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RESEARCH ARTICLE

FARS-ADL across Ataxias: Construct Validity, Sensitivity to Change, and Minimal Important Change

Andreas Traschütz, MD, PhD,[1,2] Zofia Fleszar, MD,[2,3] Holger Hengel, MD,[2,3] Thomas Klockgether, MD,[4,5] Friedrich Erdlenbruch, MD,[6] Björn H. Falkenburger, MD,[7,8] Thomas Klopstock, MD,[9,10,11] Özgür Öztop-Çakmak, MD,[12] José Luiz Pedroso, MD,[13] Filippo M. Santorelli, MD,[14] Ludger Schöls, MD,[2,3] RFC1 Study Group, PREPARE Consortium, and Matthis Synofzik, MD[1,2*]

[1]*Research Division "Translational Genomics of Neurodegenerative Diseases," Hertie-Institute for Clinical Brain Research and Center of Neurology, University of Tübingen, Tübingen, Germany*
[2]*German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany*
[3]*Department of Neurodegenerative Diseases and Hertie-Institute for Clinical Brain Research and Center of Neurology, University of Tübingen, Tübingen, Germany*
[4]*Department of Neurology, University Hospital Bonn, Bonn, Germany*
[5]*German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany*
[6]*Department of Neurology and Center for Translational Neuro- and Behavioral Sciences (C-TNBS), Essen University Hospital, University of Duisburg-Essen, Essen, Germany*
[7]*Department of Neurology, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany*
[8]*German Center for Neurodegenerative Diseases (DZNE), Dresden, Germany*
[9]*Department of Neurology, Friedrich-Baur-Institute, Ludwig-Maximilians-University of Munich, Munich, Germany*
[10]*German Center for Neurodegenerative Diseases (DZNE), Munich, Germany*
[11]*Munich Cluster for Systems Neurology (SyNergy), Munich, Germany*
[12]*Koç University, Department of Neurology, Istanbul, Turkey*
[13]*Department of Neurology and Neurosurgery, School of Medicine, Federal University of São Paulo (UNIFESP), São Paulo, Brazil*
[14]*IRCCS Fondazione Stella Maris, Pisa, Italy*

ABSTRACT: Background: Patient-focused outcomes present a central need for trial-readiness across all ataxias. The Activities of Daily Living part of the Friedreich Ataxia Rating Scale (FARS-ADL) captures functional impairment and longitudinal change but is only validated in Friedreich Ataxia.
Objective: Validation of FARS-ADL regarding disease severity and patient-meaningful impairment, and its sensitivity to change across genetic ataxias.
Methods: Real-world registry data of FARS-ADL in 298 ataxia patients across genotypes were analyzed, including (1) cross-correlation with FARS-stage, Scale for the Assessment and Rating of Ataxia (SARA), Patient-Reported Outcome Measure (PROM)-ataxia, and European Quality of Life 5 Dimensions visual analogue scale (EQ5D-VAS); (2) sensitivity to change within a trial-relevant 1-year median follow-up, anchored in Patient Global Impression of Change (PGI-C); and (3) general linear modeling of factors age, sex, and depression (nine-item Patient Health Questionnaire [PHQ-9]).
Results: FARS-ADL correlated with overall disability ($rho_{FARS\text{-}stage} = 0.79$), clinical disease severity ($rho_{SARA} = 0.80$), and patient-reported impairment ($rho_{PROM\text{-}ataxia} = 0.69$, $rho_{EQ5D\text{-}VAS} = -0.37$), indicating comprehensive construct validity. Also at item level, and validated within genotype (SCA3, RFC1), FARS-ADL correlated with the corresponding SARA effector domains; and all items correlated to EQ5D-VAS quality of life. FARS-ADL was sensitive to change at a 1-year interval, progressing only in patients with worsening PGI-C. Minimal important change was 1.1. points based on intraindividual variability in patients with stable PGI-C. Depression was captured using FARS-ADL (+0.3 points/PHQ-9 count) and EQ5D-VAS, but not FARS-stage or SARA.
Conclusion: FARS-ADL reflects both disease severity and patient-meaningful impairment across genetic ataxias, with sensitivity to change in trial-relevant timescales in patients perceiving change. It thus presents a promising patient-focused outcome for upcoming

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*__Correspondence to:__ Dr. Matthis Synofzik, Research Division "Translational Genomics of Neurodegenerative Diseases," Hertie-Institute for Clinical Brain Research and Center of Neurology, University of Tübingen, Hoppe-Seyler-Str. 3, 72076 Tübingen, Germany; E-mail: matthis.synofzik@uni-tuebingen.de

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Key Words: ataxia; clinical outcome assessment; activities of daily living; trial readiness

With a growing understanding of the underlying molecular mechanisms, an increasing number of genetic ataxias—far beyond Friedreich's ataxia (FA)—will enter the stage of interventional trials within the next years.[1] The selection of clinical outcome assessments (COA) for these trials presents a key challenge for academia and industry, in particular compliance with regulatory requirements for patient-focused drug development.[2] Common COAs like the Scale for the Assessment and Rating of Ataxia (SARA) are questioned in their meaningfulness to real life by both patients and regulatory agencies.[1,3,4] Thus, future trials might not take such clinician-reported outcomes like the SARA but rather activities of daily living (ADL) or patient-reported outcome measures (PROMs) as key outcomes, as now increasingly seen in recent U.S. Food and Drug Administration approvals for other neurological diseases.[5,6] For such an endpoint scenario, these outcomes would need to have construct validity for both disease severity and patient-meaningful impairment. Furthermore, they must be sensitive to change in a 1-year, maximal 2-year, trial period and reflect patient-meaningful change.

