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Remote Observational Research for Multiple Sclerosis

A Natural Experiment

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Abstract

Background and Objectives

Prospective, deeply phenotyped research cohorts monitoring individuals with chronic neurologic conditions, such as multiple sclerosis (MS), depend on continued participant engagement. The COVID-19 pandemic restricted in-clinic research activities, threatening this longitudinal engagement, but also forced adoption of televideo-enabled care. This offered a natural experiment in which to analyze key dimensions of remote research: (1) comparison of remote vs in-clinic visit costs from multiple perspectives and (2) comparison of the remote with in-clinic measures in cross-sectional and longitudinal disability evaluations.

Methods

Between March 2020 and December 2021, 207 MS cohort participants underwent hybrid in-clinic and virtual research visits; 96 contributed 100 "matched visits," that is, in-clinic (Neurostatus-Expanded Disability Status Scale [NS-EDSS]) and remote (televideo-enabled EDSS [tele-EDSS]; electronic patient-reported EDSS [ePR-EDSS]) evaluations. Clinical, demographic, and socioeconomic characteristics of participants were collected.

Results

The costs of remote visits were lower than in-clinic visits for research investigators (facilities, personnel, parking, participant compensation) but also for participants (travel, caregiver time) and carbon footprint ($p < 0.05$ for each). Median cohort EDSS was similar between the 3 modalities (NS-EDSS: 2, tele-EDSS: 1.5, ePR-EDSS: 2, range 0.6.5); the remote evaluations were each noninferior to the NS-EDSS within ±0.5 EDSS point (TOST for noninferiority, $p < 0.01$ for each). Furthermore, year to year, the % of participants with worsening/stable/improved EDSS scores was similar, whether each annual evaluation used NS-EDSS or whether it switched from NS-EDSS to tele-EDSS.

Discussion

Altogether, the current findings suggest that remote evaluations can reduce the costs of research participation for patients, while providing a reasonable evaluation of disability trajectory longitudinally. This could inform the design of remote research that is more inclusive of diverse participants.

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The UCSF MS EPIC Team members are listed in Appendix 2 at the end of the article.

Glossary

DMT = disease-modifying treatment; **EDSS** = Expanded Disability Status Scale; **EPIC** = Expression/genomics, Proteomics, Imaging, and Clinical; **ePR-EDSS** = electronic patient-reported EDSS; **MS** = multiple sclerosis; **NS-EDSS** = Neurostatus EDSS; **tele-EDSS** = televideo-enabled Expanded Disability Status Scale.

The global crisis imposed by the SARS-CoV-2 pandemic forced change across the health system, including broader recognition of glaring and long-simmering disparities in research and care,[2] and accelerating adoption of remote care.[3] Historically, observing the natural history of multiple sclerosis (MS) relied on prospective cohorts collecting reproducible evaluations longitudinally with regular visits and high retention rates. This approach yielded critical insights about the role of disease-modifying treatments (DMTs) on disability progression,[4] the silent progression underlying even "stable" disease,[5] and changing epidemiology. A number of digital tools and remote assessments have been validated to enrich in-clinic evaluations.[6] Such evaluations were brought to the fore when COVID-19–related shelter-in-place edicts (e.g., in California in March, 2020) immediately stopped all in-person observational research visits. To maintain active engagement by study participants, by April 2020, research protocols, including the prospective UCSF MS EPIC study, were modified to "go virtual."

The resulting hybrid virtual/in-clinic research setting provided a natural experiment to evaluate critical aspects of remote research previously challenging to test. The current analysis leverages this natural experiment to test 2 specific hypotheses. The first hypothesis was that overall costs of remote research would be lower. Here, various perspectives were included: participant (e.g., travel), research (e.g., clinic room use), and societal (e.g., carbon footprint). The second hypothesis was that the remote evaluations deployed, a televideo-enabled Expanded Disability Status Scale (tele-EDSS)[7] and an electronic patient-reported EDSS (ePR-EDSS),[8] were each noninferior to the gold standard disability assessment (Neurostatus EDSS) when compared cross-sectionally, and further longitudinally, to demonstrate that using them interchangeably at annual evaluations would not affect changes in global disability. While this research cohort's shift to virtual visits occurred in response to a global pandemic, the lessons learned could inform the feasibility of more inclusive, less costly, prospective cohort studies in MS and other chronic neurologic conditions.

