Clinical Outcome Assessments (COAs) in Ataxias

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ERN-RD Webinar
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Learning objectives

By the end of this webinar you will be able

- to apply ataxia staging systems,
- to know the most important properties of two clinical ataxia scales, SARA and FARS,
- to discuss the relevance of INAS,
- to understand the use of performance-based tests in ataxia, and
- to assess the importance of patient-related outcome measures in ataxia.

Webinar outline

- Staging systems
- Clinical scales
- Quantitative performance measures
- Patient-related outcome measures

Standard for clinical assessment

Ataxia Global Initiative Working Group
Clinical Outcome Assessments (COAs)
Sep 2021

The goal of the working group on COAs is to define a set of data including a graded catalogue of COAs that will serve as the standard for future sharing of clinical data and joint clinical studies. To keep the hurdles for contribution of data to common analyses and studies low, it was agreed to define a mandatory dataset (minimal dataset) that can ideally be obtained during a routine clinical consultation, and a more demanding extended dataset that is useful for research purposes. Data collection via phone alone is not recommended

Minimal dataset

The minimal dataset includes core data that provide basic information on demographics, clinical and genetic status, disability, ataxia severity, and neurological status. It includes the following items:

- *Identifier*
  A unique identifier with large geographic reach is desirable (e.g. EUPID), but further discussions with stakeholders are required.
- *Participation in previous study/registry*
  If yes, study acronym and (old) identifier should be entered.
- *Core demographic data*
- *Genetic information*
  Detailed genetic data according to common standards need to be recorded. The query must be suitable for SCAs, recessive ataxias, and sporadic ataxias. Information on performed tests and negative results needs to be included. For this purpose, the genetic CRF from ARCA registry can be used.
- *Disability status*
- FARS disease stage scaling (0-6): 0 normal; 1 minimal signs detected by physician; 2 symptoms present as recognized by patient, cannot run; 3 symptoms are overt, mild disability, periodic holding to a wall or walker; 4 walking requires a walker, moderate disability; 5 confined but can navigate a wheelchair, can perform some activities of daily living; 6 confined to wheelchair or bed with total dependency [1]
- *Patient's global impression* (7-point scale related to functional impairment due to ataxia compared to the situation one year ago)
- SARA [2]

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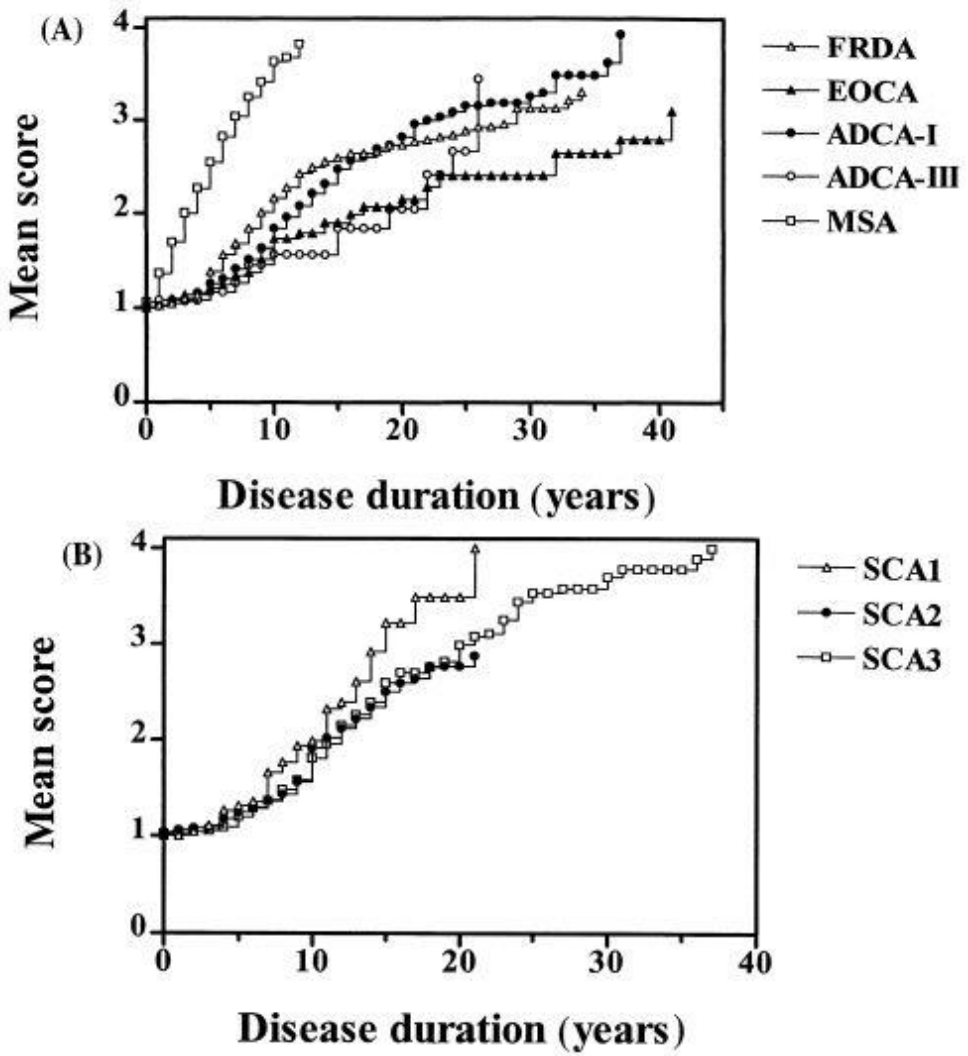
Ataxia staging systems

- Stage 0 — No gait difficulties
- Stage 1 — Gait difficulties
- Stage 2 — Loss of independent gait, as defined by permanent use of a walking aid or reliance on a supporting arm
- Stage 3 — Confinement to wheelchair
- Stage 4 — Death



Klockgether et al. Brain 1998 Apr;121:589-600

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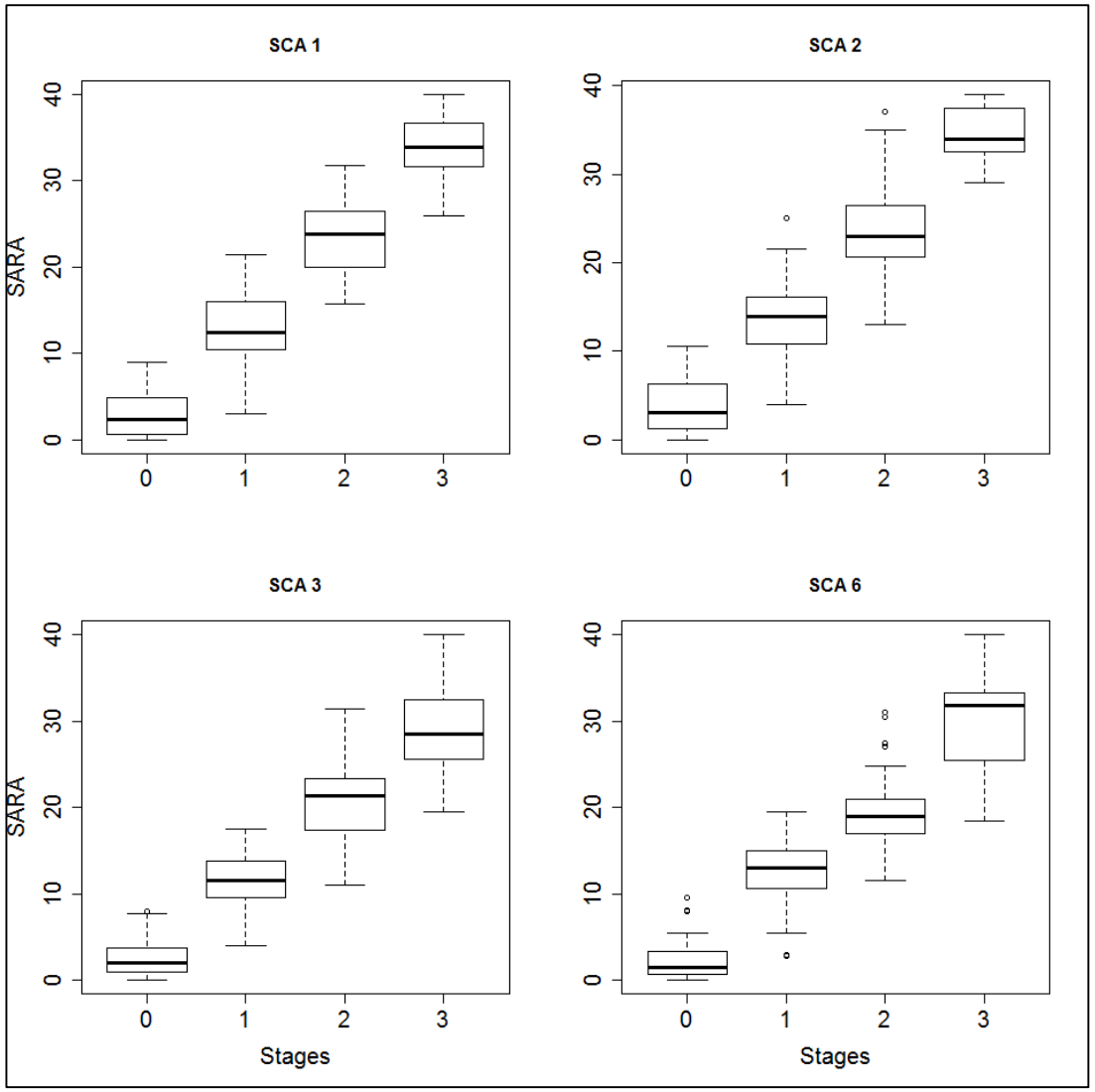