The ADL part of the Friedreich Ataxia Rating Scale (FARS-ADL), which primarily reflects patient-derived information on daily living with ataxia, might provide such an endpoint that captures patients' functional status and health-related quality of life over time.[7] Indeed, the FARS-ADL reflects abilities relevant to daily life[8] and has already shown sensitivity to change in FA.[9] However, its validity for disease severity and patient-meaningful impairment and its sensitivity to change remain to be demonstrated for all other ataxias. The large majority of genetic degenerative ataxias result in a qualitatively similar (albeit not same) set of ataxia and non-ataxia signs and impairments, which in turn leads to a similar overlapping set of functional ADL impairments, which is being captured by the FARS-ADL. Thus, the FARS-ADL might work, at least in principle, for many degenerative ataxias.

Leveraging prospective cross-sectional and longitudinal registry-based real-world data across ataxia genotypes, we here analyze (1) the construct validity of the FARS-ADL in relation to overall disability (FARS-stage), clinical disease severity (SARA), and patient-reported impairment (PROM-ataxia, quality of life); (2) its intra-individual sensitivity to change and minimal important change (MIC) within a trial-relevant 1-year timescale; and (3) how the FARS-ADL might be influenced by other non-ataxia features, such as demographic factors (age, sex) and depression.

Patients and Methods

Cohort and Recruitment

Real-world registry data from four prospective longitudinal observation studies of degenerative ataxia were analyzed for all patients who had received a concurrent assessment using FARS-ADL and SARA from January 2012 through August 2022. This comprised 275 visits for 223 patients with genetically confirmed autosomal-recessive or unsolved early-onset ataxia from the ARCA (Autosomal-Recessive Cerebellar Ataxia) registry[10] (multicenter data available to the study principal investigator site Tübingen), 162 visits for 52 patients with FA (EFACTS [European Friedreich's Ataxia Consortium for Translational Studies] registry),[11] 115 visits for 46 patients with genetically confirmed or unsolved autosomal-dominant spinocerebellar ataxia (SCA registry),[12] and 18 visits for 10 patients with sporadic late-onset ataxia (SPORTAX registry)[13] (for the last three registries: all data from the principal investigator site Tübingen). After exclusion of patients below 18 years of age (n = 19), duplicates in the ARCA and EFACTS registries (n = 14), and follow-up visits after <6 or >24 months (n = 119, to achieve comparable follow-up intervals), the final study cohort comprised 298 cross-sectional and 110 longitudinal visits (Fig. 1A). Data collection was approved by the Institutional Review Board of the Medical Faculty of the University of Tübingen (598/2011BO1), and all subjects provided written informed consent.

Clinical Outcome Assessments

FARS-ADL consists of nine items rating functional impairment in ADLs (speech, cutting food/handling utensils, dressing, hygiene, falling, walking, sitting) as well as swallowing and bladder function.[7] It was applied by the clinician as a structured patient interview, with its five standard prespecified severity levels per item and optional 0.5-point increments between item levels if strongly felt appropriate (total score: from 0 [no ADL impairments] to 36 points [most severe ADL impairments]). The SARA is based on the clinical examination of ataxia severity and comprises eight items with variable severity levels from normal to maximum impairment (gait: 0–8; stance: 0–6 and sitting: 0–4; speech: 0–6; finger chase, nose-finger test, fast alternating hand movements, and heel-shin slide: 0–4 points), yielding total scores from 0 (no ataxia) to 40 (most severe ataxia).[4]

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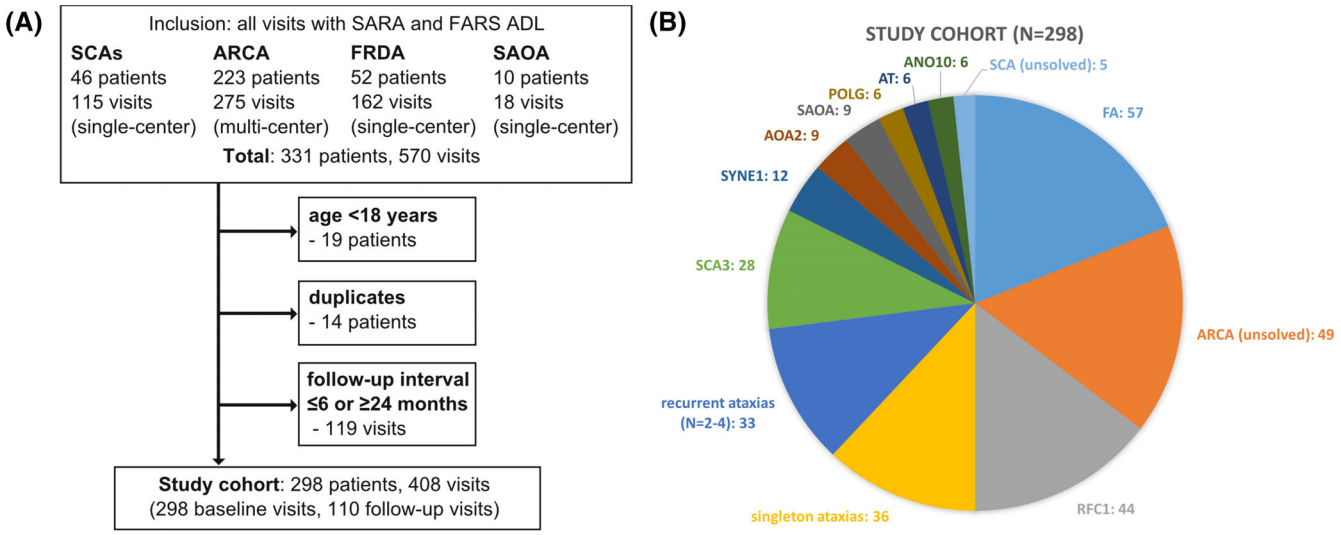