Methods

Participants

The UCSF Expression/genomics, Proteomics, Imaging, and Clinical (EPIC) study is a single-center prospective observational research cohort of participants with MS evaluated annually since July 2004 (epicstudy.ucsf.edu/). Patients (age 18–65 years) receiving care at the University of California, San Francisco MS Center between July 2004 and September 2005 were invited to participate. Ambulatory participants and those with a recent onset of clinically definite MS (2001 International Panel Diagnostic Criteria)[9] or clinically isolated syndrome were preferentially recruited, although individuals with all clinical subtypes of the disease participate. Participant retention at 10-year follow-up exceeded 91%.[10] The UCSF ORIGINS cohort is a more recent cohort study prospectively enrolling since 2015, adults being evaluated within 90 days of a first suspected demyelinating attack, with similar design.

Visit Details

Per typical protocol until March 2020, participants were seen annually for a clinical MRI of the brain and cervical and thoracic spine, neurologic evaluation including the EDSS and MSFC4, visual testing including ocular coherence tomography and low-contrast visual acuity, and blood biomarker collection. After March 2020, visits were changed overnight to remote visits in most conditions, with in-person visits initially restricted to first-onset ORIGINS participants in whom neuroimaging, neurodiagnostics, and biosamples were clinically indicated to establish a diagnosis.

Then, between March 2021 and December 2021, a further 100 participants were seen who received both an in-person Neurostatus EDSS evaluation and a video-enabled televideo-enabled disability evaluation (tele-EDSS) evaluation within 14 days, in addition to completing an ePR-EDSS self-report. ORIGINS participants continued to be prioritized, but EPIC participants were seen as well. In previous studies,[7,8] the order of in-person and remote evaluations had been counterbalanced, but there were no differences in agreement according to the order. Here, for convenience, all NS-EDSS evaluations happened first, followed by the remote evaluations within 14 days; the order of the 2 remote evaluations was counterbalanced.

Measures Collected

Demographic details include age, sex, race, ethnicity, and zip code. Zip code was used to access the following geolocation characteristics from publicly available resources: distance from the clinic,[11] socioeconomic indicators from the US Census,[12] neighborhood walking score,[13] and COVID-19–related infection and death data.[14] Clinical (MS) characteristics include disease duration, MS type, MS DMT, and disability evaluations as per below. Visit characteristics included length of visit, room usage, and costs of in-visit components based on 2021 research recharge costs (excluding the additional costs of all other research infrastructure activities that are independent of specific visits themselves).

Clinical Evaluations

For in-person visits, the Neurostatus EDSS (NS-EDSS) evaluation was performed by a Neurostatus[15]-certified neurologist. Remote evaluations consisted of 2 evaluations recently validated against the gold standard NS-EDSS[15]; each showed correlation of >0.88 and >85% agreement within 1 point with the NS-EDSS.[7,8] Previous studies found that agreement increased with EDSS score of the studied population and that some functional systems (vision, brainstem, sensory) were more challenging to approximate remotely.

Tele-EDSS

As detailed previously,[7] a Neurostatus-trained neurologist performed the evaluation through the HIPAA-compliant Zoom televideo platform, instructing and guiding the participant through the examination. An aide was present only if on request by the participant or if deemed to be warranted by the investigator. Instructions and scoring were programmed into a REDCap survey so that the examiner could follow a template, ensuring accuracy of data capture. A low-cost ($6 USD) neurologic evaluation kit modified from that previously described[7] to include a vision card and a red piece of paper but not a tuning fork was mailed to participants in advance of their evaluation.

ePR-EDSS

As detailed previously,[8] participants were guided by the study personnel to access the online tool using a free, open access website (openmsbioscreen.org). Then, participants completed a series of questions evaluating their function, and a score was automatically generated and recorded.

Standard Protocol Approvals, Registrations, and Patient Consents

The UCSF Institutional Review Board approved the protocol, and written informed consent was obtained from all participants.

Statistical Analyses

Participants' clinical, demographic, and sociodemographic features for all EPIC + ORIGINS participants seen between March 2020 and December 2021 were first characterized using descriptive statistics.

Student *t* tests were used to test the hypothesis that costs for remote visits would be lower than for in-clinic measures for disability assessments.

To test the hypothesis that the quality of data extracted would be similar, for the 100 visits with all 3 measures available, all 3 modalities were compared. The primary analysis was a TOST (2 one-sided test) for noninferiority[16] with the NS-EDSS as the primary outcome. Disability evaluations were further compared using 3 analyses: Pearson correlations, unweighted Kappa statistics, and a Bland-Altman plot to visualize agreement by contrasting the difference between the 2 scores against the reference score. A previously reported analysis of various patient-reported EDSS scores was replicated for the current measures, to further evaluate the utility of the tele-EDSS and ePR-EDSS scores.[6] Then, to evaluate the effect on overall characterization of the cohort's disability level of alternating modes of disability evaluation, the year-to-year change in disability evaluations was compared in participants who received NS-EDSS at 2 annual time points, as well as in participants who received NS-EDSS at 1 time point followed by tele-EDSS the subsequent year. This mimicked a situation in which a neurologist might alternate between in-clinic and televideo-enabled evaluations. As previously reported,[10] clinically significant disability was defined as worsening by an increase in the EDSS[17] of 1.5 points if the baseline EDSS score was 0, by 1.0 point if the baseline EDSS score was between 1.0 and 5.0, and by a 0.5 point increase for baseline EDSS scores of 5.5 or higher. A similar analysis was performed for time points changing from NS-EDSS to ePR-EDSS.

