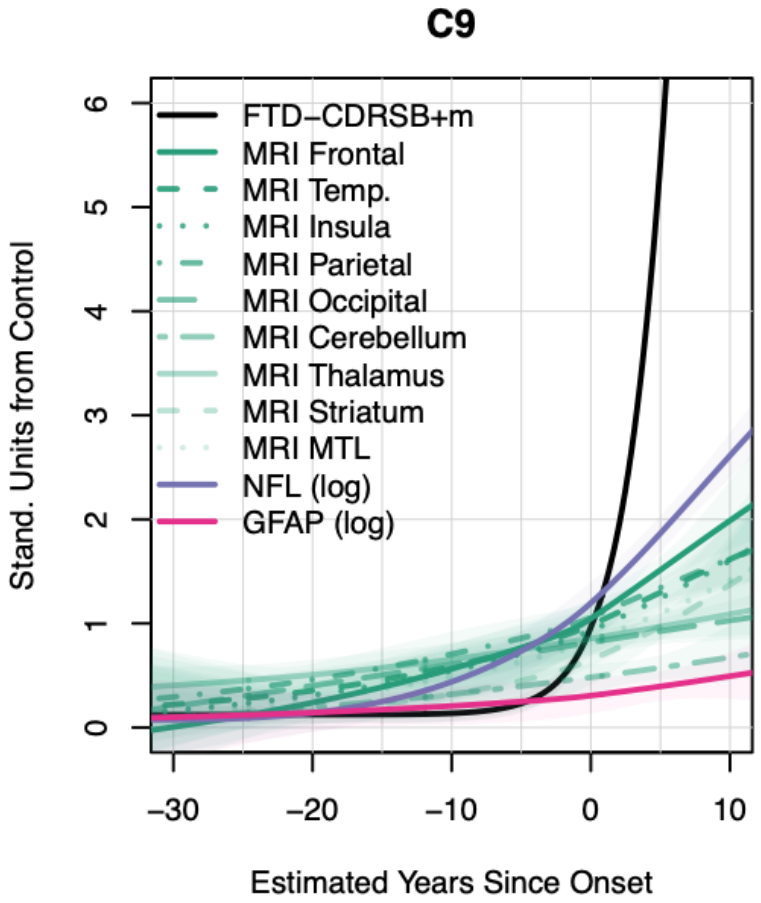
- **Use predicted Disease Age for optimal clinical trial enrollment**
  - Enroll too early – No power
  - Enroll too late – Treatment may not be effective
  - Enroll an earlier patient population that will likely progress ***and*** benefit



FPI
FTD Prevention Initiative

DA Estimation Algorithm

Progression curves for multiple endpoints from FTD DPM

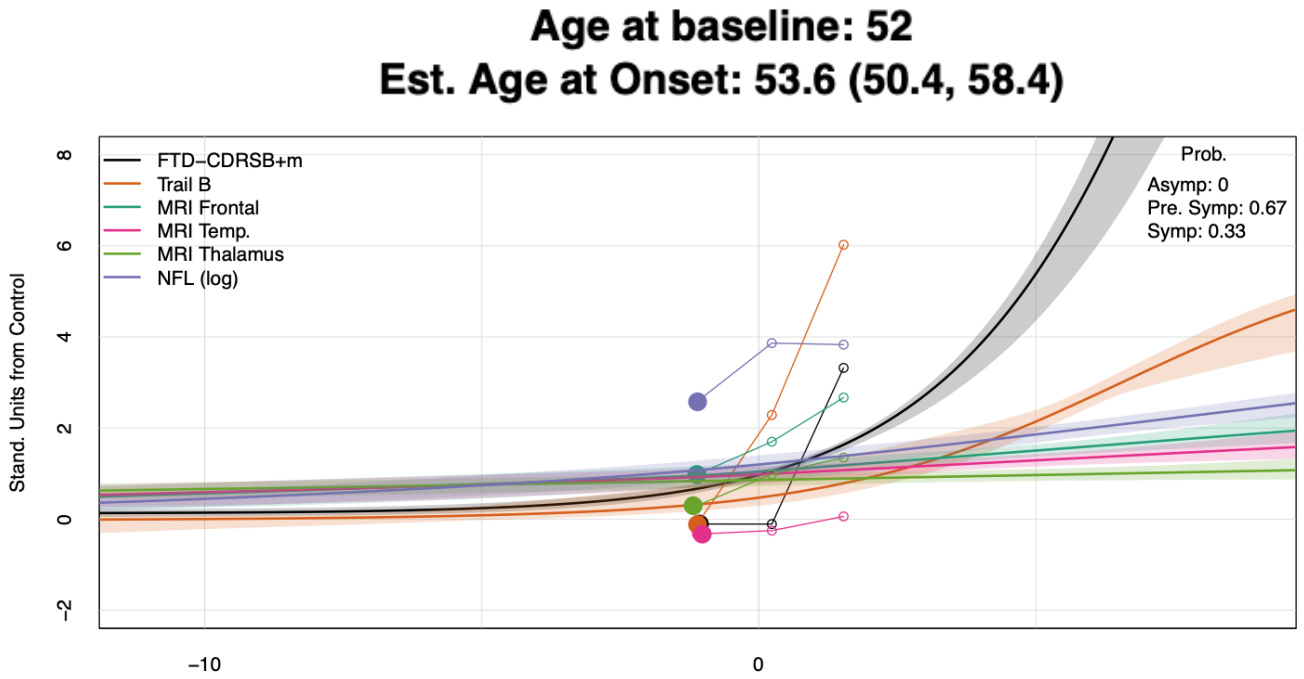


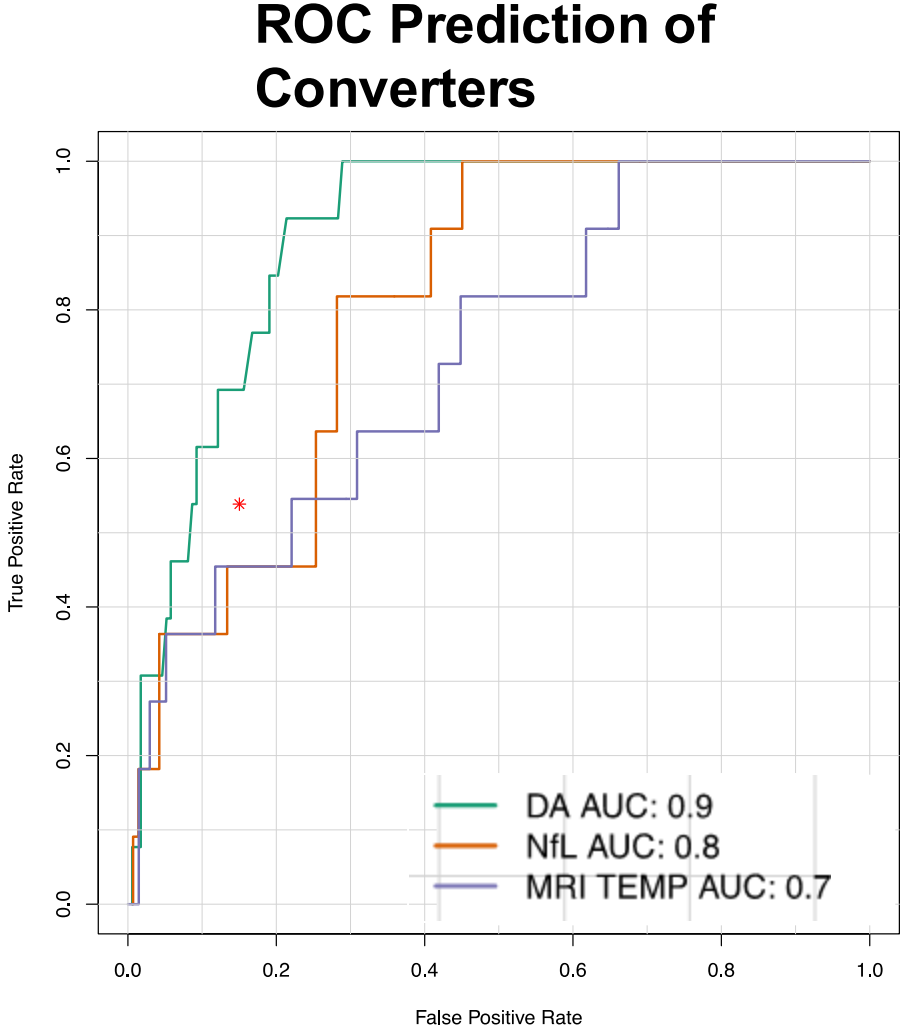
Observed Baseline values

Baseline Information Participant 1	
Mutation	C9
Global CDR	0
FTD-CDRSB+m	0
MRI Temp	0 SD from control
MRI Front	1 SD from control
MRI Thalmus	.5 SD from control
NFL (log)	2.5 SD from control

FPI
FTD Prevention

Disease age validation for individual patients





Disease age-based targeted enrollment

Early symptomatic treatment trial (all CDR+NACC-FTLD Global = 1 enriched with 0 and 0.5 participants)										
Genetic Group	Estimated number of eligible participants	Inclusion criteria	Primary endpoint: sample size estimates (50% treatment effect)							
			CDR+NACC-FTLD-SB		Neuropsychological tests		NfL (log)		MRI volume	
			1.5 yr	2 yr	1.5 yr	2 yr	1.5 yr	2 yr	1.5 yr	2 yr
C9orf72 MRI =temporal NP = Trails B	94	ALL CDR 0.5 and 1	188	129	340	203	811	483	639	367
	37	All CDR 1 and (CDR 0 and 0.5 if NfL > 3)	161	115	370	222	1,806	782	645	358
	83	All CDR 1 and (CDR 0 and 0.5 if DA > −2.5)	176	124	400	207	740	423	678	360
	67	All CDR 1 and (CDR 0 and 0.5 if DA > 0)	117	**79**	275	161	628	384	669	359

- Using disease age as an enrollment criterion substantially reduces sample sizes for clinical trials

Conclusions

- Recruitment challenges are a major bottleneck to identifying an effective treatment for f-FTLD.
- Disease progression models are a powerful tool for addressing barriers to clinical trials in f-FTLD
- Models will need to include global samples to ensure applicability across cohorts
- Other directions include endpoint development and use of digital health technologies for higher enrollment and more frequent remote monitoring

FPI
FTD Prevention Initiative

Acknowledgements

Thank you to all the participants, carers and family members who take part in the familial FTD research.

Thank you to all the FPI researchers and investigators.

FPI Executive Committee:
Jonathan Rohrer
Adam Boxer
Hilary Heuer
Lucy Chisman-Russell

Cohort Leads:
Howie Rosen
Brad Boeve
Rebekah Ahmed
Brigid Ryan
Agustin Ibanez
Adeline Ng Su Lyn
Qin Chen
EJ Kim
Survarna Alladi
Manabu Ikeda

Data Infrastructure
Joe Hesse
Adam Staffaroni
Rose George
Richel Leung

Project Management:
Sophie Farley
Eve Ferry-Bolder
Leah Forsberg

GENFI Acknowledgments

To all the participants, carers and family members who take part in the GENFI study

- UCL: Jonathan Rohrer
- Cambridge: James Rowe
- Brescia UNIBS: Barbara Borroni
- Milano UNIMI: Daniela Galimberti
- Milano INCB: Pietro Tiraboschi
- Toronto: Mario Masellis, Carmela Tartaglia
- London Ontario: Liz Finger
- Rotterdam: John van Swieten, Lize Jiskoot, Harro Seelaar
- Firenze: Sandro Sorbi
- Stockholm: Caroline Graff
- Quebec: Robert Laforce
- Lisboa: Alexandre Mendonca
- Leipzig: Matthias Schroeter
- Oulu: Anne Remes
- Amsterdam: Yolande Pijnenburg
- Manchester: Alex Gerhard
- Oxford: Chris Butler
- Barcelona: Raquel Sánchez-Valle
- San Sebastian: Fermin Moreno
- Paris: Isabelle Le Ber
- Lille: Florence Pasquier
- Lund: Maria Landqvist Waldo
- Ulm: Markus Otto
- Tubingen: Matthis Synofzik
- Munchen: Johannes Levin, Adrian Danek
- Leuven: Rik Vandenberghe
- Montreal: Simon Ducharme
- Coimbra: Isabel Santana
- Ghent: Tim Van Langenhove
- Copenhagen: Jørgen Nielsen

ALLFTD
ARTFL LEFFTDS Longitudinal Frontotemporal Lobar Degeneration

Study mPIs: Brad Boeve, Adam Boxer, Howard Rosen

Special Thanks to ALLFTD Participants and Their Families

Current Clinical Site PIs and Study Clinicians

Brian Appleby
Sami Barmada
Ece Bayram
Hugo Botha
Andrea Bozoki
David Clark
Ryan Darby
Gregg Day
Bradford Dickerson
Kimiko Domoto-Reilly
Fanny Elahi
Doug Galasko
Nupur Ghoshal
Neill Graff-Radford
Jon Graff-Radford
Ian Grant
Chad Hales
Sam Holden
Lawrence Honig
Robin Hsiung
Edward Huey
David Irwin
David Knopman
Justin Kwan
Maria Lapid
Gabriel Leger
Irene Litvan
Peter Ljubenkov
Ian Mackenzie
Joseph Masdeu
Lauren Massimo
Stu McCarter
Scott McGinnis
Mario Mendez
Toji Miyagawa
Georges Nassan
Chiadi Onyike
Belen Pascual
Tanav Popli
Peter Pressman
Vijay Ramanan
Julio Rojas-Martinez
Erik Roberson
Allison Snyder
Campbell Sullivan
Carmela Tartaglia
Ren VandeVrede
Dylan Wint
Zbignew Wszolek

Neuropsychologists

Ciaran Considine
Julie Fields
Kate Rankin
Katya Rascovsky
Adam Staffaroni
Sandra Weintraub
Bonnie Wong

Genetic Counselors

Laynie Dratch
Emily Dwosh
Jamie Fong
Ralitza Gavrilova
Jill Goldman
Diane Lucente
Liya Rabkina

Participant and Family Engagement Board

Katherine Brandt (co-chair)
Brad Grems (co-chair)
Board members (rotating; 2-year terms)

Management

Hilary Heuer
Leah Forsberg

DMS Core

Walter Kremers
John Kornak
Nellie Brushaber
Tyler Kolander
Carly Mester
Penny Dacks
Carrie Milliard
Sweatha Reddy

Biofluid Core

Len Petrucelli
Adam Boxer
Suzanne Schindler
Tania Gendron
Argentina Lario Lago

Genetics Core

Dan Geschwind
Rosa Rademakers
Marisa Da Silva Ramos

Neuroimaging Core

Kejal Kantarci
Howard Rosen
Denise Reyes
Yann Cobigo
Chris Schwarz
Kaely Thostenson

Neuropathology Core

Bill Seeley
Dennis Dickson
Ian Mackenzie

Mobile App

Adam Staffaroni
Jack Taylor
Sreya Dhanam

Biospecimen Sharing - NCRAD

Tatiana Foroud
Kelley Faber
Corinne Kim
Jazmyn Dickinson

Data Sharing - NACC

Walter Kukull
Sara Biber

Image Sharing - LONI

Art Toga
Karen Crawford

Scientific Advisory Board

Eric Reiman
Rhoda Au
Alison Goate
Bruce Miller
John Morris
Ron Petersen
Andy Singleton

ALLFTD Funding Partners and Patient Advocacy Groups:

NIH National Institute on Aging
NIH National Institute of Neurological Disorders and Stroke
FTD DISORDERS REGISTRY
AFTD The Association for Frontotemporal Degeneration FIND HELP·SHARE HOPE
CurePSP UNLOCKING THE SECRETS OF BRAIN DISEASE
ALZHEIMER'S ASSOCIATION
BLUEFIELD PROJECT Curing FTD
RAINWATER Charitable Foundation
Tau Consortium
Alzheimer's Drug Discovery Foundation
cure MAPT FTD
END THE LEGACY

Endpoint Selection in Progressive Diseases and Considerations for Clinical Trials: A Case Study from NeuroNEXT

46th ANNUAL MEETING

May 18-21, 2025

VANCOUVER
CANADA

SCT
SOCIETY FOR CLINICAL TRIALS

NeuroNEXT

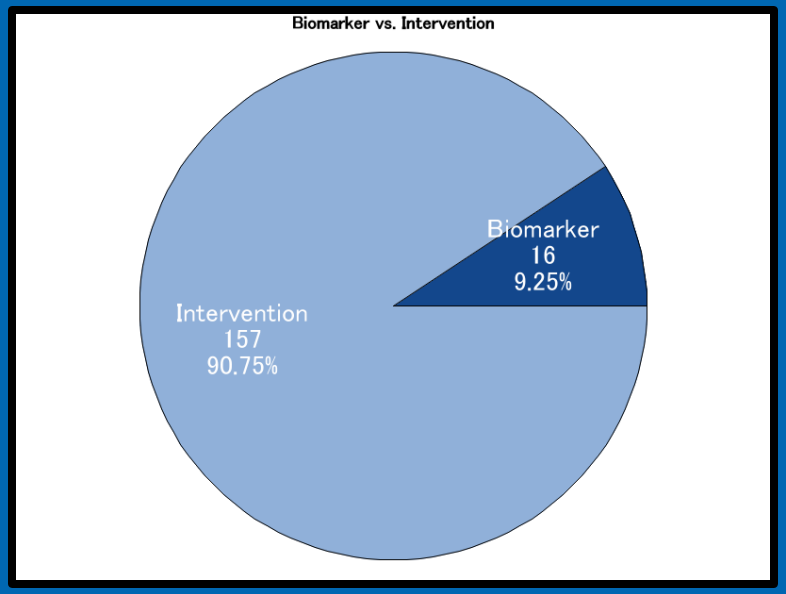
Network for Excellence in Neuroscience Clinical Trials:
Designed to conduct studies in neurological diseases through partnerships with academia, private foundations, and industry to:

- Test promising new therapies
- Increase efficiency of clinical trials
- Respond quickly as new opportunities arise to test promising treatments in neurological diseases

NeuroNEXT

Since the inception of NeuroNEXT in 2011, the Network has received 184 proposals from 90 different institutions/companies covering 65 different diseases!

- Majority of proposals to date involve phase 2 clinical trials



NeuroNEXT

A priori specified & justified "go"/"no go" criteria important

- Screen out ineffective treatments
- Determine if new treatment is sufficiently promising to justify inclusion in large-scale randomized trials
- Without specified a priori criteria, investigators may subjectively highlight positive "trends" – could be real effect of "chance" finding
- A design that meets "go" criteria if any of multiple endpoints show hint of effect will almost always "go" forward – even if treatment does not work

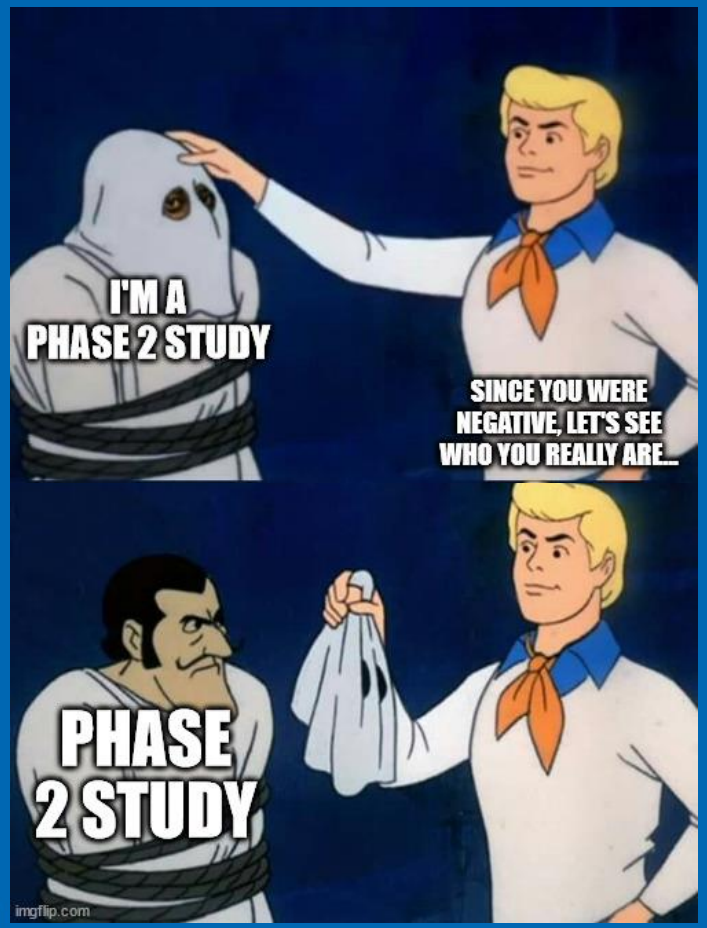
NeuroNEXT

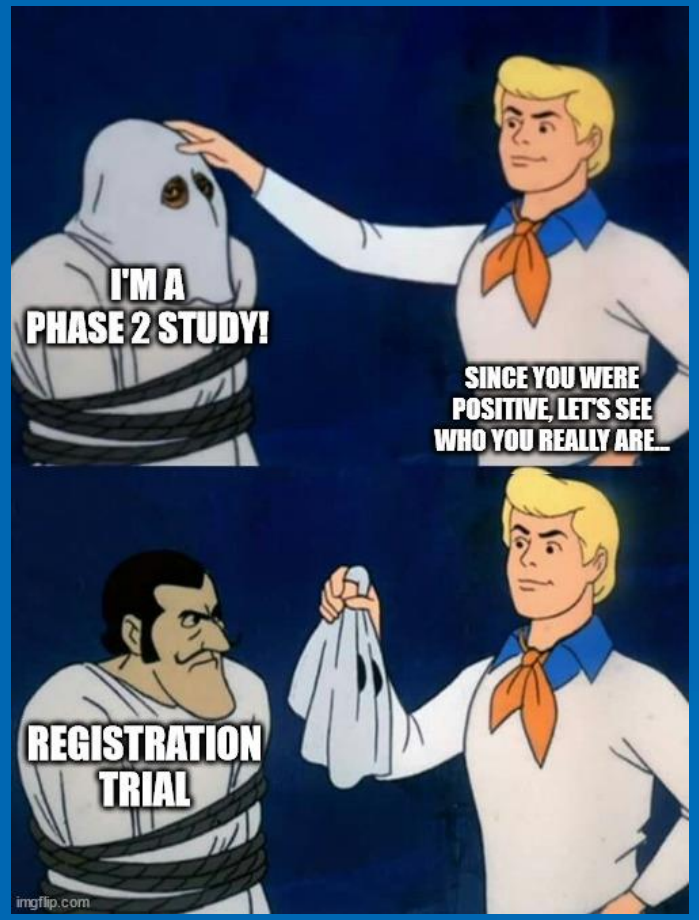
Completed Phase 2 Clinical Trials

- NN102 Ibudilast in ***Progressive Multiple Sclerosis***
- NN103 Rituximab in ***Myasthenia Gravis***
- NN104 3K3A-APC in ***Acute Stroke***
- NN105 SRX246 for Irritability in ***Huntington's Disease***
- NN107 AFQ056 for Language Learning in ***Fragile X Syndrome***
- NN108 Topiramate for ***Cryptogenic Sensory Peripheral Neuropathy***
- NN110 Light Therapy for ***Parkinson's Disease***

NeuroNEXT

Phase 2?? --- Or Phase 3 in Disguise!!