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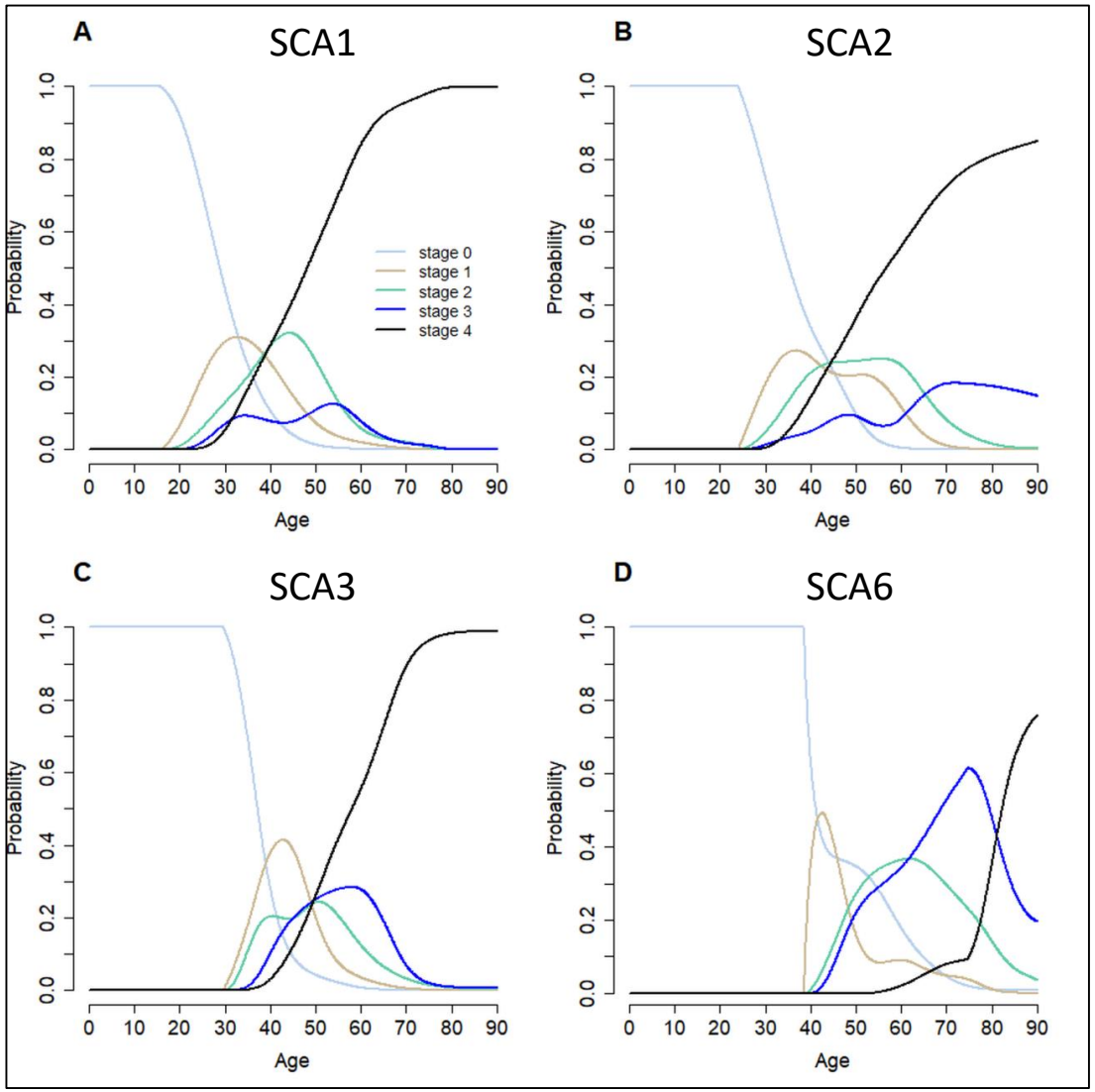

Klockgether et al. Brain 1998 Apr;121:589-600

Ataxia staging systems

FARS part I

I. FUNCTIONAL STAGING FOR ATAXIA

Increment by 0.5 may be used if the status is about the middle between two stages.

STAGE ☐☐

STAGE 0:	Normal.
STAGE 1.0:	Minimal signs detected by physician during screening. Can run or jump without loss of balance. No disability.
STAGE 2.0:	Symptoms present, recognized by patient, but still mild. Cannot run or jump without losing balance. The patient is physically capable of leading an independent life, but daily activities may be somewhat restricted. Minimal disability.
STAGE 3.0:	Symptoms are overt and significant. Requires regular or periodic holding onto wall/furniture or use of a cane for stability and walking. Mild disability. (Note: many patients postpone obtaining a cane by avoiding open spaces and walking with the aid of walls/ people etc. These patients are grades as stage 3.0)
STAGE 4.0:	Walking requires a walker, Canadian crutches or two canes. Or other aids such as walking dogs. Can perform several activities of daily living. Moderate disability.
STAGE 5.0:	Confined but can navigate a wheelchair. Can perform some activities of daily living that do not require standing or walking. Severe disability.
STAGE 6.0:	Confined to wheelchair or bed with total dependency for all activities of daily living. Total disability.

Lynch et al. Neurology 2006;66:1711-6

Ataxia staging systems

Recommendation

- Use the FARS Functional Staging for Ataxia at every routine visit

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Multiple choice question (1)

Which of the following statements is correct?

1. The staging system introduced by Klockgether et al. is finer graded than the FARS Functional Staging.
2. The FARS Functional Staging can be easily applied by telephone interview.
3. Staging systems are useful as outcome measures in clinical trials.
4. **The staging systems used in ataxia are mainly based on walking disability.**
5. Correct use of ataxia staging systems requires longstanding clinical experience.

Clinical ataxia scales

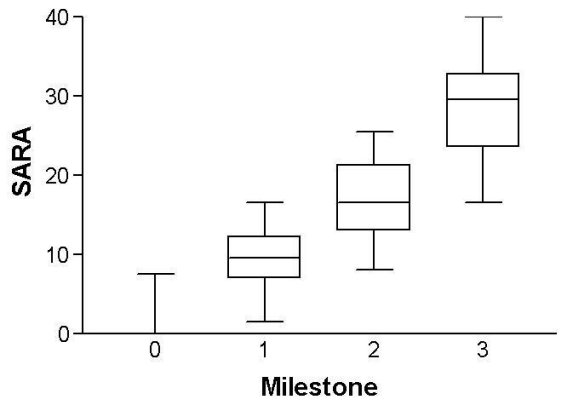
	Disease	Items	Weight (%)	Publication
ICARS	Ataxia	19	Postural/gait 34 Limb 52 Speech 8 Oculomotor 6	Trouillas et al. J Neurol Sci. 1997
SARA	SCA, FRDA, Sporadic ataxia	8	Postural/gait 45 Limb 40 Speech 15	Schmitz-Hübsch et al. Neurology 2006
FARS part III	FRDA	23	Postural/gait 24 Limb 39 Speech 8 Others 29	Lynch et al. Neurology 2006
NESSCA	SCA3	18	Postural/gait 10 Limb 8 Speech 10 Oculomotor 10 Others 62	Kieling et al. Eur J Neurol 2008
BARS	Ataxia	5	Postural/gait 27 Limb 53 Speech 13 Oculomotor 7	Schmahmann et al. Mov Disord. 2009

