Motor unit number estimation in adult patients with spinal muscular atrophy treated with nusinersen

Christian Schneider | Meike K. Wassermann | Nicolai B. Grether | Gereon R. Fink | Gilbert Wunderlich | Helmar C. Lehmann

Abstract

Background and purpose: The aim was to assess the organization and short-term changes of motor units in adult patients with spinal muscular atrophy (SMA) treated with nusinersen.

Methods: In this single-centre cross-sectional and longitudinal study 15 adult patients with SMA type 3 were assessed and compared to 15 age-matched healthy controls and nine patients with amyotrophic lateral sclerosis. Moreover, 10 patients with SMA were followed up after 4–8 months. All patients were investigated clinically and by the motor unit number estimation method MScanFit of the abductor pollicis brevis muscle.

Results: The number of motor units ($p < 0.001$) was significantly lower in patients with SMA compared to healthy controls at study entry. Mean unit amplitude, median amplitude and largest unit ($p < 0.001$) were significantly increased in patients with SMA. Patients with amyotrophic lateral sclerosis showed a significant reduction of compound muscle action potential ($p = 0.005$) and number of motor units ($p = 0.03$) compared to patients with SMA, accompanied by a larger median amplitude ($p = 0.03$). A prospective analysis identified patients with the ability to walk to improve the number of motor units ($p = 0.046$) accompanied by a decreased median amplitude ($p = 0.03$). Electrophysiological measures showed a moderate to strong correlation with clinical scores.

Conclusion: Patients with SMA show loss of motor units in distal muscles. MScanFit variables indicate that compound muscle action potential amplitudes are maintained by collateral sprouting. Prospective analyses suggest that milder affected adult patients with SMA preferentially benefit from nusinersen treatment through recovery of smaller motor units. Correlations with clinical scores underline the potential of MScanFit as a surrogate marker.

Keywords: amyotrophic lateral sclerosis, motor unit number estimation, nusinersen, spinal muscular atrophy
**INTRODUCTION**

Spinal muscular atrophy (SMA) is a clinically heterogenic motor neuron disease caused by a homozygous disruption of the SMN1 gene on chromosome 5q. This leads to a progressive loss of motor function. The disease is subdivided according to its clinical phenotypes which range from severe motor deficits in infants to mild late onset symptoms in adulthood (i.e., SMA types 1–4).

In 2017–2018, the antisense oligonucleotide nusinersen (Spinraza®, Biogen, Cambridge, MA, USA) was approved by the Food and Drug Administration and European Medicines Agency to treat patients with SMA. Despite good knowledge about the effects of this treatment in infants and children [1,2], little is known about the benefit of nusinersen in adults, especially regarding electrophysiological measures. A recent large observational study suggested treatment-related clinical improvement in adults, which was determined by functional rating scores [3].

MScanFit is a new motor unit number estimation (MUNE) method. Its use and advantages compared to other MUNE methods have mainly been proven in patients with amyotrophic lateral sclerosis (ALS) [4]. Recent studies showed that MScanFit might serve as a surrogate marker for disease progression, and allows insights into disease pathology (i.e., collateral sprouting) [5]. Hereby, in different SMA subtypes a marked loss of motor unit function has been observed; however, no observation of nusinersen-treated patients was made, no comparison to healthy controls and no prospective data were reported [6].

In our study, the aim was to characterize motor unit organization in adult patients with SMA compared to healthy controls and patients with ALS, and to investigate prospectively short-term motor unit changes during nusinersen treatment using MScanFit.

**MATERIAL and METHODS**

Patients and ethical approval

Fifteen adult patients with genetically confirmed SMA, assigned to type 3 in accordance with their clinical onset, participated in this study. All patients were treated with nusinersen according to the manufacturer’s recommendations at the Department of Neurology, University Hospital of Cologne. The number of treatment courses before study entry are listed in Table 1. The Hammersmith Functional Motor Scale Expanded (HFMSE) and the Revised Upper Limb Module (RULM) were used to evaluate the clinical status of patients with SMA (see Table 1). Additionally, the 6-min walk test was included for patients with the ability to walk. All scores were performed by trained physiotherapists, blinded to electrophysiological investigations, before each nusinersen application.