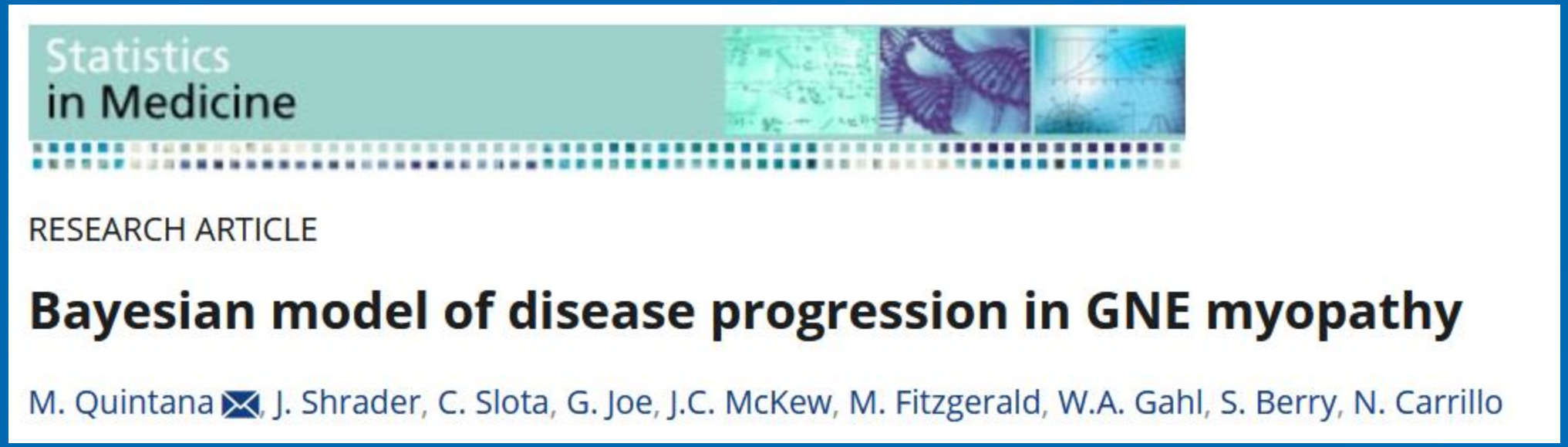




GNE Myopathy

- Rare, progressive muscle disease caused by mutations in the GNE gene, leading to a deficiency in sialic acid production
- Typically characterized by bilateral foot drop and other muscle weakness
- Often appears in early adulthood
- Condition progresses slowly – eventually affecting muscles throughout the body (though the quadriceps are often spared)
- Estimated prevalence: 6/1,000,000

GNE Myopathy Disease Progression Model

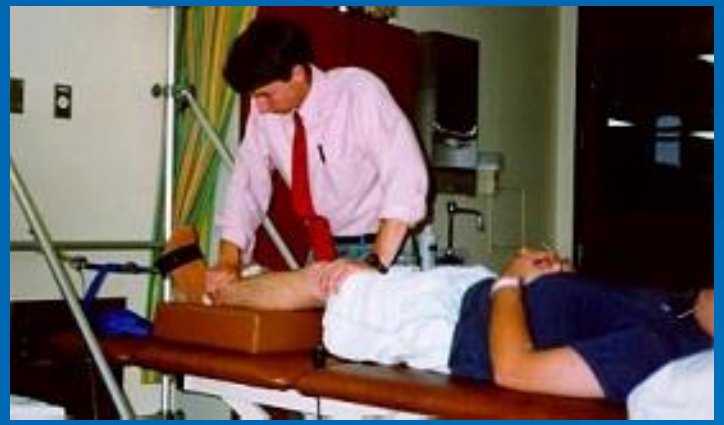


- *Statistics in Medicine*. 2018;1–16. https://doi.org/10.1002/sim.8050

GNE Myopathy Disease Progression Model

Simultaneously model percent strength of Quantitative Muscle Assessment (SMA) for each of 6 primary muscles

- Ankle Dorsiflexion
- Knee Flexion
- Knee Extension
- Hand Grip
- Elbow Flexion
- Shoulder Abduction



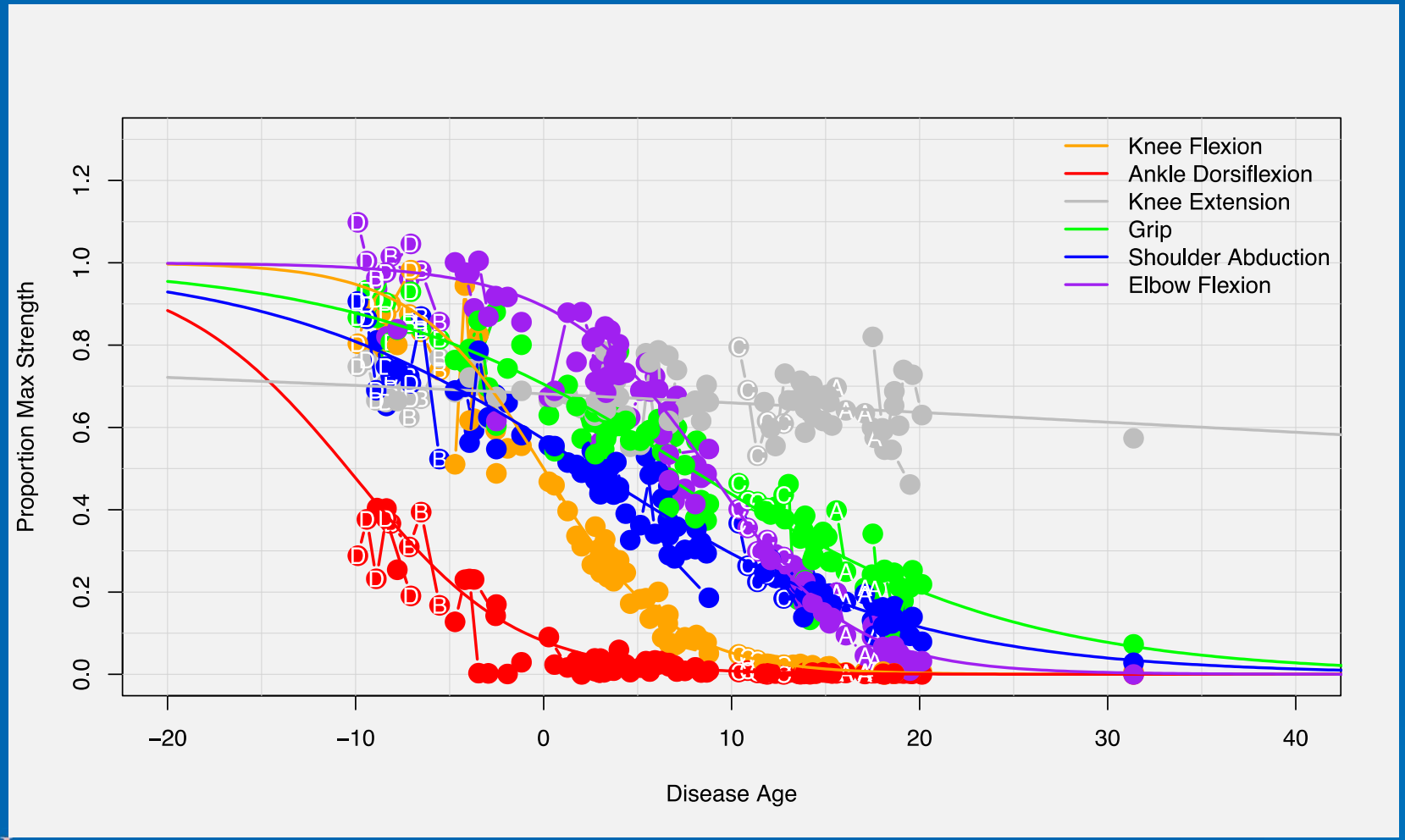
Muscle strength expressed as a proportion of participant's predicted normal values for their sex, age, and body mass index

GNE Myopathy Disease Progression Model

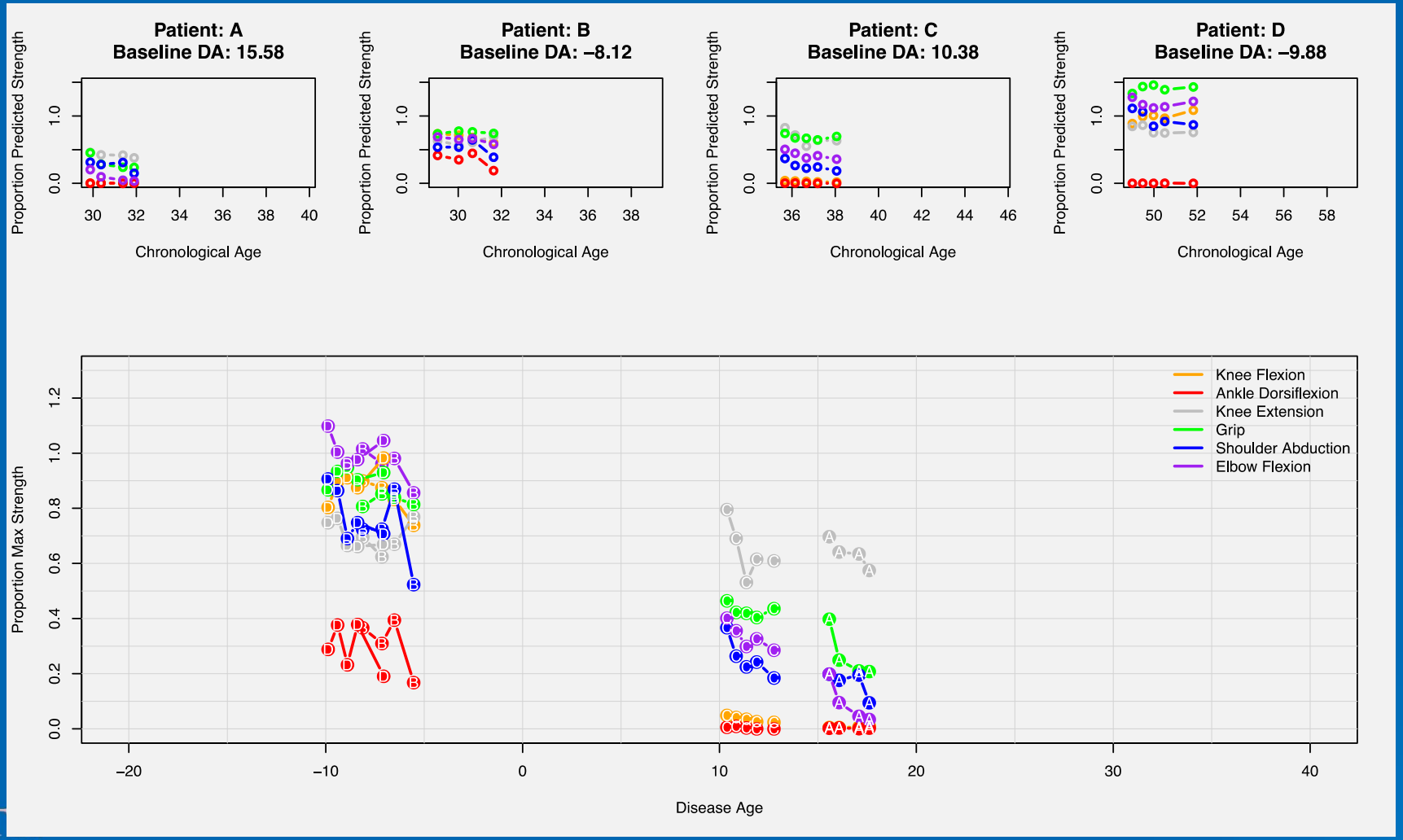
Estimate "Disease Age" for each subject based on 6 muscle scores

- Assume disease age is defined as 0 when the proportion of knee flexion strength is 0.50
- Estimate timing and rate of decline for each muscle under natural progression / placebo

GNE Myopathy Disease Progression Model



GNE Myopathy Disease Progression Model



GNE Myopathy Disease Progression Model

- **Treatment Effect:** Constant % slowing in the rate of decline across all muscles under treatment compared to the rate of decline in placebos
- **Alternative Interpretation:** Slowing in number of years it will take to reach milestones incorporates treatment effect parameter (γ) that measures proportional change in rate of decline jointly across all muscle groups
  - Example: 50% slowing in rate of decline = Will take participant twice as many years to reach milestone under treatment

GNE Myopathy Disease Progression Model

- Model incorporates treatment effect parameter (γ) that measures proportional change in rate of decline jointly across all muscle groups
  - γ = 1 → Effect of treatment same as placebo
  - γ < 1 → Treatment slows disease progression
  - Γ = 0 → Treatment has stopped progression

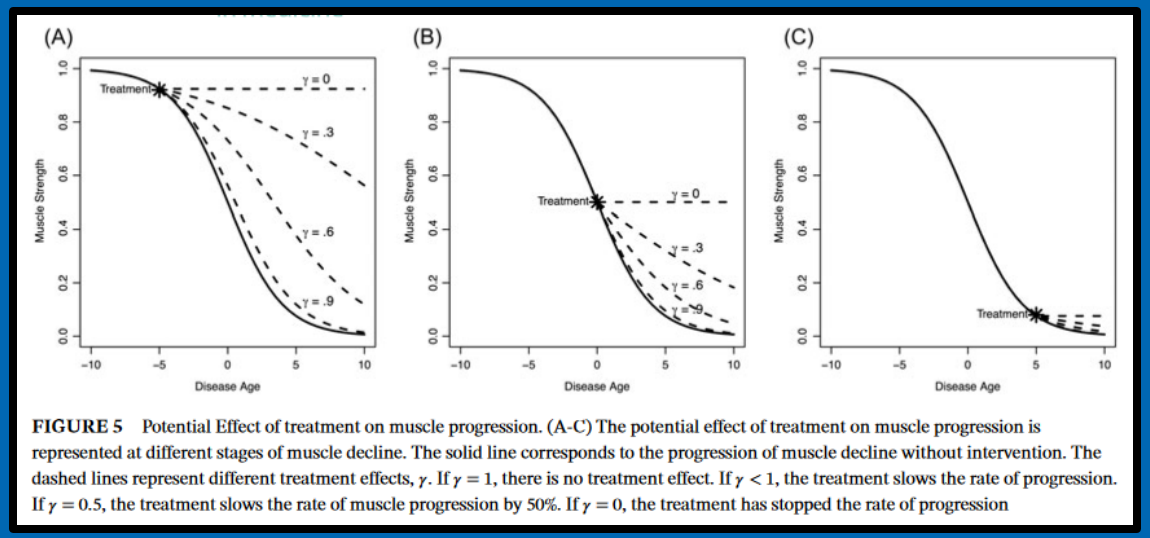


FIGURE 5 Potential Effect of treatment on muscle progression. (A-C) The potential effect of treatment on muscle progression is represented at different stages of muscle decline. The solid line corresponds to the progression of muscle decline without intervention. The dashed lines represent different treatment effects, γ. If $\gamma = 1$, there is no treatment effect. If $\gamma < 1$, the treatment slows the rate of progression. If $\gamma = 0.5$, the treatment slows the rate of muscle progression by 50%. If $\gamma = 0$, the treatment has stopped the rate of progression

NN109 – MAGINE Study

A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Evaluate the Efficacy of ManNAc in Subjects with GNE Myopathy

PIs: Anthony Amato (Brigham & Women's); Francis Rossigni (NIH)

Primary Objective:

To evaluate efficacy of ManNAc in subjects with GNE myopathy as measured by ability of ManNAc to slow progression of muscle strength decline compared to placebo.

NN109 – MAGINE Study

Design and Power:

- N = 50 Enrolled; 2:1 Treatment vs. Control
- Follow all participants for a minimum of two years
- Assume 10% annual rate of LTFU
- Treatment effects: 0% (Null) vs. 40-50% slowing in progression

% Reduction	Power
50%	0.892
45%	0.817
40%	0.715
0%	0.011

NN109 – MAGINE Study

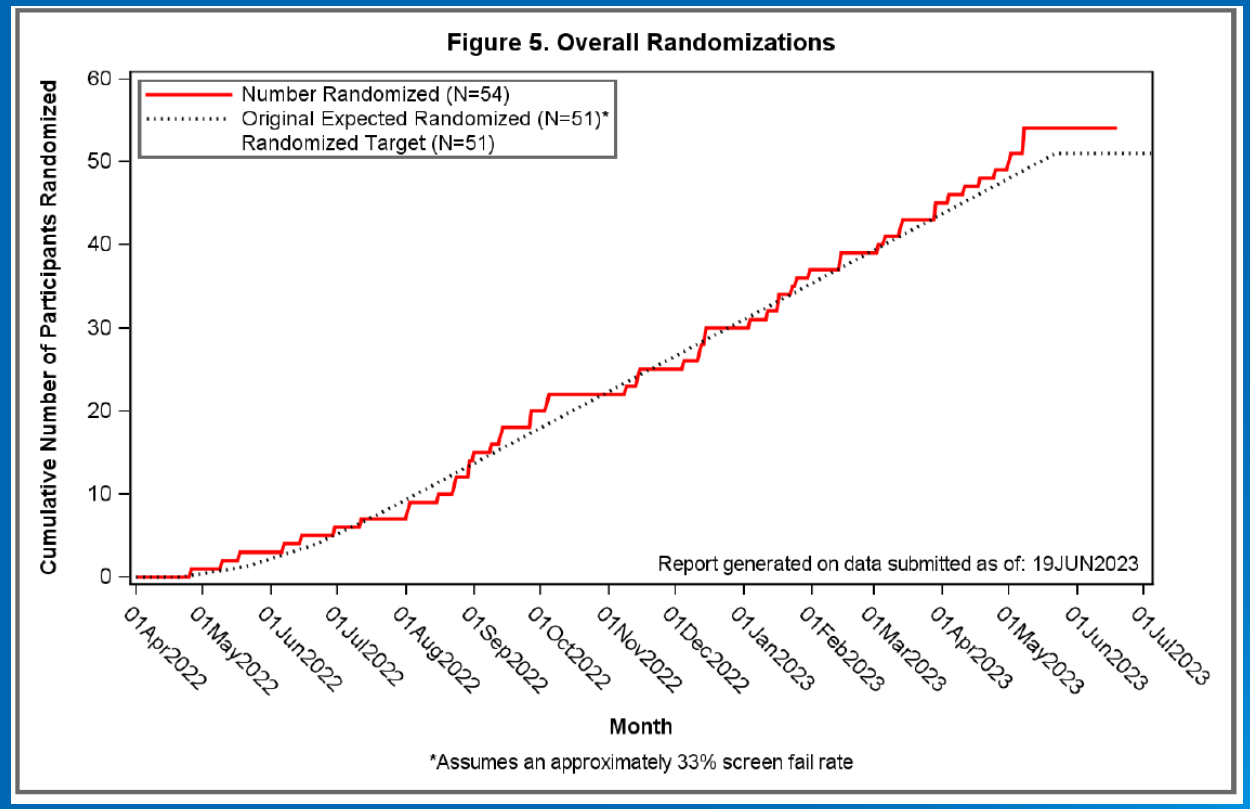
At least 96 patients are needed to detect a 50% reduction with other potential primary endpoints – and power is reduced to 80%

Table 2. Comparison Sample size with other Available Endpoints		
Primary Endpoint	**1-year decline Mean (SD)[1]**	**Sample size[2] (80% power; gamma 0.50)**
Composite total strength (%predicted)	-2.01 (5.66)	252
Composite UE strength (% predicted)*	-1.67 (5.28)	318
Composite LE strength (% predicted)*	-2.28 (6.85)	288
Composite UE strength (kg)*	–4.52 (10.2)	164
subset 6MWT >200m[3]	–5.66 (10.9)	120
Composite LE strength (kg)*	–9.55 (20.6)	150
subset 6MWT >200m[3]	–11.4 (20.72)	106
6MWT (meters)	-10.7 (32.7)	296
IBMFRS total score	-0.49 (1.65)	352
HAP maximum activity score	-3.24 (7.96)	192
AMAT total score	-1.47 (2.52)	96

NN109 – MAGINE Study

Enrollment Completed: May 2023

- Final Consented: 68
- Final Randomized: 54
- Follow-up to continue through Q3 2025
- Close out activities to continue through Q4 2025



Modeling Informative Censoring in Progressive Disease Trials

Session: "Stopping Progress: Finding Effective Treatments Using Disease Progression Modeling"

Thomas Jensen, MS

Biostatistician

Berry Consultants

Statistical Innovation

SCT Conference
Vancouver, BC
20 May 2025

Overview

- Motivation
  - What does regulatory guidance say about informative censoring?
- Methods
  - Joint model framework for handling informative censoring in a repeated measures analysis
- Application
  - REMAP-ILD trial planning with joint model primary analysis

Regulatory Guidance for Informative Censoring

Regulatory Guidance for Informative Censoring

Guidance for Sponsors, Clinical Investigators, and IRBs

Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials

Food and Drug Administration. "Guidance for sponsors, clinical investigators, and IRBs: Data retention when subjects withdraw from FDA-regulated clinical trials." *Rockville, MD. Available online at: https://www. fda. gov/regulatory-information/search-fda-guidance-documents/dataretention-when-subjects-withdraw-fda-regulated-clinical-trials(accessed June 19, 2019)* (2008).

Regulatory Guidance for Informative Censoring

Guidance for Sponsors, Clinical Investigators, and IRBs

Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials

There is long-standing concern with the removal of data, particularly when removal is non-random, a situation called "informative censoring."

The validity of a clinical study would also be compromised by the exclusion of data collected during the study. There is long-standing concern with the removal of data, particularly when removal is non-random, a situation called "informative censoring." FDA has long advised "intent-to-treat" analyses (analyzing data related to all subjects the investigator intended to treat), and a variety of approaches for interpretation and imputation of missing data have been developed to maintain study validity.[6] Complete removal of data, possibly in a non-random or informative way, raises great concerns about the validity of the study.

Food and Drug Administration. "Guidance for sponsors, clinical investigators, and IRBs: Data retention when subjects withdraw from FDA-regulated clinical trials." *Rockville, MD. Available online at: https://www. fda. gov/regulatory-information/search-fda-guidance-documents/dataretention-when-subjects-withdraw-fda-regulated-clinical-trials(accessed June 19, 2019)* (2008).

Regulatory Guidance for Informative Censoring

Guidance for Sponsors, Clinical Investigators, and IRBs

Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials

Complete removal of data, possibly in a non-random or informative way, raises great concerns about the validity of the study.

exclusion of
removal of data,
censoring."
all subjects the
on and
imputation of missing data have been developed to maintain study validity.[6] Complete removal of data, possibly in a non-random or informative way, raises great concerns about the validity of the study.

Food and Drug Administration. "Guidance for sponsors, clinical investigators, and IRBs: Data retention when subjects withdraw from FDA-regulated clinical trials." *Rockville, MD. Available online at: https://www. fda. gov/regulatory-information/search-fda-guidance-documents/dataretention-when-subjects-withdraw-fda-regulated-clinical-trials(accessed June 19, 2019)* (2008).

Regulatory Guidance for Informative Censoring

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

2 July 2010
EMA/CPMP/EWP/1776/99 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on Missing Data in Confirmatory Clinical Trials

European Medicines Agency. *Guideline on Missing Data in Confirmatory Clinical Trials*. Rev. 1, 20 Sept. 2010, www.ema.europa.eu/en/documents/scientific-guideline/guideline-missing-data-confirmatory-clinical-trials_en.pdf.

Regulatory Guidance for Informative Censoring

2 July 2010
EMA/CPMP/EWP/1776/99 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on Missing Data in Confirmatory Clinical Trials

Whilst it is unavoidable that some data are missing from all confirmatory clinical trials, it should be noted that just ignoring missing data is not an acceptable option when planning, conducting or interpreting the analysis of a confirmatory clinical trial.

It should be the aim of those conducting clinical trials to achieve complete capture of all data from all patients, including those who discontinue from treatment. Whilst it is unavoidable that some data are missing from all confirmatory clinical trials, it should be noted that just ignoring missing data is not an acceptable option when planning, conducting or interpreting the analysis of a confirmatory clinical trial. The reason for missing data and handling of missing data in the analysis represent critical factors in the regulatory assessment of all confirmatory clinical trials. The main focus of this guideline is issues associated with the analysis of the primary efficacy endpoint where patients are followed up over time.

European Medicines Agency. *Guideline on Missing Data in Confirmatory Clinical Trials*. Rev. 1, 20 Sept. 2010, www.ema.europa.eu/en/documents/scientific-guideline/guideline-missing-data-confirmatory-clinical-trials_en.pdf.

Regulatory Guidance for Informative Censoring

the loss of these non-completers could lead to an underestimate of variability and hence artificially narrow the confidence interval for the treatment effect.

Guideline on Missing Data in Confirmatory Clinical Trials

4.1. Power and Variability

The sample size and the variability of the outcomes affect the power of a clinical trial. The power of a trial will increase if the sample size is increased or if the variability of the outcomes is reduced.

If missing values are handled by simply excluding any patients with missing values from the analysis, this will result in a reduction in the number of cases available for analysis and therefore normally result in a reduction of the statistical power. Clearly, the greater the number of missing values, the greater the likely reduction in power. Hence every effort should be made to minimize the amount of missing data.

Conversely, non-completers might be more likely to have extreme values (treatment failure leading to dropout, extremely good response leading to loss of follow-up). Therefore, the loss of these non-completers could lead to an underestimate of variability and hence artificially narrow the confidence interval for the treatment effect. If the methods used to handle missing data do not adequately take this into account, the resulting confidence interval cannot be considered a valid summary of the uncertainty of the treatment effect.

European Medicines Agency. *Guideline on Missing Data in Confirmatory Clinical Trials*. Rev. 1, 20 Sept. 2010, www.ema.europa.eu/en/documents/scientific-guideline/guideline-missing-data-confirmatory-clinical-trials_en.pdf.

Regulatory Guidance for Informative Censoring

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

the loss of these non-completers could lead to an underestimate of variability and hence artificially narrow the confidence interval for the treatment effect.

The comparability of the treatment groups. A consequence of this may be a bias in the estimation of the treatment effect.

ls

4.1. Power and Variability

The sample size and the variability of the outcomes affect the power of a clinical trial. The power of a trial will increase if the sample size is increased or if the variability of the outcomes is reduced.

4.2. Bias

Bias is the most important concern resulting from missing data. If patients are excluded from the analysis, this may affect:

- The comparability of the treatment groups. A consequence of this may be a bias in the estimation of the treatment effect.
- The representativeness of the study sample in relation to the target population (external validity).

European Medicines Agency. *Guideline on Missing Data in Confirmatory Clinical Trials*. Rev. 1, 20 Sept. 2010, www.ema.europa.eu/en/documents/scientific-guideline/guideline-missing-data-confirmatory-clinical-trials_en.pdf.

Regulatory Guidance for Informative Censoring

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Therefore, approaches that investigate different MNAR scenarios such as a pattern mixture model (PMM), a selection model (SEM) and a shared parameter model (SPM) may be useful.

Guideline on Missing Data in Confirmatory Clinical Trials

Generally, MNAR data is difficult to rule out, and it is not clear whether even a small amount of MNAR data could have an impact on the study results in a particular experiment. Therefore, approaches that investigate different MNAR scenarios such as a pattern mixture model (PMM), a selection model (SEM) and a shared parameter model (SPM) may be useful. A combined strategy incorporating several methods for handling missingness (e.g. assume dropouts due to lack of efficacy and adverse events are MNAR and lost to follow-up are MAR) may also be considered. As described above, methods that do not assume MCAR or MAR such as PMMs may offer a flexible framework to explore the impact of treating different types of missing data as MNAR and evaluating the impact different modelling strategies have on the estimated treatment effect.

European Medicines Agency. *Guideline on Missing Data in Confirmatory Clinical Trials*. Rev. 1, 20 Sept. 2010, www.ema.europa.eu/en/documents/scientific-guideline/guideline-missing-data-confirmatory-clinical-trials_en.pdf.

