

Challenges of assessing Progression in Ataxias -- and Consequences for trials and approvals

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Disclosures

- Friedreich's Ataxia Research Alliance
- National Ataxia Foundation
- Ataxia UK and others
- Biogen, PTC Therapeutics, Larimar Tx, Biohaven Ltd, Lexeo Tx, Takeda Pharmaceuticals and Solaxa

Tools to Assess Progression in Ataxia - Clinical Outcome Assessments

Established Measures

- Patient Reported Outcomes (PRO)
 - Activities of Daily Living
 - Quality of Life
- Clinician Reported Outcomes (ClinRO)
 - Rating Scales:
SARA, mFARS, ... , others
- Performance Outcomes (PerfO)
 - Timed Walking, Peg Board
- (Observer Reported, ObsRO)

Under Development

- Digital Outcome Measures
 - Gait / Balance
 - Functional Tests
 - Speech
- Indirect or Surrogate Measures
 - Imaging (e.g. MRI)
 - Biomarker (in Blood or other Tissues)
 - Electrophysiology (Nerve Conduction)
- Cognitive Testing

What are Rating Scales?

- “Compartmentalized Quantification [...] of Ataxia Symptoms”
--> Breaking down ataxia to different symptoms
- Elaborate Statistics Required
- Fair Assessment, but how to balance?
- Required to detect even small changes that are important and meaningful to Patients

SARA (40)

Speech
1 (6)

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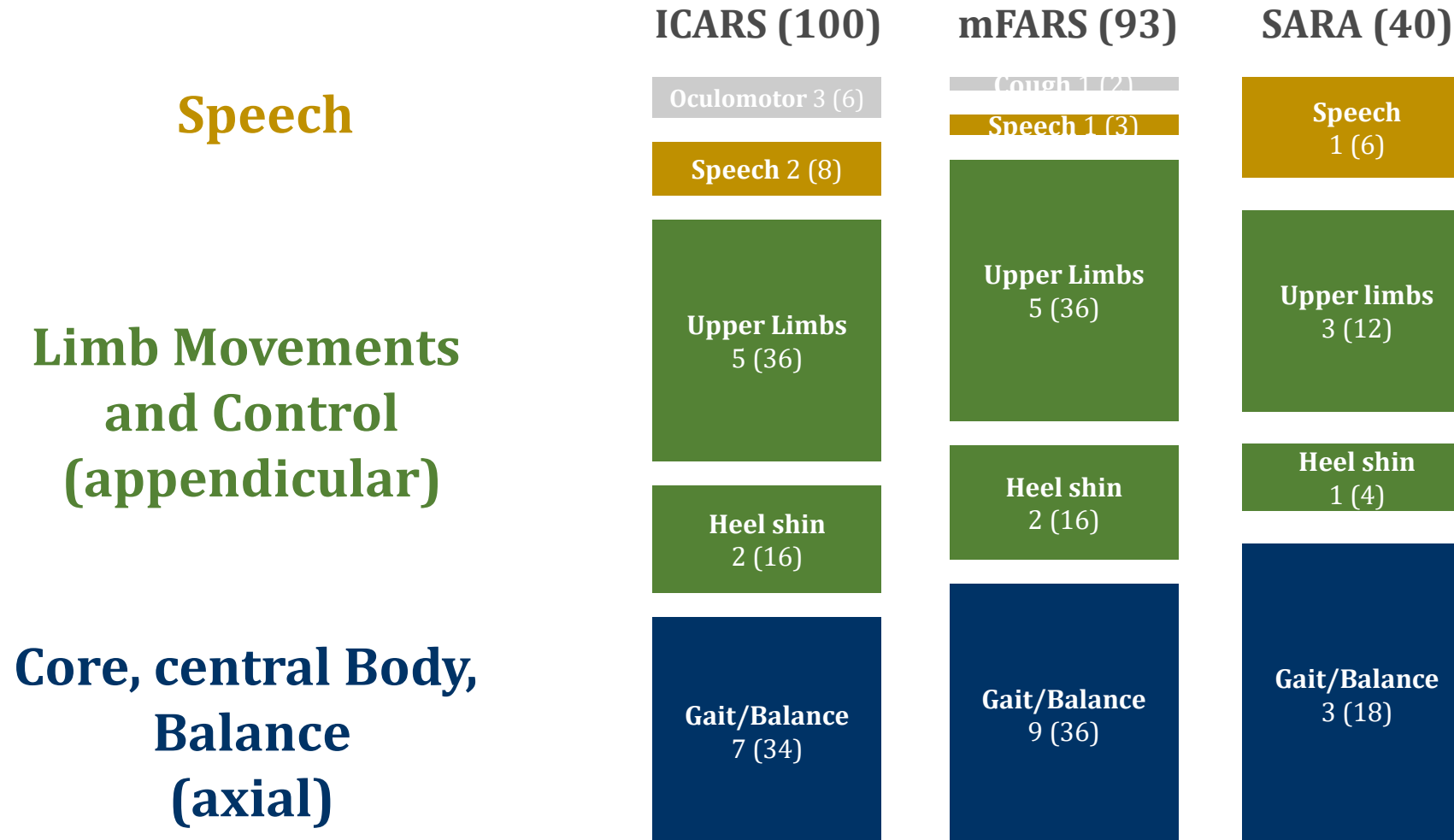
Upper limbs
3 (12)