FIG. 1. Recruitment and cohort. (**A**) Flow chart of inclusion and exclusion criteria, with recruitment from four real-world registries, including patients with autosomal-dominant spinocerebellar ataxia (SCA), autosomal-recessive cerebellar ataxia (ARCA) or unsolved early-onset ataxias enriched for ARCAs, Friedreich ataxia (FA), and sporadic late-onset ataxia (SAOA). (**B**) Distribution of diagnoses and genotypes in the study cohort. [Color figure can be viewed at wileyonlinelibrary.com]

To determine construct validity, demographic data of patients (age, sex) and concurrent cross-sectional clinician-reported and patient-reported outcomes from the same assessment day were retrieved from the registries and analyzed as available. These outcomes included disease staging of the FARS as a measure of overall disability (FARS stage, n = 259 patients, ranging from 0 = normal to 6 = bedridden/unable to navigate wheelchair),[7] the visual analogue scale of the European Quality of Life 5 Dimensions scale as a measure of quality of life (EQ5D-VAS, n = 214, ranging from 0 = "The worst health you can imagine" to 100 = "The best health you can imagine"),[14] and the nine-item Patient Health Questionnaire as a diagnostic instrument for depression (PHQ-9, n = 176, total score: 0–27; mild depression: 5–9, moderate: 10–14, moderately severe: 15–19, severe: 20–27).[15] In a subset of 30 patients, the PROM-ataxia was available after its recent translation into German language.[16] As a 70-item questionnaire, the PROM-ataxia asks for the frequency of ataxia-related symptoms and the severity of functional impairment based on the previous 2-week experience, yielding a total score (range: 0–280) and subscores for its three domains: "physical" (0–144), "activities of daily living" (0–68), and "mental health" (0–68 points).

Statistical Analysis

Construct validity—specifically convergent validity—of the FARS-ADL was analyzed by calculating the cross-sectional correlation matrix for the rank-ordered alignment of FARS-stage, SARA, FARS-ADL, PROM ataxia, and EQ5D-VAS. This order followed the a priori hypothesis based on the model proposed by Wilson and Cleary[17] that such respective COAs would—along a gradual spectrum—increasingly reflect nonbiological, that is, psychosocial factors (eg, individual motivational, affective, or coping factors) or nonmedical factors (eg, individual life preferences, social support)—from an objective rating of overall disability on the left side (FARS-stage) to a fully self-rated overall health-related quality of life on the right side (EQ5D-VAS). Item-level correlations of the FARS-ADL to the SARA were calculated to determine its convergent validity in the corresponding effector domains (eg, gait, sitting, speech). Patient meaningfulness of the FARS-ADL and each of its items was analyzed by item-level correlations to EQ5D-VAS quality of life. Spearman's correlations were chosen to account for nonparametric distributions and nonlinear associations.

Sensitivity to change in the FARS-ADL was analyzed and compared to the SARA by calculating the intra-individual difference in scores between the follow-up and baseline assessments. Using an anchor-based method, patient meaningfulness of the change was determined based on the Patient Global Impression of Change (PGI-C) relative to baseline,[18] which was available for 107 of 110 longitudinal assessments, and stratified into three levels of "worsening" (n = 61), "stable/no change" (n = 39), and "improvement/better" (n = 7). To determine the MIC of the FARS-ADL, we calculated the upper limit of the 95% confidence interval (CI) of score changes in patients with stable PGI-C.[19] Potential bias between patients with and without follow-up data was excluded by comparing categorical data (sex) with Fisher's exact test, and continuous data (age or outcome scores) with Mann-Whitney tests.

To estimate the impact of demographic factors and depression on the FARS-ADL and other ataxia outcomes,

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we performed general linear modeling (GLM) for each COA, selecting the respective score of the outcome as dependent variable of the model, and age, sex, and PHQ-9 score as independent variables.

Descriptive statistics, test statistics, and Spearman's correlations were calculated using Prism 9 (GraphPad Software, La Jolla, CA). SPSS 25 (IBM, Armonk, NY) was used to perform GLM (function GENLIN).

Results

Cohort Characteristics

The study cohort comprised 298 ataxia patients across a representative spectrum of degenerative ataxias, with FA (n = 57), RFC1 disease (n = 44), and SCA3 (n = 28) as most frequent recurrent genotypes (Fig. 1B). Demographic characteristics and the distribution of COAs spanned the full range of ataxia severities (Table 1). Patients with longitudinal follow-up (n = 110; median interval: 12 months, interquartile range: 11–13) were less likely to have RFC1 disease (n = 3; Supplement S1) but were otherwise not biased in demographic characteristics (age: $P = 0.812$, sex: $P = 0.180$), severity of ataxia (FARS-ADL: $P = 0.278$, SARA: $P = 0.272$), or presence of depressive symptoms (PHQ-9: $P = 0.534$) compared to patients without follow-up.

TABLE 1 *Characteristics of the study cohort*

Characteristic	N	Median	IQR	Range
Demographics				
Age (y)	298	49	33–61	18–85
Sex (% female)	298	51	–	–
Outcome measures				
FARS-stage	259	3	2–4.5	0–6
SARA	298	13.5	9.5–18.5	0–40
FARS-ADL	298	11	6–16	0–36
PROM-ataxia	30	104	78–123	14–203
EQ5D-VAS	214	64	50–75	0–100
PHQ-9	176	5	2–9	0–24

Abbreviations: IQR, interquartile range; FARS-ADL, Friedreich Ataxia Rating Scale Activities of Daily Living; SARA, Scale for the Assessment and Rating of Ataxia; PROM-ataxia, Patient-Reported Outcome Measure for ataxia; EQ5D-VAS, European Quality of Life 5 Dimensions Visual Analogue Scale; PHQ-9, nine-item Patient Health Questionnaire.