Regulatory Guidance for Informative Censoring

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Therefore, approaches that investigate different MNAR scenarios such as a pattern mixture model (PMM), a selection model (SEM) and a shared parameter model (SPM) may be useful.

E.g., a joint model

Guideline on Missing Data in Confirmatory Clinical Trials

Generally, MNAR data is difficult to rule out, and it is not clear whether even a small amount of MNAR data could have an impact on the study results in a particular experiment. Therefore, approaches that investigate different MNAR scenarios such as a pattern mixture model (PMM), a selection model (SEM) and a shared parameter model (SPM) may be useful. A combined strategy incorporating several methods for handling missingness (e.g. assume dropouts due to lack of efficacy and adverse events are MNAR and lost to follow-up are MAR) may also be considered. As described above, methods that do not assume MCAR or MAR such as PMMs may offer a flexible framework to explore the impact of treating different types of missing data as MNAR and evaluating the impact different modelling strategies have on the estimated treatment effect.

European Medicines Agency. *Guideline on Missing Data in Confirmatory Clinical Trials*. Rev. 1, 20 Sept. 2010, www.ema.europa.eu/en/documents/scientific-guideline/guideline-missing-data-confirmatory-clinical-trials_en.pdf.

Joint Models of Repeated Measures and Time-to-Event Outcomes

Conventional methods vs joint models (with shared parameters)

Conventional Methods

- Random coefficient models:
  - $p(y_i;\boldsymbol{\theta}) = \int p(y_i \mid \boldsymbol{b_i}, \boldsymbol{\theta}) p(\boldsymbol{b_i};\boldsymbol{\theta}) d\boldsymbol{b_i}$

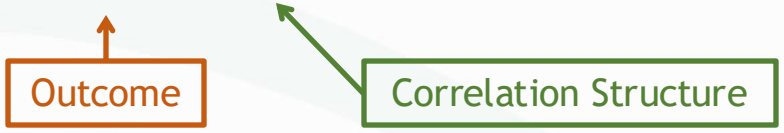
Outcome

Random Effects

Conventional Methods

- Random coefficient models:
  - $p(y_i;\boldsymbol{\theta}) = \int p(y_i \mid \boldsymbol{b_i}, \boldsymbol{\theta}) p(\boldsymbol{b_i};\boldsymbol{\theta}) d\boldsymbol{b_i}$

- MMRM models:
  - $p(y_i;\boldsymbol{\theta}) = p(y_i \mid \boldsymbol{\theta}, \boldsymbol{\Sigma})$



Conventional Methods

- Random coefficient models:
  - $p(y_i;\boldsymbol{\theta}) = \int p(y_i \mid \boldsymbol{b_i}, \boldsymbol{\theta}) p(\boldsymbol{b_i};\boldsymbol{\theta}) d\boldsymbol{b_i}$

Outcome

Random Effects

- MMRM models:
  - $p(y_i;\boldsymbol{\theta}) = p(y_i \mid \boldsymbol{\theta}, \boldsymbol{\Sigma})$

Outcome

Correlation Structure

- Notice: data missingness label, m_i not modeled!
  - Both assume m_i is "ignorable"

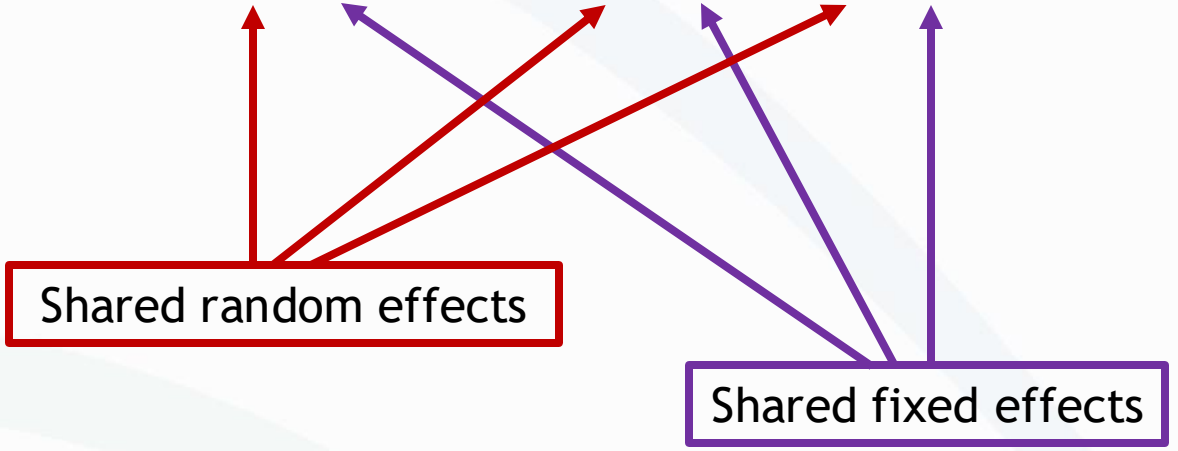
Joint Model Framework

- Joint Model with shared parameters:
  - $p(y_i, m_i; \boldsymbol{\theta}) = \int p(y_i \mid \boldsymbol{b_i}, \boldsymbol{\theta}) p(m_i \mid \boldsymbol{b_i}, \boldsymbol{\theta}) p(\boldsymbol{b_i}; \boldsymbol{\theta}) d\boldsymbol{b_i}$

Rizopoulos, Dimitris. *Joint models for longitudinal and time-to-event data: With applications in R*. CRC press, 2012.

Joint Model Framework

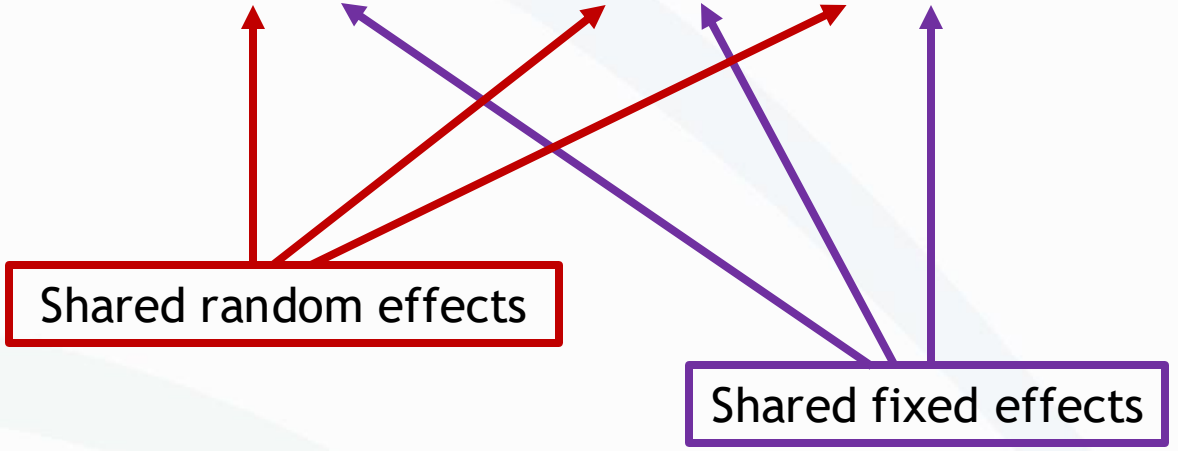
- Joint Model with shared parameters:
  - $p(y_i, m_i; \boldsymbol{\theta}) = \int p(y_i \mid \boldsymbol{b_i}, \boldsymbol{\theta}) p(m_i \mid \boldsymbol{b_i}, \boldsymbol{\theta}) p(\boldsymbol{b_i}; \boldsymbol{\theta}) d\boldsymbol{b_i}$



Rizopoulos, Dimitris. *Joint models for longitudinal and time-to-event data: With applications in R*. CRC press, 2012.

Joint Model Framework

- Joint Model with shared parameters:
  - $p(y_i, m_i; \boldsymbol{\theta}) = \int p(y_i \mid \boldsymbol{b_i}, \boldsymbol{\theta}) p(m_i \mid \boldsymbol{b_i}, \boldsymbol{\theta}) p(\boldsymbol{b_i}; \boldsymbol{\theta}) d\boldsymbol{b_i}$



- **Explicitly models the missingness mechanism driving m_i**
- Does <u>not</u> assume missing data are “ignorable”

Rizopoulos, Dimitris. *Joint models for longitudinal and time-to-event data: With applications in R*. CRC press, 2012.

Joint Model Specification

- Joint model:
  - $p(y_i, m_i; \boldsymbol{\theta}) = p(y_i, s_i; \boldsymbol{\theta}) = \int p(\, y_i \mid \boldsymbol{b_i}, \boldsymbol{\theta}\,) p(\, s_i \mid \boldsymbol{b_i}, \boldsymbol{\theta}\,) p(\boldsymbol{b_i}; \boldsymbol{\theta}) d\boldsymbol{b_i}$

Model survival times s_i

Joint Model Specification

- Joint model:
  - $p(y_i, m_i; \boldsymbol{\theta}) = p(y_i, s_i; \boldsymbol{\theta}) = \int p(\, y_i \mid \boldsymbol{b_i}, \boldsymbol{\theta}\,) p(\, s_i \mid \boldsymbol{b_i}, \boldsymbol{\theta}\,) p(\boldsymbol{b_i}; \boldsymbol{\theta}) d\boldsymbol{b_i}$

- Repeated measures submodel:
  - $y_{ij} = f\left(t_j; \boldsymbol{\theta}, \boldsymbol{b_i}\right) + \epsilon_{ij};\ \ i = 1, \ldots, N;\ \ \ j = 1, \ldots, J_i$

    where $f\left(t_j; \boldsymbol{\theta}, \boldsymbol{b_i}\right)$ is some function of mixed effects.

Joint Model Specification

- Joint model:
  - $p(y_i, m_i; \boldsymbol{\theta}) = p(y_i, s_i; \boldsymbol{\theta}) = \int p(\, y_i \mid \boldsymbol{b_i}, \boldsymbol{\theta}\,) p(\, s_i \mid \boldsymbol{b_i}, \boldsymbol{\theta}\,) p(\boldsymbol{b_i}; \boldsymbol{\theta}) d\boldsymbol{b_i}$

- Repeated measures submodel:
  - $y_{ij} = f\left(t_j; \boldsymbol{\theta}, \boldsymbol{b_i}\right) + \epsilon_{ij}; \;\; i = 1, \ldots, N, \;\; j = 1, \ldots, J_i$

    where $f\left(t_j; \boldsymbol{\theta}, \boldsymbol{b_i}\right)$ is some function of mixed effects.

- Time-to-event submodel:
  - $h_i(s) = h_0(s) \exp\left(\boldsymbol{\eta} * g(s; \boldsymbol{\theta}, \boldsymbol{b_i})\right)$

    where $\boldsymbol{\eta}$ is the **association** between the repeated measures and time-to-event outcomes

Joint Model Specification

- Joint model:
  - $p(y_i, m_i; \boldsymbol{\theta}) = p(y_i, s_i; \boldsymbol{\theta}) = \int p(y_i \mid \boldsymbol{b_i}, \boldsymbol{\theta}) p(s_i \mid \boldsymbol{b_i}, \boldsymbol{\theta}) p(\boldsymbol{b_i}; \boldsymbol{\theta}) d\boldsymbol{b_i}$

- Repeated measures submodel:
  - $y_{ij} = f(t_j; \boldsymbol{\theta}, \boldsymbol{b_i}) + \epsilon_{ij};\ i = 1, \ldots, N;\ \ j = 1, \ldots, J_i$

    where $f(t_j; \boldsymbol{\theta}, \boldsymbol{b_i})$ is some function of mixed effects.

- Time-to-event submodel:
  - $h_i(s) = h_0(s) \exp(\boldsymbol{\eta} * g(s; \boldsymbol{\theta}, \boldsymbol{b_i}))$

    where $\boldsymbol{\eta}$ is the association between the repeated measures and time-to-event outcomes

f and g *not necessarily* the same function

Joint Model Specification

- Joint model:
  - $p(y_i, m_i; \boldsymbol{\theta}) = p(y_i, s_i; \boldsymbol{\theta}) = \int p(y_i \mid \boldsymbol{b_i}, \boldsymbol{\theta}) p(s_i \mid \boldsymbol{b_i}, \boldsymbol{\theta}) p(\boldsymbol{b_i}; \boldsymbol{\theta}) d\boldsymbol{b_i}$

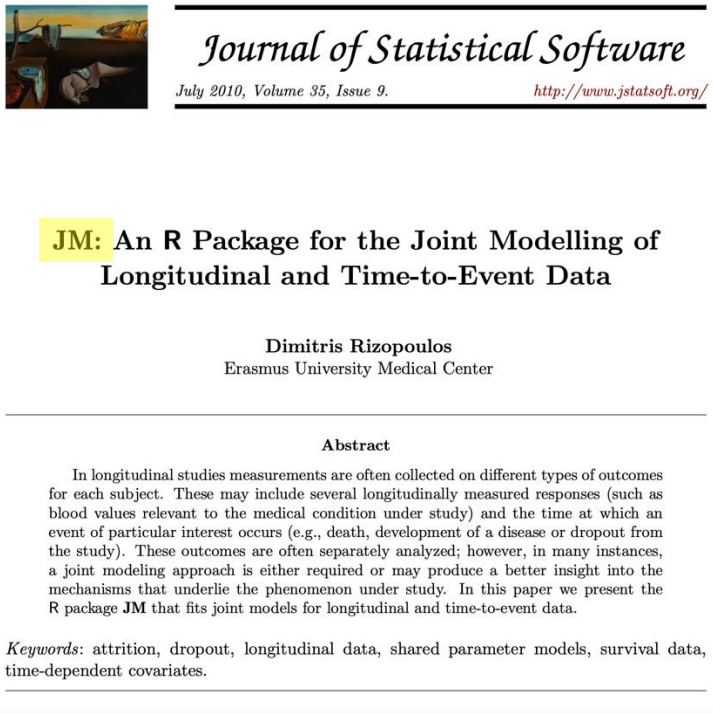
- Repeated measures submodel:
  - $y_{ij} = f(t_j; \boldsymbol{\theta}, \boldsymbol{b_i}) + \epsilon_{ij}$; $i = 1, \ldots, N; \quad j = 1, \ldots, J_i$
    where $f(t_j; \boldsymbol{\theta}, \boldsymbol{b_i})$ is some function of mixed effects.

- Time-to-event submodel:
  - $h_i(s) = h_0(s) \exp(\boldsymbol{\eta} * g(s; \boldsymbol{\theta}, \boldsymbol{b_i}))$
    where η is the association between the repeated measures and time-to-event outcomes

Shared parameters

Joint Model Applications

- Software available in R
  - Frequentist (***JM***; left) and Bayesian (***rstanarm***; right)



Journal of Statistical Software
July 2010, Volume 35, Issue 9. http://www.jstatsoft.org/

JM: An R Package for the Joint Modelling of Longitudinal and Time-to-Event Data

Dimitris Rizopoulos
Erasmus University Medical Center

Abstract

In longitudinal studies measurements are often collected on different types of outcomes for each subject. These may include several longitudinally measured responses (such as blood values relevant to the medical condition under study) and the time at which an event of particular interest occurs (e.g., death, development of a disease or dropout from the study). These outcomes are often separately analyzed; however, in many instances, a joint modeling approach is either required or may produce a better insight into the mechanisms that underlie the phenomenon under study. In this paper we present the R package **JM** that fits joint models for longitudinal and time-to-event data.

Keywords: attrition, dropout, longitudinal data, shared parameter models, survival data, time-dependent covariates.

Estimating Joint Models for Longitudinal and Time-to-Event Data with rstanarm

Sam Brilleman

2024-01-16

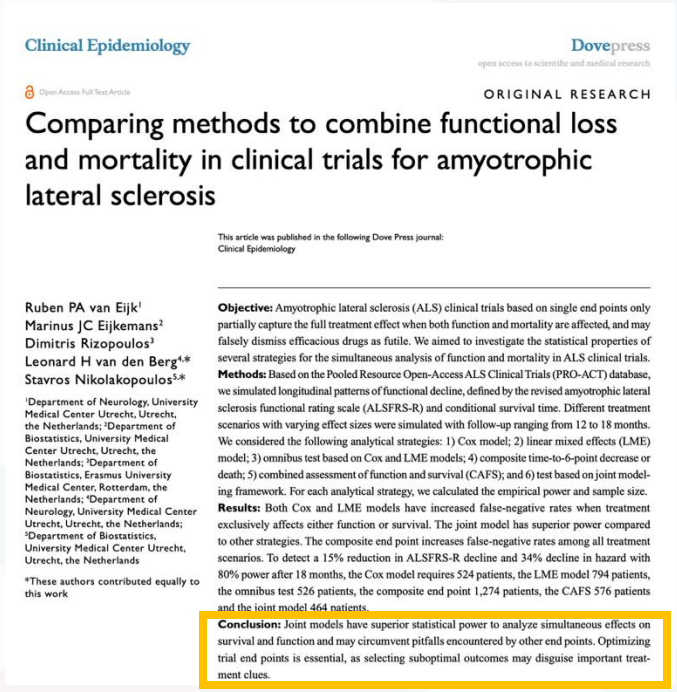
- Preamble
- Introduction
- Technical details
  - Model formulation
    - Longitudinal submodel(s)
    - Event submodel
    - Association structures
    - Assumptions
    - Log posterior distribution
  - Model predictions
    - Individual-specific predictions for in-sample individuals (for $0 \leq t \leq T_i$)
    - Individual-specific predictions for in-sample individuals (for $t > C_i$)
    - Individual-specific predictions for out-of-sample individuals (i.e. dynamic predictions)
    - Population-level (i.e. marginal) predictions
    - Standardised survival probabilities
  - Model extensions
    - Delayed entry (left-truncation)
    - Multilevel clustering
  - Model comparison
    - LOO/WAIC in the context of joint models
- Usage examples
  - Dataset used in the examples
  - Fitting the models
    - Univariate joint model (current value association structure)
    - Univariate joint model (current value and current slope association structure)
    - Multivariate joint model (current value association structures)
  - Posterior predictions
    - Predicted individual-specific longitudinal trajectory for in-sample individuals
    - Predicted individual-specific survival curves for in-sample individuals
    - Combined plot of longitudinal trajectories and survival curves
    - Predicted individual-specific longitudinal trajectory and survival curve for out-of-sample individuals (i.e. dynamic predictions)
    - Predicted population-level longitudinal trajectory
    - Standardised survival curves
- References

Rizopoulos, Dimitris. "JM: An R package for the joint modelling of longitudinal and time-to-event data." *Journal of statistical software* 35 (2010): 1-33.

Brilleman, Sam. *Estimating Joint Models for Longitudinal and Time-to-Event Data with rstanarm*. R package vignette, version 2.32.1, 16 Jan. 2024, https://cran.r-project.org/web/packages/rstanarm/vignettes/jm.html.

Joint Model Applications

- Examples of joint model analyses in ALS (left)



Clinical Epidemiology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Comparing methods to combine functional loss and mortality in clinical trials for amyotrophic lateral sclerosis

This article was published in the following Dove Press journal:
Clinical Epidemiology

Ruben PA van Eijk[1]
Marinus JC Eijkemans[2]
Dimitris Rizopoulos[3]
Leonard H van den Berg[4,*]
Stavros Nikolakopoulos[5,*]

[1]Department of Neurology, University Medical Center Utrecht, Utrecht, the Netherlands; [2]Department of Biostatistics, University Medical Center Utrecht, Utrecht, the Netherlands; [3]Department of Biostatistics, Erasmus University Medical Center, Rotterdam, the Netherlands; [4]Department of Neurology, University Medical Center Utrecht, Utrecht, the Netherlands; [5]Department of Biostatistics, University Medical Center Utrecht, Utrecht, the Netherlands

*These authors contributed equally to this work

Objective: Amyotrophic lateral sclerosis (ALS) clinical trials based on single end points only partially capture the full treatment effect when both function and mortality are affected, and may falsely dismiss efficacious drugs as futile. We aimed to investigate the statistical properties of several strategies for the simultaneous analysis of function and mortality in ALS clinical trials.

Methods: Based on the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database, we simulated longitudinal patterns of functional decline, defined by the revised amyotrophic lateral sclerosis functional rating scale (ALSFRS-R) and conditional survival time. Different treatment scenarios with varying effect sizes were simulated with follow-up ranging from 12 to 18 months. We considered the following analytical strategies: 1) Cox model; 2) linear mixed effects (LME) model; 3) omnibus test based on Cox and LME models; 4) composite time-to-6-point decrease or death; 5) combined assessment of function and survival (CAFS); and 6) test based on joint modeling framework. For each analytical strategy, we calculated the empirical power and sample size.

Results: Both Cox and LME models have increased false-negative rates when treatment exclusively affects either function or survival. The joint model has superior power compared to other strategies. The composite end point increases false-negative rates among all treatment scenarios. To detect a 15% reduction in ALSFRS-R decline and 34% decline in hazard with 80% power after 18 months, the Cox model requires 524 patients, the LME model 794 patients, the omnibus test 526 patients, the composite end point 1,274 patients, the CAFS 576 patients and the joint model 464 patients.

Conclusion: Joint models have superior statistical power to analyze simultaneous effects on survival and function and may circumvent pitfalls encountered by other end points. Optimizing trial end points is essential, as selecting suboptimal outcomes may disguise important treatment clues.

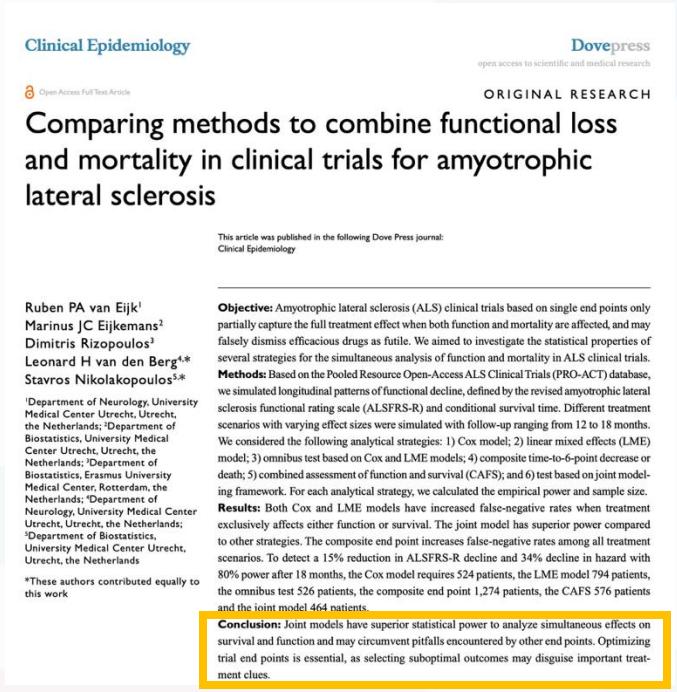
Conclusion: Joint models have superior statistical power to analyze simultaneous effects on survival and function and may circumvent pitfalls encountered by other end points. Optimizing trial end points is essential, as selecting suboptimal outcomes may disguise important treatment clues.

Van Eijk, Ruben PA, et al. "Comparing methods to combine functional loss and mortality in clinical trials for amyotrophic lateral sclerosis." *Clinical epidemiology* (2018): 333-341.

Kreuter, Michael, et al. "Impact of lung function decline on time to hospitalisation events in systemic sclerosis-associated interstitial lung disease (SSc-ILD): a joint model analysis." *Arthritis Research & Therapy* 24 (2022): 1-9.

Joint Model Applications

- Examples of joint model analyses in ALS (left) and ILD (right) studies



Clinical Epidemiology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Comparing methods to combine functional loss and mortality in clinical trials for amyotrophic lateral sclerosis

This article was published in the following Dove Press journal:
Clinical Epidemiology

Ruben PA van Eijk[1]
Marinus JC Eijkemans[2]
Dimitris Rizopoulos[3]
Leonard H van den Berg[4,*]
Stavros Nikolakopoulos[5,*]

[1]Department of Neurology, University Medical Center Utrecht, Utrecht, the Netherlands; [2]Department of Biostatistics, University Medical Center Utrecht, Utrecht, the Netherlands; [3]Department of Biostatistics, Erasmus University Medical Center, Rotterdam, the Netherlands; [4]Department of Neurology, University Medical Center Utrecht, Utrecht, the Netherlands; [5]Department of Biostatistics, University Medical Center Utrecht, Utrecht, the Netherlands

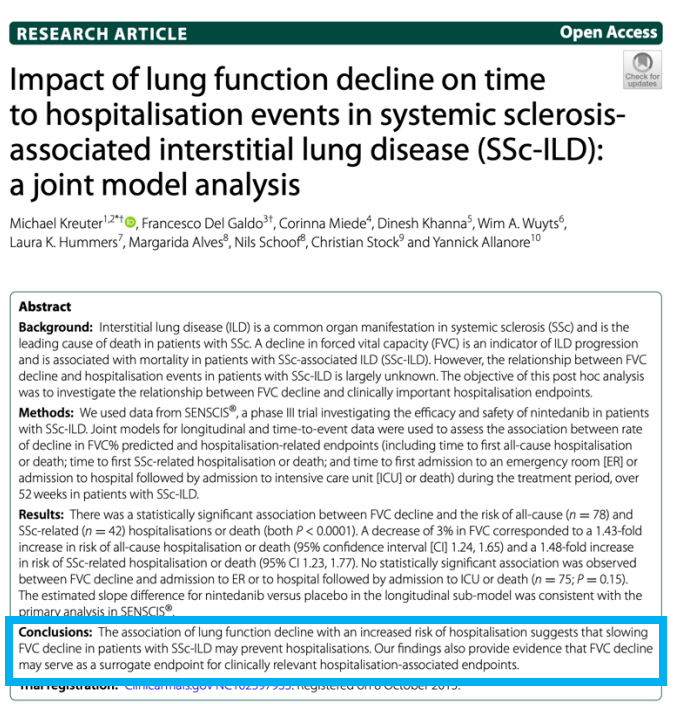
*These authors contributed equally to this work

Objective: Amyotrophic lateral sclerosis (ALS) clinical trials based on single end points only partially capture the full treatment effect when both function and mortality are affected, and may falsely dismiss efficacious drugs as futile. We aimed to investigate the statistical properties of several strategies for the simultaneous analysis of function and mortality in ALS clinical trials.