Heel shin
1 (4)

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Gait/Balance
3 (18)

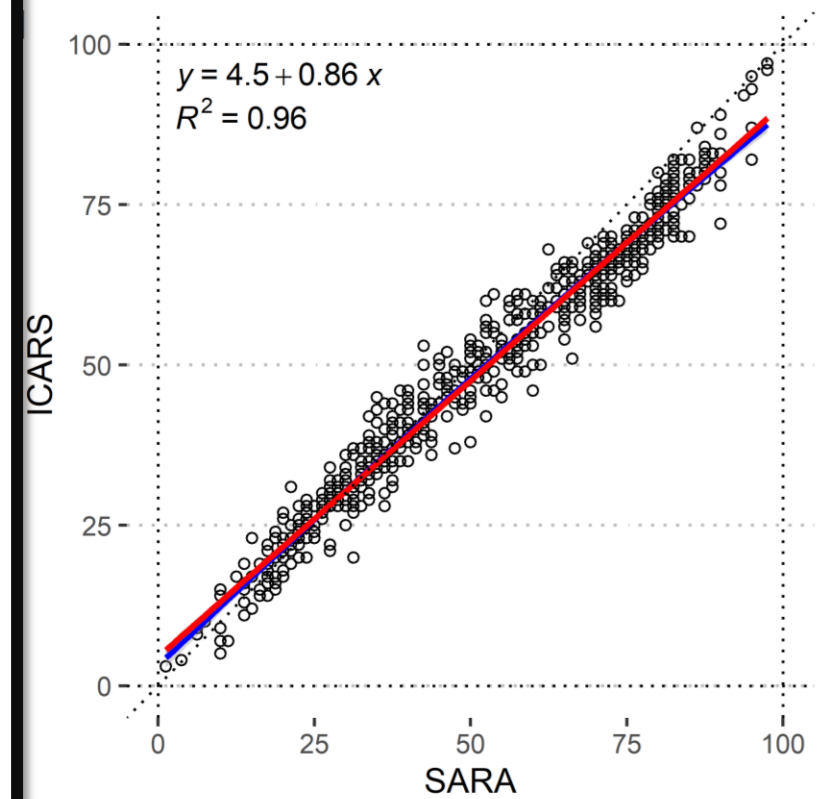
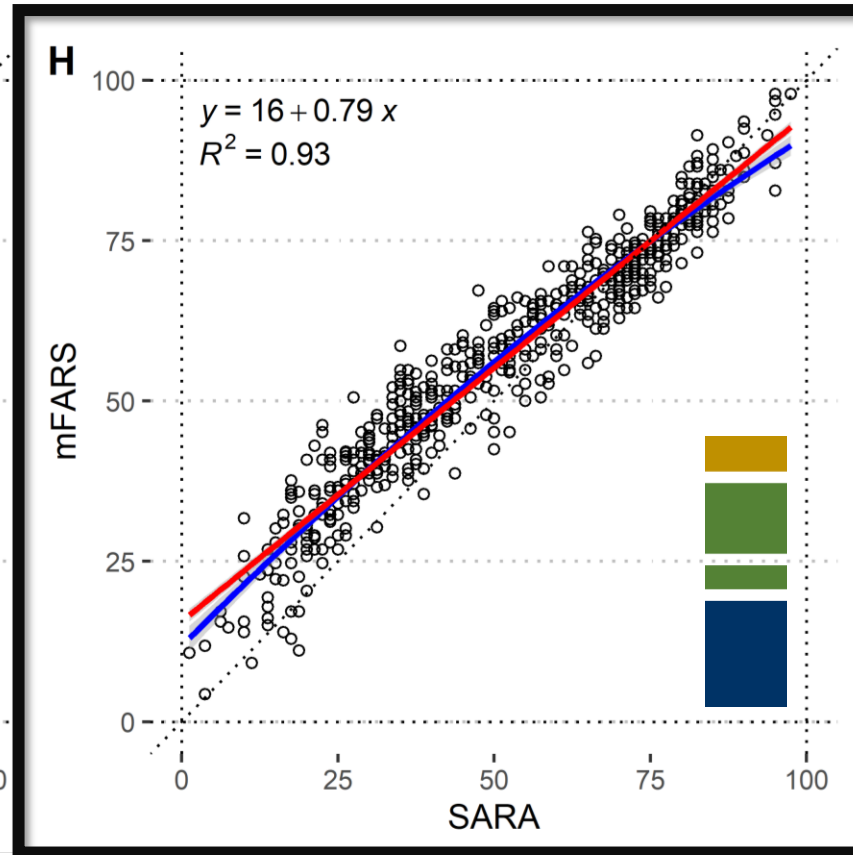
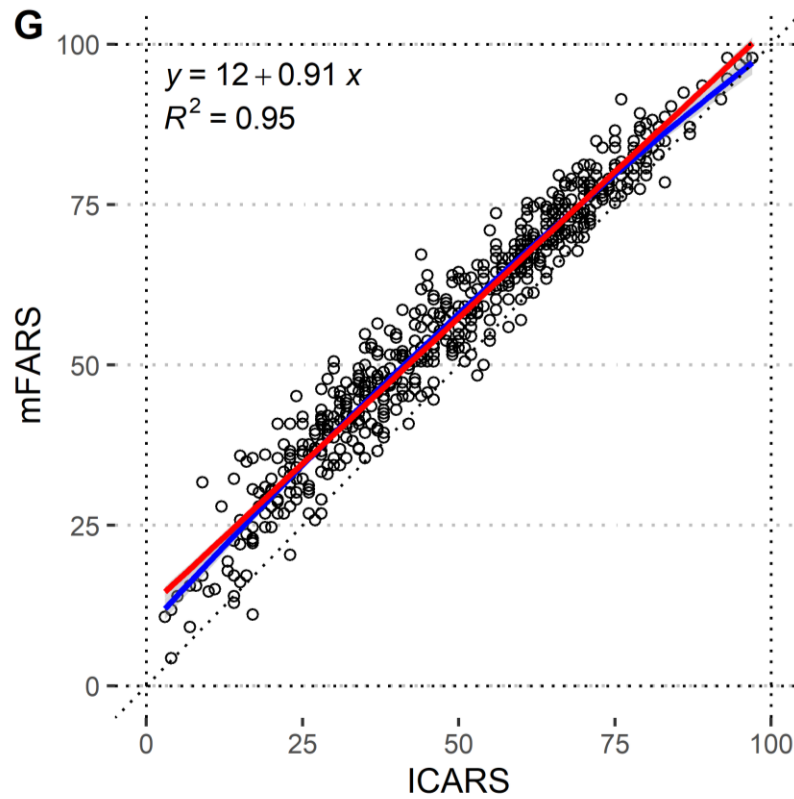
Ataxia Rating Scales