Convergent Validity of FARS-ADL

FARS-ADL was correlated to FARS-stage (rho = 0.78, n = 259), SARA (rho = 0.80, n = 298), PROM-ataxia (rho = 0.79, n = 30), and EQ5D-VAS (rho = −0.37, n = 214; all $P < 0.001$), indicating comprehensive convergent validity. The strength of the correlation coefficients of the FARS-ADL—and also among FARS-stage, SARA, PROM-ataxia, and EQ5D-VAS—was consistent with the hypothesized rank order: correlations successively decreased with the distance between two COAs along the spectrum from overall disability on the one end to patient-reported overall health-related quality of life on the other end, whereas adjacent COAs along the spectrum showed the highest correlations (Fig. 2A).

To determine the convergent validity of FARS-ADL for individual effector domains of ataxia, we analyzed its cross-correlations at the item level (see Fig. 2B, shown are all correlations with an at least weak correlation of |rho| ≥ 0.2, all $P < 0.001$). FARS-ADL and SARA showed several strong cross-correlations in the corresponding effector domains ("hot-spot correlation domains," see Fig. 2B), in particular between FARS-ADL *walking* and SARA *gait* (rho = 0.86) and *stance* (rho = 0.77), or between the corresponding *sitting* or *speech* items (both rho = 0.77). The FARS-ADL upper-limb item *cutting/handling food* was moderately correlated to the SARA item *alternating hand movements* (rho = 0.58). FARS-ADL items *dressing* and *hygiene* showed no specific associations with SARA items. This pattern was also qualitatively observed within each of the main genotypes (RFC1, FA, SCA3) and all other genotypes covered in this cohort, with minor nuances in the relative item correlations, thus demonstrating that it was not just carried by FA patients (Supplement S2). All FARS-ADL items were correlated to EQ5D-VAS quality of life, with the highest correlation for *walking* (rho = 0.34).

To investigate the potential differences between FARS-ADL and PROM-ataxia—as the current only PROM sensu strictu specifically tailored to ataxia—cross-correlations of the FARS-ADL were further analyzed at the level of individual PROM-ataxia domains (Fig. 2C). FARS-ADL was correlated to all domains of the PROM-ataxia, including a strong correlation to its *ADL* domain (rho = 0.82, $P < 0.001$). In turn, only the *ADL* domain of the PROM-ataxia was correlated to all COAs, from FARS-stage (rho = 0.51, $P = 0.005$) to EQ5D-VAS (rho = 0.65, $P = 0.006$). Neither the *physical* ($P = 0.203$) nor the *mental* domain ($P = 0.520$) of the PROM-ataxia reflected overall disability in the FARS-stage, and the correlation between the *mental* domain and EQ5D-VAS quality of life was of moderate effect size and only borderline statistical significance (rho = 0.48, $P = 0.050$).

Sensitivity to Change in FARS-ADL Reflecting Patient-Meaningful Change

Sensitivity to change in the FARS-ADL was analyzed in comparison to SARA (Fig. 3; see Supplement S3 for item-level analysis). Averaged across all patients, the total score of both scales progressed by 0.5 points each within the median 1-year follow-up interval, reaching

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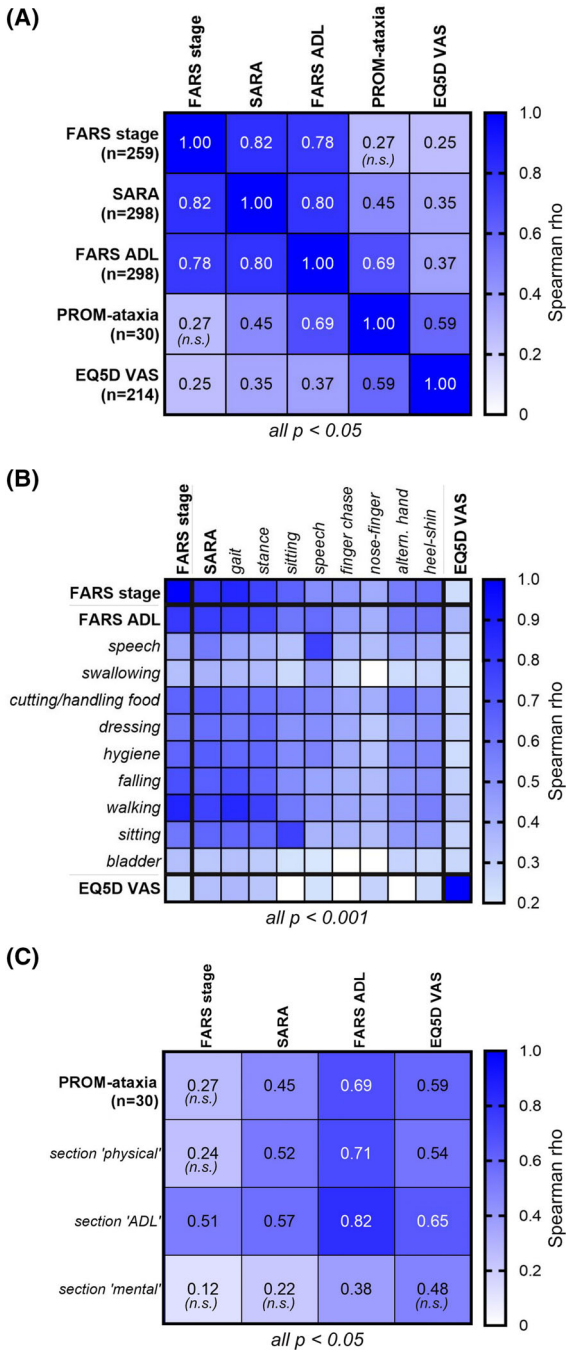


