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Functional Outcome Measures to Optimize Drug Development in Spinal and Bulbar Muscular Atrophy

Results From a Meta-Analysis of the Global SBMA Dataset

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Abstract

Background and Objectives

Spinal and bulbar muscular atrophy (SBMA) is a rare, slowly progressive, and debilitating disease without effective treatments available. Lack of reliable biomarkers and sensitive outcome measures makes clinical research conduct challenging. The primary objective of this study was to identify clinically meaningful and statistically sensitive outcome measures enabling the evaluation of therapeutic interventions in late-stage clinical trials.

Methods

This study was a meta-analysis of SBMA patient-level data from 6 observational studies conducted in Italy, South Korea, Denmark, United Kingdom, Japan, and United States. Patients with confirmed SBMA genetic diagnosis and differing severity were enrolled following individual site protocols. Routine assessments were performed longitudinally for approximately 3 years, including one or more clinical outcomes, such as SBMA functional rating scale (SBMAFRS), 6-minute walk test (6MWT), quantitative muscle testing (QMT), and Adult Myopathy Assessment Tool (AMAT). A modified scale, m-SBMAFRS, was derived by including only lower limb and trunk subscales having lower variability and larger effect size compared with the others. Changes from baseline at follow-up time points were calculated for all measures, and percent changes using random slope models were calculated to compare clinical measure performances. A survey conducted on 196 patients by the Coordination of Rare Diseases at Sanford (CoRDS), elucidating the impact of specific disease aspects on patients' lives, was also evaluated to corroborate these research outcomes.

Results

This global SBMA dataset analyzed data from 278 men (mean age = 59.7 ± 10.8 years, mean disease duration = 17.7 ± 11.9 years). Patients progressed on SBMAFRS (−4.7 ± 6.2 points after 38 months with 1-year standard response mean [SRM] = 0.6) and 6MWT (distance walked decreased by −53.2 ± 87.0 meters after 26 months with 1-year SRM = 0.5). These measures

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Glossary

6MWT = 6-minute walk test; **ADLs** = activities of daily living; **ALSFRS** = Amyotrophic Lateral Sclerosis Functional Rating Scale; **AMAT** = Adult Myopathy Assessment Tool; **CoRDS** = Coordination of Rare Diseases at Sanford; **FARS** = Friedreich Ataxia Rating Scale; **QMT** = quantitative muscle testing; **SBMA** = spinal and bulbar muscular atrophy; **SBMAFRS** = SBMA functional rating scale; **SRM** = standard response mean.

showed lower variability and larger effect size than AMAT and QMT (1-year SRM = 0.1 and −0.2, respectively) and confirmed SBMA linear progression across a range of disease stages. The m-SBMAFRS also showed a significant yearly decline of 0.9 ± 1.5 points (SRM = 0.6) and more consistent performance with less variability across clinical sites. The CoRDS survey confirmed the relevance of lower limb strength and mobility, which correlated with higher quality-of-life metrics and were reported by patients as predominant disease issues.

Discussion

We generated a comprehensive global SBMA dataset, enabling the identification of sensitive functional end points for clinical trials. Possible limitations relate to data collection nuances across sites that a single study protocol could override.

Introduction

Spinal and bulbar muscular atrophy (SBMA), also known as Kennedy disease, is an adult-onset, slowly progressive neuromuscular disorder marked by muscle atrophy and weakness due to primary muscle toxicity and the loss of lower motor neurons in the brainstem and spinal cord.[1-3] Muscle weakness also affects bulbar control, loss of which can lead to aspiration-induced pneumonia.[4] SBMA is caused by a CAG trinucleotide repeat expansion in the *androgen receptor gene (AR)* on the X-chromosome.[5,6] The disease occurs on androgen binding to the AR protein and, as such, only manifests in men and presents with additional complications of androgen insensitivity and metabolic dysfunction, which may lead to gynecomastia and insulin resistance, respectively.

The disease onset is usually in the 3rd to 5th decade of life, and the prevalence is estimated to be 1 to 2 per 100,000,[7] although this is believed to be an underestimation because some patients are misdiagnosed with other neuromuscular disorders, such as amyotrophic lateral sclerosis.[8]

There are no curative treatments for SBMA. Clinical studies aimed at suppressing or reducing androgen production[9,10] or increasing anabolic activity[11] have not shown convincing therapeutic benefits. Major hurdles for the development of new treatments are the slowly progressive and multifaceted aspects of SBMA that are difficult to measure, given the lack of biomarkers and sensitive outcome measures.