Individual Items

	mFARS	SARA	ICARS
Bulbar Function	A3. (2) Cough	4. (6) Speech	15. (4) Fluency
	A4. (3) Speech		16. (4) Clarity
Appendicular Function	B1. (6) Finger/Finger	5. (4) Finger chase	8. (8) Knee-tibia test
	B2. (8) Nose/Finger	6. (4) Nose/Finger	9. (8) Heel to Knee
	B3. (8) Dysmetria	7. (4) Fast Altering Hand mov.	10. (8) Finger to Nose dysmetria
	B4. (6) Rapid Altering Mov.		11. (8) Finger to Nose tremor
	B5. (8) Finger Taps		12. (8) Finger/Finger
	C1. (8) Heel/shin slide	8. (4) Heel/shin slide	13. (8) Pron., sup., alter. Mov.
	C2. (8) Heel/shin tap		14. (4) Archimedes spiral
Axial Function	E1. (4) Sitting		1. (8) Walking
	E2A. (4) Stance Feet Apart		2. (4) Gait Speed
	E2B. (4) – with eyes closed	1. (8) Gait	3. (6) Stand eyes open
	E3A. (4) Stance Feet Together	2. (6) Stance	4. (4) Spread of feet, eyes open
	E3B. (4) – with eyes closed	3. (4) Sitting	5. (4) Body sway eyes open
	E4. (4) Tandem Stance		6. (4) Body sway eyes closed
	E5. (4) Stance on Dominant Foot		7. (4) Sitting Position
	E6. (3) Tandem Walk		
Oculomotor Disorders	E7. (5) Gait		17. (3) Nystagmus
			18. (2) Ocular pursuit
			19. (1) Dysmetria of saccade

Correlations: mFARS vs SARA vs ICARS



Issues with Appendicular Function Assessment

- Variability in Healthy People
 - Children ($\sim < 12$) & Elderly ($\sim > 65$ y)
- Placebo Effects
- Practice Effects
- Clinical Relevance difficult to argue

Two Approaches to a Systemic Disorder

*Assess “whole” System
in one Scale*

*Focus on Representative
Symptom*

Clinical Trial Design Challenges

- Outcome Selection
- Trial Population - often only a subset of patients that might benefit
- Study Durations – many ataxias are progression relatively slowly
- Natural History Comparator Groups