Methods: Based on the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database, we simulated longitudinal patterns of functional decline, defined by the revised amyotrophic lateral sclerosis functional rating scale (ALSFRS-R) and conditional survival time. Different treatment scenarios with varying effect sizes were simulated with follow-up ranging from 12 to 18 months. We considered the following analytical strategies: 1) Cox model; 2) linear mixed effects (LME) model; 3) omnibus test based on Cox and LME models; 4) composite time-to-6-point decrease or death; 5) combined assessment of function and survival (CAFS); and 6) test based on joint modeling framework. For each analytical strategy, we calculated the empirical power and sample size.

Results: Both Cox and LME models have increased false-negative rates when treatment exclusively affects either function or survival. The joint model has superior power compared to other strategies. The composite end point increases false-negative rates among all treatment scenarios. To detect a 15% reduction in ALSFRS-R decline and 34% decline in hazard with 80% power after 18 months, the Cox model requires 524 patients, the LME model 794 patients, the omnibus test 526 patients, the composite end point 1,274 patients, the CAFS 576 patients and the joint model 464 patients.

Conclusion: Joint models have superior statistical power to analyze simultaneous effects on survival and function and may circumvent pitfalls encountered by other end points. Optimizing trial end points is essential, as selecting suboptimal outcomes may disguise important treatment clues.



RESEARCH ARTICLE Open Access

Impact of lung function decline on time to hospitalisation events in systemic sclerosis-associated interstitial lung disease (SSc-ILD): a joint model analysis

Michael Kreuter[1,2*†], Francesco Del Galdo[3†], Corinna Miede[4], Dinesh Khanna[5], Wim A. Wuyts[6], Laura K. Hummers[7], Margarida Alves[8], Nils Schoof[8], Christian Stock[9] and Yannick Allanore[10]

Abstract

Background: Interstitial lung disease (ILD) is a common organ manifestation in systemic sclerosis (SSc) and is the leading cause of death in patients with SSc. A decline in forced vital capacity (FVC) is an indicator of ILD progression and is associated with mortality in patients with SSc-associated ILD (SSc-ILD). However, the relationship between FVC decline and hospitalisation events in patients with SSc-ILD is largely unknown. The objective of this post hoc analysis was to investigate the relationship between FVC decline and clinically important hospitalisation endpoints.

Methods: We used data from SENSCIS®, a phase III trial investigating the efficacy and safety of nintedanib in patients with SSc-ILD. Joint models for longitudinal and time-to-event data were used to assess the association between rate of decline in FVC% predicted and hospitalisation-related endpoints (including time to first all-cause hospitalisation or death; time to first SSc-related hospitalisation or death; and time to first admission to an emergency room [ER] or admission to hospital followed by admission to intensive care unit [ICU] or death) during the treatment period, over 52 weeks in patients with SSc-ILD.

Results: There was a statistically significant association between FVC decline and the risk of all-cause ($n = 78$) and SSc-related ($n = 42$) hospitalisations or death (both $P < 0.0001$). A decrease of 3% in FVC corresponded to a 1.43-fold increase in risk of all-cause hospitalisation or death (95% confidence interval [CI] 1.24, 1.65) and a 1.48-fold increase in risk of SSc-related hospitalisation or death (95% CI 1.23, 1.77). No statistically significant association was observed between FVC decline and admission to ER or to hospital followed by admission to ICU or death ($n = 75$; $P = 0.15$). The estimated slope difference for nintedanib versus placebo in the longitudinal sub-model was consistent with the primary analysis in SENSCIS®.

Conclusions: The association of lung function decline with an increased risk of hospitalisation suggests that slowing FVC decline in patients with SSc-ILD may prevent hospitalisations. Our findings also provide evidence that FVC decline may serve as a surrogate endpoint for clinically relevant hospitalisation-associated endpoints.

Conclusion: Joint models have superior statistical power to analyze simultaneous effects on survival and function and may circumvent pitfalls encountered by other end points. Optimizing trial end points is essential, as selecting suboptimal outcomes may disguise important treatment clues.

Conclusions: The association of lung function decline with an increased risk of hospitalisation suggests that slowing FVC decline in patients with SSc-ILD may prevent hospitalisations. Our findings also provide evidence that FVC decline may serve as a surrogate endpoint for clinically relevant hospitalisation-associated endpoints.

Van Eijk, Ruben PA, et al. "Comparing methods to combine functional loss and mortality in clinical trials for amyotrophic lateral sclerosis." *Clinical epidemiology* (2018): 333-341.

Kreuter, Michael, et al. "Impact of lung function decline on time to hospitalisation events in systemic sclerosis-associated interstitial lung disease (SSc-ILD): a joint model analysis." *Arthritis Research & Therapy* 24 (2022): 1-9.

REMAP-ILD

Joint model primary analysis for REMAP-ILD trial

REMAP-ILD

- **R**andomized,
  Embedded,
  Multifactorial,
  Adaptive,
  Platform

  Interstitial
  Lung
  Disease.

- Website: https://remap-ild.org/

- Currently in planning stage.

- Primary analysis is a joint analysis of forced vital capacity (FVC) and survival times.

Adaptive multi-interventional trial platform to improve patient care for fibrotic interstitial lung diseases

Leticia Kawano-Dourado [1,2,3] Tejaswini Kulkarni [4] Christopher J Ryerson,[5] Pilar Rivera-Ortega,[6] Bruno Guedes Baldi [2] Nazia Chaudhuri,[7] Manuela Funke-Chambour,[8] Anna-Maria Hoffmann-Vold,[9,10] Kerri A Johannson [11] Yet Hong Khor [12,13] Sydney B Montesi,[14] Lucilla Piccari [15] Helmut Prosch,[16] María Molina-Molina,[17] Jacobo Sellares Torres [18] Iazsmin Bauer-Ventura,[19] Sujeet Rajan,[20] Joseph Jacob [21,22] Duncan Richards [23] Lisa G Spencer,[24] Barbara Wendelberger,[25] Tom Jensen,[25] Melanie Quintana,[25] Michael Kreuter,[26] Anthony C Gordon [27] Fernando J Martinez,[28] Naftali Kaminski [29] Victoria Cornelius,[30] Roger Lewis,[31] Wendy Adams,[32] Gisli Jenkins [33] REMAP-ILD consortium

ABSTRACT

Background Fibrotic interstitial lung diseases (fILDs) are a heterogeneous group of lung diseases associated with significant morbidity and mortality. Despite a large increase in the number of clinical trials in the last 10 years, current regulatory-approved management approaches are limited to two therapies that prevent the progression of fibrosis. The drug development pipeline is long and there is an urgent need to accelerate this process. This manuscript introduces the concept and design of an innovative research approach to drug development in fILD: a global Randomised Embedded Multifactorial Adaptive Platform in fILD (REMAP-ILD).

Methods Description of the REMAP-ILD concept and design: the specific terminology, design characteristics (multifactorial, adaptive features, statistical approach), target population, interventions, outcomes, mission and values, and organisational structure.

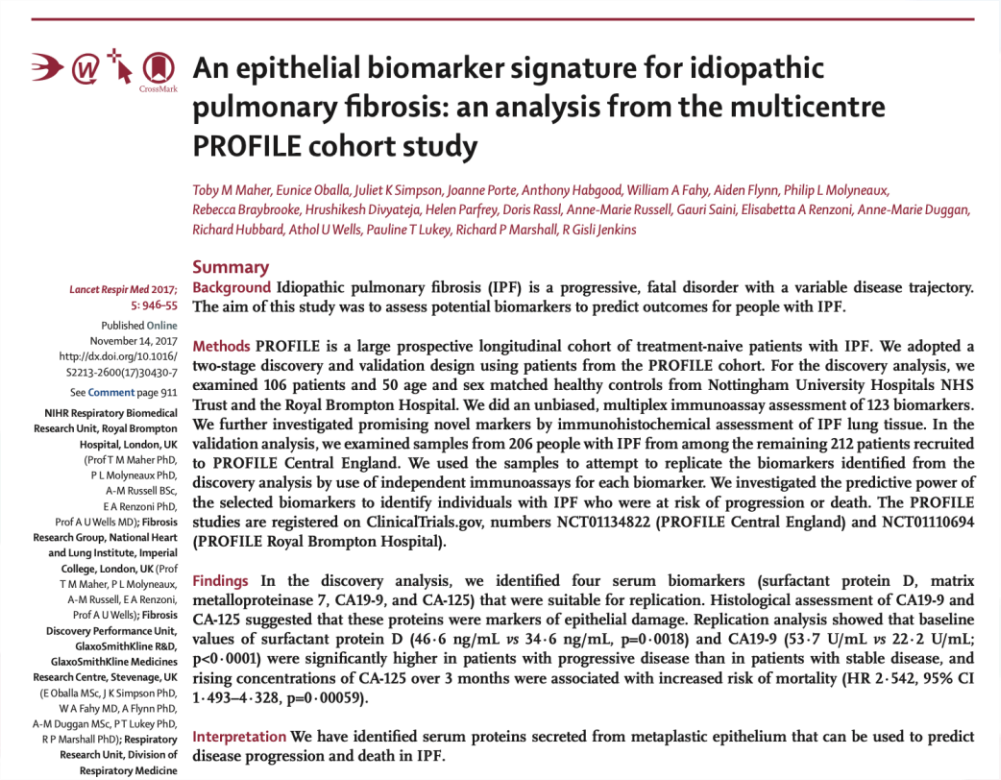
BACKGROUND

Interstitial lung diseases (ILDs) are a group of pulmonary disorders that occur due to a variety of causes, including many different environmental and genetic factors.[1–4] ILDs are often subcategorised as fibrotic, inflammatory or fibroinflammatory based on clinical and radiological features, and in some cases, supplemented with immunological and histological data. Patients with fibrotic ILD (fILD) typically have a poor prognosis, with significant morbidity and mortality.[5–8] There is an urgent unmet need for better pharmacological and non-pharmacological therapies for patients affected by fILD.[9]

Standard of care for fILD varies substantially, even for those fILDs where guidelines exist. The heterogeneity in the management of fILD reflects the lack of robust evidence in the field.[10–13] Conversely, development of new therapeutic agents has been limited by the complexity and heteroge-

REMAP-ILD Planning

- **PROFILE** and **INJUSTIS** cohorts followed ILD patients for 2+ years
  - FVC and survival data for N=892 analyzed with joint model



An epithelial biomarker signature for idiopathic pulmonary fibrosis: an analysis from the multicentre PROFILE cohort study

Toby M Maher, Eunice Oballa, Juliet K Simpson, Joanne Porte, Anthony Habgood, William A Fahy, Aiden Flynn, Philip L Molyneaux, Rebecca Braybrooke, Hrushikesh Divyateja, Helen Parfrey, Doris Rassl, Anne-Marie Russell, Gauri Saini, Elisabetta A Renzoni, Anne-Marie Duggan, Richard Hubbard, Athol U Wells, Pauline T Lukey, Richard P Marshall, R Gisli Jenkins

Lancet Respir Med 2017; 5: 946–55
Published Online November 14, 2017 http://dx.doi.org/10.1016/S2213-2600(17)30430-7
See Comment page 911

NIHR Respiratory Biomedical Research Unit, Royal Brompton Hospital, London, UK (Prof T M Maher PhD, P L Molyneaux PhD, A-M Russell BSc, E A Renzoni PhD, Prof A U Wells MD); **Fibrosis Research Group, National Heart and Lung Institute, Imperial College, London, UK** (Prof T M Maher, P L Molyneaux, A-M Russell, E A Renzoni, Prof A U Wells); **Fibrosis Discovery Performance Unit, GlaxoSmithKline R&D, GlaxoSmithKline Medicines Research Centre, Stevenage, UK** (E Oballa MSc, J K Simpson PhD, W A Fahy MD, A Flynn PhD, A-M Duggan MSc, P T Lukey PhD, R P Marshall PhD); **Respiratory Research Unit, Division of Respiratory Medicine**

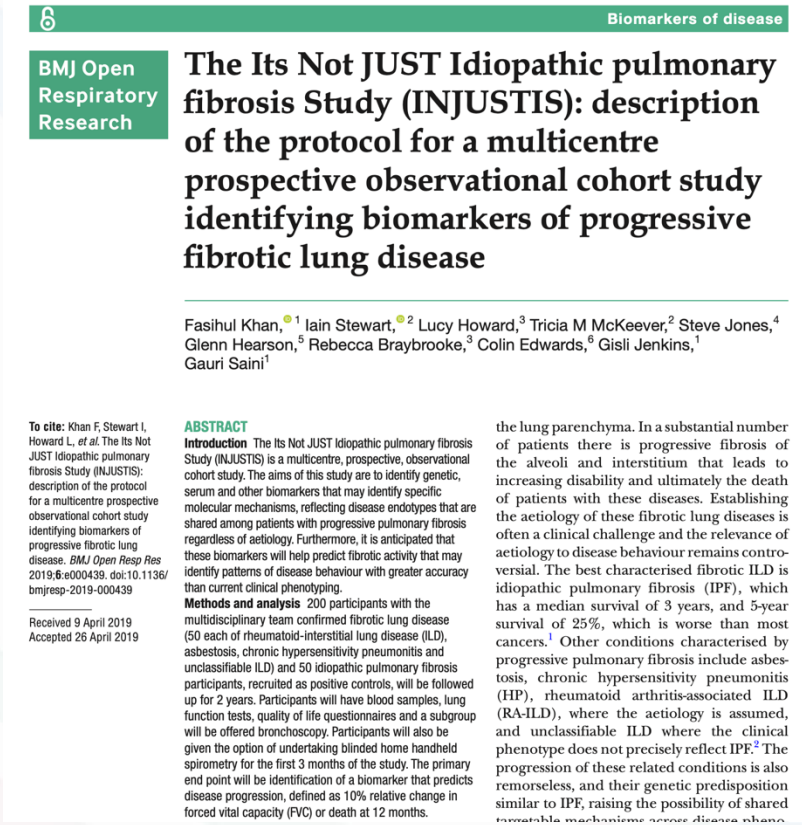
Summary

Background Idiopathic pulmonary fibrosis (IPF) is a progressive, fatal disorder with a variable disease trajectory. The aim of this study was to assess potential biomarkers to predict outcomes for people with IPF.

Methods PROFILE is a large prospective longitudinal cohort of treatment-naive patients with IPF. We adopted a two-stage discovery and validation design using patients from the PROFILE cohort. For the discovery analysis, we examined 106 patients and 50 age and sex matched healthy controls from Nottingham University Hospitals NHS Trust and the Royal Brompton Hospital. We did an unbiased, multiplex immunoassay assessment of 123 biomarkers. We further investigated promising novel markers by immunohistochemical assessment of IPF lung tissue. In the validation analysis, we examined samples from 206 people with IPF from among the remaining 212 patients recruited to PROFILE Central England. We used the samples to attempt to replicate the biomarkers identified from the discovery analysis by use of independent immunoassays for each biomarker. We investigated the predictive power of the selected biomarkers to identify individuals with IPF who were at risk of progression or death. The PROFILE studies are registered on ClinicalTrials.gov, numbers NCT01134822 (PROFILE Central England) and NCT01110694 (PROFILE Royal Brompton Hospital).

Findings In the discovery analysis, we identified four serum biomarkers (surfactant protein D, matrix metalloproteinase 7, CA19-9, and CA-125) that were suitable for replication. Histological assessment of CA19-9 and CA-125 suggested that these proteins were markers of epithelial damage. Replication analysis showed that baseline values of surfactant protein D (46·6 ng/mL *vs* 34·6 ng/mL, p=0·0018) and CA19-9 (53·7 U/mL *vs* 22·2 U/mL; p<0·0001) were significantly higher in patients with progressive disease than in patients with stable disease, and rising concentrations of CA-125 over 3 months were associated with increased risk of mortality (HR 2·542, 95% CI 1·493–4·328, p=0·00059).

Interpretation We have identified serum proteins secreted from metaplastic epithelium that can be used to predict disease progression and death in IPF.



BMJ Open Respiratory Research

The Its Not JUST Idiopathic pulmonary fibrosis Study (INJUSTIS): description of the protocol for a multicentre prospective observational cohort study identifying biomarkers of progressive fibrotic lung disease

Fasihul Khan,[1] Iain Stewart,[2] Lucy Howard,[3] Tricia M McKeever,[2] Steve Jones,[4] Glenn Hearson,[5] Rebecca Braybrooke,[3] Colin Edwards,[6] Gisli Jenkins,[1] Gauri Saini[1]

To cite: Khan F, Stewart I, Howard L, *et al*. The Its Not JUST Idiopathic pulmonary fibrosis Study (INJUSTIS): description of the protocol for a multicentre prospective observational cohort study identifying biomarkers of progressive fibrotic lung disease. *BMJ Open Resp Res* 2019;**6**:e000439. doi:10.1136/bmjresp-2019-000439

Received 9 April 2019
Accepted 26 April 2019

ABSTRACT

Introduction The Its Not JUST Idiopathic pulmonary fibrosis Study (INJUSTIS) is a multicentre, prospective, observational cohort study. The aims of this study are to identify genetic, serum and other biomarkers that may identify specific molecular mechanisms, reflecting disease endotypes that are shared among patients with progressive pulmonary fibrosis regardless of aetiology. Furthermore, it is anticipated that these biomarkers will help predict fibrotic activity that may identify patterns of disease behaviour with greater accuracy than current clinical phenotyping.

Methods and analysis 200 participants with the multidisciplinary team confirmed fibrotic lung disease (50 each of rheumatoid-interstitial lung disease (ILD), asbestosis, chronic hypersensitivity pneumonitis and unclassifiable ILD) and 50 idiopathic pulmonary fibrosis participants, recruited as positive controls, will be followed up for 2 years. Participants will have blood samples, lung function tests, quality of life questionnaires and a subgroup will be offered bronchoscopy. Participants will also be given the option of undertaking blinded home handheld spirometry for the first 3 months of the study. The primary end point will be identification of a biomarker that predicts disease progression, defined as 10% relative change in forced vital capacity (FVC) or death at 12 months.

the lung parenchyma. In a substantial number of patients there is progressive fibrosis of the alveoli and interstitium that leads to increasing disability and ultimately the death of patients with these diseases. Establishing the aetiology of these fibrotic lung diseases is often a clinical challenge and the relevance of aetiology to disease behaviour remains controversial. The best characterised fibrotic ILD is idiopathic pulmonary fibrosis (IPF), which has a median survival of 3 years, and 5-year survival of 25%, which is worse than most cancers.[1] Other conditions characterised by progressive pulmonary fibrosis include asbestosis, chronic hypersensitivity pneumonitis (HP), rheumatoid arthritis-associated ILD (RA-ILD), where the aetiology is assumed, and unclassifiable ILD where the clinical phenotype does not precisely reflect IPF.[2] The progression of these related conditions is also remorseless, and their genetic predisposition similar to IPF, raising the possibility of shared

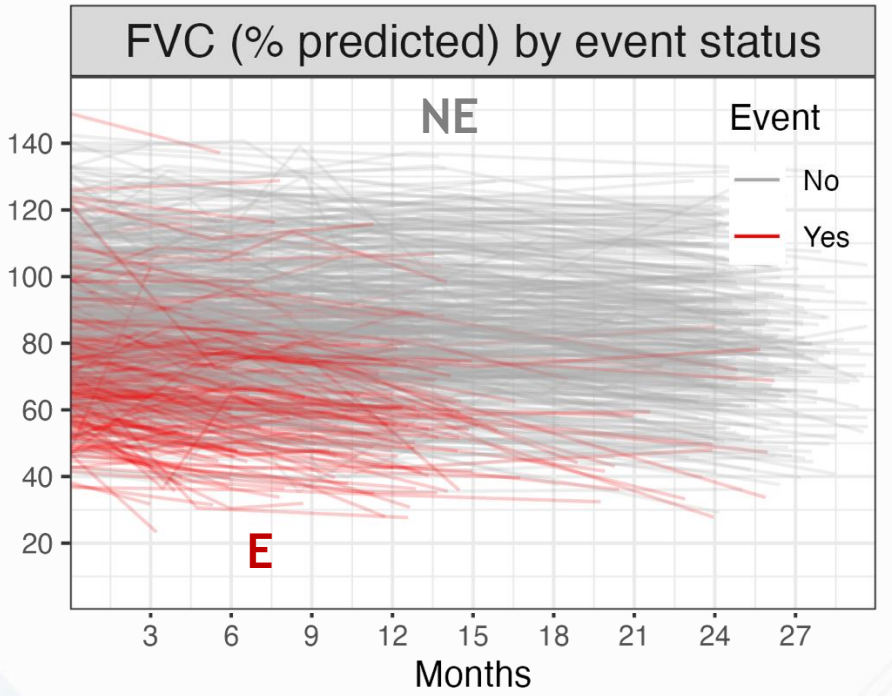
Maher, Toby M., et al. "An epithelial biomarker signature for idiopathic pulmonary fibrosis: an analysis from the multicentre PROFILE cohort study." *The Lancet Respiratory Medicine* 5.12 (2017): 946-955.

Khan, Fasihul, et al. "The Its Not JUST Idiopathic pulmonary fibrosis Study (INJUSTIS): description of the protocol for a multicentre prospective observational cohort study identifying biomarkers of progressive fibrotic lung disease." *BMJ open respiratory research* 6.1 (2019): e000439.