Our objective was to identify statistically sensitive and clinically meaningful functional end points to improve the measurement of treatment effects in clinical studies and to serve as primary end points leading, if positive, to regulatory approval of new treatments. In this study, we have aggregated and analyzed patient-level data across multiple longitudinal natural history studies of SBMA worldwide that resulted in a deeper understanding of SBMA progression and symptomatology. Furthermore, this effort enabled the identification of sensitive clinical measures that could support the design of more effective interventional clinical studies.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

Our global SBMA dataset included complete, longitudinal SBMA patient-level data (n = 278) across 6 individual studies that were approved by their respective ethics committees. Patients were enrolled in Italy, through the Italian SBMA Registry Study Group within the NMD Registry,[12] supported by Fondazione Telethon ETS and the Associazione del Registro,[13] in Denmark;[14] at the NIH;[15] in South Korea, through the Kyungpook National University motor neuron disease registry;[16] and at the University of College London (UCL, United Kingdom), supported by Neuro Research Trust and KD-UK. In addition, data from the Nido Biosciences–sponsored observational study were included from patients enrolled at NIH, UCL, and Nagoya University (Japan), and none of these patients recruited overlapped with those in other registries. Patients at the NIH were enrolled under protocol NCT04944940, approved by the NIH Institutional Review Board. All participants at Nagoya were enrolled in the observational study, approved by the Ethics Review Committee of Nagoya University Graduate School of Medicine (approval number: 2021-0433). All patients provided their written informed consent for participation in each individual study.

Global SBMA Dataset and Clinical Measures

The data included in the global SBMA dataset have been collected by individual clinical sites and included in their respective observational studies over the period of July 2011 and March 2024. Most of the 278 patients had approximately 3 years of follow-up while a minority of patients were followed

for up to 6 years. Demographics and baseline disease characteristics were provided for all patients, and changes in functional and clinical assessments over time were calculated.

Each study reported several functional assessments at scheduled intervals of approximately 8–12 months. These included the SBMAFRS, the 6-minute walk test (6MWT), the Adult Myopathy Assessment Tool (AMAT), and quantitative muscle testing (QMT).

SBMAFRS is a validated functional rating scale developed from the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) to specifically address the disability profile of patients with SBMA.[17] It is a questionnaire-based scale that measures physical function in activities of daily living (ADLs) and consists of 5 main subscales measuring bulbar, upper limb, lower limb, truncal, and respiratory functions. Specific domains within each subscale are scored based on 5 response options from 0 (worst) to 4 (normal). A higher score indicates better functioning. Because the variability in clinical assessments represents a tangible risk for the development of successful treatments of SBMA, we explored the possibility to further reduce intrinsic noise in the SBMAFRS by evaluating its subscales and the specific items within each subscale across all the patients in the global SBMA dataset. Therefore, the modified SBMAFRS was generated by only scoring the trunk and lower limb subscale items.

The 6MWT is a relatively simple measure widely adopted as an outcome measure in several neuromuscular conditions. From a standing start, the participant is asked to walk for 6 minutes as quickly as possible. Assistive devices, orthoses, and ankle braces are allowed. The distance traveled in 6 minutes is recorded. Adult Myopathy Assessment Tool is a performance-based instrument that rates physical function and muscle endurance, with higher scores indicating better performance; it includes 7 timed functional tasks and 6 endurance tasks (0 = worst, 45 = best).[18] The QMT measures the strength of specific muscle groups using a dynamometer or robotic-based quantification.[19] Clinical laboratory parameters were also assessed including androgen, lipid, metabolic, and blood panels (Supplemental Material; eAppendix 1).

CoRDS Survey Dataset

The Coordination of Rare Diseases at Sanford (CoRDS) has developed a voluntary global online survey that was administered to 196 patients with confirmed SBMA diagnosis from June 28, 2021, to February 13, 2023. After establishing SBMAFRS and 6MWT as sensitive outcome measures, we wanted to determine their clinical meaningfulness by interrogating the CoRDS survey where patients directly addressed the relevance and extent of the disease-related symptoms in their lives.

Patients completed the CoRDS profile along with the CoRDS standard questionnaire and the Kennedy Disease/SBMA questionnaire. The CoRDS standard questionnaire included dozens of self-reported questions regarding symptomology and quality of life (QoL) with 5 categorical answers from poor to excellent, along with questions on what patients considered the primary disease-related problem they experience and the approximate age they first noticed specific symptoms. The Kennedy Disease/SBMA questionnaire probed 12 of the 14 items constituting the SBMAFRS. Additional details on these questionnaires can be found in the Supplemental Material (eAppendix 2).

Data Quality Control

The onset age of SBMA symptoms was removed if the age at interview was less than the onset age of symptoms. Outliers in the changes over time in functional assessments were assessed using the following formula: Outlier $> \mu\left(\left|\frac{\Delta_{\text{Baseline}}}{\text{Follow}} - \text{up Time}\right|\right) + 3 * \sigma\left(\left|\frac{\Delta_{\text{Baseline}}}{\text{Follow}} - \text{up Time}\right|\right)$. If outlying observations were inconsistent with other reported functional assessments, outliers were removed from analyses. In total, 2 patients were removed from the SBMAFRS, 6MWT, AMAT, and QMT assessments.

Analyses

Random slope models from the lmerTest R package[20] were used to assess changes over time in patients. Degrees of freedom were estimated using the Satterthwaite approximation, which were then used to calculate test statistics and p values. Slopes (B), or the average monthly change over time across patients, and subject-specific SDs, which measure individual variability in changes over time, were reported from these models. Pearson product-moment correlations were conducted to investigate the relationships between variables. Significance was determined using a p value threshold of < 0.05 and an effect size cutoff of $r > |0.25|$. The standard response mean (SRM) for all the clinical outcome measures was derived by dividing the mean change of each score by the SD of the respective change score.