FIG. 2. Convergent validity of FARS-ADL (Friedreich Ataxia Rating Scale Activities of Daily Living) with clinician- and patient-reported ataxia outcomes. (**A**) Cross-sectional correlation between total score levels, with a priori hypothesis-driven rank-ordered alignment of outcomes from clinician-reported overall disease severity (FARS-stage) on the left to patient-reported overall health-related quality of life (EQ5D-VAS [European Quality of Life 5 Dimensions Visual Analogue Scale]) on the right. Note that correlation coefficients are highest between adjacent outcomes and monotonically decrease with their distance in the correlation matrix. (**B**) Cross-correlations at the item level, above a threshold of at least weak correlation (|rho| ≥ 0.2). Note the "hot spots" of correlation between FARS-ADL and SARA (Scale for the Assessment and Rating of Ataxia) items in corresponding motor domains of ataxia (eg, gait, sitting, or speech). (**C**) Cross-correlations to the PROM-ataxia (Patient-Reported Outcome Measure for ataxia) and its individual domains. [Color figure can be viewed at wileyonlinelibrary.com]

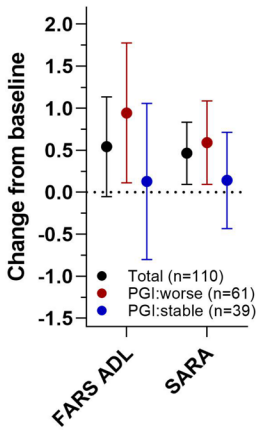


FIG. 3. Sensitivity to change within trial-relevant 1-year timescale. Longitudinal change between follow-up and baseline for the total score of FARS-ADL (Friedreich Ataxia Rating Scale Activities of Daily Living) compared to the SARA. Data presented as average across all patients (black) and stratified using Patient Global Impression of Change (PGI-C). Changes plotted as mean and 95% confidence intervals, indicating significant progression when zero (dashed line) is not included. Progression of FARS-ADL and SARA was limited to patients with subjective worsening of ataxia. [Color figure can be viewed at wileyonlinelibrary.com]

significance for the total SARA (95% CI: [0.09–0.83], $P = 0.015$) and a trend for the total FARS-ADL ([−0.06 to 1.14], $P = 0.075$). Stratification by PGI-C showed that the FARS-ADL worsened in patients with worsening PGI-C by 0.9 points ([0.11–1.78], $P = 0.027$, n = 39), whereas FARS-ADL scores were stable in patients reporting stable PGI-C ([−0.80 to 1.06], P = 0.782, n = 39).

The worsening of the FARS-ADL in patients with worsening PGI-C was also observed in genotypes other than FA, demonstrating that it was not just carried by FA patients (Supplement S4). The same pattern was observed for longitudinal changes in SARA, with specific progression by 0.6 points for worsening PGI-C ([0.09–1.09], $P = 0.021$) but nonprogression in stable PGI-C ([−0.43 to 0.71], $P = 0.622$). Based on the upper bound of the 95% CI in patients with stable PGI-C, the estimated MIC was 1.1 points for FARS-ADL and 0.7 points for SARA.

Impact of Demographic Factors and Depression on FARS-ADL

Higher FARS-ADL scores were associated with higher PHQ-9 scores in multivariate GLM, with an increase of 0.3 points in FARS-ADL per PHQ-9 count ($P = 0.009$), thus indicating that FARS-ADL also reflects depression as psychosocial aspects in ataxia (Table 2; for confirmation also in non-FA genotypes, see Supplement S5). The relative impact of depression was even larger on self-rated quality of life, with a loss of 1.5 points in EQ5D-VAS per PHQ-9 count ($P < 0.001$). In contrast, PHQ-9 scores were not associated with FARS-stage

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TABLE 2 *Impact of demographic factors and depression*

Model variable	FARS-stage (n = 148)		SARA (n = 176)		FARS-ADL (n = 176)		EQ5D-VAS (n = 176)	
	β	*P*	β	*P*	β	*P*	β	*P*
Intercept	2.661	<0.001	14.360	<0.001	7.482	<0.001	74.886	<0.001
Sex	–	0.668	–	0.778	–	0.980	–	0.687
Age	0.012	0.080	–	0.579	–	0.242	–	0.279
PHQ-9 score	0.004	0.845	0.216	0.085	0.299	0.009	−1.542	<0.001

General linear model with respective ataxia outcome as dependent variable and sex, age, and PHQ-9 core as independent variables. β is the regression coefficient, normalized to scale range in the last line of the table.
Abbreviations: FARS-ADL, Friedreich Ataxia Rating Scale Activities of Daily Living; SARA, Scale for the Assessment and Rating of Ataxia; EQ5D-VAS, European Quality of Life 5 Dimensions Visual Analogue Scale.

($P = 0.845$) or SARA ($P = 0.085$), in line with the fact that both are clinician-reported outcomes of overall disability and clinical disease severity, with less integration of more global patient daily life activities. The FARS-ADL (and also none of the other COA outcomes) was not associated with age or sex.

Discussion

To explore whether the FARS-ADL could serve as valid, patient-meaningful, and change-sensitive COA across ataxias, the present study leveraged a large prospective cross-genotype ataxia cohort to analyze the cross-sectional convergent validity of the FARS-ADL for disease severity and patient-meaningful impairment, and its sensitivity to patient-meaningful change within trial-relevant timescales.