Data were analyzed using R[18] and Python 3.8.10[19] software packages. Application programming interfaces were used to pull zip code–level geolocation, socioeconomic status, and COVID data (see details in Figure 1). Geospatial visualization and overlay used folium[24] Python library.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

Participants and Visit Characteristics

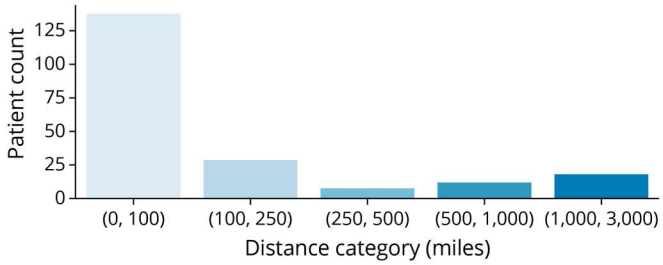
Overall, 207 individual adults with MS were seen during the study timeframe (March 2020 through December 2021), using a combination of in-clinic and remote visits, as shown in eFigure 1 (links.lww.com/NXI/A788). Their clinical characteristics, outlined in Table 1, include mean age of 42.3 years (SD 11.4), 70% women, >70% with over 15 years of education, and mean disease duration of 2.2 years (SD 4.6). One quarter (25%) were on no DMT, 37% were on monoclonal antibodies, 20% on oral therapies, and 18% on first-line self-injectable therapies. Of these, 96 participants received matched visits, i.e., all 3 disability assessment modalities within 14 days of one another, 4 participants contributed 2 sets of matched visits >6 months apart, for a total of 100 matched visits. Mean time interval between in-clinic and remote assessments was 7.6 days (SD 3.2). Participants with matched visits seemed to represent a slightly younger cohort with more recent MS onset (Table 1) because this was the group prioritized for imaging and biosample collection to confirm diagnosis and initiate treatment during the pandemic; however, this was not a statistically significant difference.

Sociodemographic Characteristics

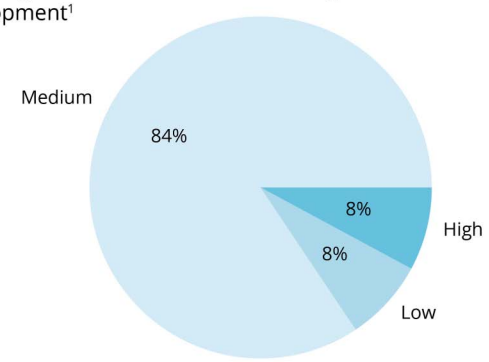
Participant sociodemographic characteristics were evaluated (Figure 1): median one-way driving distance was 35 miles, some participants traveling much further (up to 2,966 miles

Figure 1 Selected Sociodemographic Characteristics of the 207 Participants Seen Remotely During the Study Period

A. One-way driving distance between the participant's zip code and the clinic



B. Median household income in participants' zip code, according to the 2021 California Housing and Community Development[1]



C. Distribution of selected demographic characteristics

SES/COVID	Mean	Standard	Minimum	Median	Maximum
One-way distance (miles)	273	601	1	35	2,966
Duration (min)	259	533	5	45	2,635
Roundtrip CO_2 (kg)	186	408	0	24	2,017
COVID cases/100k	18,114	4,003	13,019	16,668	31,959
COVID deaths/100k	146	82	59	109	499
Median household income	$82,149.65	$32,084.33	$22,517.00	$80,383.50	$165,534.00
Walk score	47.3	39.0	-	49.0	100.0

Sources: The US Census,[12] neighborhood walking score,[13] and COVID19-related infection and death data.[14]

(A) One-way driving distance between the participant's zip code and the clinic. (B) Median household income in participants' zip code, according to 2021 California Housing and Community Development. (C) Distribution of demographic characteristics.

one-way) to attend study visits. Only a minority (8%) of the participants lived in zip codes considered to be low-income by 2021 California Housing and Community Development,[1] with 84% living in medium-income zip codes and 8% in zip codes considered to be high income. By comparison, the proportion of people living in low-income, medium-income, and high-income zip codes in the San Francisco Metropolitan Area (San Francisco, Oakland, Hayward) was 23%, 47%, and 30% for this period.[20] There were no correlations with $r > 0.3$ or $p < 0.05$ when the association between NS-EDSS and the selected sociodemographic variables was evaluated.