Power and sample size calculations for a hypothetical Phase 3 trial were also estimated where the SBMA database was used to randomly generate simulated patients. Simulations were performed on the m-SBMAFRS using mixed-effect models for repeated measures that include subject-specific random intercepts and slopes. The treatment-by-time interactions were tested at a one-sided significance level of 0.025.

Data Availability

Data not provided in the article because of space limitations may be shared (anonymized) at the request of any qualified investigator for purposes of replicating procedures and results.

Results

Patient Demographics and Baseline Disease Characteristics

Data from 278 patients collected through individual registries or studies in Denmark, Italy, Japan, South Korea, United Kingdom,

and United States were integrated into a curated dataset (Table 1). No review protocol was registered for this meta-analysis. While a large number of patient data were provided by a single country (Italy), there was an even distribution of patients across clinical sites, ranging from 25 to 46 patients each. The average age of patients included in this dataset was 59.7 ± 10.8 years at baseline. All patients had a genetically confirmed diagnosis of SBMA, with an average number of CAG repeats of 45.4 ± 3.9, and had an average disease duration of 17.7 ± 11.9 years. Inconsistencies across clinical sites in the determination of disease duration were apparent because the time of disease onset was defined by the first symptom experienced at some sites while others defined it by the start of muscle weakness.

The disease severity at baseline was measured by 4 different functional assessments: the QMT, the AMAT, the 6MWT, and the SBMAFRS (Table 1). Fewer sites collected QMT or AMAT scores while the 6MWT and SBMAFRS scores were consistently reported for virtually every patient.

Patients had an average SBMAFRS score of 43.4 ± 6.6 at baseline and walked an average distance of 373 ± 142.4 meters as measured by the 6MWT. In addition, a subgroup of patients had an average QMT score of 264.9 ± 98.5 kg and an average AMAT score of 30.1 ± 9.1.

SBMAFRS and 6MWT Are Consistent Measurements of SBMA Progression

Average changes from baseline were calculated at several time points for SBMAFRS and 6MWT with patients declining based on the SBMAFRS by −1.2 ± 2.6 points at 6 months; by −1.6 ± 2.5 points between 6 and 14 months; by −2.7 ± 3.3 points between 14 and 26 months; by −3.6 ± 3.5 points between 26 and 38 months; and by −4.7 ± 6.2 points beyond 38 months from baseline (Figure 1).

Changes based on the 6MWT were −17.8 ± 13.1 meters at 6 months; −27.1 ± 56.5 meters between 6 and 14 months; −41.9 ± 79.8 meters between 14 and 26 months; and −53.2 ± 87.0 meters beyond 26 months (Figure 1).

To compare the performance of different clinical functional measurements in the combined dataset, we calculated the percent change from baseline over the course of all available follow-up assessments using random slope models. Significance was determined using a p value threshold of < 0.05 and $r > |0.25|$. Data related to the QMT had the shortest number of longitudinal assessments with only up to approximately 20 months of postbaseline measurements while the other clinical measurements had follow-up assessments up to 80 months after baseline.

As shown in Figure 2, statistically significant changes from baseline were measured for AMAT, 6MWT, and SBMAFRS but not QMT. In brief, the slope indicates the average rate of change per month, the t reflects the t-statistic, the SD shows the within-patient variability for changes over time, R indicates a Pearson product-moment correlation coefficient, and p values are from random slope models. The SBMAFRS and 6MWT had the largest effect size as measured with the slope coefficient and t-statistic, with SBMAFRS also having the lowest variability across all measurements, as measured by the SD.

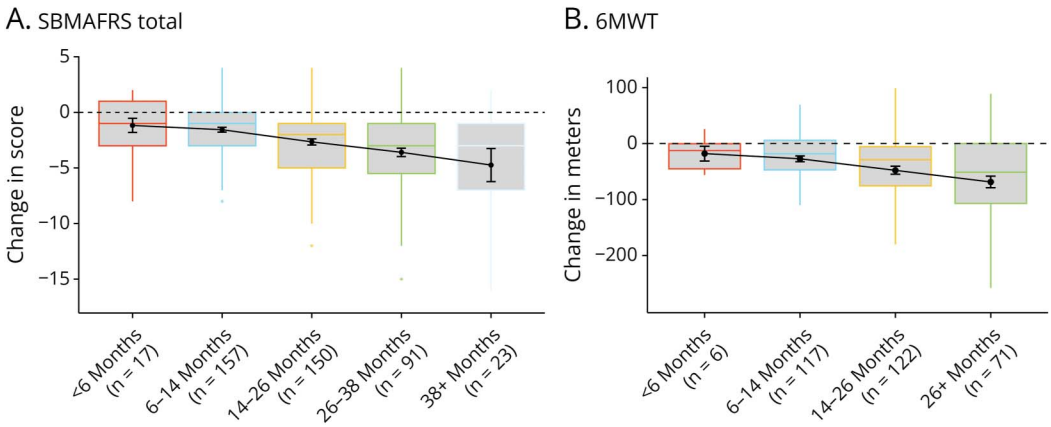
When looking at changes over 1 year, on average, patients progressed by 1.5 ± 2.4 points (SRM = 0.6) as measured by the SBMAFRS and experienced a decrease in the distance walked of 25.4 ± 49.0 meters (SRM = 0.5) as measured by the 6MWT (eFigure 1A). Changes in SBMAFRS and 6MWT seem to be consistent across patients at different clinical sites, that is, mean changes consistently manifest as decreases, and clearly confirmed that SBMA progresses over time in a linear fashion, irrespective of disease severity. Based on SBMAFRS and 6MWT assessments, 71.6% and 74.4% of patients, respectively, had significant decline over time (eFigure 1B), whereas only 53.1% and 54.6% of patients declined based on QMT and AMAT, respectively (SRM = 0.1 and −0.2, respectively). These results strongly suggest that the SBMAFRS and the 6MWT are sensitive functional outcome measures in patients with SBMA to consistently measure changes over time.