Berry Consultants

REMAP-ILD Planning
Application of real world data

- Line plot shows individual trajectories of FVC progression over 2.5 years
  - Red lines indicate person had an event (died) during the study
  - **Low FVC correlated with high mortality!**

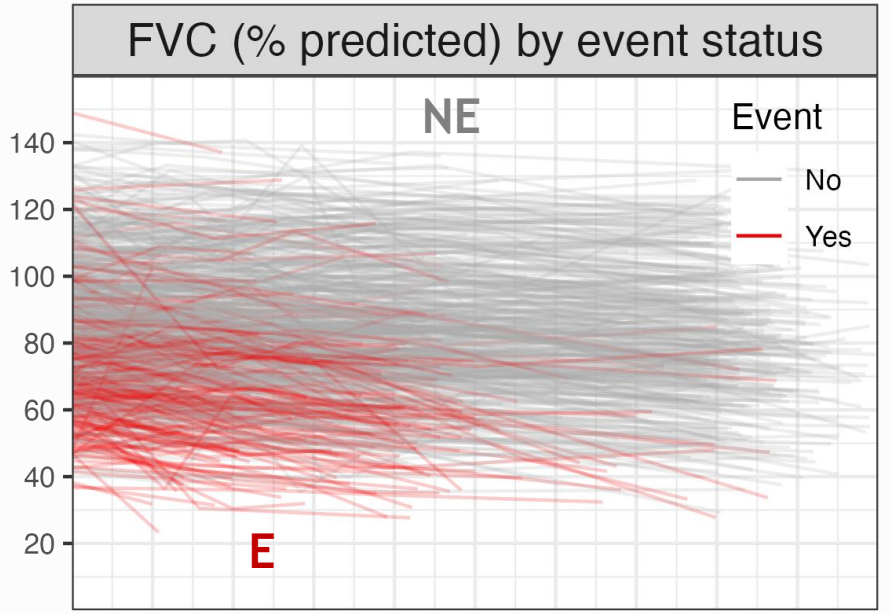


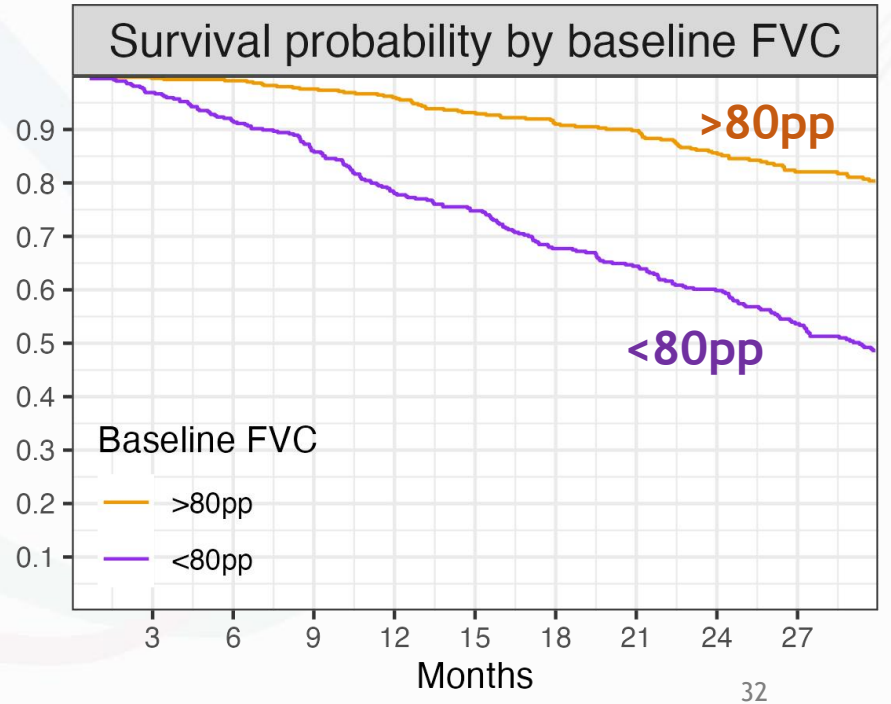
Individual-level data from PROFILE and INJUSTIS cohort studies

REMAP-ILD Planning
Application of real world data

- Line plot shows individual trajectories of FVC progression over 2.5 years
  - Red lines indicate person had an event (died) during the study
  - **Low FVC correlated with high mortality!**

- Kaplan-Meier plot shows separate curves by baseline FVC value
  - **Again, low FVC correlated with high mortality!**





Individual-level data from PROFILE and INJUSTIS cohort studies

Berry Consultants

REMAP-ILD Model

- Repeated measures submodel:
  - $y_{ij} = \boldsymbol{\mu_i(t_j)} + \epsilon_{ij}$

Model-estimated FVC **"Value"**

REMAP-ILD Model

- Repeated measures submodel:
  - $y_{ij} = \boldsymbol{\mu_i(t_j)} + \epsilon_{ij}$

Model-estimated FVC "**Value**"

- Time-to-event (mortality) submodel:
  - $h_i(s) = h_0(s)\exp\left(\eta_1 \boldsymbol{\mu_i(t_j)} + \eta_2 \boldsymbol{\mu_i'(t_j)}\right)$

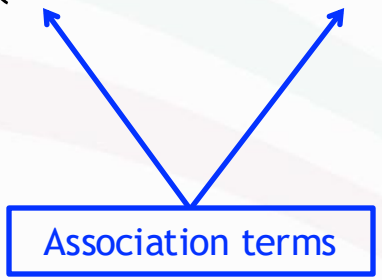
FVC "**Value**"

FVC "**Slope**"

REMAP-ILD Model

- Repeated measures submodel:
  - $y_{ij} = \boldsymbol{\mu_i(t_j)} + \epsilon_{ij}$

- Time-to-event (mortality) submodel:
  - $h_i(s) = h_0(s)\exp\left(\eta_1 \boldsymbol{\mu_i(t_j)} + \eta_2 \boldsymbol{\mu_i'(t_j)}\right)$



	$\Pr(< 0 \mid \textbf{Data})$
η_1	1.000
η_2	1.000

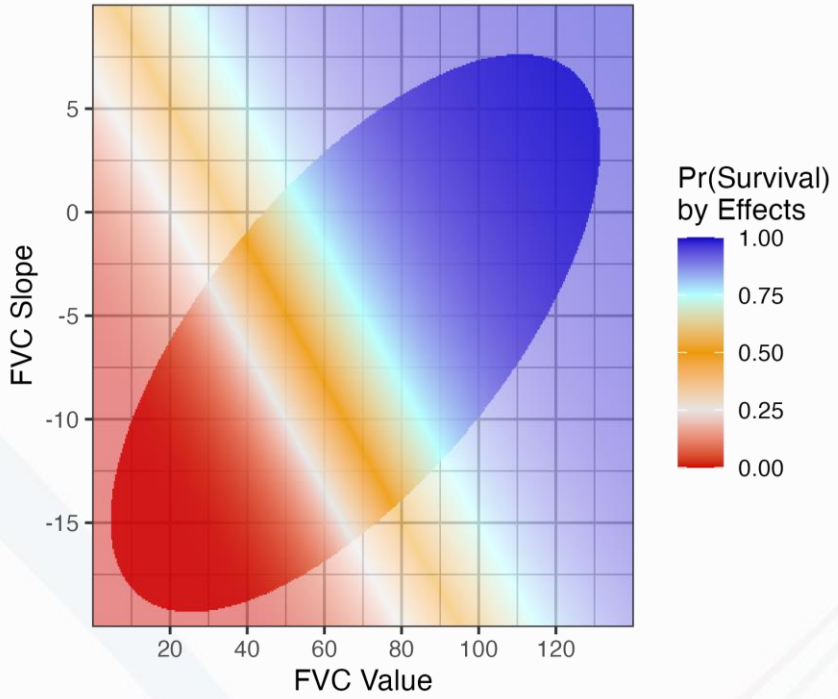
REMAP-ILD Model

- Repeated measures submodel:
  - $y_{ij} = \boldsymbol{\mu_i(t_j)} + \epsilon_{ij}$

- Time-to-event (mortality) submodel:
  - $h_i(s) = h_0(s)\exp\left(\eta_1 \boldsymbol{\mu_i(t_j)} + \eta_2 \boldsymbol{\mu_i'(t_j)}\right)$

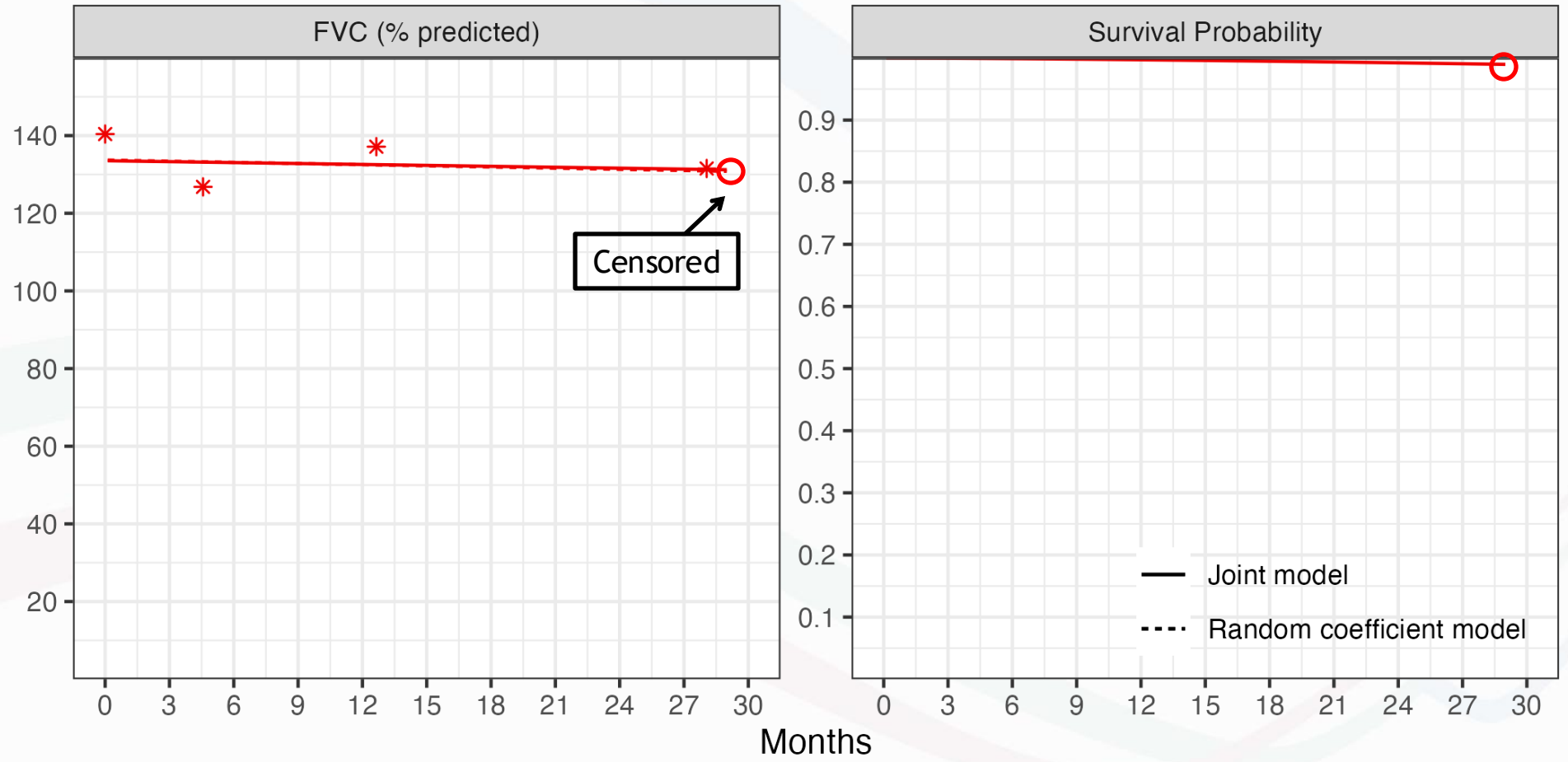
Association terms

Survival Probability at 2.5 years by FVC "Value" (**x**) and FVC "Slope" (**y**)



	$\Pr(< 0 \mid \textbf{Data})$
η_1	**1.000**
η_2	**1.000**

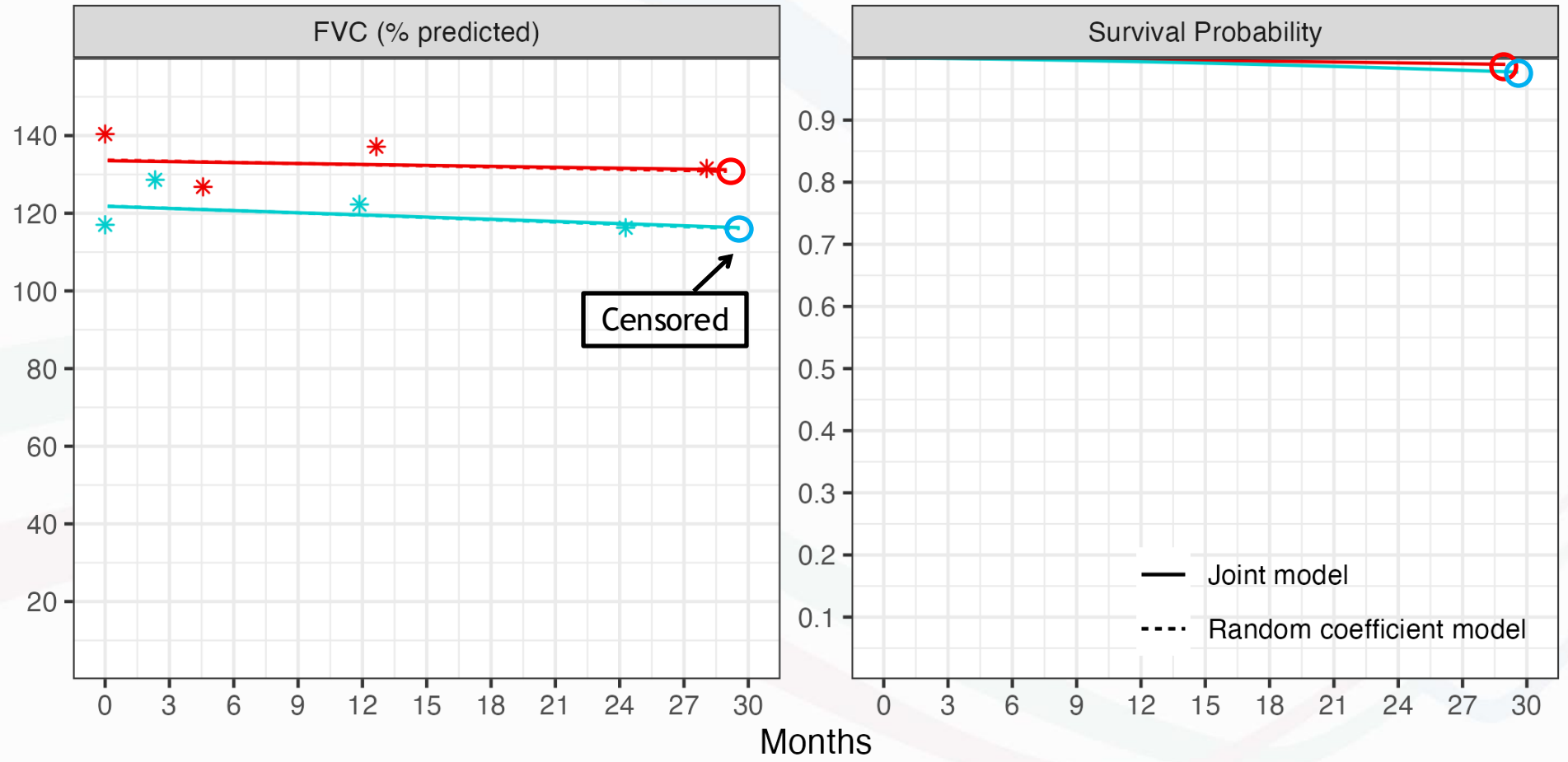
REMAP-ILD Model Fit



Individual-level data from PROFILE and INJUSTIS cohort studies

Berry Consultants

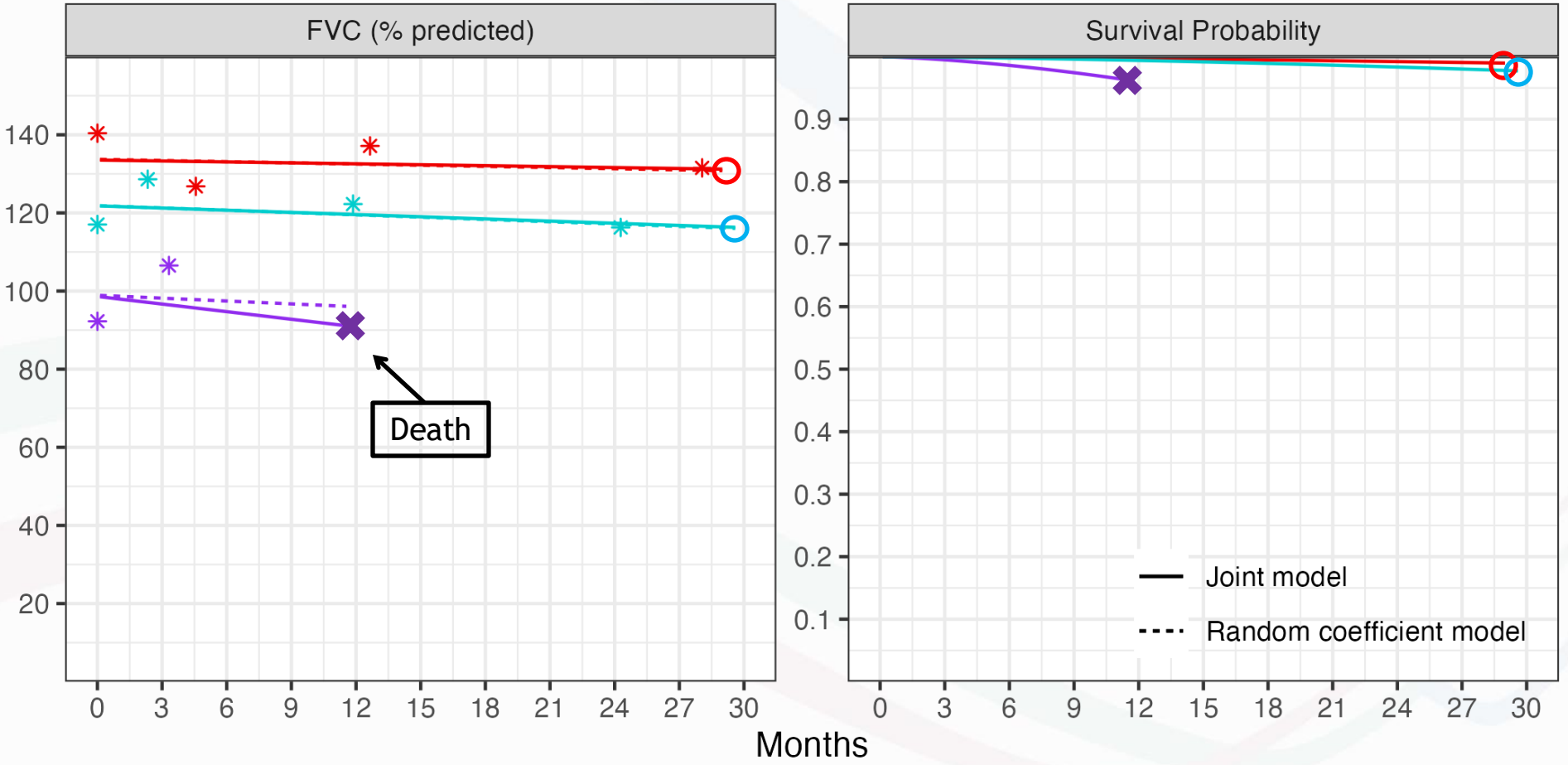
REMAP-ILD Model Fit



Individual-level data from PROFILE and INJUSTIS cohort studies

Berry Consultants

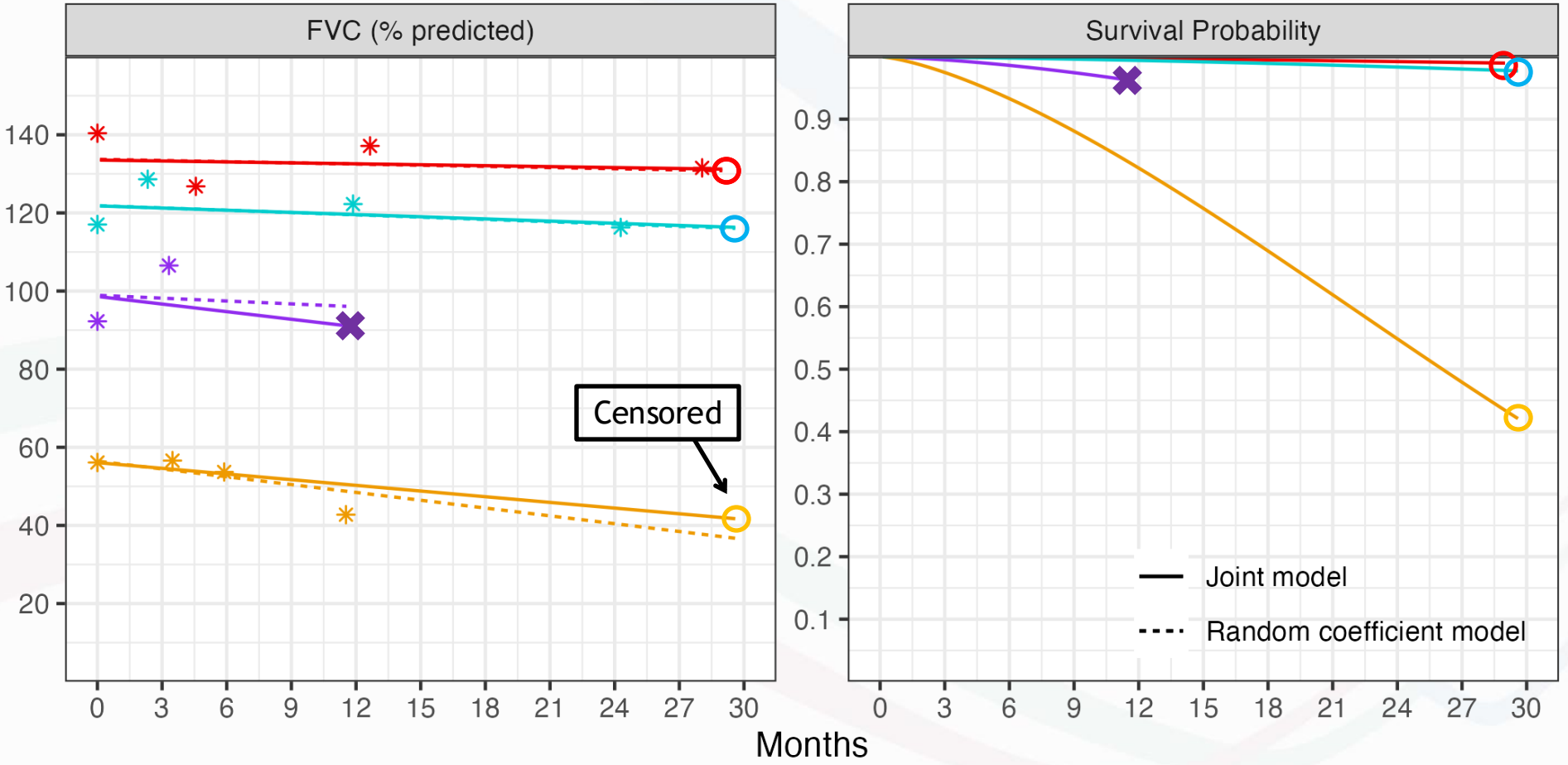
REMAP-ILD Model Fit



Individual-level data from PROFILE and INJUSTIS cohort studies

Berry Consultants

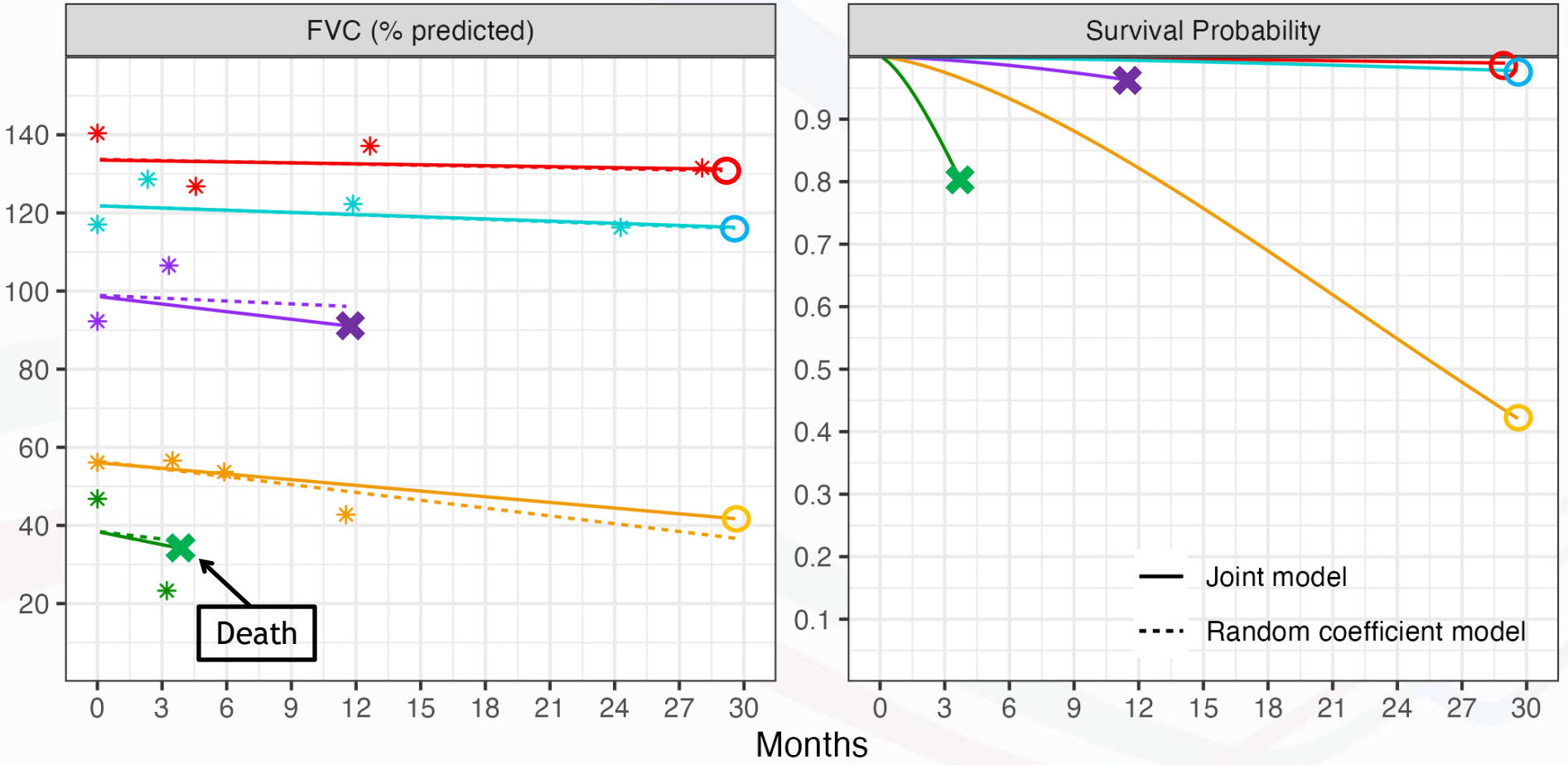
REMAP-ILD Model Fit



Individual-level data from PROFILE and INJUSTIS cohort studies

Berry Consultants

REMAP-ILD Model Fit



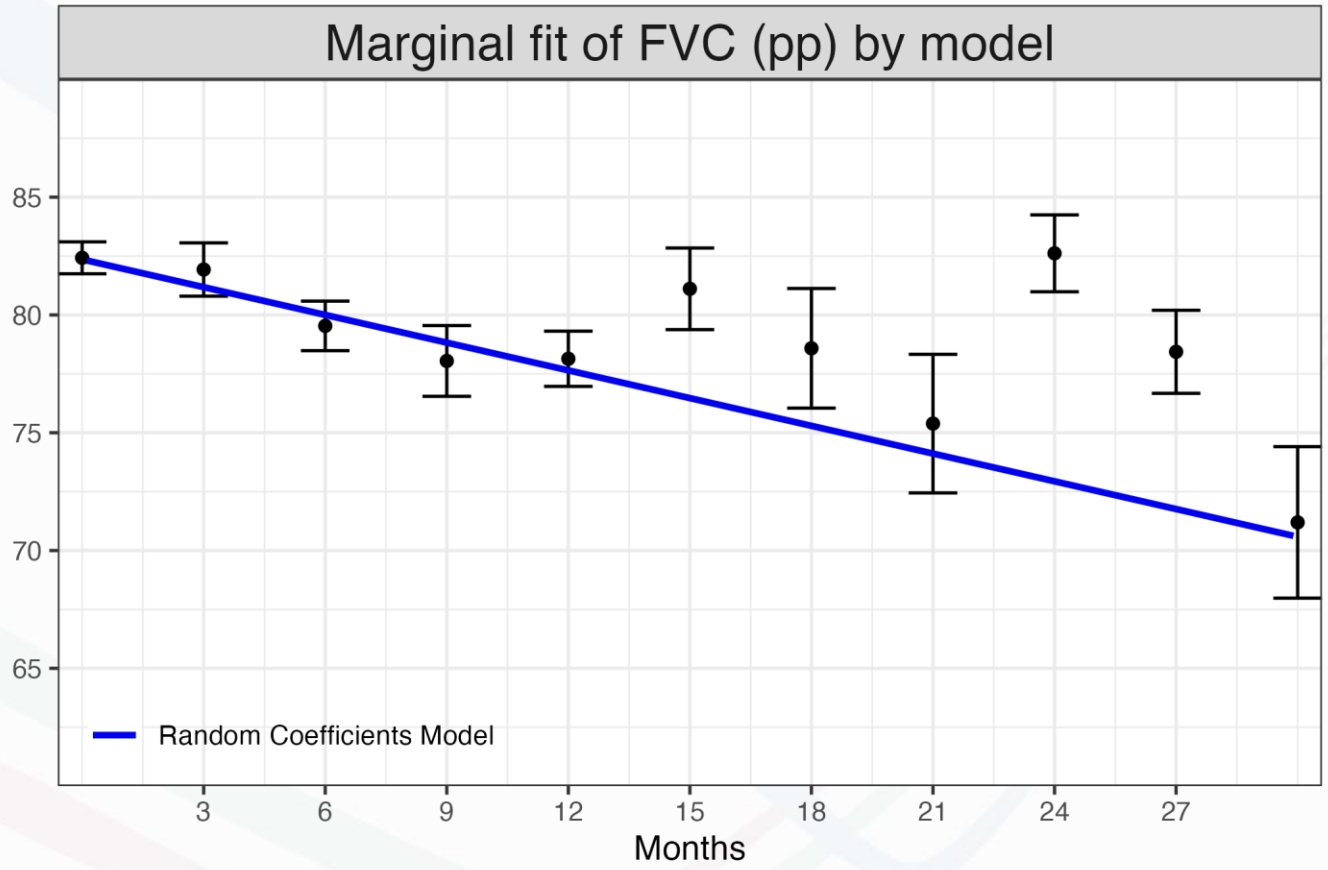
Individual-level data from PROFILE and INJUSTIS cohort studies