To illustrate the COVID-19 burden of our participants, as well as possible transmission averted by conducting remote research visits, Figure 2 represents the home zip code of research participants who resided in California. In-person visits were avoided from both low (immediate San Francisco Bay Area) and high (Central Valley of California, Los Angeles area) COVID-19 prevalence areas.

Hypothesis 1: Comparison of Cost Categories Between In-Clinic and Remote Visits

The costs of remote and in-clinic visits were compared, using selected cost categories: to research study (e.g., study personnel, examination rooms), individual research participants (e.g., travel time), and society (CO_2 footprint). Table 2 provides a comparison of the costs (direct and opportunity) of in-person vs remote visits for the 100 matched visits. We imputed total costs assuming all participants received the full set of in-clinic and remote evaluations. Research participation for in-clinic visits represents a substantial cost to participants regarding both transit time and overall visit time. Looking at commensurate cost items, the remote visits were significantly less costly for research team, participants, and carbon footprint ($p < 0.05$ for all analyses).

Hypothesis 2: Noninferiority of Remote vs In-Clinic Disability Evaluations

Cross-sectional Comparisons of Disability Evaluations Using Tele-EDSS, ePR-EDSS, and EDSS

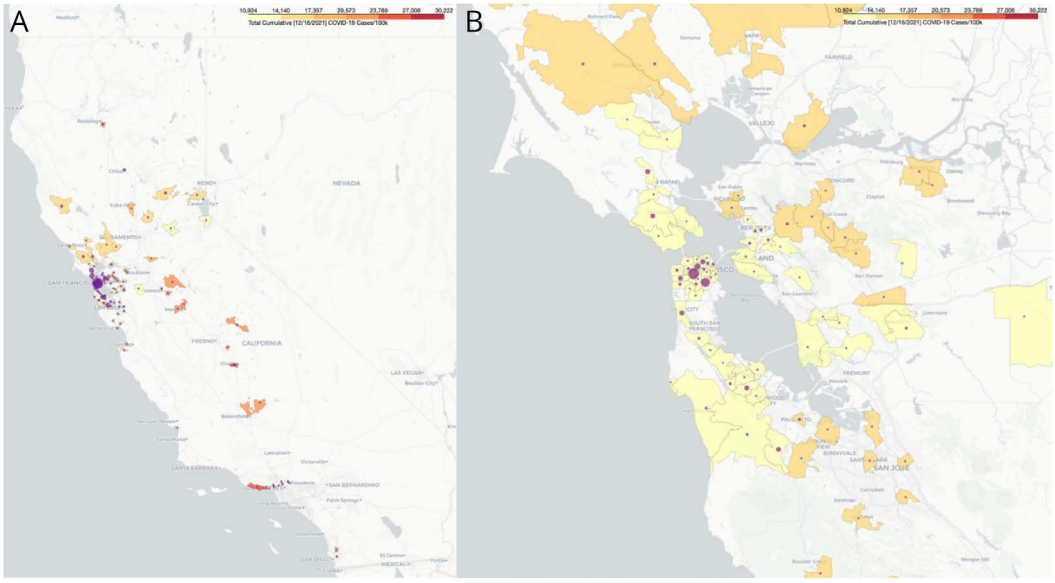
Disability outcomes were first compared for the 100 participants who had matched visits, i.e., all 3 measures were obtained within 14 days (tele-EDSS, ePR-EDSS, and in-clinic NS-EDSS). As shown in Table 1, their mean age (SD) was 41 years (11.7 SD) and their mean disease duration was 1.4 years (SD 3.4). Overall participants' scores were similar across the 3 measures (Figure 3). Distribution of each was 0–6.5. The tele-EDSS had a lower mean (1.7) and median (1.5) score than the NS-EDSS (2.0, 2.0) and the ePR-EDSS (2.0, 2.0). Using a TOST for noninferiority, both PR-EDSS ($p = 0.000012$) and

Table 1 Demographic and Clinical Characteristics of All Participants Seen Between March 2020 and December 2021 (N = 207), Including the 96 Participants Who Contributed 100 Visits With Matched Disability Modalities (NS-EDSS, Tele-EDSS, ePR-EDSS)