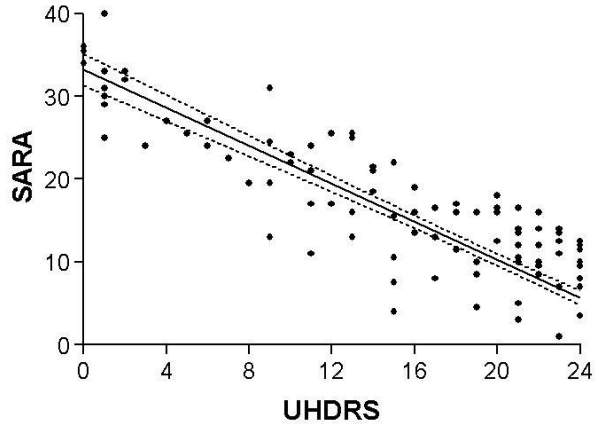
Scale for the Assessment and Rating of Ataxia (SARA)

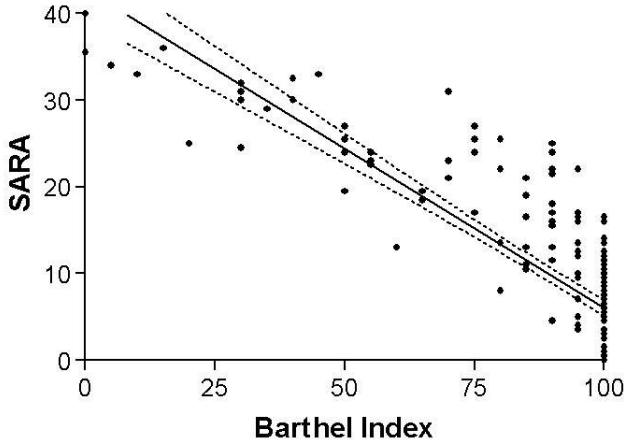
The Scale for the Rating and Assessment of Ataxia (SARA) is a clinical rating scale based on a standard neurological exam. SARA has 8 items (gait, stance, sitting, speech, finger-chase, nose-finger, fast alternating movements, heel-shin).

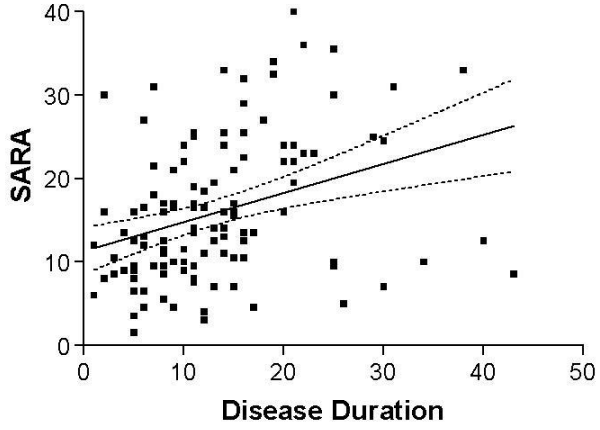
Five validation trials in 617 ataxia patients (SCA, FRDA, sporadic ataxia) providing evidence for