Ten patients were investigated prospectively: at study entry and at follow-up, 4–8 months later (mean 4.7 ± 1.34 SD). Measurements of all patients were compared to 15 healthy age-matched controls (seven males and eight females; mean age 39.67 years, range 21–63) and 10 patients with ALS (seven males and three females; mean age 65.6 years, range 51–81), who were included as an additional reference group. However, one of the 10 investigated patients with ALS could not be included in further data analysis as no reproducible motor unit potential could be evoked as the patient was clinically too severely affected. Patients with ALS were diagnosed according to the revised El Escorial criteria [7], and disease severity was stratified using the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) (mean 32.4 ± 8.62 SD, range 19–44). Patients with ALS and SMA were clinically matched by disease severity using the ALSFRS-R (p = 0.13).

Participants were excluded before the electrophysiological investigations if they had one of the following conditions: (i) polyneuropathy, (ii) diabetes mellitus, (iii) neurotoxic medication or (iv) affection of the investigated nerve by fracture, carpal tunnel syndrome or herniated cervical intervertebral disc.

The study was approved by the local ethics committee (Ethikkommission der Medizinischen Fakultät der Universität zu Köln). All participants provided written informed consent before admission to the study. This single-centre cross-sectional and longitudinal study was conducted in 2020 and 2021 and was carried out in accordance with the Declaration of Helsinki.

**Motor unit number estimation**

All participants of the study were investigated by the MUNE method MScanFit. The MScanFit recordings for MUNE were

| Patients with SMA (n = 15) |  |
|---------------------------|--|
| Age (years)               | 38.27 ± 11.73 (23–58) |
| Sex                       |  |
| Males (n = 10)            |  |
| Females (n = 5)           |  |
| SMA type                  |  |
| SMA type III (n = 15)     |  |
| HFMSE (max.: 66)          | 31 ± 17.62 (2–59) |
| RULM (max.: 37)           | 29 ± 8.65 (11–37) |
| Number of nusinersen courses at entry | 6.93 ± 3.06 (1–10) |

Notes: Clinical status was assessed by the Hammersmith Functional Motor Scale Expanded (HFMSE) and the Revised Upper Limb Module (RULM). Values are expressed as mean ± standard deviation (SD). Values in parenthesis show the range. n = number of patients.
made using the MSCAN-R protocol within the Software QtracS (©Institute of Neurology, University College London, UK). The recording set-up included an isolated bipolar constant current stimulator (DS5, Digitimer Ltd), a HumBug Noise Eliminator (50/60 Hz, Digitimer Ltd) and an Isolated Amplifier/Filter (D440-2, Digitimer Ltd).

The recordings were undertaken by stimulating the median nerve of the dominant arm of the participant (patients with SMA, patients with ALS and healthy controls). Therefore the participant’s hand and forearm were cleansed with Nuprep Skin Preparation Gel (Weaver and Company) and alcohol (Spitacid, ECOLAB, DE). The active recording electrode (BlueSensor NF-50-K, Ambu, DE) was placed on the belly of the M. abductor pollicis brevis with the reference electrode (BlueSensor NF-50-K, Ambu) located over the proximal phalanx of the thumb. The ground electrode (Neuroline 714 Ground, Ambu) was placed on the dorsum of the hand. The stimulation electrodes (BlueSensor Q-50-K, Ambu) were placed on the median nerve at the wrist. The stimulating cathode was placed at the point where the lowest stimulus intensity was needed to stimulate the nerve, and the anode was placed proximally along the median nerve. To eliminate noise or artefacts caused by movement, the fingers were taped together and the arm was placed in a relaxed position. The skin temperature was measured and maintained between 32 and 36°C [8].

According to the MSCAN-R protocol, first a detailed compound muscle action potential (CMAP) scan from maximum to minimum detectable response was performed. The stimulus was manually set to a just supramaximal level. After recording a prescan consisting of 20 CMAPs generated by a supramaximal stimulus, the stimulus intensity was automatically decreased in regular steps until the motor response disappeared. At the end of each scan, a postscan with a further 20 CMAPs was recorded (Figure 1). Prescan and postscan periods were performed to assess baseline noise and response variability.

The following parameters were set for stimulation: (i) scan steps 0.2%, (ii) interstimulus interval 0.6 s and (iii) stimulus widths 0.2 ms [9].