	All remotely evaluated participants				Participants with matched visits			
	N	Mean	SD	Total %	N	Mean	SD	Total %
Age	207	42.3	11.4		96	41.4	11.7	
Disease duration	207	2.2	4.6		96	1.4	3.4	
Sex								
Female	145			70.0%	66			68.8%
Male	62			30.0%	30			31.3%
Race								
Asian or Pacific Islander	8			3.9%	8			8.3%
Black or African American	7			3.4%	4			4.2%
Hispanic or Latino	15			7.2%	8			8.3%
Native American	0			0.0%	4			4.2%
White	169			81.6%	69			71.9%
Other	7			3.4%	3			3.1%
Unknown	1			0.5%	0			0.0%
Education								
≤10	4			1.0%	0			0.0%
11 to 15	44			21.3%	15			15.6%
>15	146			70.5%	71			74.0%
DMT								
Self-Injectable								
Glatiramer	32			15.5%	13			13.5%
Interferon beta-1A	6			2.9%	3			3.1%
Monoclonal antibody							0.0%	
Ocrelizumab	48			23.2%	19			19.8%
Rituximab	17			8.2%	8			8.3%
Natalizumab	12			5.8%	6			6.3%
Oral							0.0%	
Fingolimod	21			10.1%	8			8.3%
Dimethyl fumarate	18			8.7%	8			8.3%
Teriflunomide	1			0.5%	1			1.0%
None/unknown	52			25.1%	30			31.3%
MS type								
Relapsing (CIS, RR)	174			84.1%	88			91.7%
Progressive (PP, SP, PR)	25			12.1%	4			4.2%
Undetermined	8			3.9%	4			4.2%

Abbreviations: CIS = clinically isolated syndrome; DMT = disease-modifying treatment; EDSS = Expanded Disability Status Scale; ePR-EDSS = electronic patient-reported EDSS; NS-EDSS = Neurostatus EDSS; tele-EDSS = televideo-enabled EDSS.
The 2 groups did not differ significantly in any characteristic ($p > 0.05$ for each comparison).

Figure 2 Overlay of California Resident Study Participants' Residence and COVID-19 Infection Rates in Their Communities (Infections per 100,000 People Ever, as of December 2021)



Panel A represents a map of all (n = 174) participants who were California residents. Panel B represents participants from the San Francisco Bay Area (n = 120). The purple circles represent individual participants in a given area code (larger circles = more participants). The hue of the areas corresponding to participants' zip codes represents the cumulative COVID-19 cases as of December 2021 in that specific zip code.

tele-EDSS ($p = 0.0067$) were noninferior to NS-EDSS within ±0.5 EDSS point.

When comparing each of the 3 modalities, the correlation became higher as the disability level increased (Figure 4). Notably, 86% of all tele-EDSS scores showed agreement within 1 point to NS-EDSS scores.

When specific functional systems were compared across the 3 protocols, some showed more clear agreement than others (eFigure 2, links.lww.com/NXI/A788). Overall, the NS-EDSS seemed to identify higher vision scores than the other modalities, while brainstem and cerebral difficulties were higher in the ePR-EDSS modality. More detailed comparisons of the 3 modalities can be found in eFigure 2.

Longitudinal Comparisons of Changes in Disability

While differences between the modalities were anticipated at the individual level (potentially because of a combination of interobserver differences, differences in functional status at the time of the examination, and differences in the modalities themselves), it was also important to determine whether at the group level, differences in modality used from one research visit to another could influence global characterization of disability progression for the cohort. To accomplish this, both absolute change in EDSS and distribution of participants according to disability change (progression, stability, improvement) were analyzed for the participants who received sequential NS-EDSS examinations annually (i.e., 1 year apart) vs participants who received an NS-EDSS and then a subsequent tele-EDSS for the following visit. The timeframe of analysis was narrowed to 2018–2022. As shown in Figure 5, various timeframes were selected to evaluate annual changes in the NS-EDSS. Overall, the mean and median change in EDSS from one year to the other hovered around 0 regardless of the evaluation modality. When comparing year-to-year proportion of participants whose disability remained stable vs progressed or improved, using the 1-year NS-NS EDSS change from EPIC participants 2004–2018 as reference, for the period 2018–2022, there was valid statistical equivalence for 1-year NS-NS ($p = 0.000006$), NS-tele ($p = 0.000017$), and NS-PR ($p = 0.0196$) (Figure 5).

Discussion

The forced adoption of remote evaluations brought about by the COVID-19 pandemic provided a natural experiment in which to compare virtual and in-clinic observational assessments. With validated remote evaluation tools readily available, the research infrastructure was able to pivot and rapidly engage participants. In the current analyses, remote evaluations were noted to be less costly overall, and on a cohort-level, switching to remote visits did not seem to influence the rate of perceived annual disability progression.