- reliability
- validity
- linearity
- sensitivity to change









Schmitz-Hübsch et al. Neurology 2006;66:1717-20

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Download

http://www.ataxia-study-group.net/html/about/ataxiascales

SARA Online Training Tool

https://ataxia-global-initiative.net/resources/sara-training-tool/

Schmitz-Hübsch et al. Neurology 2006;66:1717-20

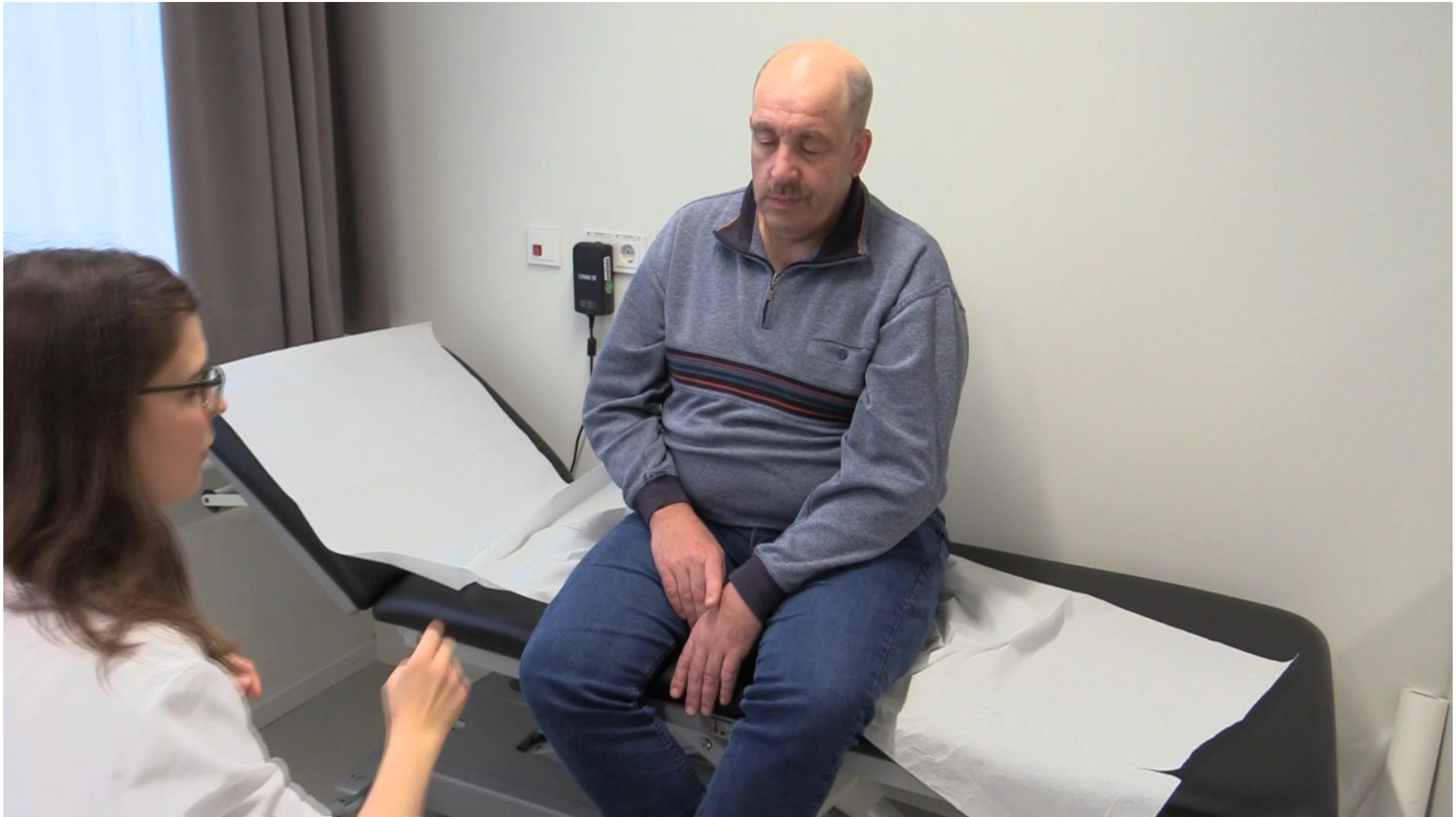
Item 1: Gait

Item 2: Stance

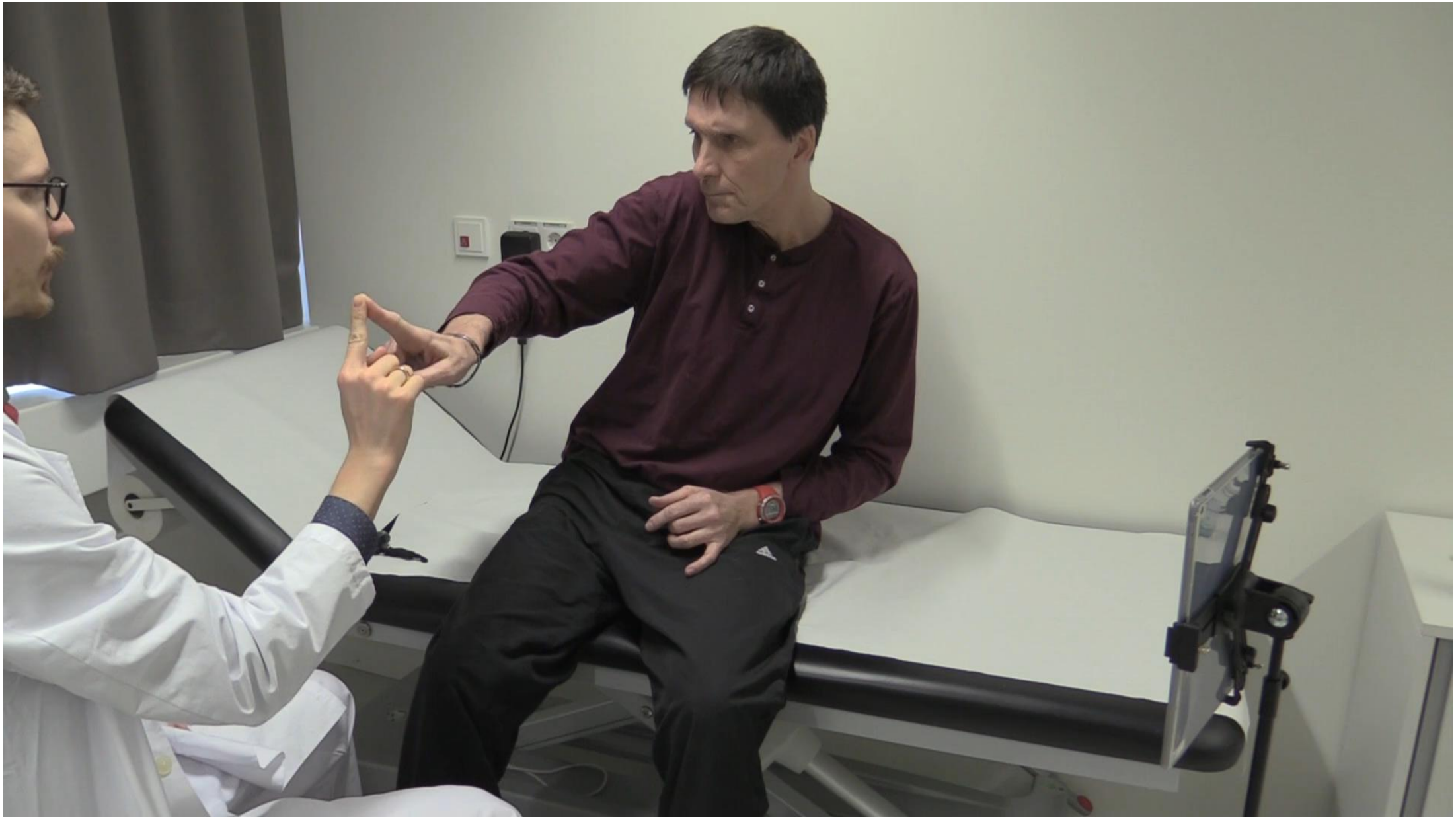
Item 3 - Sitting

Proband is asked to sit on an examination bed without support of feet, eyes open and arms outstretched to the front.