Table 1 Baseline Demographics and Disease Characteristics

Sample	N	Age Avg (±SD)	No. of CAG repeats Avg (±SD)	Disease duration Avg (±SD)	QMT Avg kg (SD)	AMAT Avg (SD)	6MWT Avg meter (±SD)	SBMAFRS Avg (±SD)
All	278	59.7 (10.8)	45.4 (3.9)	17.7 (11.9)	264.9 (98.5)	30.1 (9.1)	373.0 (142.4)	43.4 (6.6)
Denmark	29	57 (13.2)	43.4 (3.6)	17.8 (10.4)	—	—	388.8 (198.7)	42.7 (8.7)
Italy	110	62.1 (10.7)	45.1 (3.2)	25.6 (11.9)	—	29.4 (9.9)	390.6 (123.8)	45.0 (6.3)
South Korea	39	53.7 (10.2)	46.3 (4.6)	10.7 (6.5)	—	—	345.1 (128.3)	41.7 (5.6)
Nido Biosciences	25	58.4 (6.8)	45.6 (3.6)	9.4 (6.3)	295.2 (90.7)	—	419.6 (144.1)	40.9 (3.8)
UCL	29	62.8 (10.8)	43.7 (4.0)	8.2 (6.6)	—	34.2 (8.8)	329.7 (138.6)	42.4 (7.3)
NIH	46	54.6 (9.0)	47.2 (4.0)	15.0 (8.8)	253.1 (99.9)	29.0 (6.8)	—	—

Note: slight discrepancies in the collection of disease duration across clinical sites result in a wide range of duration.

Figure 1 Linear Changes in SBMA Functional Outcome Measures



Boxplots illustrating the progressive decline in the SBMA functional rating scale (SBMAFRS) and 6-minute walk test (6MWT) scores among patients with SBMA. These plots show changes from baseline with lower (25th percentile) and upper (75th percentile) hinges and whiskers extending to 1.5 times the interquartile range. The horizontal line at the center and black dot within each boxplot represent the median and mean values, respectively, while error bars depict standard errors. SBMA, spinal and bulbar muscular atrophy.

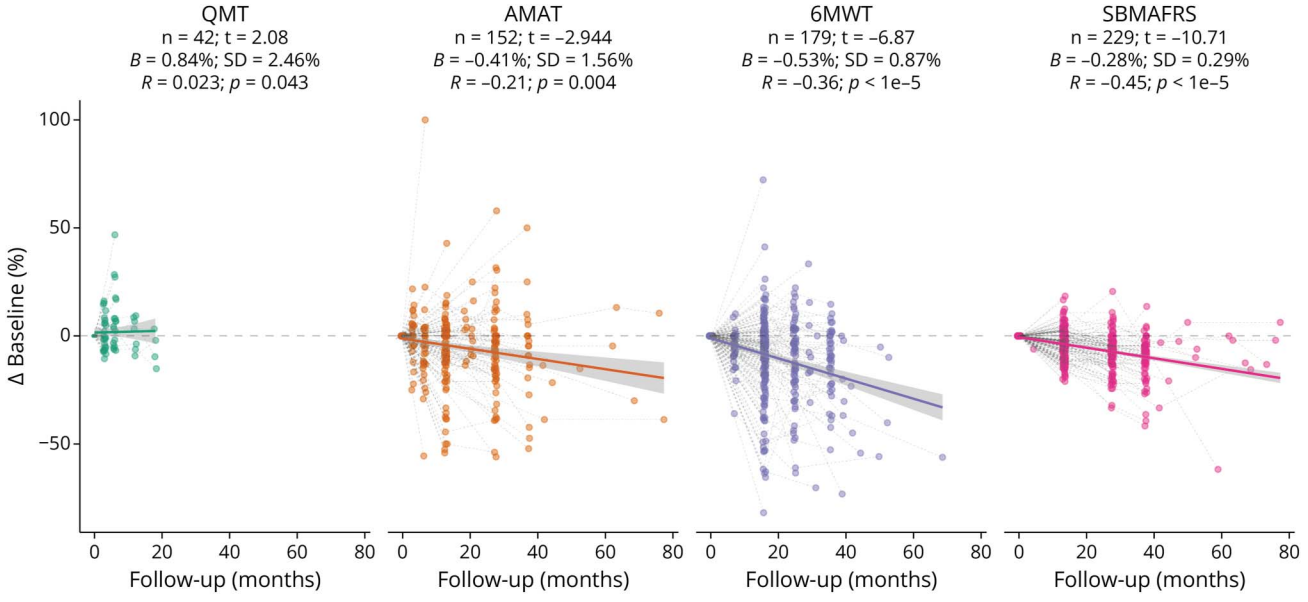
m-SBMAFRS Provides More Consistent Performance Across Clinical Sites