The registered CMAP scan was then analysed by the automated computer-based MScanFit component within the software QtracP (©Institute of Neurology, University College London). The program generates a model based on the variance and slope of the recorded CMAP scan. The model is then refined by multiple optimization processes to reduce the discrepancy between the model and the recorded scan [9].

From the fitted model, multiple parameters were derived: (i) MscPeak, the maximum CMAP amplitude (mV); (ii) MSFNUnits, the estimated number of motor units; (iii) MscD50, a value that represents the number of CMAP scan discontinuities (size-ordered from largest to smallest), which, when added up, exceed 50% of the CMAP amplitude [10] (iv) MSFMeanUnitAmp, the mean value of the amplitudes of single motor unit potentials (µV); (v) MSFLargestAmp, the amplitude of the largest motor unit (mV); and (vi) MSFMedianAmp (%), the median of the amplitudes of single motor unit potentials expressed as a percentage of CMAP.

**Statistical analysis**

Statistical analysis was performed using the software QtracP (©Institute of Neurology, University College London) and SPSS Statistics 27 (IBM).

The distribution of variables was evaluated by the Shapiro–Wilk test, and homogeneity of variances was assessed by the Levene test. As some parameters were not normally distributed or had unequal

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**FIGURE 1** Characteristic CMAP scans of normal controls (NC) (a), patients with spinal muscular atrophy (SMA) (b) and amyotrophic lateral sclerosis (ALS) (c). Scans show a response recorded from the M. abductor pollicis brevis from just supramaximal stimulation to minimum detectable response, including prescans and postscans with 20 stimuli at the same intensity to detect baseline noise and variability of responses. Recordings show characteristic discontinuities of the CMAP scan in patients with motor neuron disease (b), (c).
variances, the Mann–Whitney U test was used to compare group
data for patients and controls. The Wilcoxon signed-rank test was
performed to compare paired MScanFit recordings at entry and at
follow-up. If not mentioned otherwise, results are presented as me-
dian (first quartile, third quartile).

To analyse the relationship between clinical scores and electro-
physiological measurements, Spearman's correlation was used. The
strength of the correlation was classified as Rho 0.00–0.19 (very
weak), 0.20–0.39 (weak), 0.40–0.59 (moderate), 0.60–0.79 (strong),
0.80–1.0 (very strong). Results with \( p < 0.05 \) were considered
significant.

**Data accessibility**

The data that support the findings of this study are stored on a
secured server at the University Hospital of Cologne, Germany,
and are available from the corresponding author on reasonable
request.

**RESULTS**

The characteristics of patients with SMA are shown in Table 1. Eight
patients were functionally classified as wheelchair users. The re-
main ing seven patients were able to walk independently.

The numbers of motor units recorded from the abductor pollicis
brevis muscle were lower in patients with SMA compared to healthy
controls (\( p < 0.001 \)), even though CMAP amplitude did not differ
between the two groups (\( p = 1 \)). Compared to patients with ALS,
the number of motor units and peak CMAP amplitude were higher
in patients with SMA (motor units, \( p = 0.03 \); CMAP, \( p = 0.005 \))
(Figure 2).

Axonal loss was increased reflected by a decrease of the D50
value, and measures of re-innervation showed larger motor unit
amplitudes in patients with SMA compared to healthy controls
(D50, \( p = 0.007 \); mean unit amplitude, \( p < 0.001 \); largest amplitude,
\( p < 0.001 \); median amplitude, \( p < 0.001 \); see Table 2). Compared
to patients with ALS, axonal loss reflected by the D50 value was
less pronounced in patients with SMA (\( p = 0.32 \)). The median