Item 5: Finger-chase

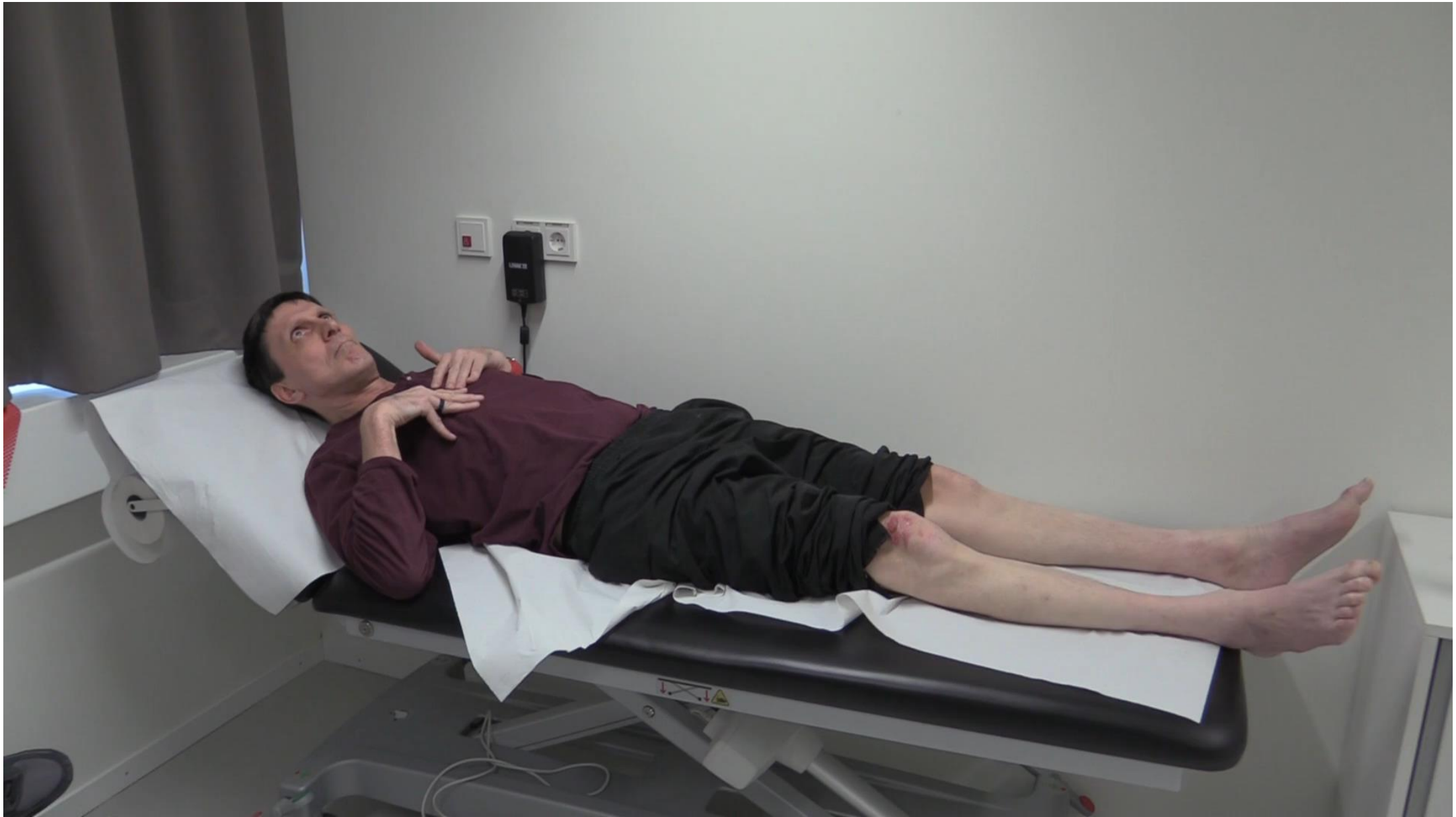


Item 6: Nose-finger

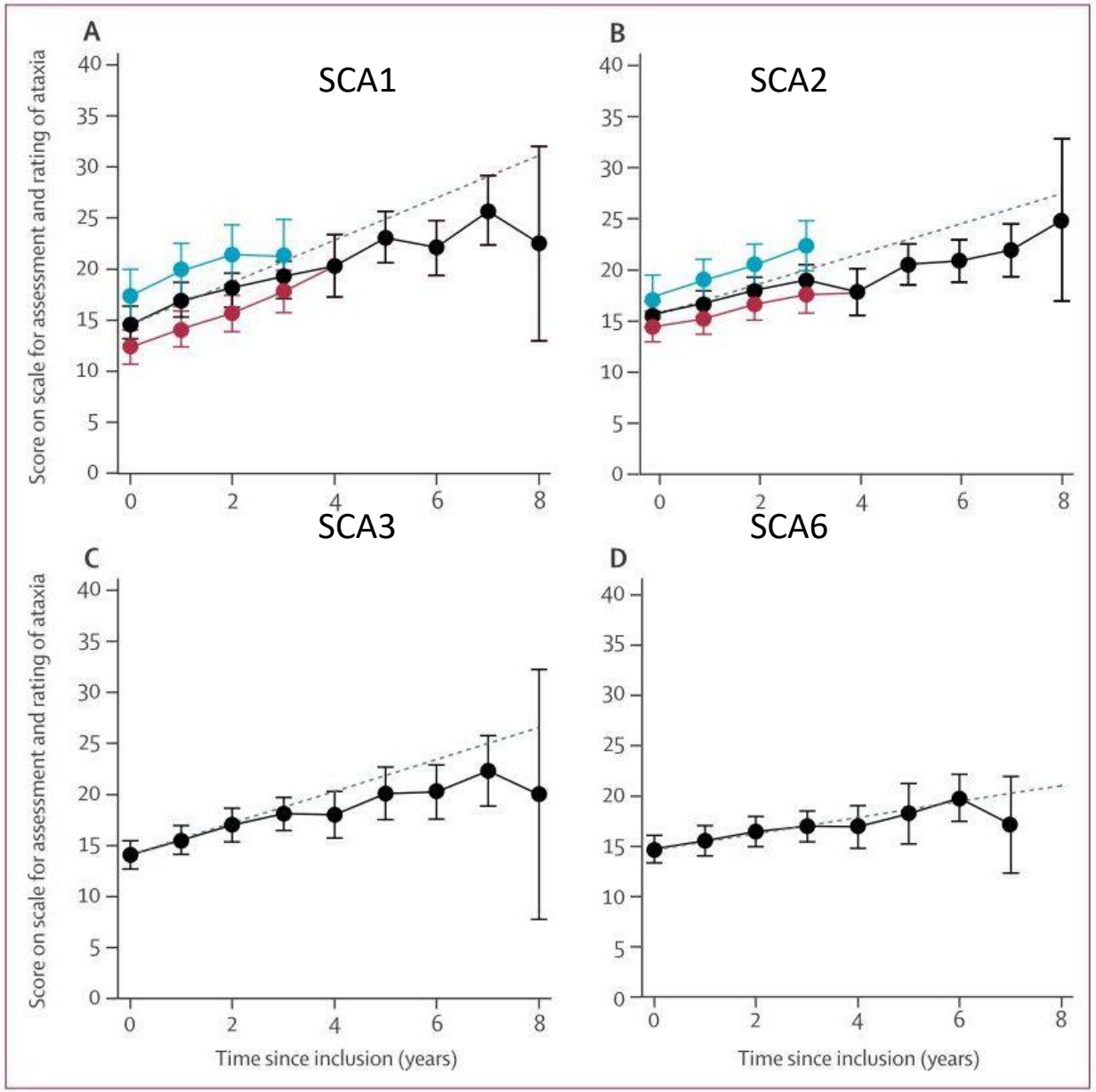


Item 7: Fast alternating movements

Item 8: Heel-shin



SARA progression in SCAs



EUROSCA

Linear mixed and pattern mixture modelling

- SARA progression was linear in all genotypes.
- SARA progression was fastest in SCA1, intermediate in SCA2 and SCA3, slowest in SCA6.

Jacobi et al. Lancet Neurol 2015;14:1101-8

Friedreich Ataxia Rating Scale (FARS)

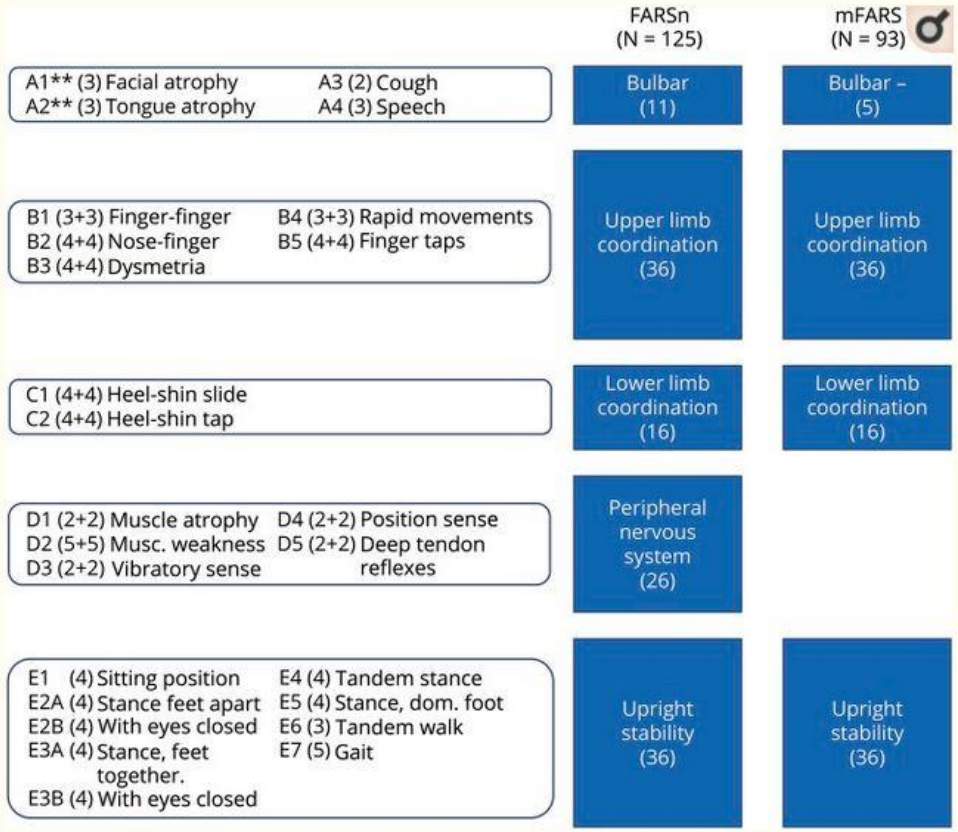


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Figure 1

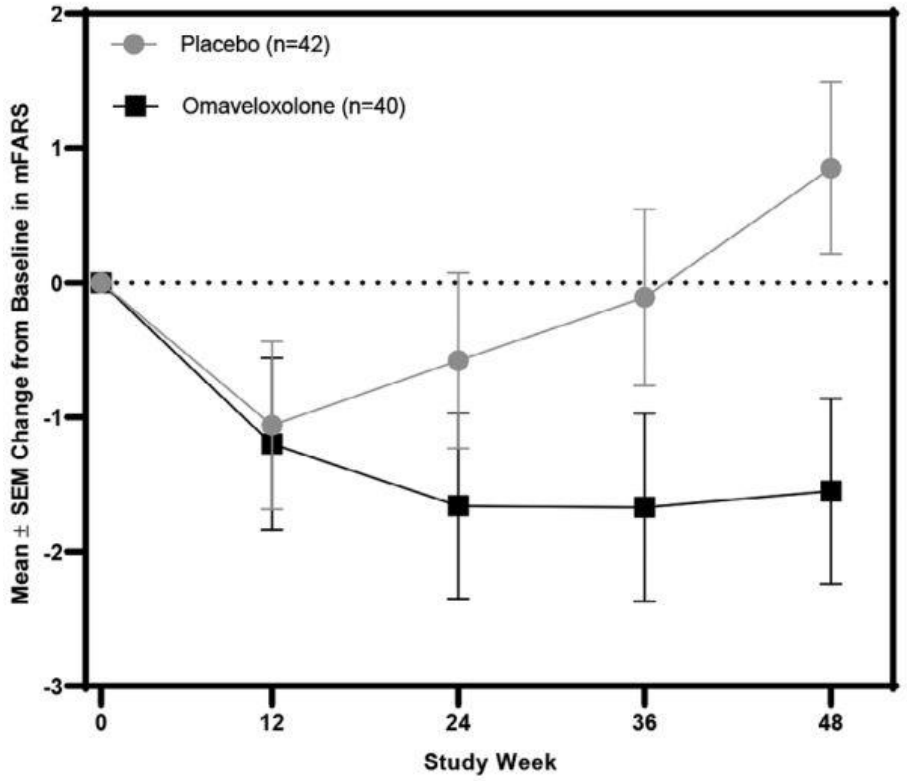
Measurement model of the neurologic examination of the FARSn and the modified FARS (mFARS)

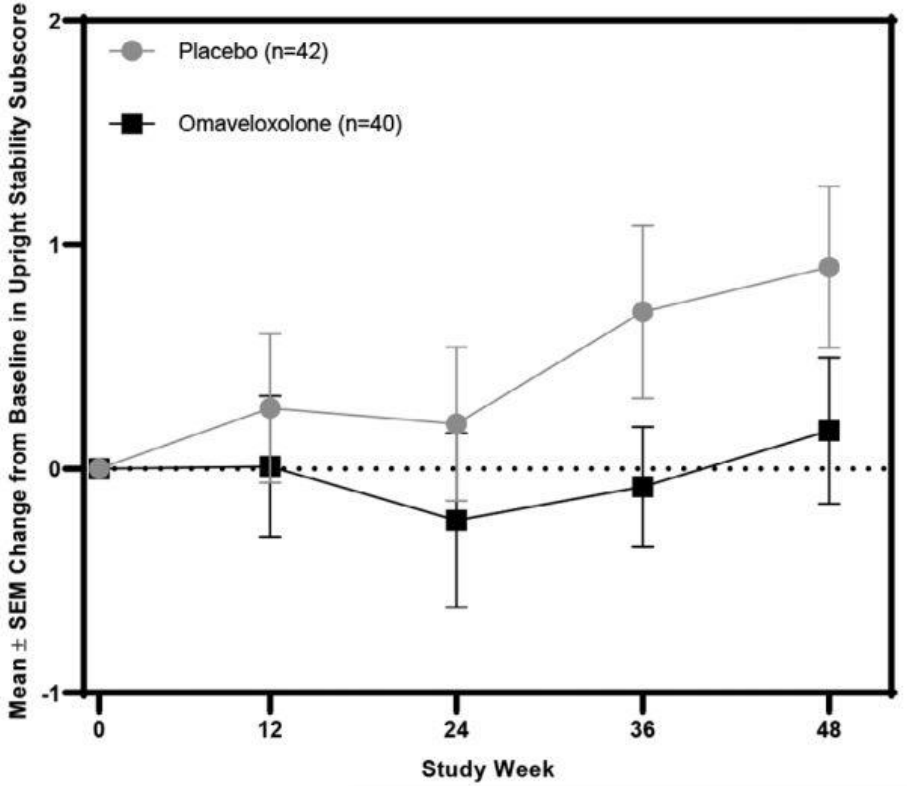
Maximum score/subscale/item scores are shown in brackets. Items in subscales B, C, and D are conducted separately on lateral sides; ** items A1 and A2 are excluded in the mFARS examination. FARS = Friedreich Ataxia Rating Scale; mFARS = modified FARS.