Convergent Validity for Disease Severity and Patient-Meaningful Impairment

With significant correlations between the FARS-ADL and all the FARS-stage, SARA, PROM-ataxia, and EQ5D-VAS across many different ataxias, this study provides first evidence for the convergent validity of the FARS-ADL for both disease severity and patient-meaningful impairment beyond FA. Furthermore, the pattern of cross-correlations between these COAs confirmed our a priori hypothesis of their systematic order along a gradual spectrum of decreasing clinician/"objective" factors and increasing patient-related/subjective factors based on the model by Wilson and Cleary.[17] In particular, we observed that correlations successively decreased with the distance between two COAs along the spectrum from clinician-rated "objective" overall disability (FARS-stage) on the one end to subjective rating of overall health-related quality of life (EQ5D-VAS) on the other. In turn, correlations were highest for adjacent COAs along this spectrum. At a center position, FARS-ADL was markedly correlated to both clinician-reported outcomes (FARS-stage, SARA) and patient-reported outcomes (PROM-ataxia, EQ5D-VAS), thus indicating that it might partly reflect both clinician-reported disease severity and patient-meaningful impairment. Regarding clinician-reported disease severity, the strong correlations of the FARS-ADL with FARS-stage and SARA are consistent with—and extend—previous validation studies in FA.[11,20,21] Regarding patient meaningfulness, the correlation between FARS-ADL and EQ5D-VAS was actually higher than previously shown in FA.[11] This correlation probably reflects the broad spectrum of ataxia severities and genotypes that spanned almost the complete scoring range of outcomes (and thus statistically facilitated cross-correlations between them). Yet, subject to future in-depth studies, it may also indicate that FARS-ADL might capture quality of life in other genetic ataxias even better than in FA.

At the item level, FARS-ADL showed certain "hot spots" of strong correlations to the SARA in several corresponding effector domains of ataxia, particularly for *speech*, *walking/falling*, and *sitting*. This pattern was qualitatively also observed within each of the main genotypes covered in this cohort (RFC1, FA, SCA3), with only minor nuances in the relative item correlations (Supplement S1), thus demonstrating that it was not just carried by FA patients. Moreover, all FARS-ADL items were correlated to the EQ5D-VAS. These item-level correlations further underline the construct validity of the FARS-ADL for disease severity and patient-meaningful impairment even in individual ataxia domains. In the upper-limb domain, the moderate correlation of the FARS-ADL item only to SARA *alternating hand movements* was probably due to the metric limitations of SARA's appendicular items, as demonstrated previously.[22,23] FARS-ADL items *dressing* and *hygiene* probably showed less specific correlations to individual SARA items because these ADLs depend on multiple ataxia domains at the same time. For FARS-ADL items *swallowing* and *bladder function*, which are not covered by the SARA score, the correlation to EQ5D-VAS quality of life is consistent with the importance of these functions according to patients' and caregivers' voices,[8] and both items thus appear to present patient-meaningful domains in the FARS-ADL.

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Convergence of FARS-ADL and PROM-Ataxia—with Activities of Daily Living as the Key Component in Patient-Focused Outcomes

The present study shows that the FARS-ADL differentially captures all domains of the Patient-Reported Outcome Measure of ataxia (PROM-ataxia), with strong correlations to *physical* symptoms and impairment, very strong correlations to *ADL*, and weak correlations to its *mental* domain of cognitive-affective symptoms and impairment.[16] This convergence with a PROM primarily developed with patient input indicates that the FARS-ADL can be validly taken to capture patient-relevant ADL in ataxia trials. This is of particular importance because existing longitudinal FARS-ADL data over several years could inform trial planning in key ataxias such as FA; SCA1, SCA2, and SCA3; ARSACS; and SPG7.

The correlations between individual PROM-ataxia domains and other COAs provide additional insight into the validity of patient-focused outcomes in general. Notably, only the *ADL* domain of the PROM-ataxia reflected all other ataxia outcomes, that is, overall disability (FARS-stage), clinical disease severity (SARA), and patient-reported quality of life (EQ5D-VAS). In contrast, the *physical* domain was less correlated to quality of life and not correlated to the FARS-stage, and the *mental* domain was not correlated to any COA except FARS-ADL. Regarding validity, ADL thus appears to be the key component in patient-focused outcomes of ataxia.

Sensitivity to Patient-Meaningful Change in Trial-Relevant Timescales

The FARS-ADL has shown sensitivity to change in large natural history studies of FA.[9,24] This study now presents the first longitudinal analysis of the FARS-ADL in ataxias other than FA, showing that the FARS-ADL is sensitive to change across different ataxia genotypes—and even within a trial-relevant timescale of only 1 year. This was true for those patients who also actually perceived a change: FARS-ADL showed significant and specific progression only in patients with worsening PGI-C and stability in patients with stable PGI-C. This indicates that the FARS-ADL captures not just intraindividual change per se but in fact *patient-meaningful* change. The same type of change—progression in patients who perceive worsening but stability in patients who perceive stability—was observed for the SARA, thus confirming and extending previous findings on sensitivity to patient-meaningful change for the SARA in SCA1, SCA2, SCA3, and SCA6,[19,25] now demonstrating that this finding might actually apply *across* manifold ataxias. Here we show for the first time that this also holds true for the FARS-ADL. This is of importance as other primarily patient-reported outcome scales like the Friedreich Ataxia Impact Scale have failed to detect significant change over 1 to 2 years,[26,27] and also the more recent PROM-ataxia has not yet demonstrated sensitivity to change, in particular in such short time frames.[16] Our study raises the possibility that FARS-ADL could be, in principle, better placed within the spectrum of COAs than usual patient-reported outcomes as it allows to capture both disease severity and patient-meaningful impairment, not only cross-sectionally but also over time.

Although sensitivity to change is a necessary requirement for COAs, their MIC is also essential for implementation as endpoint in clinical trials.[18] Based on patients with stable PGI-C, the present study provides a first estimate for the MIC of the FARS-ADL (1.1 points). For the SARA score, the observed MIC of 0.7 points extends a previous study reporting an MIC of 1.1 points in a mixed cohort of SCA1, SCA2, SCA3, and SCA6 based on the same method.[19] Of note, the chosen method provides a rather conservative estimate for the design of future trials. With a mean FARS-ADL progression of 0.9 points in the subgroup with worsening PGI-C, patients may effectively experience a discrete score increase of 1 point as a meaningful change.