**FIGURE 2** MScanFit variables of patients with spinal muscular atrophy (SMA), amyotrophic lateral sclerosis (ALS) and healthy controls
(NC). (a) Peak CMAP amplitudes are not significantly different between patients with SMA and healthy controls (SMA, 7.64 [4.05, 10.88];
NC, 8.1 [6.11, 9.17]; ALS, 3.31 [1, 4.54]). Other variables show significant changes of patients with SMA and ALS compared to controls. One
of the 10 investigated patients with ALS could not be included in the data analysis as no reproducible motor unit potential could be evoked.
(b) Number of motor units (SMA, 43 [25, 66]; NC, 92 [67, 120]; ALS, 9 [5, 42]); (c) D50 values (SMA, 30 [15, 35]; NC, 34 [32, 38]; ALS, 17 [6.5,
32]) and (d) mean unit amplitude (SMA, 165 [131.3, 211.7]; NC, 74.9 [62.9, 111.9]; ALS, 166.7 [126.4, 301.45]). Horizontal solid lines indicate
medians, and dashed lines represent first and third quartiles (Q1, Q3). Asterisks indicate the \( p \) values (*\( p < 0.05 \), **\( p < 0.01 \), ***\( p < 0.001 \),
****\( p < 0.0001 \), *****\( p < 0.00001 \) )
amplitude expressed as the percentage of the CMAP was higher in ALS \((p = 0.03)\); other variables did not differ significantly.

Electrophysiological measures of patients with SMA showed a moderate to strong statistical correlation with clinical scores (HFSME, RULM). In particular, the number of motor units showed a strong correlation with both HFMSE \((\text{Rho} = 0.67, p = 0.009)\) and RULM \((\text{Rho} = 0.63, p = 0.01)\) (Figure 3).

Overall, the analysis of MScanFit variables and clinical scores showed no significant differences between the first (study entry) and second investigation (follow-up) \((n = 10)\) (Figure 4). However, the subgroup analysis of patients with SMA with the ability to walk \((n = 6)\) versus wheelchair users \((n = 4)\) demonstrated an improvement of the number of motor units at follow-up in patients with an ability to walk \((p = 0.046)\), accompanied by a reduced median amplitude \((p = 0.03)\).

### Table 2: Statistical analysis of MScanFit derived parameters of patients with SMA, ALS and healthy controls

|                  | Median (Q1, Q3) |  |  |  | p for Mann–Whitney U test |
|------------------|----------------|----------------|----------------|----------------|------------------------|
|                  | SMA \(n = 15\) | NC \(n = 15\) | ALS \(n = 9\) |                | SMA vs. NC  | SMA vs. ALS | ALS vs. NC  |
| Age              | 36 (26, 52)    | 34 (31, 54)    | 65 (59.75, 71)| 0.77           | <0.001**** | <0.001**** |
| MUNE             | 43 (25, 66)    | 92 (67, 120)   | 9 (5, 42)     | 0.03           | <0.001**** | <0.001**** |
| D50              | 30 (15, 35)    | 34 (32, 38)    | 17 (6.5, 32)  | 0.07           | 0.32       | 0.005**   |
| Mean unit (µV)   | 165 (131.3, 211.7) | 74.9 (62.9, 111.9) | 166.7 (126.4, 301.45) | <0.001**** | 0.68       | 0.001**   |
| Largest unit (mV) | 0.68 (0.43, 0.97) | 0.32 (0.28, 0.44) | 0.53 (0.33, 0.79) | <0.001*** | 0.14       | 0.08      |
| Median unit (%)  | 1.62 (1.3, 3.36) | 0.94 (0.69, 1.2) | 8.75 (1.99, 18.55) | <0.001**** | 0.03*      | <0.001**** |
| Peak CMAP (mV)   | 7.64 (4.05, 10.88) | 8.1 (6.11, 9.17) | 3.31 (1.45, 4.54) | 1              | 0.005**    | <0.001**** |

Notes: Results with \(p < 0.05\) were considered significant. Asterisks indicate the \(p\) values (*\(p < 0.05\), **\(p < 0.01\), ***\(p < 0.001\), ****\(p < 0.0001\), *****\(p < 0.00001\)).

Abbreviations: ALS, amyotrophic lateral sclerosis; CMAP, compound muscle action potential; MUNE, motor unit number estimation; NC, normal controls; SMA, spinal muscular atrophy.