Berry Consultants

REMAP-ILD Model Marginal Fit

Fit: $\frac{1}{n}\sum_i \mu_i(t)$

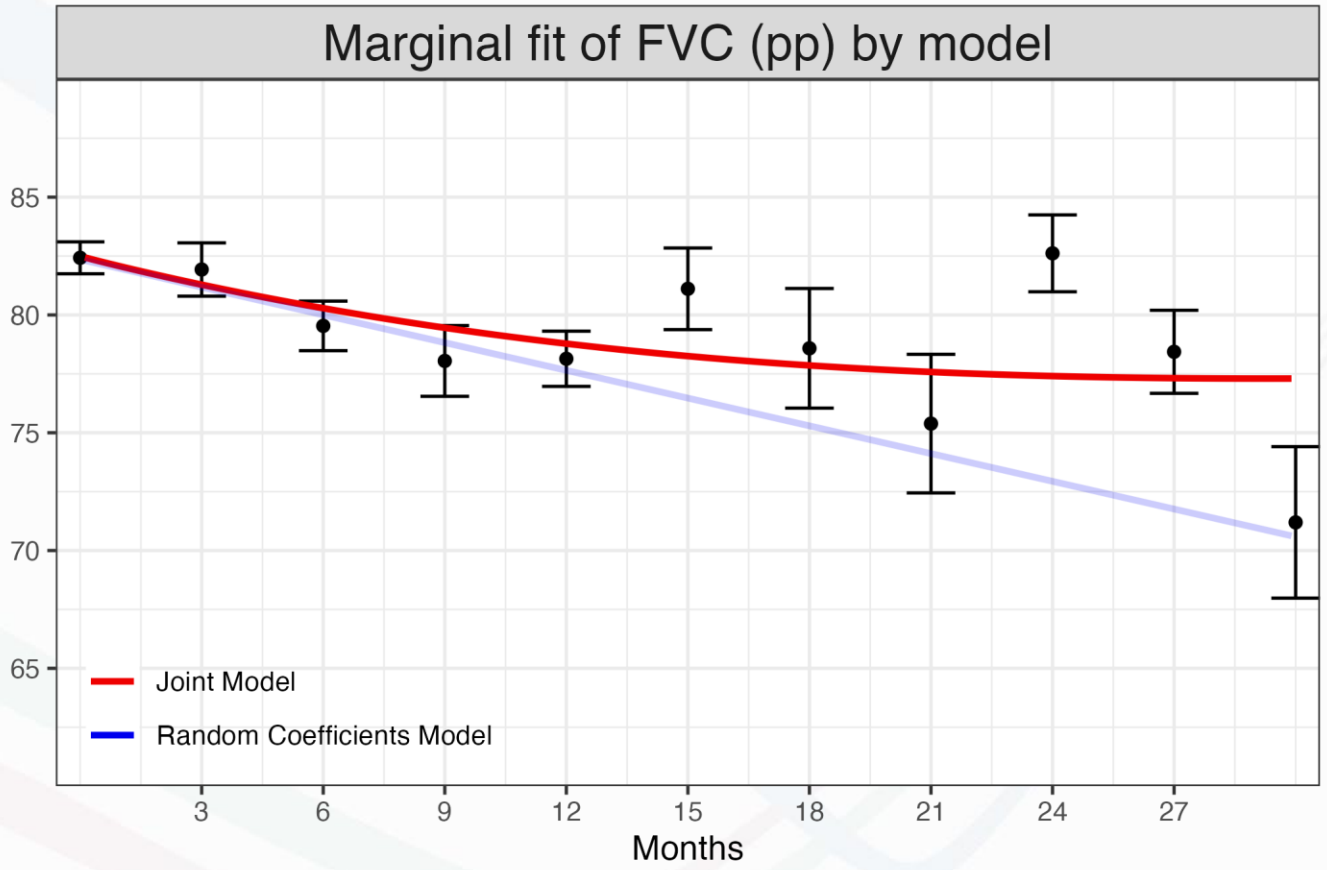
- Marginal model fit (line) vs data means (dots)
- Observed data are non-linear because due to survival events
- Random coefficients model cannot fit the non-linearity because survival events unaccounted for



REMAP-ILD Model Marginal Fit

Fit: $\frac{\sum_i \mu_i(t) s_i(t)}{\sum_i s_i(t)}$

- Marginal model fit (line) vs data means (dots)
- Observed data are non-linear because due to survival events
- Joint model fits the non-linearity by accounting for survival events



Collaborators

BERRY

Barbara Wendelberger, PhD
Senior Statistical Scientist at Berry Consultants

Melanie Quintana, PhD
Director and Senior Statistical Scientist at Berry Consultants

Roger Lewis, MD, PhD
Senior Medical Scientist at Berry Consultants

REMAP-ILD

Chris Ryerson, MD
Professor of Medicine
University of British Columbia, Canada

R. Gisli Jenkins, MD
REMAP-ILD Global Lead & Margaret Turner Warwick Chair of Thoracic Medicine
National Heart & Lung Institute, Imperial, UK

Iain Stewart, PhD
Advanced Research Fellow
National Heart & Lung Institute, Imperial, UK

Leticia Kawano-Dourado, MD
REMAP-ILD Global Head of Operations
HCor Research Institute & University Sao Paulo, Brazil & MAGIC Evidence Ecosystem Foundation, Norway

Pilar Rivera Ortega, MD
Clinical and Research Lead
Interstitial Lung Disease Unit at Wythenshawe Hospital, UK

Wendy Adams
Director of Research
Action for Pulmonary Fibrosis, UK

REMAP-ILD Consortium

END

- Thomas Jensen, MS
- Biostatistician at Berry Consultants
- tomjensen@berryconsultants.net

Defining treatment effects in progressive disease, addressing similarities and differences related to deltas, slowing, reduction, and variance
--Lessons Learned from the DIAN-TU Platform Trial

Guoqiao Wang
Department of Neurology, Division of Biostatistics, Washington University School of Medicine, USA

Conflict of interest

Guoqiao Wang, the biostatistics core co-leader for the DIAN-TU platform trial, is supported by funding from various sources, including NIH/NIA, Alzheimer's Association, Eli Lilly and Company, F. Hoffman-LaRoche Ltd., Avid Radiopharmaceuticals (a subsidiary of Eli Lilly and Company), GHR Foundation, and an anonymous organization. In addition, in-kind support has been offered by Cogstate and Signant.

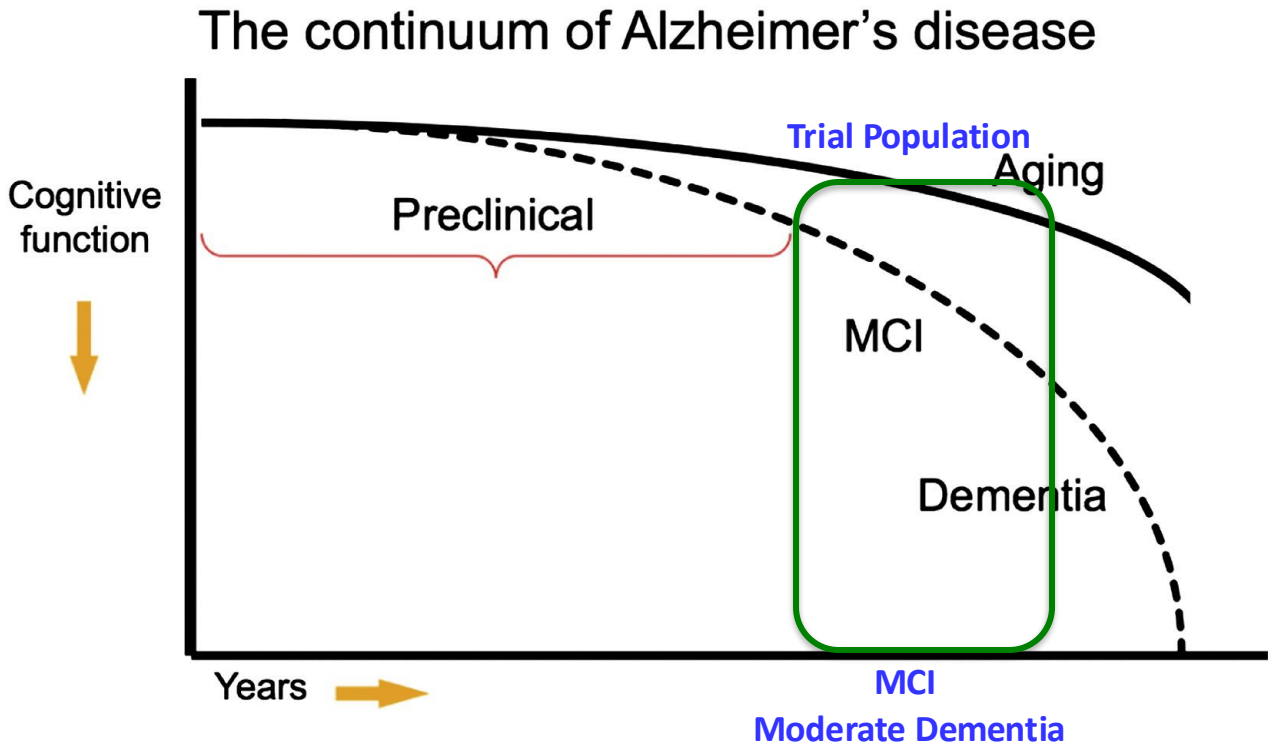
Furthermore, Guoqiao Wang discloses serving on the DSMB for Eli Lilly and Company, Amydis Corporate, and Abata Therapeutics, as well as working as a statistical consultant for Alector, Inc. and Eisai, Inc. He also serves as DSMB member for another five studies funded by NIH.

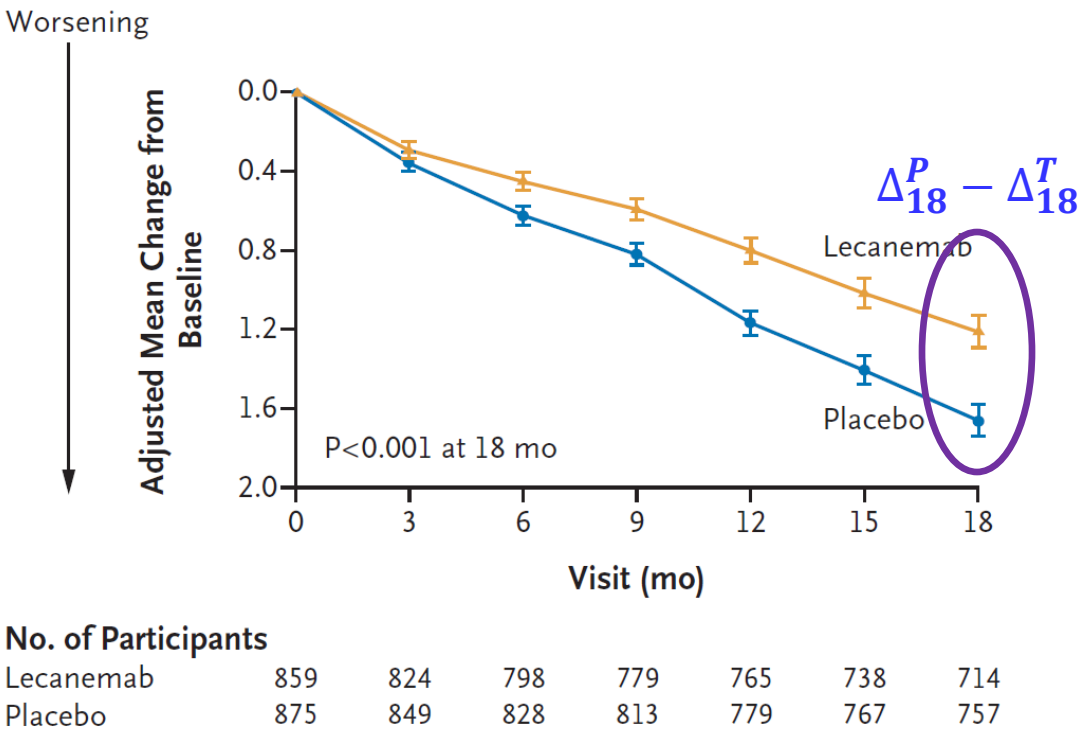
Outlines

- **Redefine How to Evaluate Treatment Effect in Progressive Disease**
  - Traditional: Mean Difference
  - Alternative: Relative Proportional Reduction
- **A Metric that Unifies Various Ways of Defining Treatment Effects**
  - Mean difference
  - Time savings/delay in disease progression
  - Hazard ratio reduction
- **A Metric that Offers Greater Possibility**

Part I: Redefine How to Evaluate Treatment Effect in Rare Disease (Dominantly Inherited Alzheimer's Disease)

Alzheimer's disease





No. of Participants

Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

- **Left**: Natural disease progression trajectory of Alzheimer's disease
- **Right**: Snapshot of disease progression trajectory in a real clinical trial (compare means using mixed model for repeated measures (MMRM))

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., ... & Phelps, C. H. (2011). Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & dementia*, *7*(3), 280-292.

Van Dyck, C. H., Swanson, C. J., Aisen, P., Bateman, R. J., Chen, C., Gee, M., ... & Iwatsubo, T. (2023). Lecanemab in early Alzheimer's disease. *New England Journal of Medicine*, *388*(1), 9-21.

Clinical Trials for Rare vs Sporadic Alzheimer's disease

To improve the chance of success of clinical trials

- Composite outcome vs single outcome
- Selection of more homogeneous population: enrichment trials or targeted trials
- **Apply new statistical concept** (i.e., beyond MMRM)
  - New models
  - More data points for direct efficacy inference

Dominantly Inherited (i.e., Rare) AD Population

Dominantly inherited AD (DIAD):

- Multiple mutations in 3 genes (amyloid precursor protein (APP), presenilin 1 (PSEN1), or presenilin 2 (PSEN2)) but all converge on similar pathway
- Early disease onset: 40s-60s
- Good predictability for age of symptom onset (AO) within specific mutations
- **Estimated years to symptom onset (EYO)** : e.g. AO=55, age=45, EYO=-10

Primary Outcome - A Cognitive Composite

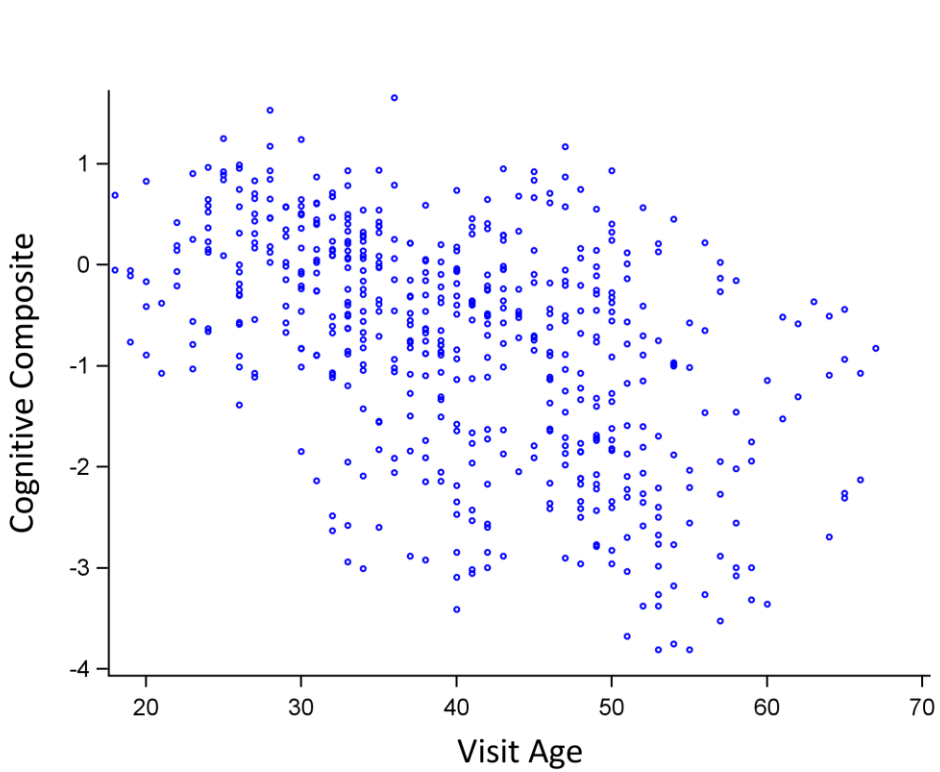
The composite endpoint, Y, is the equal weighting of Mini Mental State Examination (MM), Wechsler Adult Intelligence Scale Digit Symbol Substitution Test (W), Wechsler Memory Scale-Revised Logical Memory Delayed Recall (ME), and DIAN Word List Delayed Recall (D):

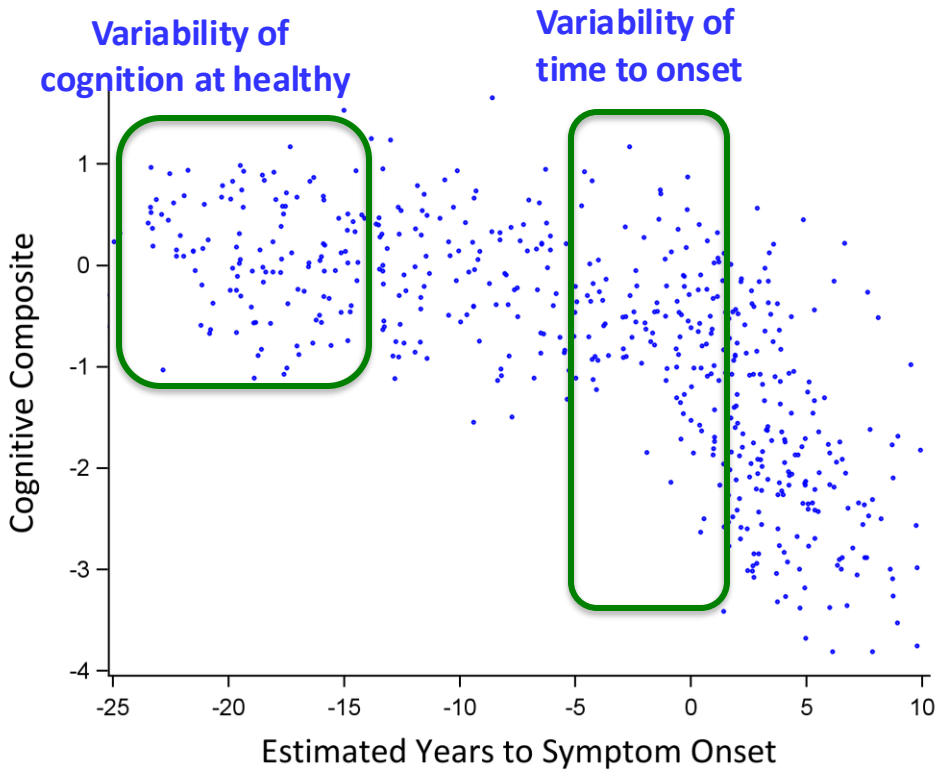
$$Y = \frac{1}{4}\left(\frac{MM - 28.79}{4.39}\right) + \frac{1}{4}\left(\frac{W - 63.87}{13.34}\right) + \frac{1}{4}\left(\frac{ME - 13.74}{3.91}\right) + \frac{1}{4}\left(\frac{D - 3.47}{2.18}\right)$$

Standardize each endpoint by the Mean and SD in relative healthy population $EYO \leq -15$

Wang, G., Berry, S., Xiong, C., Hassenstab, J., Quintana, M., McDade, E. M., ... & Dominantly Inherited Alzheimer Network Trials Unit. (2018). A novel cognitive disease progression model for clinical trials in autosomal-dominant Alzheimer's disease. *Statistics in medicine*, *37*(21), 3047-3055.

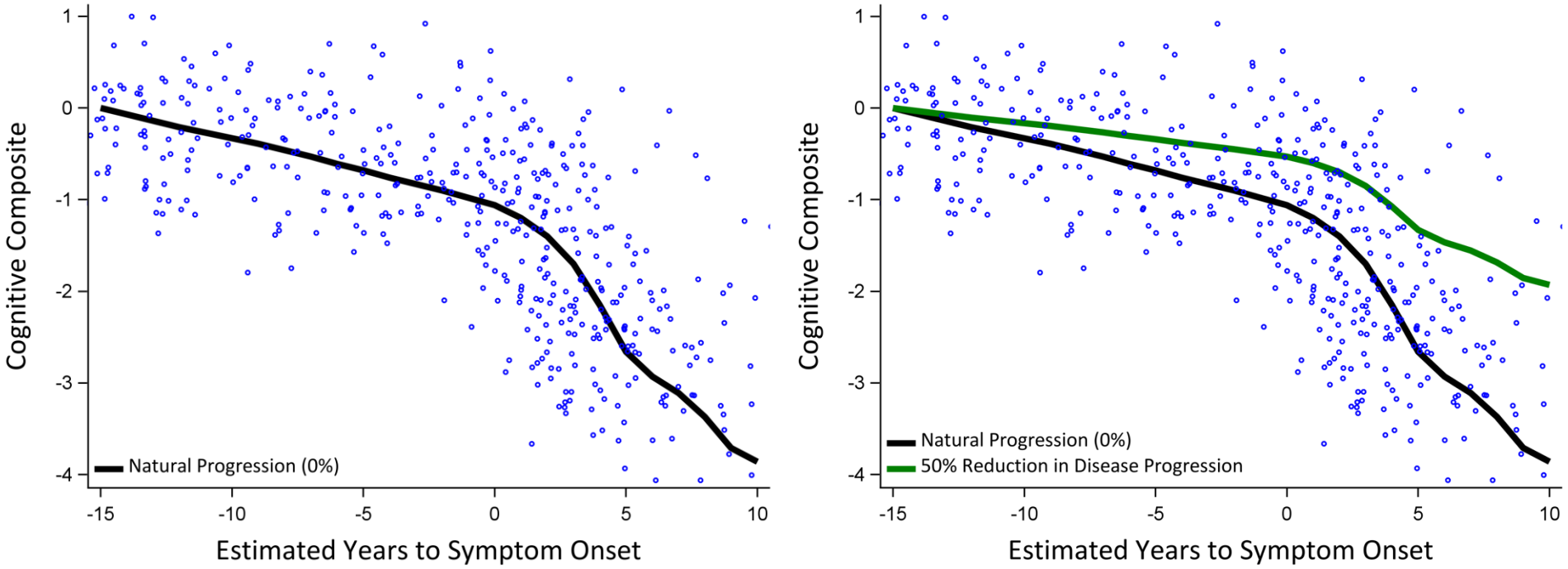
Cognitive Progression by Age and by EYO





- **Left**: Natural disease progression trajectory by age
- **Right**: Natural disease progression trajectory by estimated years to symptom onset (EYO)

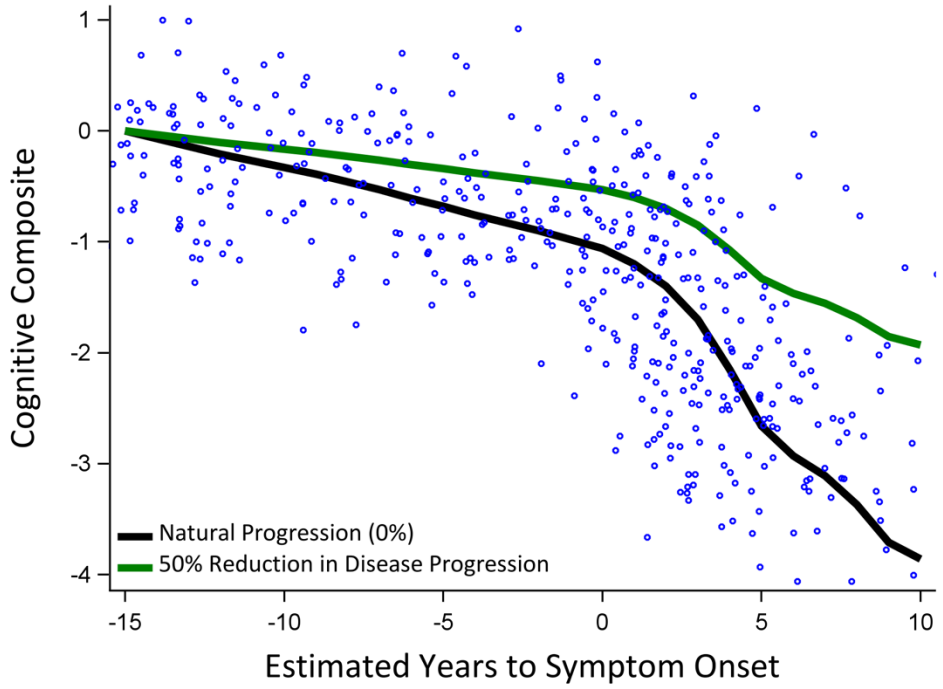
Estimated Disease Progression Trajectory with Hypothetical Treatment Effect --Redefine Treatment Effects as Proportional Reduction



- **Left**: Natural disease progression trajectory with raw data
- **Right**: Disease progression trajectory with 50% reduction in disease progression

Wang, G., Berry, S., Xiong, C., Hassenstab, J., Quintana, M., McDade, E. M., ... & Dominantly Inherited Alzheimer Network Trials Unit. (2018). A novel cognitive disease progression model for clinical trials in autosomal-dominant Alzheimer's disease. *Statistics in medicine*, *37*(21), 3047-3055.