Beyond Just Motor Coordination: FARS-ADL Integrates Psychosocial Disease Factors

The present study demonstrates that the severity of depressive symptoms, as measured using the PHQ-9, is associated with worse patient-reported FARS-ADL. Similarly, it is associated with worse patient-reported EQ5D-VAS quality of life scores but not associated with the clinician-reported FARS-stage or the SARA as clinician-rated assessments of overall disability and disease severity. This finding indicates that FARS-ADL integrates not only the neurological severity of ataxia disease or just its motor coordination component but also psychosocial factors of ataxia disease. Although the association between ADL impairments (as determined by the FARS-ADL) and depression does not prove causation, such causality is rather likely and probably bidirectional. The highly significant associations of PHQ-9 only with FARS-ADL and EQ5D-VAS suggest that the more negative patient self-perception of their functional ability status was the consequence of depression. Conversely, given at least a statistical trend for a positive association between SARA and PHQ-9 scores, depressive symptoms may also partly be the consequence of ataxia severity, either biologically as part of a cerebellar cognitive-affective syndrome,[28] and/or the psychosocial consequence of the profound impact of the disease on functional independence and social participation.[29,30]

Notably, the association of PHQ-9 (ie, depression) was stronger to the EQ5D-VAS than to the FARS-ADL, with worsening of scores relative to the scoring range that was almost twice as large (1.5% vs. 0.8% per PHQ-9 score). This is consistent with the order of

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ataxia outcomes along a gradual spectrum of objective/biological versus subjective/evaluative factors, as suggested by the general outcome framework by Wilson and Cleary[17]—and now for the first time applied to ataxias and here corroborated by empirical data. Based on their cross-correlations, it seems that current ataxia COAs fall on a gradual spectrum, from an objective rating of overall disability (FARS-stage) to clinical disease severity (SARA), to functional impairment (FARS-ADL), and to overall health-related quality of life (EQ5D-VAS), along which these COAs appear to increasingly integrate psychosocial factors.[17] This makes these respective latter ataxia outcomes increasingly holistic and patient focused, as requested by regulatory authorities. At the same time, however, this also makes them increasingly susceptible to disease-unrelated factors, including characteristics of the individual (symptom amplification, motivation and values, cultural perspectives, and daily living patterns), characteristics of the environment (social and economic support, geocultural ecosystems), or nonmedical factors that affect overall health-related quality of life.[17] Statistically, this reduces sensitivity to longitudinal change and therapy response, which are usually primarily targeted at disease factors per se. At some point, this may even violate other regulatory requirements, namely that COAs should not be "overly influenced by external factors."[2] With its construct validity for both disease severity and patient-meaningful impairment, and its capacity to capture patient-meaningful change, the FARS-ADL may thus be placed at a regulatory "sweet spot" of COAs in ataxia.

Limitations

Overall, the present study aimed to validate the FARS-ADL as a patient-focused outcome in ataxia with a large, cross-genotype cohort, including ultra-rare ataxias for which thorough separate validation will inherently not be possible. We assumed that the FARS-ADL would capture functional impairment generically across ataxia diseases, given that they qualitatively affect the same ataxia-related functions. This assumption is being corroborated by the qualitatively similar item-level correlations between FARS-ADL and SARA for RFC1, SCA3, and FA (Supplement S2). However, given that different ataxia genotypes gradually vary in how they affect different functions, validity of the FARS-ADL for disease severity and patient-meaningful impairment and its sensitivity to change remain to be demonstrated in other ataxias. In addition, given the limited sample size, results from our longitudinal data should be interpreted with caution, especially in the rarer and milder genotypes. In particular, absolute values for annual change, or the differential sensitivity of individual items, will likely differ between genetic ataxias and may not be significant in milder genotypes. Moreover, the size of our cohort limited the possibility to analyze the relative impact of demographic factors or depression on the PGI-C and the sensitivity to change in different COAs. Our cross-validation with PROM-ataxia needs to be confirmed in larger studies as soon as its translations into other languages are more widely available and applied. Although our study provides first hints of the FARS-ADL performance also in different ataxia genotypes of trial relevance beyond FA (eg, SCA3 and RFC1), additional studies are now required to validate the FARS-ADL and its sensitivity to change in individual ataxia genotypes and larger cohorts, particularly those where molecular treatment trials are on the horizon. ■

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Additional Study Group Contributors of the PREPARE Consortium

Martina Minnerop, MD Institute of Neuroscience and Medicine (INM-1), Research Centre Juelich, Juelich, Germany

Department of Neurology, Center for Movement Disorders and Neuromodulation, Medical Faculty, Heinrich Heine University, Düsseldorf, Germany

Institute of Clinical Neuroscience and Medical Psychology, Medical Faculty, Heinrich-Heine University, Germany

Alexander Münchau, MD Institute of Systems Motor Science, Neurogenetics, University of Lübeck, Lübeck, Germany

Ivana Ricca, MD IRCCS Fondazione Stella Maris, Pisa, Italy

Dagmar Timmann, MD Department of Neurology and Center for Translational Neuro- and Behavioral Sciences (C-TNBS), Essen University

Hospital, University of Duisburg-Essen, Essen, Germany

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Andreas Thieme, MDDepartment of Neurology and Center for Translational Neuro- and Behavioral Sciences (C-TNBS), Essen University

Hospital, University of Duisburg-Essen, Essen, Germany

Additional Study Group Contributors of the RFC1 Study Group

Nazan Akkaya, MD Department of Neurology, Koç University, Istanbul, Turkey

Orlando G.P. Barsottini Department of Neurology, Federal University of São Paulo (UNIFESP), Sao Paulo, Brazil

Paula Camila Alves, MD Department of Neurology and Neurosurgery, School of Medicine, Federal University of São Paulo (UNIFESP), São Paulo SP, Brazil

Chiara Pane, MD Department of Neurosciences, Reproductive and Odontostomatological Sciences, Federico II University, Naples, Italy

Richard H. Roxburgh, MD Centre for Brain Research Neurogenetics Research Clinic, University of Auckland, Auckland, New Zealand

Francesco Saccà, MD Department of Neurosciences, Reproductive and Odontostomatological Sciences, Federico II University, Naples, Italy

Sara Satolli, MD IRCCS Fondazione Stella Maris, Pisa, Italy

Atay Vural, MD Department of Neurology, Koç University, Istanbul, Turkey

Data Availability Statement

Anonymized data will be made available upon reasonable request.