**Figure 3** Correlations of clinical scores (HFMSE and RULM) and electrophysiological measures. (a), (b) Number of motor units (HFMSE, \(\text{Rho} = 0.67, p = 0.009\); RULM, \(\text{Rho} = 0.63, p = 0.01\)) and (c), (d) CMAP amplitude (HFMSE, \(\text{Rho} = 0.54, p = 0.046\); RULM, \(\text{Rho} = 0.75, p = 0.001\)), showing moderate to strong correlations with clinical scores. Results with \(p < 0.05\) were considered significant.
Motor unit reorganization in distal muscles of patients with SMA

Our results demonstrate a marked loss of motor units in the abductor pollicis brevis muscle in patients with SMA compared to healthy controls, despite overall equal peak CMAP amplitudes in the two groups. These findings are similar to those observed in 24 treatment-naïve patients with type 2–4 SMA [6]. However, so far no MScanFit variables of adult patients with SMA have been compared to healthy controls [6]. Thus, our results prove that MUNE by MScanFit can detect changes in muscles before they become apparent on conventional electrophysiological techniques such as neurography. Further, our data show that distal muscles are regularly involved in patients with SMA despite the proximal-dominant phenotype of the disease. Likewise, in a study that investigated motor unit loss in patients with ALS, MScanFit was reported to be superior to CMAP amplitude analysis to distinguish patients with ALS from healthy controls [11].

Further analysis of MScanFit variables showed an increased amplitude of single motor units in patients with SMA compared to healthy controls at study entry indicating that peak CMAP is maintained by collateral sprouting in the disease’s natural course. The comparison to clinically matched patients with ALS revealed greater axonal and motor unit loss in the ALS cohort. These results reflect the clinical experience of a more pronounced involvement of distal muscle groups in patients with ALS compared to the SMA. Despite the differences of these motor neuron diseases, the knowledge about motor unit loss and remodelling in ALS using MScanFit allows a more detailed interpretation of the observed changes in patients with SMA; therefore an ALS reference group was included [4,5].

Our data showed a moderate to strong correlation with clinical scores. This observation and the lack of group differences of CMAP variables of adult patients with SMA have been compared to healthy controls [6]. Thus, our results prove that MUNE by MScanFit can detect changes in muscles before they become apparent on conventional electrophysiological techniques such as neurography. Further, our data show that distal muscles are regularly involved in patients with SMA despite the proximal-dominant phenotype of the disease. Likewise, in a study that investigated motor unit loss in patients with ALS, MScanFit was reported to be superior to CMAP amplitude analysis to distinguish patients with ALS from healthy controls [11].
amplitudes in healthy controls and patients with SMA suggest a potential use of MScanFit to monitor disease progression in motor unit disorders and show its advantages over conventional electrophysiological studies. These observations are in line with the strong clinical correlation of MScanFit variables and clinical scores in patients with ALS described before [4,8,12].

**Prospective analysis of nusinersen-treated patients with SMA**

The overall prospective analyses of MScanFit variables and clinical data did not show significant changes in patients with SMA compared to values at study entry. However, subgroup analyses revealed a moderate but significant increase in the number of motor units in patients with an ability to walk, accompanied by a significant reduction of median amplitude, whereas in wheelchair-using patients these changes were not observed. Clinical scores could not detect significant changes in our cohort. This observation might also be explained by ceiling effects which are commonly observed in clinical scores such as RULM and HFMSE in patients with good clinical functioning [13].

As no controlled studies with nusinersen have been conducted in adult patients with SMA, potential therapy effects are expected based on case series and observational studies. A recent study described the efficacy of nusinersen treatment in adult patients with SMA, which was observed in clinical scores already at 6 months post treatment initiation [3]. In contrast, other case series reported no or only mild treatment response up to 10 months [14–16] Overall, the data raise the issue of whether clinical scores detect short-term changes in patients with SMA treated with nusinersen accurately and with sufficient sensitivity.

Despite the overall small sample size in our study and especially the small number of patients in the subgroup analysis, our data indicate that SMA patients with the ability to walk might benefit more from nusinersen administration. This finding converges with data from the initial randomized, double-blind studies in infants and children and current electrophysiological studies [1,2,17]. These studies suggested that patients with shorter disease duration were more likely to benefit from nusinersen. However, our data and current observations promote a greater role of the clinical status, rather than the actual duration [3]. As repeatability has not been tested for MScanFit, in contrast to reproducibility [12], errors due to the measurement process itself cannot definitely be excluded. Moreover, as the investigators of the electrophysiological studies were not blinded to the diagnoses of the patients, a potential bias has to be considered.

The changes in motor units were accompanied by a mean decrease of the amplitude. This finding indicates that re-innervation processes in this cohort cannot be explained by collateral sprouting, which is usually observed as a compensatory mechanism in the course of chronic neuropathies and motor neuron diseases and leads to increased motor unit amplitudes [5,11]. Additional axonal regeneration, for example canonical axon outgrowth, is needed.