The changes in SBMAFRS subscales and subscale items over time are shown in Figure 3, A and B, respectively. Average 1-year change in the scores of the subscale items was used. The SBMAFRS lower limb and trunk subscales demonstrated substantial and consistent decreases over time across the individual dataset with overall yearly changes of −7.1% ± 18.2% and −4.5% ± 10.0%, respectively (Figure 3C). By contrast, the upper limb, bulbar, and breathing subscales showed smaller effect sizes across patients and more variability across cohorts, and mean changes did not consistently manifest as decreases (eFigure 2).

When looking at changes over 1 year, the m-SBMAFRS progressed by 0.9 ± 1.5 points with a 1-year SRM of 0.6.

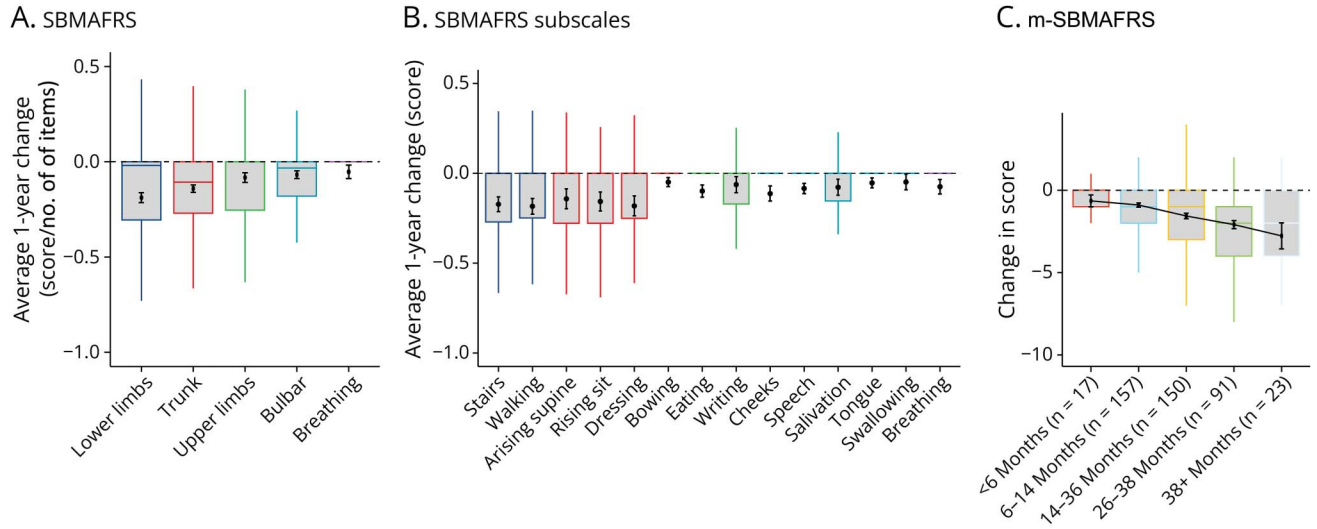
Sample size calculations were performed based on m-SBMAFRS as the primary efficacy outcome measured at visits every 3 months up to a maximum follow-up of 18 months. A

Figure 2 Comparing Longitudinal Progression Using SBMA Functional Outcome Measures



Spaghetti plots displaying changes in quantitative muscle testing (QMT), Adult Myopathy Assessment Tool (AMAT), 6MWT, SBMAFRS, and m-SBMAFRS. Each plot includes a best-fitting linear regression line and a shaded 95% CI. Random slope model statistics are reported, including sample size (N), t-statistic (t), slope coefficient (B), subject-specific SD, *p* value (P), and Pearson correlation coefficient (R). SBMA, spinal and bulbar muscular atrophy.

Figure 3 Changes in SBMAFRS Subscales and Subscale Items Over Time



Boxplots showing longitudinal changes in (A) SBMAFRS subscales and (B) specific items within each subscale, arranged to emphasize those with significant mean deterioration. Each boxplot marks the 25th and 75th percentiles at the lower and upper bounds, respectively. Whiskers extend 1.5 times the interquartile range from the hinges. Median scores are indicated by horizontal lines, with black dots and error bars representing means and standard errors. The m-SBMAFRS (C) was derived by including lower limb and trunk subscales, which show higher effect size and lower variability. SBMAFRS, SBMA functional rating scale.

treatment effect with a disease rate ratio of 0.5 was assumed, corresponding to 50% slowing in decline by an active treatment. Based on these assumptions, a maximum of 200 total participants followed for 18 months would be needed to provide more than 90% power.