Alternative Efficacy Inference Metric: Proportional (i.e., %) Reduction vs Mean Difference



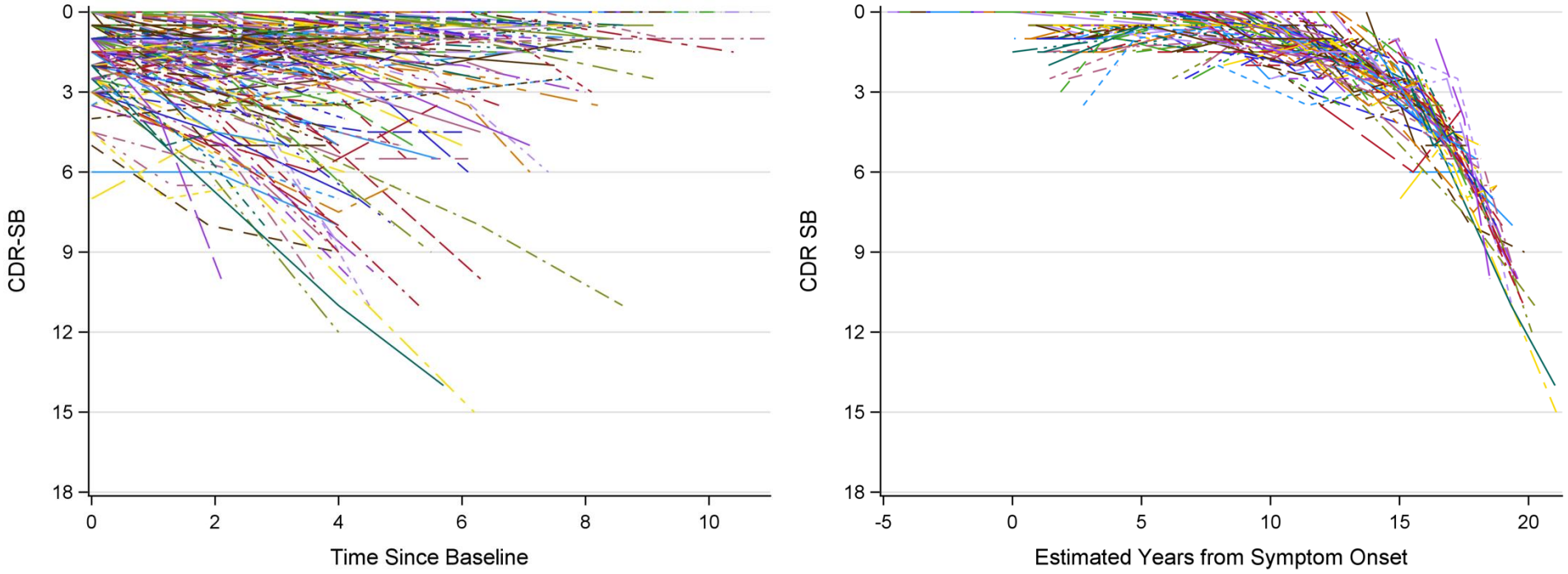
- **Mean Difference:** $\Delta_j^P - \Delta_j^T$
- $\theta = \frac{\Delta_j^P - \Delta_j^T}{\Delta_j^P}$
- $\Delta_j^T = (1-\theta)\Delta_j^P, \theta = 50\%$
- **Proportional reduction relative to the placebo decline**
- **Non-linear model**
- θ**: Estimate treatment effect across a wide range of disease stages/timepoints**

Wang, G., Berry, S., Xiong, C., Hassenstab, J., Quintana, M., McDade, E. M., ... & Dominantly Inherited Alzheimer Network Trials Unit. (2018). A novel cognitive disease progression model for clinical trials in autosomal-dominant Alzheimer's disease. *Statistics in medicine*, *37*(21), 3047-3055.

Wang, G., Liu, L., Li, Y., Aschenbrenner, A. J., Bateman, R. J., Delmar, P., ... & Xiong, C. (2022). Proportional constrained longitudinal data analysis models for clinical trials in sporadic Alzheimer's disease. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, *8*(1), e12286.

Extension to Sporadic Alzheimer's Disease

--Disease Progression Model with Random Effect in Time

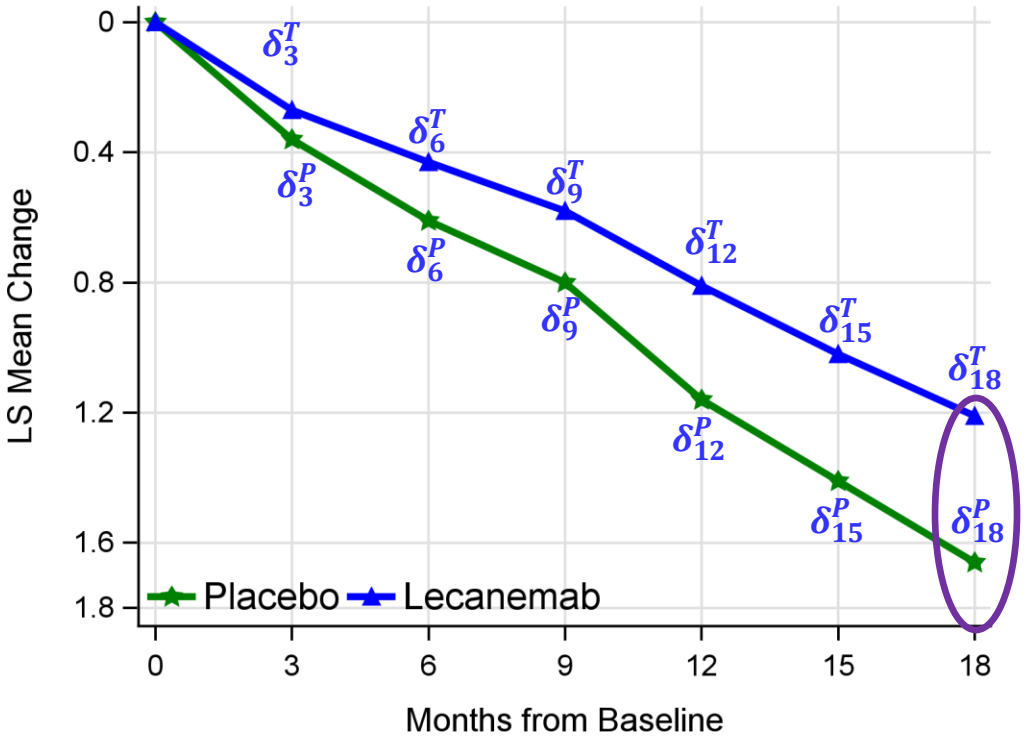


- Random effect shifts individual data left and right to form a nice DPM trajectory
- Model can output "disease stage" time variable similar to EYO

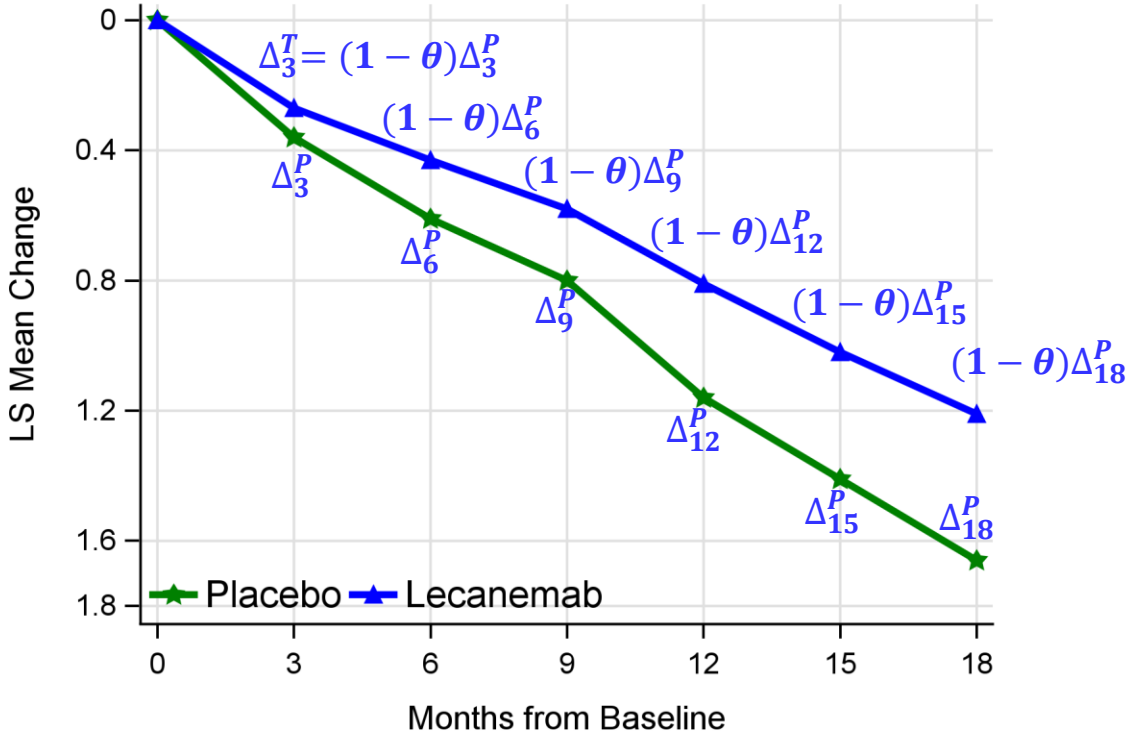
Donohue, Michael C., et al. "Estimating long-term multivariate progression from short-term data." *Alzheimer's & Dementia* 10 (2014): S400-S410.
Raket, Lars Lau. "Statistical disease progression modeling in Alzheimer disease." *Frontiers in big Data* 3 (2020): 24.
Wang, G., CTAD 2024

Proportional (%) Treatment Effect across All Post-baseline Visits

Absolute difference: $\Delta_{18}^{P} - \Delta_{18}^{T}$



Proportional (%) Reduction across Multiple Visits



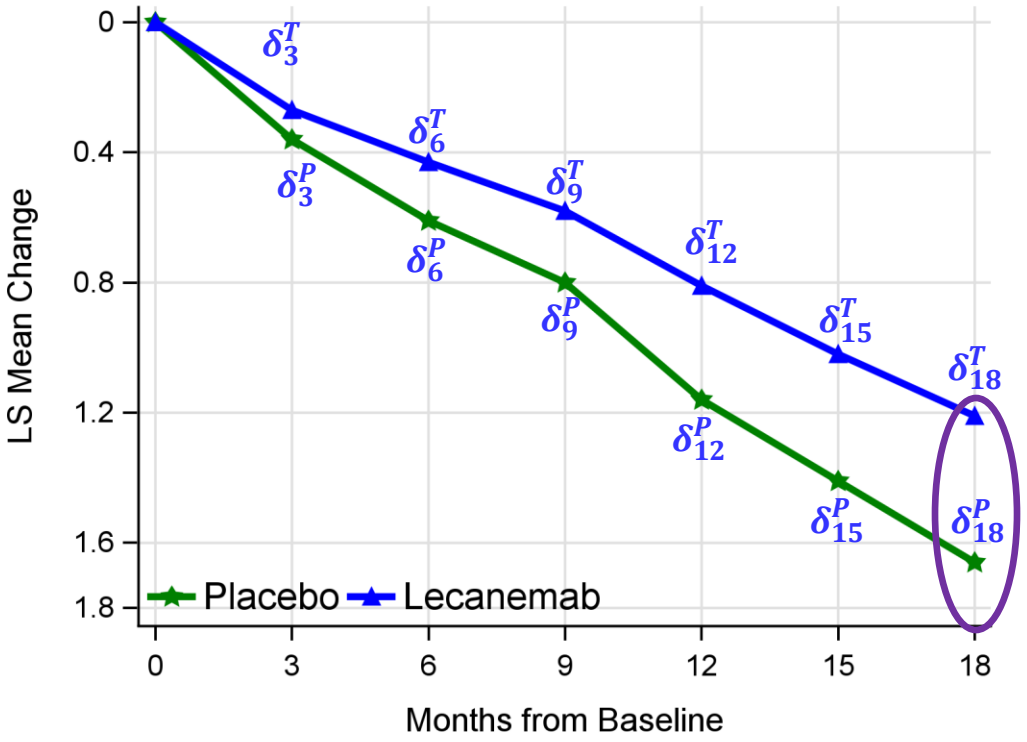
Adapted from Van Dyck, Christopher H., et al. "Lecanemab in early Alzheimer's disease." New England Journal of Medicine 388.1 (2023): 9-21.

Wang, Guoqiao, et al. "Novel non-linear models for clinical trial analysis with longitudinal data: A tutorial using SAS for both frequentist and Bayesian methods." Statistics in medicine (2024). Wang, G AAIC 2024

Part II: A Metric—Unifying Various Treatment Effects

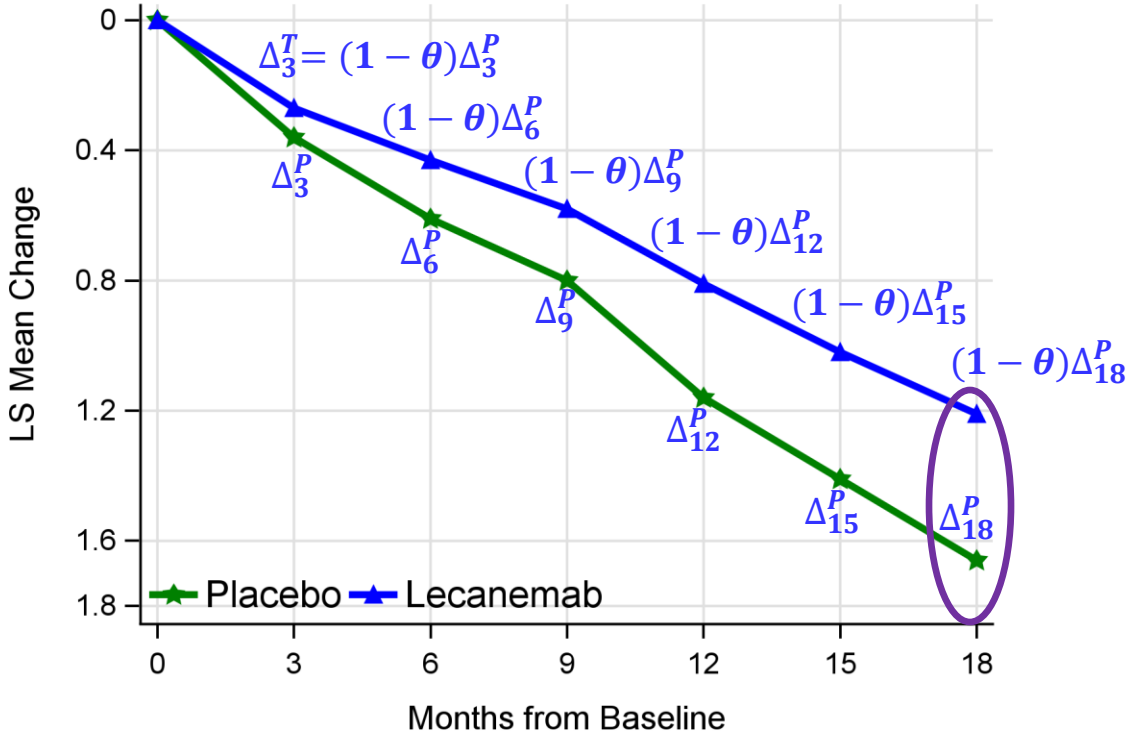
Proportional (%) Treatment Effect—
A Metric that Connects Various Treatment Efficacy Measures

Absolute difference: $\Delta_{18}^{P} - \Delta_{18}^{T} = \Delta = 0.45$



$$\frac{0.45}{1.66} \cong 27\%$$

Proportional (%) Reduction: $\theta = 27.9\%$

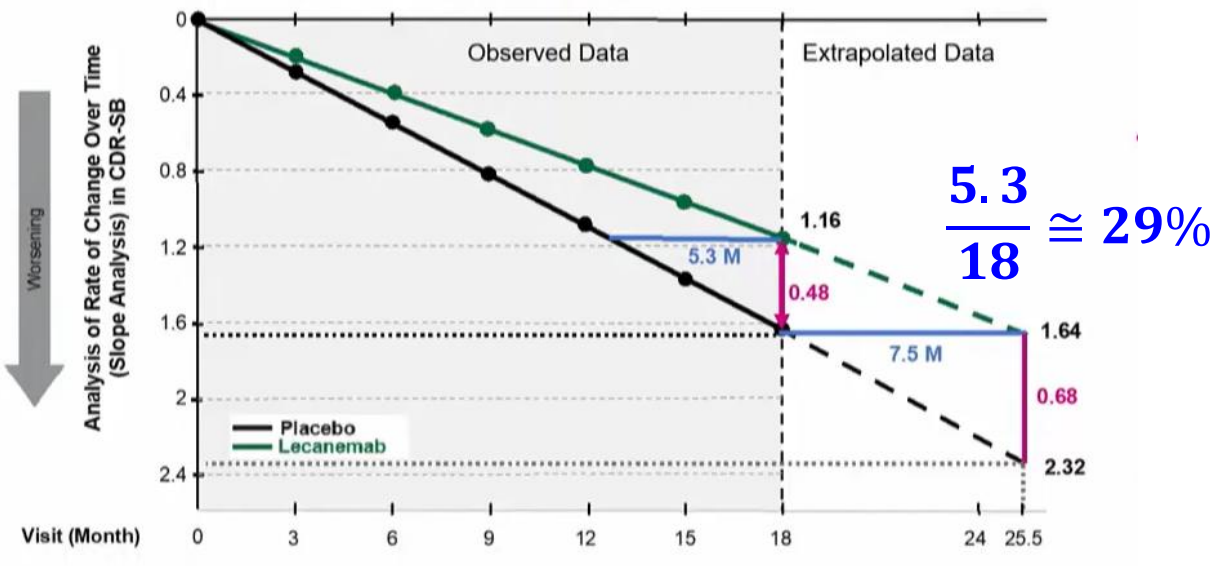


MMRM vs Proportional MMRM

Adapted from Van Dyck, Christopher H., et al. "Lecanemab in early Alzheimer's disease." New England Journal of Medicine 388.1 (2023): 9-21.
Wang, Guoqiao, et al. "Novel non-linear models for clinical trial analysis with longitudinal data: A tutorial using SAS for both frequentist and Bayesian methods." Statistics in medicine (2024). Wang, G AAIC 2024

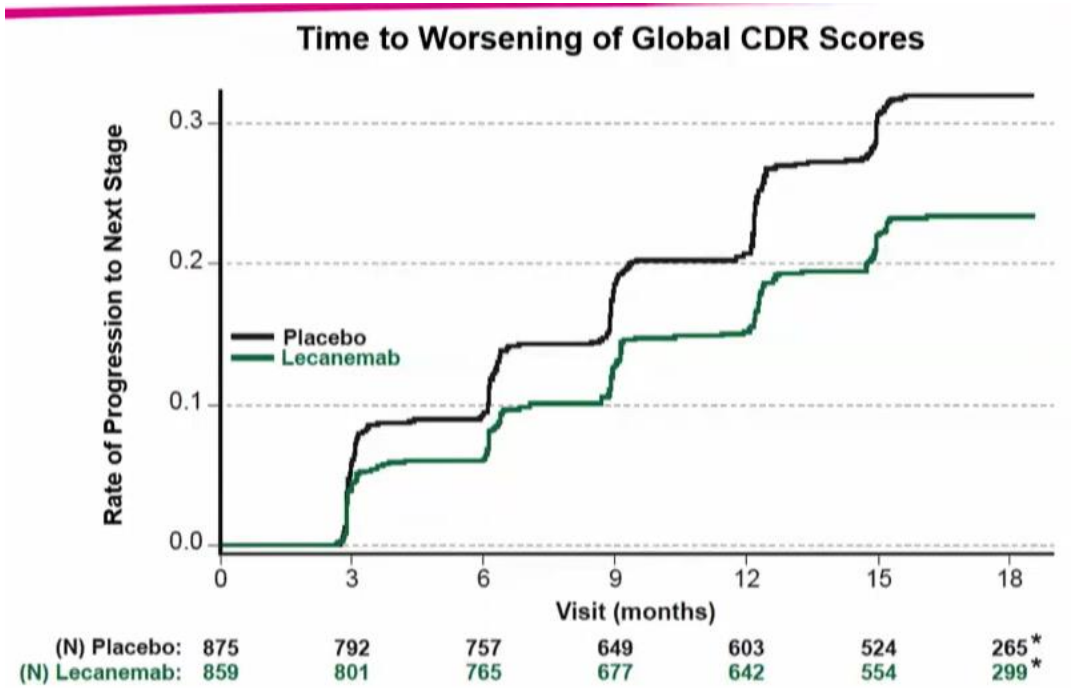
Proportional (%) Treatment Effect—
A Metric that Connects Various Treatment Efficacy Measures

Time Savings: 5.3 Months



$$\frac{5.3}{18} \cong 29\%$$

Proportional (%) Reduction in Hazard Ratio: 31%

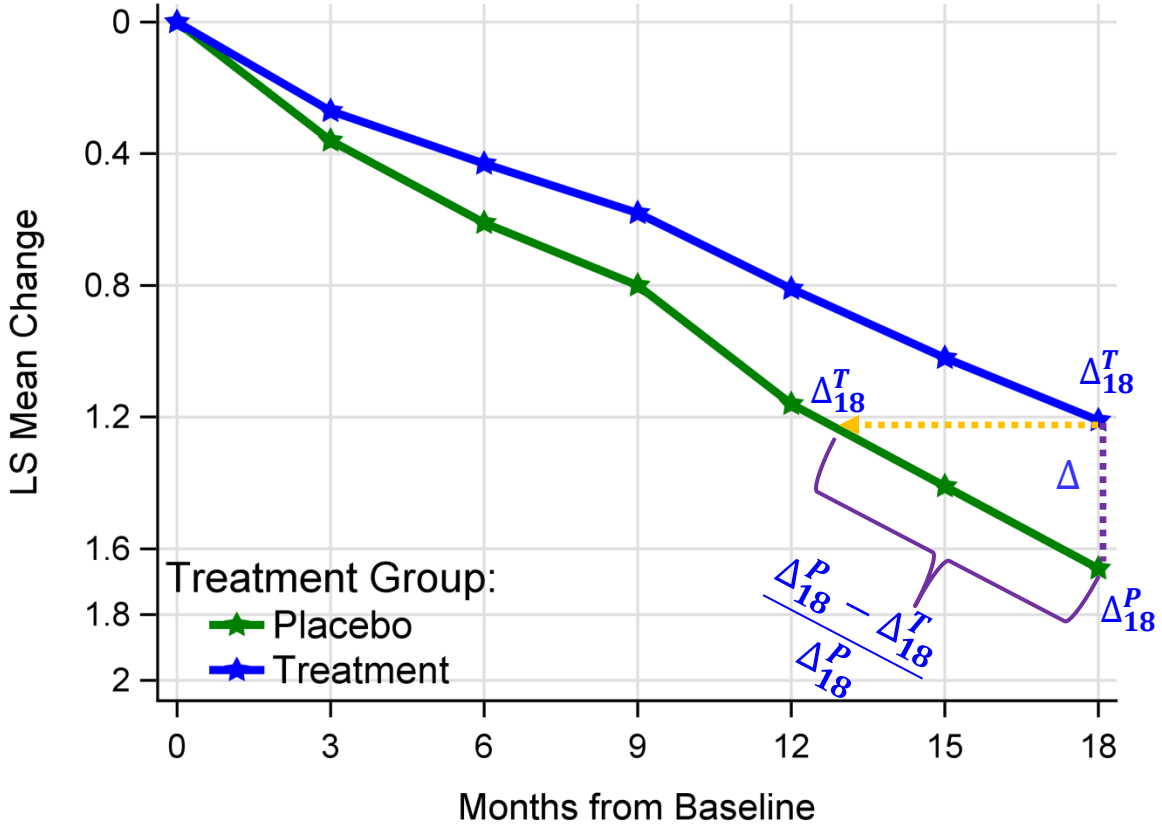


- **Notably, despite the diverse representations of these treatment effects, they converge to nearly the same number when converted to a proportional treatment effect (% Reduction).**

CTAD 2022, Van Dyck, C, et al. Wang, G AAIC 2024

Van Dyck, Christopher H., et al. "Lecanemab in early Alzheimer's disease." New England Journal of Medicine 388.1 (2023): 9-21.