Consistent with our data, in a cohort of children with SMA treated with nusinersen who were prospectively investigated using MScanFit, the first electrophysiological changes observed were a rise in the number of motor units after 6 months. This finding was explained as an increased contribution of smaller motor units [17].

A possible limitation of our study is the spread of time points (4–8 months) for the follow-up investigation. Two or more precise time points would have provided a more detailed picture of potential therapeutic benefits. However, to include more patients with this rare disease, it was decided not to rule out patients who missed out on a single appointment. Moreover, taking recent publications into account, one can assume that a separate time point analysis of 4 and 8 months does not extend the overall interpretation of the data in studies of smaller sample size but goes along with additional burden for the patient [14,15].

Besides, the effect of nusinersen on disease progression could have been interpreted more accurately if the number of courses before study entry would have been the same in all patients or if all patients had been included treatment-naive and investigated again during therapy. However, between the subgroups, there was no significant difference of nusinersen courses, arguing for our interpretation’s validity. Moreover, due to new emerging disease-modifying agents which may be administered orally, many patients have concerns starting a more invasive therapy with nusinersen, making studies with treatment-naive patients complicated and undermining the need for detailed information on the benefit of this treatment for individual patients. As MScanFit showed good reproducibility and a high sensitivity to motor unit loss in a cohort of patients with ALS [12], the implementation of this method may also yield the potential as a surrogate marker for therapy response in patients with SMA.

**Perspective**

To give a more detailed picture of reorganization of motor units in distal muscles, measurement of other muscles such as tibialis anterior muscle should be considered in the future [5]. Including other muscle groups would also be desirable when analysing treatment responses. Moreover, to verify the observed changes in our subgroup analysis and also to analyse long-term effects, larger cohorts of patients with the ability to walk versus wheelchair users should be investigated, including different time points (e.g. 3, 6, 12 months). In this context, a prospective study design comparing treated and non-treated patients longitudinally would be preferred to evaluate treatment effects more accurately.

**Interpretation**

Taken together, our data provide important insights on motor unit loss and re-innervation mechanisms in patients with SMA and depict potential benefits of nusinersen on axonal regeneration. The value of the MUNE method MScanFit as an objective parameter to evaluate
narrow treatment responses in SMA is demonstrated. Open Access funding enabled and organized by Projekt DEAL.

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CONFLICT OF INTEREST

C. Schneider, M. K. Wassermann, N. B. Grether and G. Wunderlich report no disclosures. G. R. Fink serves as an editorial board member of Cortex, Neurological Research and Practice, NeuroImage: Clinical, Zeitschrift für Neuropsychologie and DGNeurologie; receives royalties from the publication of the books Funktionelle MRT in Psychiatrie und Neurologie, Neurologische Differentialdiagnose and SOP Neurologie; received honoraria for speaking engagements from Bayer, Desitin, Ergo DKV, Forum für medizinische Fortbildung FomF GmbH, GSK, Medica Academy Messe Düsseldorf, Medicbrain Healthcare, Novartis, Pfizer and Sportärztebund NRW. H. C. Lehmann received honoraria for speaking and advisory board engagements by Akcea, Alnylam, Biogen, Celgene, CSL Behring, Grifols, Takeda; academic research support not attributed to the manuscript by Aminylam, Biogen, Grifols, Novartis. The authors received no specific fundings for this work.

AUTHOR CONTRIBUTIONS

Christian Schneider: Conceptualization (lead); formal analysis (equal); investigation (equal); project administration (lead); writing—original draft (lead); writing—review and editing (lead). Meike K. Wassermann: Data curation (lead); formal analysis (equal); investigation (equal); project administration (supporting); visualization (lead); writing—original draft (supporting). Nicolai B. Grether: Project administration (supporting); writing—original draft (supporting). Gereon R. Fink: Project administration (supporting); supervision (supporting); writing—original draft (supporting). Gilbert Wunderlich: Supervision (supporting); writing—original draft (supporting). Helmar C. Lehmann: Conceptualization (supporting); formal analysis (supporting); project administration (supporting); supervision (supporting); validation (lead); writing—original draft (supporting); writing—review and editing (supporting).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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