Relation of Clinical Outcome Measures With Disease Characteristics

We evaluated the effect of age, disease duration, and number of CAG repeats on SBMA severity and rate of disease progression. Both age and disease duration were significantly correlated with the degree of clinical impairment at baseline, as measured by SBMAFRS or 6MWT (linear regression model p = <0.001 for both), demonstrating that patients had worse SBMAFRS scores and walked shorter distances in 6 minutes at older ages and if they had longer disease duration. While no positive correlation was found between disease severity and number of CAG repeats at baseline, the degree of clinical impairment was associated with age and disease duration (eFigure 3A). No statistically significant correlations were observed between age, disease duration, and number of CAG repeats and the rate of disease progression as measured by SBMAFRS (p = 0.517, 0.239, and 0.404, respectively) or by 6MWT (p = 0.889, 0.167, and 0.280, respectively) (eFigure 3B). Similarly, clinical severity at baseline based on SBMAFRS scores did not have a significant impact on the rate of disease progression as measured by SBMAFRS or m-SBMAFRS (eFigure 2C).

Although not the focus of this study, clinical laboratory assessments were also quantified in patients with SBMA (eTable 1). Despite high variability, a few clinical laboratory results seem to change over time in a generally linear fashion (eFigure 4).

CoRDS Patient Survey Confirms Results From the Global SBMA Dataset

A total of 198 patients with an average age of 56.9 ± 12.2 years and an average disease duration of 12.4 ± 9.1 years responded to the CoRDS survey (Table 2). Patients were from different geographies including North America (n = 125), Europe (n = 39), Asia (n = 11), South America (n = 1), and Australia and New Zealand (n = 13) and had the following racial composition: 83.8% identified as White, 9.7% as Asian, 3.8% as American Indian or Alaskan Native, 1.6% as other, and 1.1% as Black or African American.

Age at onset, frequency, and distribution of disease symptoms are shown in Figure 4A. Gynecomastia and muscle cramps are reported as the earliest symptoms noticed by patients with onset in the mid-30s, followed closely by tremors and fasciculations. Virtually, all patients reported muscle weakness and muscle wasting in their mid-40s. These symptoms continue to worsen over time resulting in patients using assistive devices, with 56.6% and 32.8% using a cane or motorized device, respectively, in their early fifties and 20.2% of patients requiring the use of a walker at an average age of 55 years. Numbness and testicular wasting occurred in approximately half of the patients in their late 40s, with bulbar-related symptoms occurring in 51.0% (difficulty chewing) and 71.7% (dysphagia) in their early 50s. Using clinically assessed data from the Italian cohort, the largest in this global dataset, we found remarkable consistency regarding symptom age at onset, frequency, and progression (Figure 4B).

Table 2 Baseline Demographics of Patients With SBMA in CoRDS

Region	No. of patients	Age Avg (±SD)	Disease duration
All	198	56.9 (12.2)	12.4 (9.1)
North America	125	56.6 (12.1)	12.4 (9.7)
Europe	44	58.9 (12.0)	12.7 (7.1)
Australia and New Zealand	14	55.6 (15.0)	13.0 (10.0)
Asia	13	54.2 (10.2)	9.2 (7.7)
South America	2	71 (NA)	21.0 (NA)

Abbreviation: CoRDS = Coordination of Rare Diseases at Sanford.
Race = 83.8% White, 9.7% Asian, 3.8% American Indian or Alaskan Native, 1.6% other, and 1.1% Black or African American.

Patients were then asked what the primary problem of SBMA was, and 45.5% and 38.8% of patients reported weakness and muscle wasting or walking and mobility, respectively. Overall, less than 30% of patients reported symptoms related to bulbar function, falls, upper limb, or breathing as the major concern with their disease (Figure 5A). Finally, we wanted to understand the effect of various symptoms and their severity on patients' QoL. Higher self-reported SBMAFRS scores were shown to correlate positively with better QoL (Figure 5B). Each individual SBMAFRS subscale had a positive correlation with QoL scores with stronger correlation with the lower limb and trunk subscales, those composing the m-SBMAFRS (R = 0.36/p = 3.9e-7 and R = 0.38/p = 9.5e-8, respectively).

The SBMAFRS bulbar subscale scores did not significantly correlate with quality-of-life scores. These results confirm that impaired mobility and muscle weakness are important aspects of the disease and interventional treatments should aim to restore them.