Proportional (%) Treatment Effect—A Metric that Connects Effect on Y-axis (absolute different) and Effect on X-Axis (Time-Saving Effect)



Time savings: Time needed for the placebo to decline from Δ_{18}^{T} to Δ_{18}^{P}

Proportion of the time savings relative to the total trial duration can be approximated as:

$$\theta_T = \frac{\Delta_{18}^{P} - \Delta_{18}^{T}}{\Delta_{18}^{P}} \doteq 27\%$$

Whether measured on the y-axis (as absolute difference) or on the x-axis (as time savings):

Converting to a similar proportion by the same formula

$$\frac{5.3}{18} \cong 29\%$$

$$\frac{0.45}{1.66} \cong 27\%$$

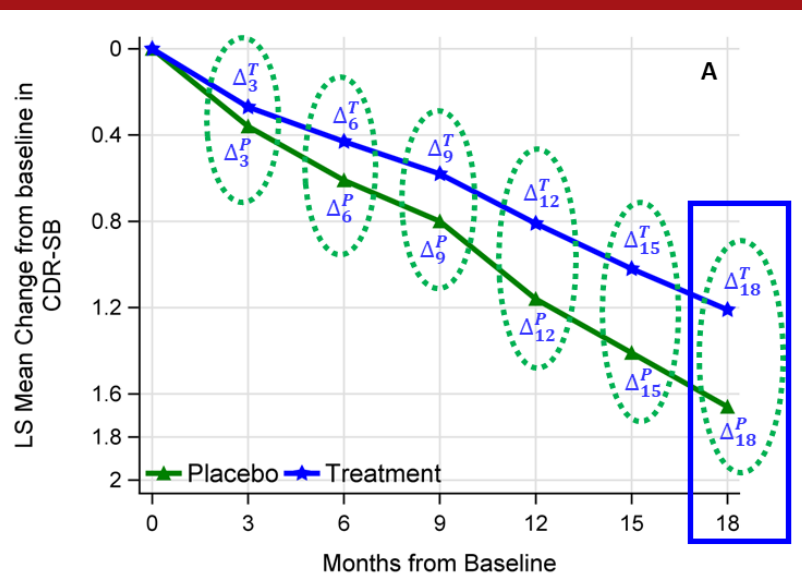
CTAD 2022, Van Dyck, C, et al., Wang, G AAIC 2024

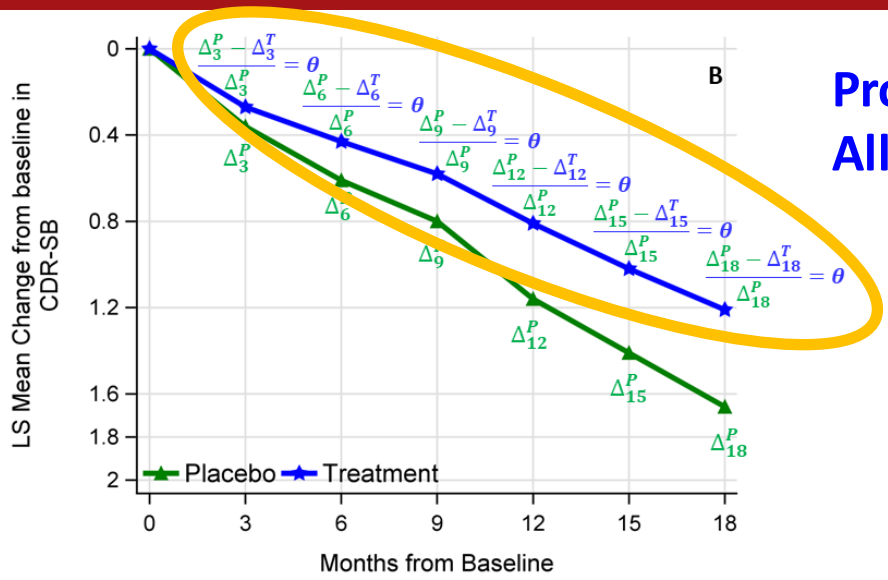
Van Dyck, Christopher H., et al. "Lecanemab in early Alzheimer's disease." New England Journal of Medicine 388.1 (2023): 9-21.

Wang, Guoqiao, et al. "Statistical considerations when estimating time-saving treatment effects in Alzheimer's disease clinical trials." *Alzheimer's & Dementia* (2024).

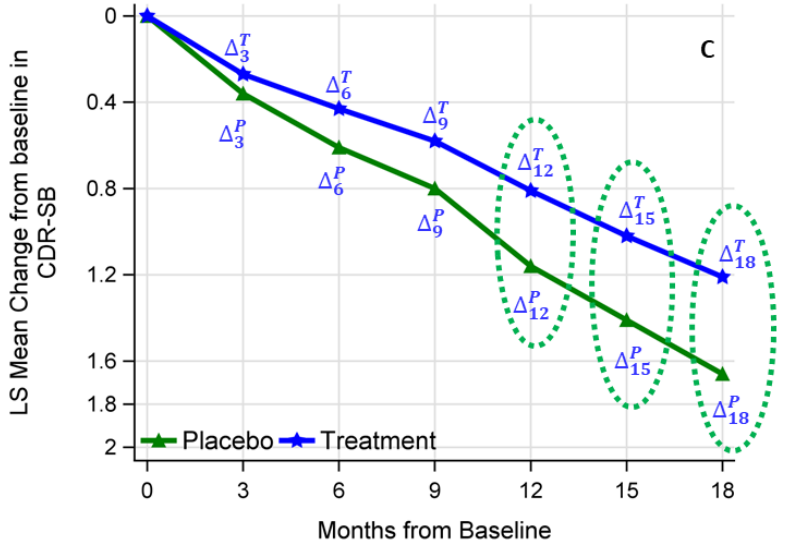
Part III: Proportional (%) Treatment Effects: Greater Flexibility and Possibility

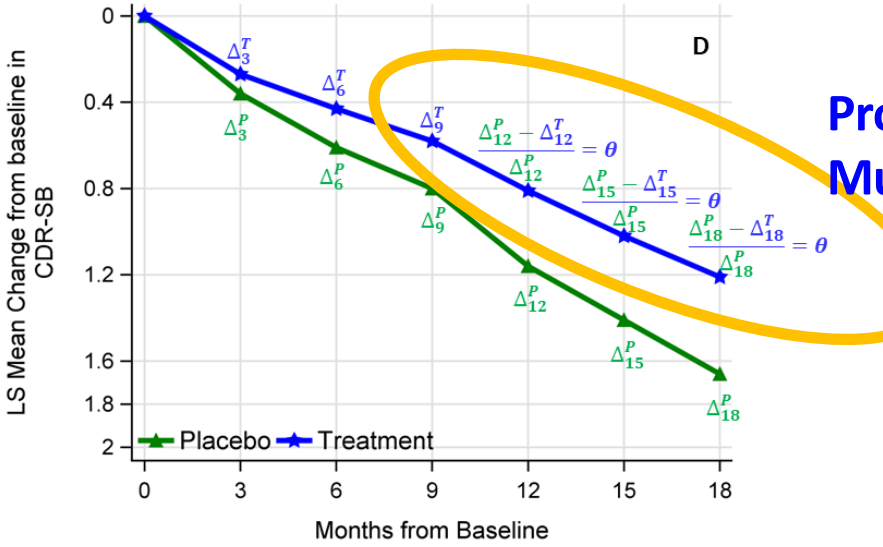
Across All (or Multiple) Post Baseline Visits in A Single Endpoint





Proportional Effect Across All Visits





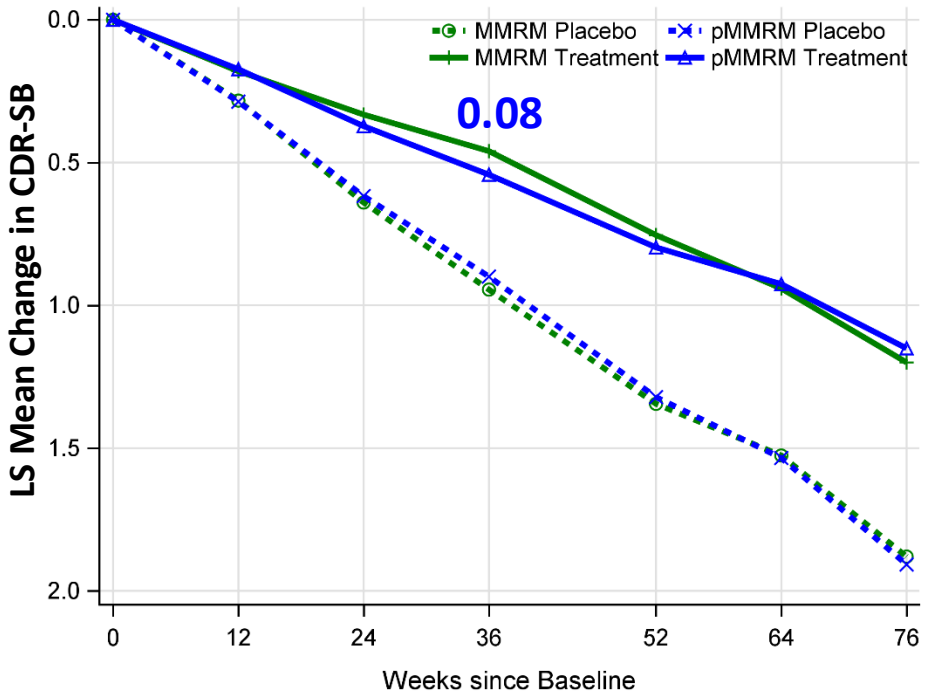
Proportional Effect Across Multiple Visits

2022, Van Dyck, C, et al. Wang, G AAIC 2024

Wang, Guoqiao, et al. "Statistical considerations when estimating time-saving treatment effects in Alzheimer's disease clinical trials." Alzheimer's & Dementia (2024).

Wang, Guoqiao, et al. "Novel non-linear models for clinical trial analysis with longitudinal data: A tutorial using SAS for both frequentist and Bayesian methods." Statistics in medicine (2024).

Proportional Effect Across Multiple Visits -- Resilient to % Variation Observed at Each Visit



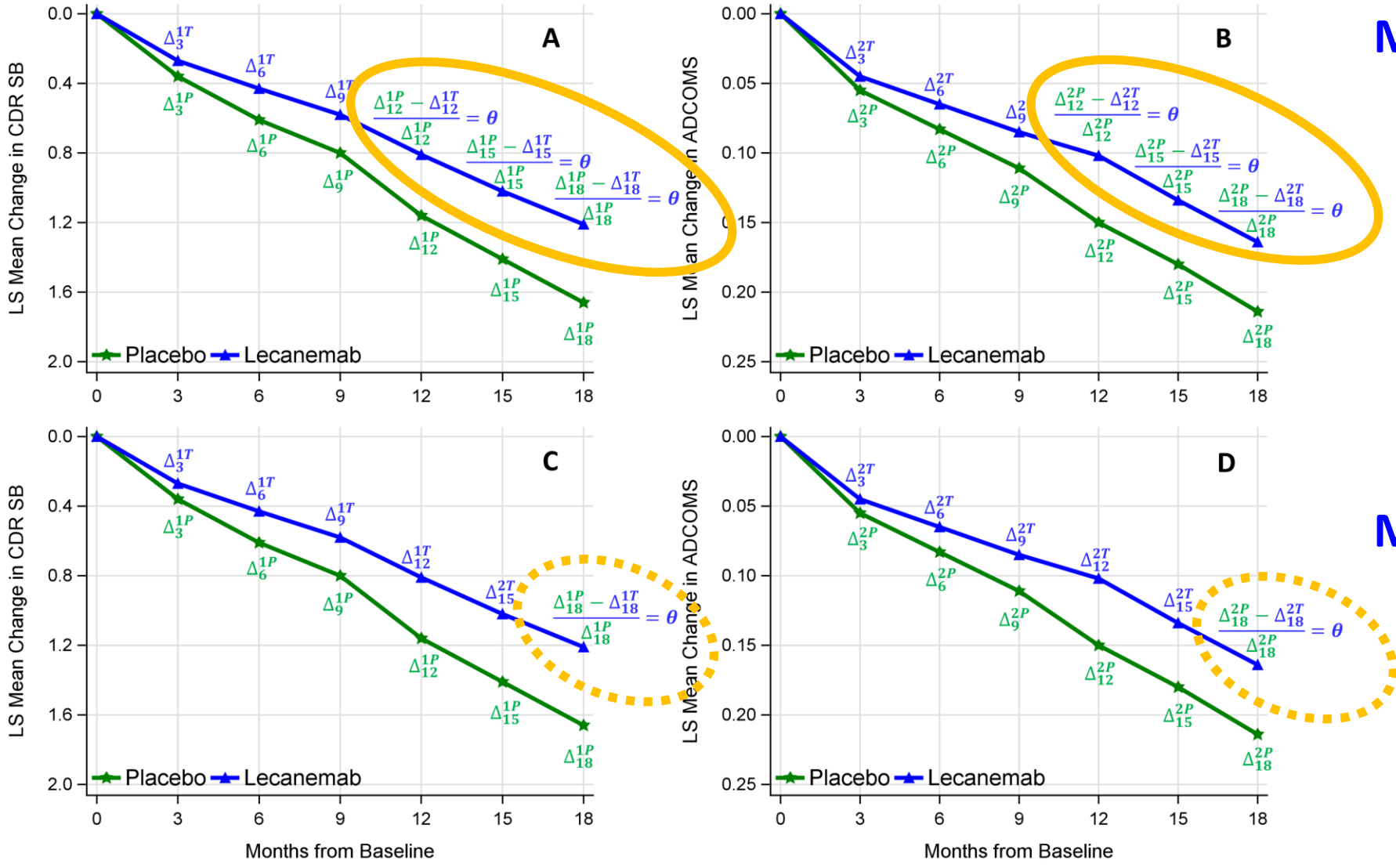
% reduction at each visit for Donanemab Phase 3 Trial (low/medium tau population)				
Weeks	Estimated % reduction	SE	95% CI	
			Lower	Upper
12	36.4%	24.1%	-10.9%	83.7%
24	48.1%	11.8%	25.0%	71.3%
36	51.3%	8.4%	34.8%	67.9%
52	43.9%	7.0%	30.1%	57.8%
64	38.3%	6.7%	25.2%	51.5%
76	36.2%	5.9%	24.6%	47.8%
% difference 36-12	14.9%	20.0%	-24.3%	54.2%
% difference 36-64	13.0%	7.1%	-1.0%	27.0%
% difference 36-76	15.2%	8.0%	-0.5%	30.8%

The differences in the % reduction, despite the magnitude, are not significant

Proportional MMRM: 39.7% (29.0%, 50.4%) vs MMRM: 36.2% (24.6%, 47.8%)

Sims, John R., et al. "Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial."*Jama* 330.6 (2023): 512-527.
Wang, Guoqiao, et al. "Statistical considerations when estimating time-saving treatment effects in Alzheimer's disease clinical trials." *Alzheimer's & Dementia* (2024).

Multivariate Endpoints and All, Multiple, or Last Visit(s)



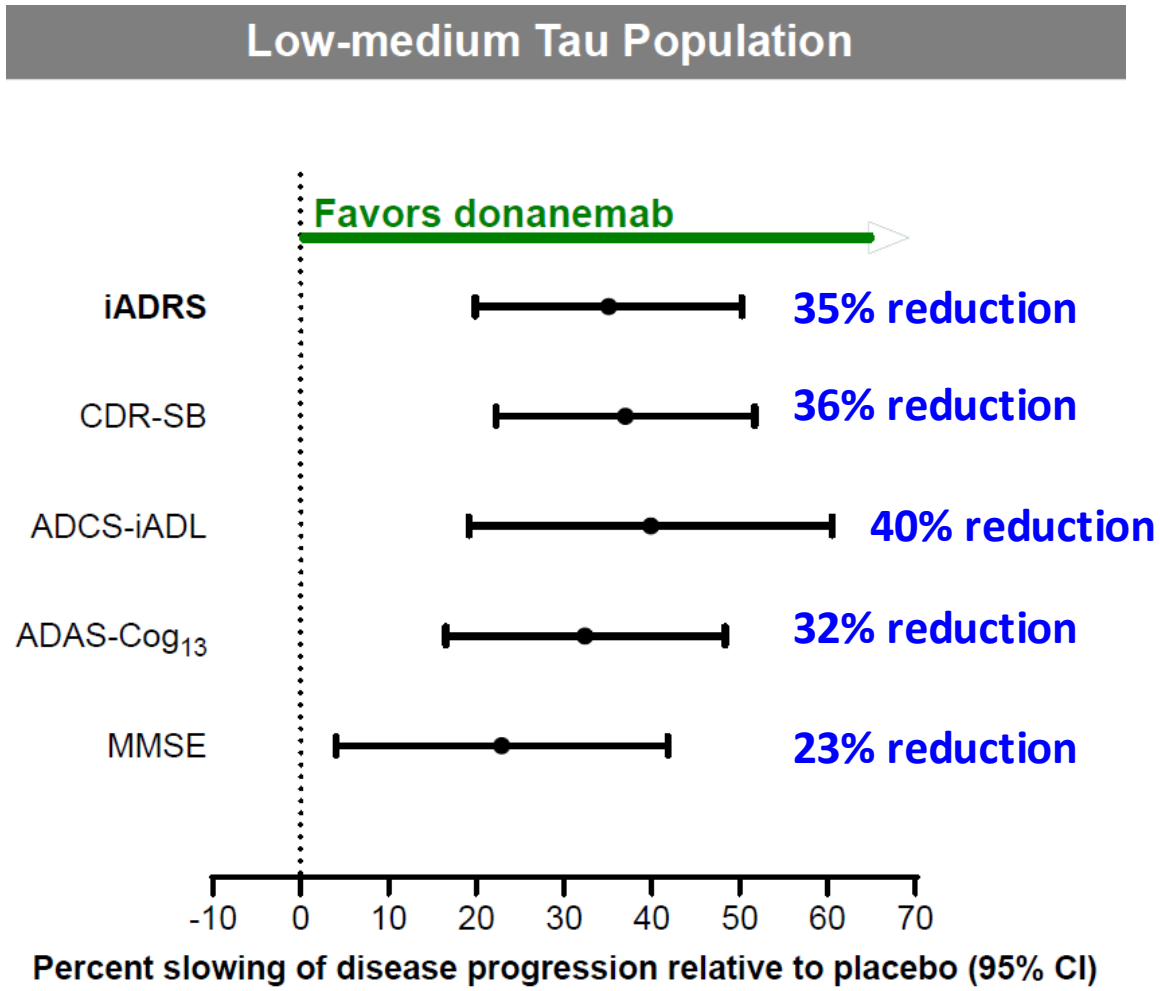
Multiple Endpoints + Multiple Visits

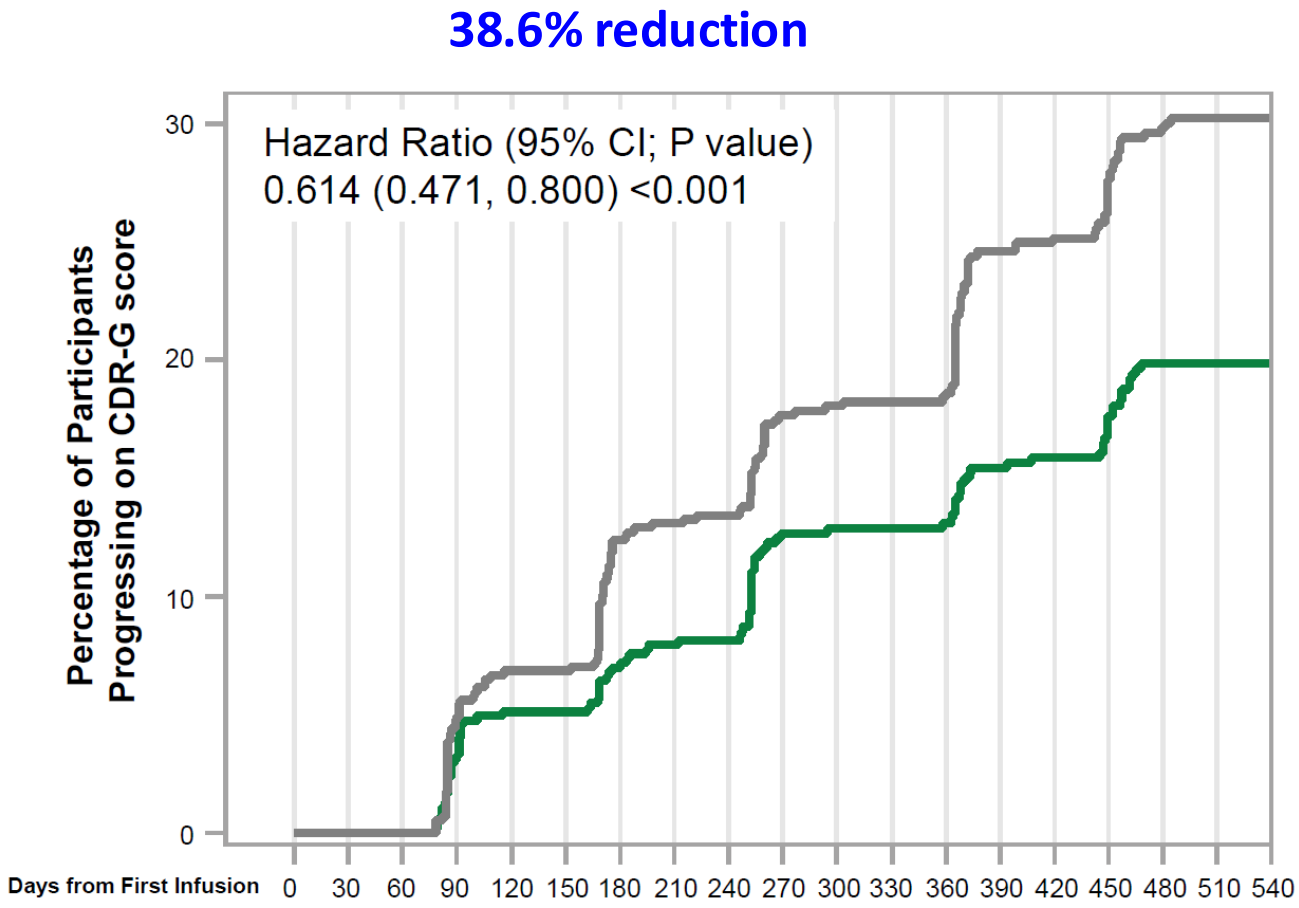
Multiple Endpoints + Last Visit

Adapted from CTAD 2022, Van Dyck, C, et al. Wang, G AAIC 2024

Wang, Guoqiao, et al. "Novel non-linear models for clinical trial analysis with longitudinal data: A tutorial using SAS for both frequentist and Bayesian methods." Statistics in medicine (2024).

Multivariate Endpoints including Survival Endpoint— and All, Multiple, or Last Visit(s)





Mintun, M. et al, AAIC 2023, Wang, G AAIC 2024

Sims, John R., et al. "Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial." *Jama* 330.6 (2023): 512-527.

Software Procedures

- SAS %nlinmix macro is the go-to computational package
  - Build upon proc mixed
- SAS **nlmixed** procedure: MMRM, pMMRM, Joint proportional model
- SAS Bayesian MCMC procedure: MMRM, pMMRM, Joint proportional model
- The estimates obtained from MMRM (covariance matrix + mean of the placebo arm) can always be used as initial values in pMMRM

Wang, Guoqiao, et al. "Novel non-linear models for clinical trial analysis with longitudinal data: A tutorial using SAS for both frequentist and Bayesian methods." Statistics in medicine (2024).

Conclusions

- **Proportional Treatment Effect Can Be An Alternative to the Difference**
  - Widely used in categorical data analysis
  - Widely used in survival analysis
  - Less popular for continuous endpoints
- **Proportional (%) Treatment Effect:**
  - Convert absolute difference into a proportion
  - Increase Power due to rescaling or combine multiple visits/endpoints
- **Proportional (%) Treatment Effect Connects Various Ways**
  - Absolute difference
  - Time savings
  - Hazard reduction

Funding acknowledgments:

DIAN Trial Unit: NIH U01AG042791, R01AG046179, R01AG053267, PI: Randall Bateman, MD; Alzheimer's Association, GHR Foundation, Anonymous Organization, Eli Lilly & Co., Roche/Genentech

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

All collaborators: Randall J. Bateman, Eric McDade, Scott Berry, Barbara Wendelberger, Yan Li, Chengjie Xiong, Jorge J Llibre-Guerra, Gary Cutter, Lon Schneider, Guogen Shan, Paul Delmar

Thank you !

Any Questions?

guoqiao@wustl.edu