Large disparities in inclusion in clinical research—as well as in clinical outcomes—have been brought into focus in recent years, magnified by the COVID-19 pandemic. In the context of MS clinical care, we and others noted possible racial, geographic, or economic disparities in telehealth adoption that preexisted before

Table 2 Comparison of Estimated Time and Costs Associated With In-clinic and Virtual Disability Evaluations From Investigator, Participant, and Societal Perspectives

		In-clinic (EDSS)	Virtual (tele-EDSS + ePR-EDSS)	*p* Value (*t* test)
Research	Total ($)	**775**	**548**	**<0.0000001**
	Per-visit personnel costs ($)			
	Clinician flat fee (approximately 30 minutes)	450	450	
	Research coordinator time before/during visit ($71/h)	177.5	82.8	
	Specific research costs ($)			
	Examination room ($45/h)	90	0	
	Testing kit + shipping	0	15	
	Participant stipend for travel costs	60	0	
Participant	**Total time (min)**	Mean 417, median 194	60	**0.00000033**
	Visit time (min)	120	60	
	Driving time (min)	Mean 297 median 74, SD 660	0	
	Total cost ($)	**Mean 29, median 15**	**0**	**0.018**
	Cost of parking ($)	25	0	
	Gasoline cost[a] ($)	Mean 64, median 10, SD 161	0	
	Stipend for travel costs ($)	60	0	
	Care partner (% visits required)	**15%**	**2%**	**0.00018**
Societal	**CO_2 emission (kg) per participant[b]**	**Mean 89, median 14, SD 215[c]**	**Approx mean 0.018[c]**	**0.00013**

Abbreviations: EDSS = Expanded Disability Status Scale; ePR-EDSS = electronic patient-reported EDSS; tele-EDSS = televideo-enabled EDSS.
[a] Round trip, at 28 mpg and $6.06/gal.
[b] Excluding carbon footprint for clinician, coordinator, receptionist.
[c] CO_2 emissions in kg; source: www.utilitybidder.co.uk/business-electricity/zoom-emissions; assume using Zoom platform at 1080p at 0.015kg/hr

the pandemic,[3] despite the savings in direct (travel) and opportunity costs (lost work) that telehealth-enabled clinical care can provide for people with MS.[21-23] When applying an equity lens to the current analyses, it is noteworthy that most of our participants, while living a range of distances from the research Center, lived in medium-income and high-income settings and most had over 15 years of education. The research cohorts (EPIC and ORIGINS) are characterized by high-quality, deep phenotyping, and excellent longitudinal retention and have made possible generation of a number of impactful insights into the evolution of MS in the modern treatment era.[4,5] Nonetheless, the costs in transit, time, and opportunity costs to individual participants are substantial. Certainly not all research services associated with a deeply phenotyped cohort were available during the pandemic; while many of the core services (clinical updates e.g., relapses or medication changes; disability evaluations) could be deployed remotely, research-grade MRIs which are typically provided for patients could not be performed virtually. Home blood draws could be performed and were used for a number of other studies during the COVID-19–related in-clinic restrictions,[24] even if not for this study. While costly ($220 per draw and shipping) to the research program, these were substantially more convenient for participants. Overall, while research participation may be counterbalanced by the provision of free MRIs that may not have been covered by insurance in some situations, the costs of travel, childcare, and other opportunity costs (e.g., work time lost) are not usually reimbursed by research participant stipends. In fact, there is a general concern by IRBs and ethical boards to limit participant incentives so as to avoid perceived coercion; yet, this carries the risk that participation in research requires costs that may exclude some patients, representing a source of inequity in clinical research.[25,26] Altogether, these lessons point to the likelihood that home-based studies could support enrollment and expand research access to more racially, geographically, and economically diverse participants.

The current cost analyses further expand on prior work demonstrating reduced patient costs associated with televideo-enabled clinical MS care[21,22,27] and research,[28] by providing estimates of cost savings to the research team, as has been done in other fields (e.g., orthopedic research[29]). Furthermore, the ecological costs of in-person visits will increasingly need to be considered in an environment of climate change.