Rummey et al. Neurology Genet 2019;5:371

FRDA: MOXIe trial

- Nuclear factor erythroid 2-related factor 2 (Nrf2) is translocated to the nucleus in response to oxidative stress and induces expression of antioxidative genes.
- Nrf2 signaling is impaired in Friedreich´s ataxia.
- Omaveloxolone is a potent Nrf2 activator.





Lynch et al. Ann Neurol 2021; 89:212–225

Inventory of Non-Ataxia Symptoms (INAS)

- The Inventory of Non-Ataxia Symptoms (INAS) is a list of 16 symptoms that may occur in SCAs.
- As a measure of the non-cerebellar involvement we defined the INAS count which is the number of non-ataxia symptoms in a patient.
- The INAS count is a dimensionless number with a range from 0 to 16.

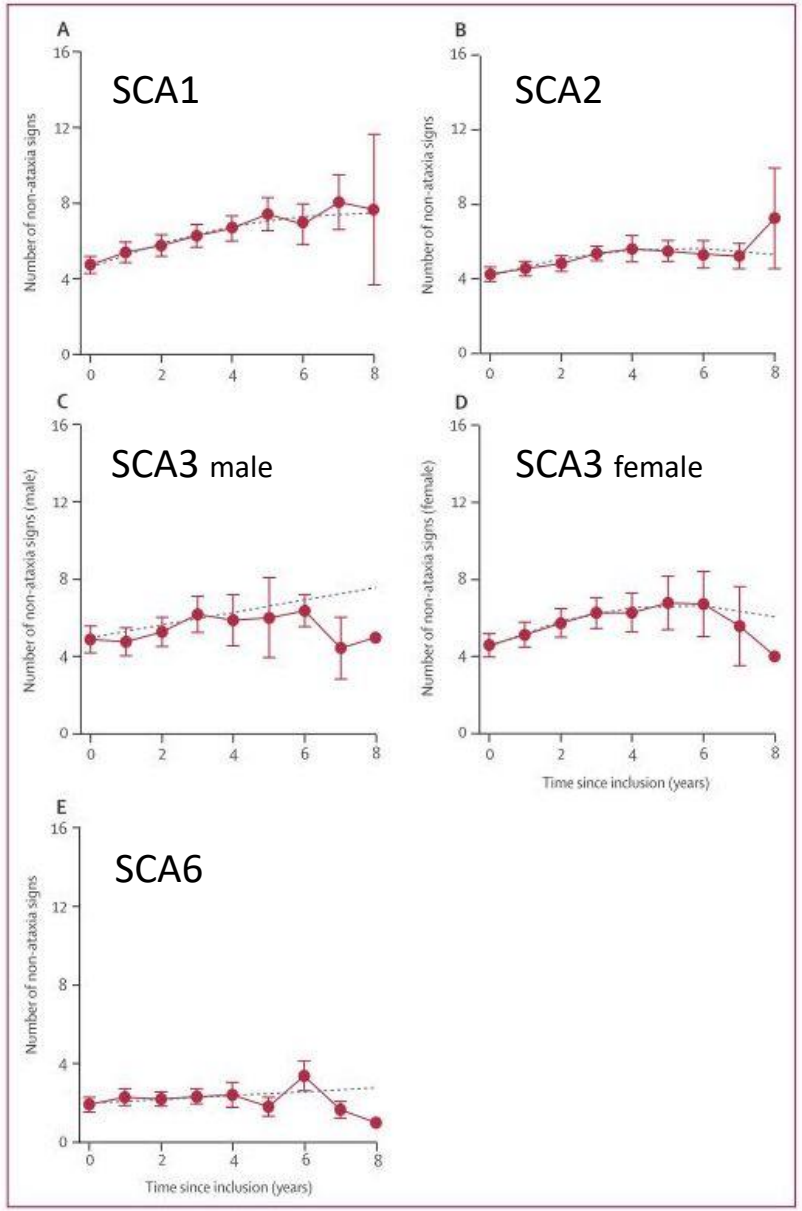
Hyperreflexia
Areflexia
Extensor plantar response
Spasticity
Paresis
Amyotrophy
Fasciculations

Myoclonus
Rigidity
Dystonia
Dyskinesia
Resting tremor

Sensory symptoms
Urinary symptoms
Cognitive impairment
Brainstem oculomotor

Jacobi et al. Cerebellum 2013;12:418-28

INAS progression in SCAs



EUROSCA

Linear mixed and pattern mixture modelling

- INAS progression reached a plateau in SCA1, SCA2 and SCA3, and was linear in SCA6.
- In SCA3, INAS progression was faster in men than in women.
- INAS progression was slowest in SCA6.

Jacobi et al. Lancet Neurol 2015;14:1101-8

Clinical scales

Recommendation

- Perform a complete neurological examination at every routine visit
- Use the SARA at every routine visit
- Consider the mFARS for clinical trials in FRDA

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Multiple choice question (2)

Which of the following statements is wrong?

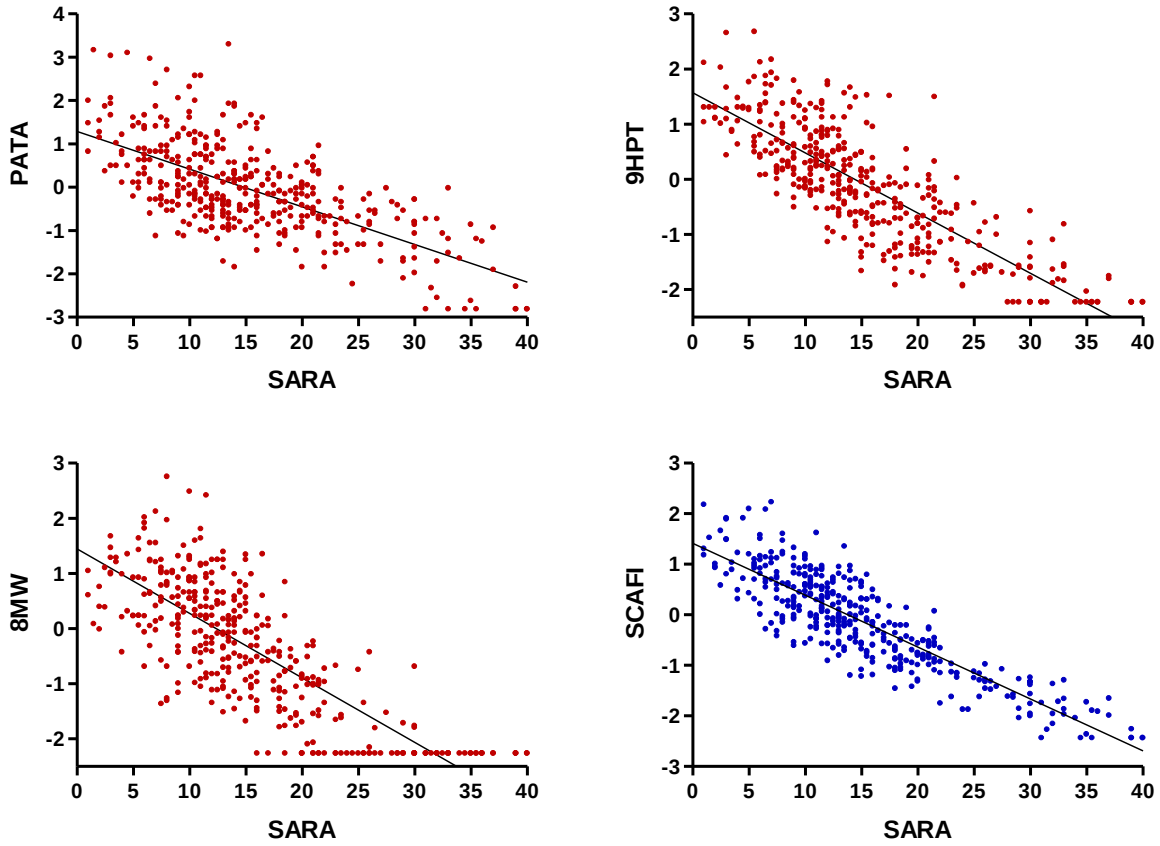
1. SARA has 8 items.
2. FARS has been specifically developed for use in Friedreich ataxia.
3. SARA has been validated in various ataxia disorders.
4. INAS is useful to assess non-ataxia symptoms in spinocerebellar ataxias.
5. **INAS requires specific instrumentation.**