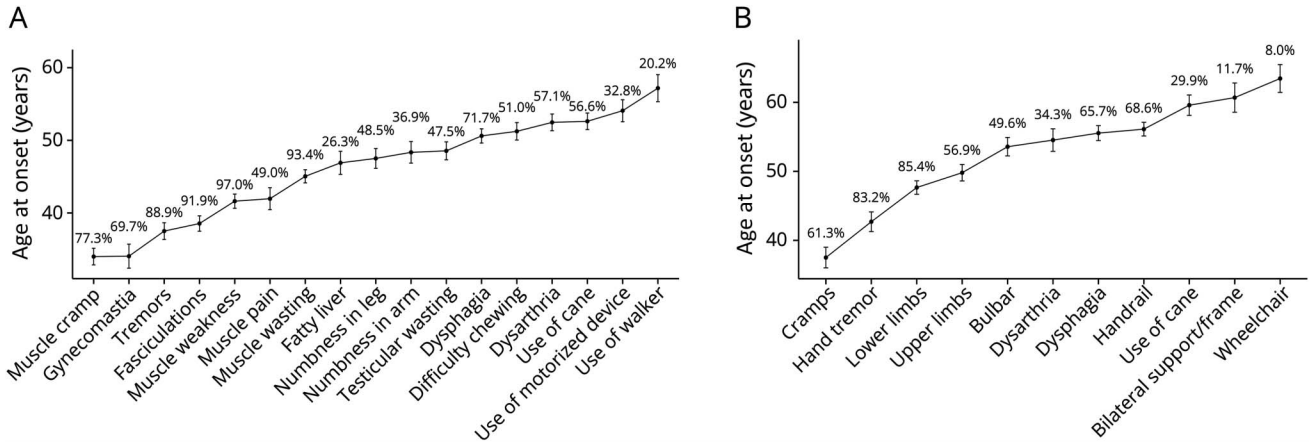
Discussion

SBMA is a slowly progressive and debilitating neuromuscular disease with multisystem involvement. Currently, there are no disease-modifying therapies approved that can cure, slow, or reverse the course of SBMA. Disease management focuses on symptomatic support and a multidisciplinary rehabilitation strategy. Given the lack of awareness regarding SBMA and the nonspecificity of the initial symptoms, patients often suffer a lengthy diagnostic journey and are often misdiagnosed with other neuromuscular diseases.

Although patients may be able to live independently early in the disease, they become increasingly impaired at a relatively young and productive age, carrying the burden of a long-term condition for a large portion of their lives. Assistance and full-time care are necessary at later stages of the disease, with social, emotional, and economic consequences affecting patients and their families. Thus, there is a significant unmet clinical need for a pharmacologic treatment able to rescue the underlying pathophysiology of the disease, modify its clinical course, and prevent long-term disability.

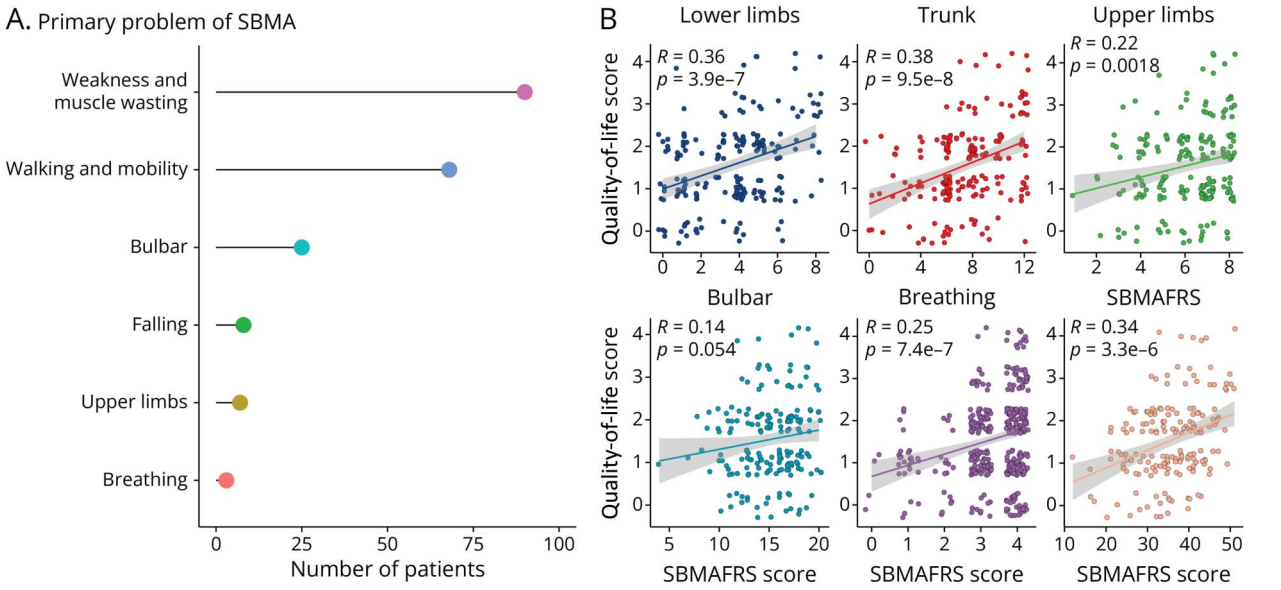
A major obstacle to the conduct of clinical research in SBMA is the lack of responsive and consistent clinical outcome measures able to capture the slow changes that characterize the disease, in a reasonable time frame. In an attempt to address these challenges and thanks to the collaboration of foresighted clinical experts worldwide, we integrated a comprehensive *global SBMA dataset*, to identify clinical

Figure 4 Age at Onset of SBMA Symptoms in Patients



Line plots depicting the average onset age of individual symptoms among patients with SBMA, comparing self-reported symptoms from the CoRDS survey and clinical assessments from the Italian SBMA cohort. Data points, color-coded by symptom frequency, show the mean and standard error. Percentages above points indicate the prevalence of each symptom within the CoRDS and Italian cohorts. CoRDS, Coordination of Rare Diseases at Sanford; SBMA, spinal and bulbar muscular atrophy.