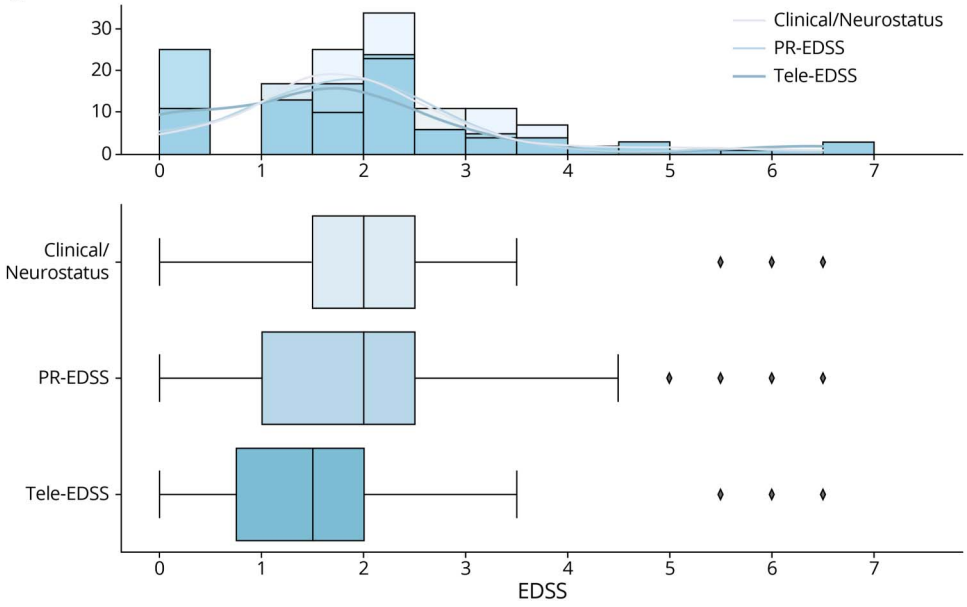
Each modality of remote evaluation (tele-EDSS and ePR-EDSS), while imperfect, was previously shown to be feasible and valid (with a correlation of almost 0.90 and reasonable agreement within 1 point with the Neurostatus EDSS). Furthermore,

Figure 3 Mean and Median Values for All 3 Disability Evaluation Modalities (Neurostatus, ePR-EDSS and Tele-EDSS) Obtained From 100 Visits (96 Participants) With Multiple Sclerosis

A

EDSS protocol	Count	Mean	Standard	Minimum	25%	50%	75%	Maximum
Clinical/Neurostatus	100.0	1.975	1.388	0.0	1.50	2.0	2.5	6.5
PR-EDSS	100.0	2.055	1.423	0.0	1.00	2.0	2.5	6.5
Tele-EDSS	100.0	1.675	1.515	0.0	0.75	1.5	2.0	6.5

B



Panel A describes the summary statistics, and Panel B visualizes these in a box plot. tele-EDSS = televideo-enabled Expanded Disability Status Scale.

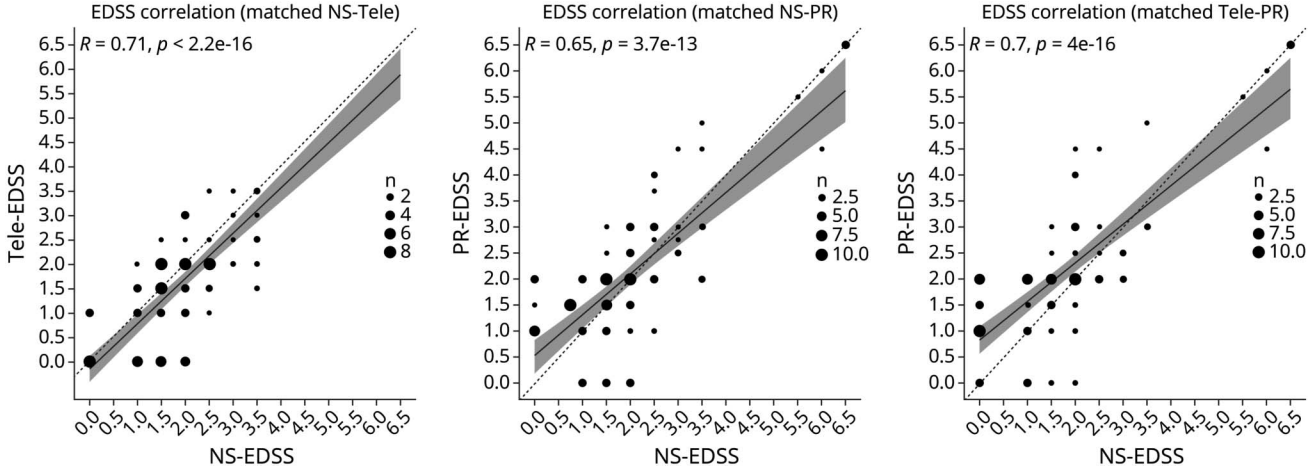
agreement was shown to increase with EDSS score (with less agreement at lower EDSS levels) and that some functional systems (vision, brainstem, sensory) were more challenging.[7,8] In this study, slightly lower correlations were observed than those previously reported. This observation is not unexpected given the greater heterogeneity in clinical examiners, as well as the low EDSS of the cohorts examined, which is associated with greater interobserver and intermodality discrepancy.[6] While neither remote modality seemed to be significantly "better" associated with the NS-EDSS, they offer different advantages. The ePR-EDSS is shorter for the participant; the tele-EDSS, while involving the added cost of a trained clinician, also enables "laying eyes" on a participant and perhaps a quality check. Ideally, both scores could be combined to better approximate an NS-EDSS.