References

1. Klockgether T, Ashizawa T, Brais B, et al. Paving the way toward meaningful trials in ataxias: an ataxia global initiative perspective. Mov Disord 2022;37(6):1125–1130.
2. Patient-Focused Drug Development. Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments. Food and Drug Administration: U.S; 2022.
3. Biohaven Provides Update on Phase 3 Clinical Trial Evaluating Troriluzole for Spinocerebellar Ataxia (SCA).
4. Schmitz-Hübsch T, du Montcel ST, Baliko L, et al. Scale for the assessment and rating of ataxia: development of a new clinical scale. Neurology 2006;66(11):1717–1720.
5. Howard JF, Utsugisawa K, Benatar M, et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. The Lancet Neurology 2017;16(12):976–986.
6. Dodick DW, Ashina M, Brandes JL, et al. ARISE: a phase 3 randomized trial of erenumab for episodic migraine. Cephalalgia 2018; 38(6):1026–1037.
7. Subramony S, May W, Lynch D, et al. Measuring Friedreich ataxia: interrater reliability of a neurologic rating scale. Neurology 2005; 64(7):1261–1262.
8. Potashman MH, Mize ML, Beiner MW, Pierce S, Coric V, Schmahmann JD. Ataxia rating scales reflect patient experience: an examination of the relationship between clinician assessments of cerebellar ataxia and patient-reported outcomes. Cerebellum 2023;22(6): 1257–1273.
9. Reetz K, Dogan I, Hilgers R-D, et al. Progression characteristics of the European Friedreich's ataxia consortium for translational studies (EFACTS): a 4-year cohort study. The Lancet Neurology 2021; 20(5):362–372.
10. Traschutz A, Reich S, Adarmes AD, et al. The ARCA registry: a collaborative global platform for advancing trial readiness in autosomal recessive cerebellar ataxias. Front Neurol 2021;12:677551.
11. Reetz K, Dogan I, Costa AS, et al. Biological and clinical characteristics of the European Friedreich's ataxia consortium for translational studies (EFACTS) cohort: a cross-sectional analysis of baseline data. The Lancet Neurology 2015;14(2):174–182.
12. Jacobi H, du Montcel ST, Bauer P, et al. Long-term disease progression in spinocerebellar ataxia types 1, 2, 3, and 6: a longitudinal cohort study. The Lancet Neurology 2015;14(11):1101–1108.
13. Giordano I, Harmuth F, Jacobi H, et al. Clinical and genetic characteristics of sporadic adult-onset degenerative ataxia. Neurology 2017;89(10):1043–1049.
14. Group TE. EuroQol-a new facility for the measurement of health-related quality of life. Health Policy 1990;16(3):199–208.
15. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16(9):606–613.
16. Schmahmann JD, Pierce S, MacMore J, L'Italien GJ. Development and validation of a patient-reported outcome measure of ataxia. Mov Disord 2021;36(10):2367–2377.
17. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life: a conceptual model of patient outcomes. JAMA 1995;273(1):59–65.
18. Patient-Focused Drug Development. Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision-Making. Food and Drug Administration: U.S; 2023.
19. Schmitz-Hübsch T, Fimmers R, Rakowicz M, et al. Responsiveness of different rating instruments in spinocerebellar ataxia patients. Neurology 2010;74(8):678–684.
20. Bürk K, Mälzig U, Wolf S, et al. Comparison of three clinical rating scales in Friedreich ataxia (FRDA). Mov Disord 2009;24(12):1779–1784.
21. Lynch D, Farmer J, Tsou A, et al. Measuring Friedreich ataxia: complementary features of examination and performance measures. Neurology 2006;66(11):1711–1716.
22. Traschütz A, Adarmes-Gomez AD, Anheim M, et al. Responsiveness of the SARA and natural history in 884 recessive and early onset ataxia patients. Ann Neurol 2023;94(3):470–485.
23. Maas R, Teerenstra S, Lima M, et al. Differential temporal dynamics of axial and appendicular ataxia in SCA3. Mov Disord 2022;37(9): 1850–1860.
24. Rummey C, Corben LA, Delatycki M, et al. Natural history of Friedreich's ataxia: heterogeneity of neurological progression and consequences for clinical trial design. Neurology 2022;36(10):2367–2377.
25. Ashizawa T, Figueroa KP, Perlman SL, et al. Clinical characteristics of patients with spinocerebellar ataxias 1, 2, 3 and 6 in the US; a prospective observational study. Orphanet J Rare Dis 2013;8(1): 1–8.
26. Tai G, Yiu EM, Corben LA, Delatycki MB. A longitudinal study of the Friedreich ataxia impact scale. J Neurol Sci 2015;352(1–2): 53–57.
27. Cano SJ, Riazi A, Schapira AH, Cooper JM, Hobart JC. Friedreich's ataxia impact scale: a new measure striving to provide the flexibility required by today's studies. Mov Disord 2009;24(7): 984–992.
28. Hoche F, Guell X, Vangel MG, Sherman JC, Schmahmann JD. The cerebellar cognitive affective/Schmahmann syndrome scale. Brain 2018;141(1):248–270.

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29. Schmitz-Hübsch T, Coudert M, Tezenas du Montcel S, et al. Depression comorbidity in spinocerebellar ataxia. Mov Disord 2011;26(5):870–876.

30. Lo RY, Figueroa KP, Pulst SM, et al. Depression and clinical progression in spinocerebellar ataxias. Parkinsonism Relat Disord 2016;22:87–92.

Supporting Data

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