Figure 5 Patient Perspective on Kennedy Disease Impact



(A) Lollipop plot representing responses to the survey question about the primary problem experienced due to Kennedy disease. Categories are derived from key terms in open-ended responses: breathing, upper limbs, falling, bulbar, walking and mobility, weakness, and muscle wasting. (B) Scatter plot correlating SBMAFRS scores with self-reported quality-of-life (QoL) metrics. QoL is rated on a scale from 0 (poor) to 4 (excellent). Pearson correlation coefficients (R) and *p* values (P) are included. Note: 1 item in the SBMAFRS (bowing) was not assessed. Points are jittered for clearer visualization.

assessments for implementation as sensitive functional, primary end points in interventional clinical trials.

We demonstrated that the SBMAFRS is a sensitive and consistent measure of disease progression with robust effect size and reduced variability compared with previously used measurements. Similarly, the 6MWT, despite its known variability in other neuromuscular diseases, seems to perform adequately in patients with SBMA, likely because of its ability to measure fatigability, which is a main feature of the disease. This contrasts with QMT, which did not achieve statistically significant changes from baseline, and AMAT, which showed a lower effect size and higher variability compared with the SBMAFRS and 6MWT. In fact, changes from baseline for QMT trended positive, which is inconsistent with the progression and symptomatology of SBMA.

In 2023, omaveloxolone received regulatory approval for patients with Friedreich ataxia based on a modified composite rating scale, the Modified Friedreich Ataxia Rating Scale (FARS) that showed better psychometric properties than the original FARS by shortening the bulbar subscale and excluding the peripheral nerve subscale.[21] This led us to explore the properties of the individual subscales of the SBMAFRS with the goal of improving the performance of the scale.

Our analysis shows that the lower limb and trunk subscales of the SBMAFRS, that is, the m-SBMAFRS composed of items showing a larger and more consistent decline over time across clinical sites, provide better performance than other subscales when measuring progression across patients and clinical sites worldwide. Furthermore, the m-SBMAFRS addresses functional domains that are more likely to show progression during the relative short duration of a clinical trial and that are most meaningful to patients. This finding is not surprising if one considers the onset and evolution of specific symptoms in SBMA with lower limb weakness and muscle atrophy being the most prominent aspects of the disease and affecting virtually every patient. By contrast, symptoms related to bulbar or respiratory functions occur later in the course of the disease and do not consistently affect all patients. Hence, the m-SBMAFRS, only including these 2 subscales, may offer an improved performance potentially resulting in higher statistical power that could facilitate the conduct of global, multicenter clinical trials in a rare disease such as SBMA. SBMAFRS, m-SBMAFRS, and 6MWT capture the linear progression of the disease with substantial yearly changes. These results seem to corroborate previous observations[4] that SBMA progresses in a linear fashion and independently of the number of CAG repeats or disease severity.

Furthermore, the independent CoRDS patient survey clearly confirmed that muscle weakness, especially in the lower limbs, and reduced mobility are highly prevalent in patients with SBMA and reported by patients themselves as primary issues related to the disease. In addition, these items had the highest correlation with QoL measures substantiating their clinical meaningfulness and relevance in patients' lives.

The evaluation of such a robust integrated clinical dataset together with patient-reported impressions enhanced our understanding of SBMA symptomatology and disease

trajectory that could inform the design of more effective clinical trials.

The main limitations of this study are inherent to the non-uniform data collection across clinical sites that may have resulted in increased variability of the outcome measures. It is also evident that the discrepancy in average disease duration across clinical sites underlies differences in capturing the age at onset of SBMA. Caution should be exercised in interpreting findings, with sparse representation like the QMT. An additional limitation is the focus on clinical, functional measures as potential primary end points addressing the most common symptoms of SBMA (i.e., ambulation and lower limb weakness) while recognizing that other aspects of the disease such as sexual dysfunction and bulbar and respiratory symptoms should be addressed through secondary end points in clinical trials. From this effort, a need clearly emerges to continue to collect and integrate patient data worldwide and to do so in a more consistent and standardized manner. The adoption of common criteria, centralized assessments, and consistency in data capture and reporting could further improve clinical measures in SBMA interventional trials.

In conclusion, this research provides valuable insights into clinical manifestations of SBMA at different disease stages and, most importantly, helped identify meaningful functional outcome measures that accurately track the intrinsically slow progression of the disease. The m-SBMAFRS could enhance the detection of significant treatment effects in large, global, multicenter clinical studies.

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Disclosure

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Continued

Appendix *(continued)*

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