Quantitative performance measures

	Components	Publication
FARS part IV	9HPT, PATA	Lynch et al. Neurology 2006;66:1711-6
SCAFI	8MW, 9HPT, PATA	Schmitz-Hübsch et al. Neurology 2008;71:486-92
CCFS	9HPT, Click Test	Tezenas et al. Brain 2008;131:1352-61

SCAFI

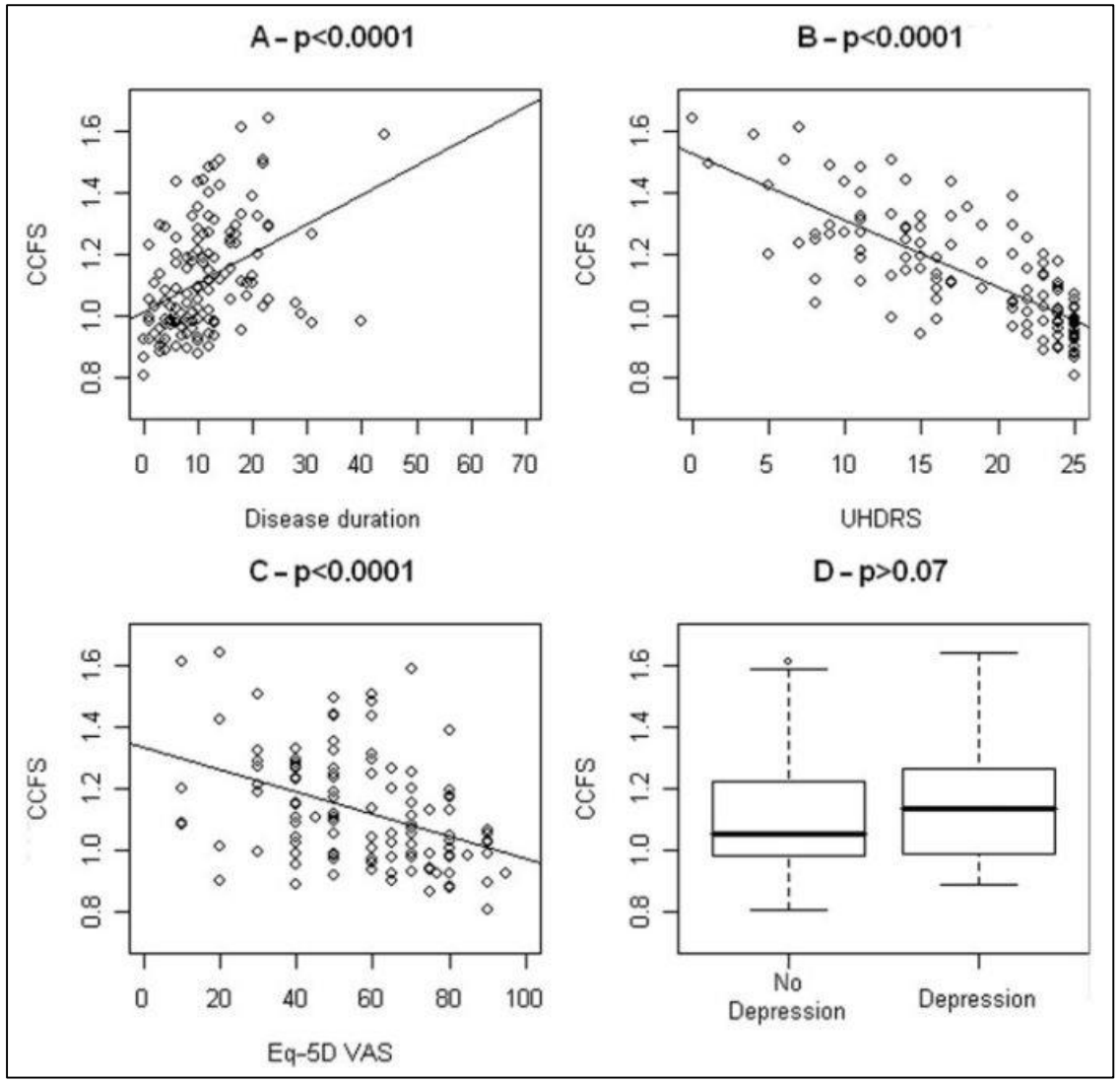
- The SCA Functional Index (SCAFI) is a quantitative and objective measure of functional performance in ataxia.
- SCAFI is based on the performance in the following three timed tests: PATA rate, nine hole peg board test (9HPT), and 8m timed walk (8MW).
- A composite functional score is formed after appropriate transformation of subtest results and compared with a reference population or baseline performance.



Schmitz-Hübsch et al. Neurology 2008;71:486-92

Composite Cerebellar Functional Severity Score (CCFS)

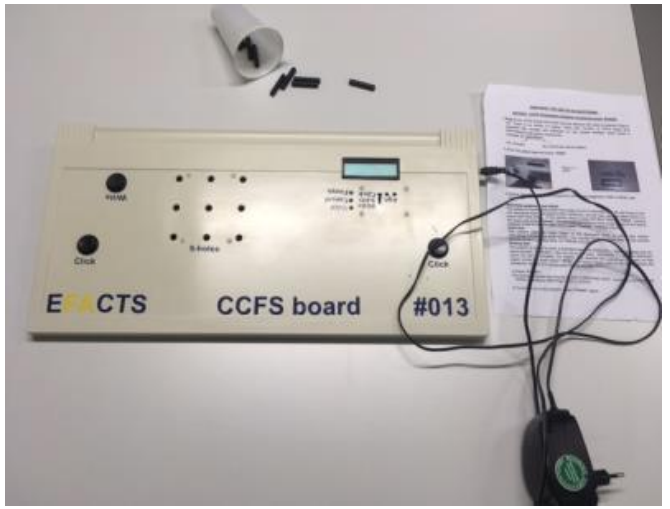
- The Composite Cerebellar Functional Severity Score (CCFS) is a quantitative and objective measure of upper limb functional performance ataxia.
- CCFS is based on the performance in the nine hole peg board test (9HPT) and the click test with the dominant hand.
- Measurements are combined to a composite score for which age-related normal values are available.



Tezenas et al. Brain 2008;131:1352-61

Click test

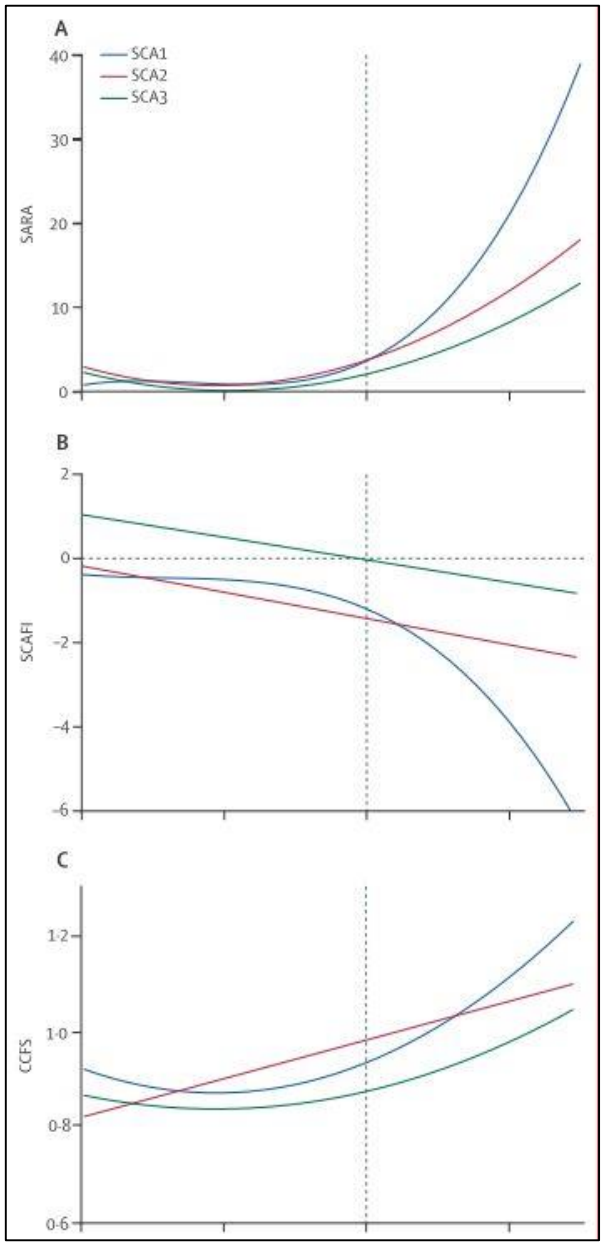
RISCA, ESMI



EFACTS

READISCA

Sensitivity to change



	Clinical scores		Brain volumetry		
	SARA	CCFS	Cerebellum (fs)	Pons (fs)	Vermis (mn)
SCA1	0.83	0.39	−1.71	−1.83	0.15
SCA2	0.77	0.17	−2.16	−1.60	0.17
SCA3	0.79	0.72	−1.47	−2.35	0.28
SCA7	0.05	0.83	−1.31	−2.06	−0.02
Control	−0.10	−0.18	−0.35	−0.07	0.03

SCAFI and CCFS lack sensitivity to change both in the pre-ataxia and ataxia stage of SCAs.

Adanyeguh et al. NeuroImage: Clinical 2018;19:858-67
Jacobi et al. Lancet Neurol 2020;19:738-47

Quantitative performance measures

Recommendation

- Use the CCFS for clinical observational studies
- Consider the use of CCFS and/or SCAFI for interventional trials

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Multiple choice question (3)

Which of the following statements is correct?

1. SCAFI is combined of subtests for walking, speech, fine manual dexterity, and writing.
2. **SCAFI and CCFS are performance-based timed tests.**
3. For SCAFI, an electronic device is available.
4. SCAFI and CCFS are more sensitive to change than clinical scales, such as SARA.
5. CCFS performance is independent of age.

Patient-related outcome measures (PROM)

	Type	Components	Publication
FARS part II	Interview	Activities of daily living (ADL)	Lynch et al. Neurology 2006;66:1711-6
CCAS	Cognitive test	Cognition	Hoche et al. Brain 2018;141:248–70
PROM-Ataxia	Questionnaire	Physical, ADL, Mental	Schmahmann et al. Mov Disord 2021; in press

FARS part II (ADL)

II. ACTIVITIES OF DAILY LIVING (increments of 0.5 may be used if strongly felt that a task falls between 2 scores)

1. Speech

0 - Normal
1 - Mildly affected. No difficulty being understood.
2 - Moderately affected. Sometimes asked to repeat statements.
3 - Severely affected. Frequently asked to repeat statements.
4 - Unintelligible most of the time.

2. Swallowing

0 - Normal.
1 - Rare choking (< once a month).
2 - Frequent choking (< once a week, > once a month).
3 - Requires modified food or chokes multiple times a week. Or patient avoids certain foods.
4 - Requires NG tube or gastrostomy feedings.

3. Cutting Food and Handling Utensils

0 - Normal.
1 - Somewhat slow and clumsy, but no help needed.
2 - Clumsy and slow, but can cut most foods with some help needed. Or needs assistance when in a hurry.
3 - Food must be cut by someone, but can still feed self slowly.
4 - Needs to be fed.

4. Dressing

0 - Normal.
1 - Somewhat slow, but no help needed.
2 - Occasional assistance with buttoning, getting arms in sleeves, etc. or has to modify activity in some way (e.g. Having to sit to get dressed; use velcro for shoes, stop wearing ties, etc.).
3 - Considerable help required, but can do some things alone.
4 - Helpless.

5. Personal Hygiene

0 - Normal.
1 - Somewhat slow, but no help needed.
2 - Very slow hygienic care or has need for devices such as special grab bars, tub bench, shower chair, etc.
3 - Requires personal help with washing, brushing teeth, combing hair or using toilet.
4 - Fully dependent

6. Falling (assistive device = score 3)

0 - Normal.
1 - Rare falling (< once a month).
2 - Occasional falls (once a week to once a month).
3 - Falls multiple times a week or requires device to prevent falls.
4 - Unable to stand or walk.

7. Walking (assistive device = score 3)

0 - Normal.
1 - Mild difficulty, perception of imbalance.
2 - Moderate difficulty, but requires little or no assistance.
3 - Severe disturbance of walking, requires assistance or walking aids.
4 - Cannot walk at all even with assistance (wheelchair bound).

8. Quality of Sitting Position

0 - Normal.
1 - Slight imbalance of the trunk, but needs no back support.
2 - Unable to sit without back support.
3 - Can sit only with extensive support (Geriatric chair, posy, etc.).
4 - Unable to sit.

9. Bladder Function (if using drugs for bladder, automatic score of 3)

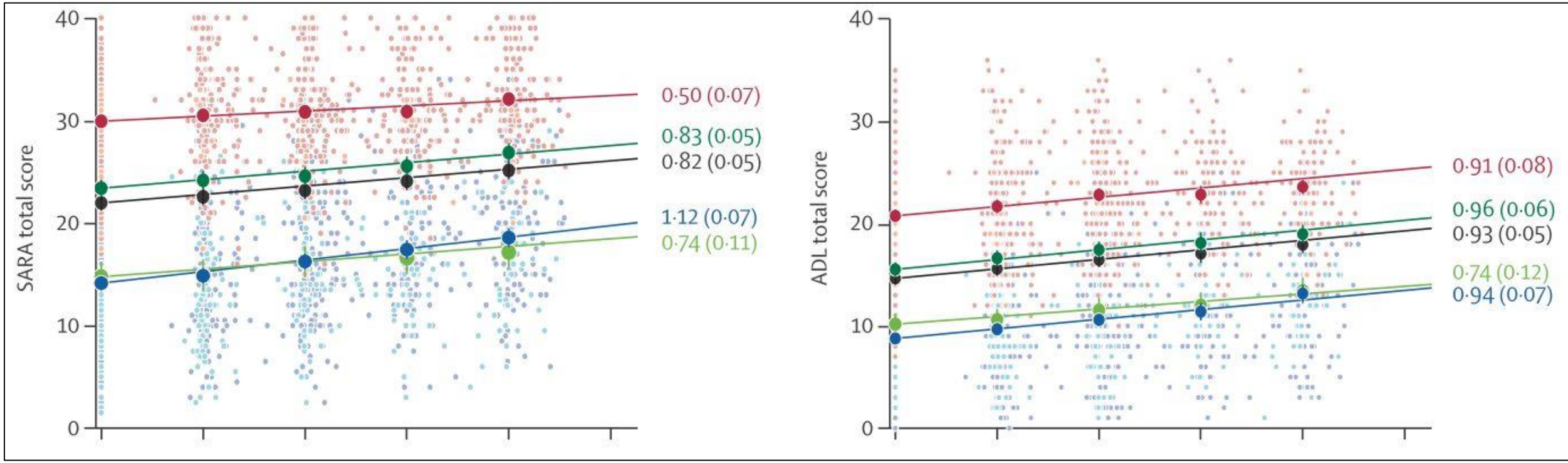
0 - Normal.
1 - Mild urinary hesitance, urgency or retention (< once a month).
2 - Moderate hesitance, urgency, rare retention/incontinence (> once a month, but < once a week).
3 - Frequent urinary incontinence (> once a week).
4 - Loss of bladder function requiring intermittent catheterization/indwelling catheter.

Lynch et al. Neurology 2006; 66:1711-6

FARS part II (ADL)

EFACTS

- FARS ADL was the most sensitive outcome measure in the EFACTS cohort.



Reetz et al. et al. Lancet Neurol 2021

Patient-related outcome measures

Recommendation

- Use the FARS-ADL and/or PROM-Ataxia in any clinical study or trial

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Multiple choice question (4)

Which of the following statements is wrong?

1. Patient-related outcome measures are becoming increasingly important in ataxia research.
2. In Friedreich ataxia, FARS ADL is highly sensitive to change.
3. **There are extensive longitudinal PROM-Ataxia data available.**
4. Among others, FARS ADL considers speech, swallowing, dressing, personal hygiene, walking, and sitting.
5. PROM-Ataxia was systematically developed starting from patient surveys and interviews.

Key points

- SARA and FARS are the most commonly used clinical scales in ataxia disorders.
- SARA can be applied to all types of ataxia, whereas FARS is specific for Friedreich ataxia.
- INAS is a simple instrument to assess non-ataxia symptoms in ataxia disorders.
- SCAFI and CCFS are timed tests to assess the severity of ataxia.
- Patient-related outcome measures are becoming increasingly important in ataxia research.