The current analysis extends prior observations about the relative merits of these evaluation modalities by examining their impact on a longitudinal cohort. When searching for possible overinterpretation of disability progression for participants who switched modalities between visits, surprisingly, on a cohort-level, the percentage of participants with stable/worsening/improving EDSS categories from year-to-year (NS-EDSS to NS-EDSS compared with NS-EDSS to tele-EDSS) was not statistically different. Numerically, there did seem to be a slightly higher percentage of participants with progression in recent years, suggesting perhaps true change brought about by the pandemic. Reports on the effects of restricted outings on patient function during the pandemic are mixed: some but not all patients experienced clinically meaningful decreases in ambulatory activity[30] and physical function.[31] While some patients reported isolation and worse mood, others enjoyed the respite.[32] Here, complementary objective data gleaned from biosensors and other modalities could be informative, as will comparison for remote with in-clinic evaluations once in-person NS-EDSS visits resume for all participants. Nonetheless, the stability of overall distribution of scores was reassuring.

This study has limitations. While a natural experiment can force change and enable interesting comparisons, it cannot replace a randomized controlled clinical trial. For example, the analyses did not account for "drop outs." Second, the cost categories included were "known" and "quantifiable" but were not complete; for example, additional nonquantified costs could have included carbon footprint of overnight mailing of blood samples or lost wages or opportunity costs for participants and care partners traveling to the Center. The current evaluation was focused on patients with recent-onset MS because they were deemed to require clinical and research prioritization for the limited in-person visits available during

Figure 4 Correlation Between Disability Scores Across the 3 Examination Modalities

EDSS matched protocol correlations	All			0–1.5			2.0–4.5			5.0–6.0+		
N	100			55			39			6		
	Spearman r (p)		% Agreement (1 point)									
NS-Tele	0.71	<0.001	86.0%	0.35	0.009	76.4%	0.50	0.001	97.4%	1.00	<0.001	100%
NS-PR	0.64	<0.001	79.0%	0.20	0.139	76.4%	0.60	<0.001	84.6%	0.98	<0.001	66.7%
Tele-PR	0.70	<0.001	80.0%	0.30	0.028	76.4%	0.26	0.105	87.2%	0.98	<0.001	66.7%



As the disability level increases, the correlation becomes higher. tele-EDSS = televideo-enabled Expanded Disability Status Scale.

the pandemic. Because overall this was mostly a low-disability and higher-income cohort, the findings would also require validation in more diverse cohorts—a goal of promoting more inclusive research. Evaluation of sensitivity to change over periods longer than 1 year will also be important. This study also did not evaluate participant preferences; while prior work has suggested strong patient satisfaction with televideo-enabled care,[21,22,27] assessing these preferences in the research realm is an important step toward supporting remote research.

This study provides pragmatic insights to expand the use of remote evaluations for clinical research in MS, whether observational or interventional—and adding to the repertoire of remote research assessments for other neurologic conditions.[33-35] In prospective observational studies, flexibility in transitioning some episodic evaluations to remote monitoring could support recruitment of more diverse (racial, disability, geographic, age, etc.) participants, promote participant access and convenience, maintain longitudinal engagement, and reduce study costs while maintaining the episodic in-person collection of biosamples, imaging, and objective assessments. Remote collection of biosensor data would naturally support and enrich the analyses. In clinical trials, the reasonable performance of the remote disability evaluation modalities against the NS-EDSS supports use of such tools in Phase IIIb or IV trials that expand enrollment to populations more varied than those narrowly proscribed by inclusion/exclusion criteria from Phase IIIa trials. This could include participants with more advanced disability (in whom the remote evaluations performed particularly well), older participants, or those who face physical, geographic, or financial challenges in accessing in-person care. For clinical trials targeting symptomatic improvements as the primary outcome (e.g., mood, fatigue, sexual dysfunction) that also require an EDSS score to benchmark overall disability, a remotely assessed EDSS might enable remote enrollment of some participants. The same concept could be applied to clinical trials targeting biosensor data acquired from patient-worn instruments as the primary outcome (e.g., for walking or dexterity).[36,37] The reduced cost of remote evaluations, paired with a larger pool of participants, could accelerate enrollment in such cases. Altogether, these observations contribute to an emerging evidence basis for the conduct of more inclusive, and possibly less costly, remote clinical trials.

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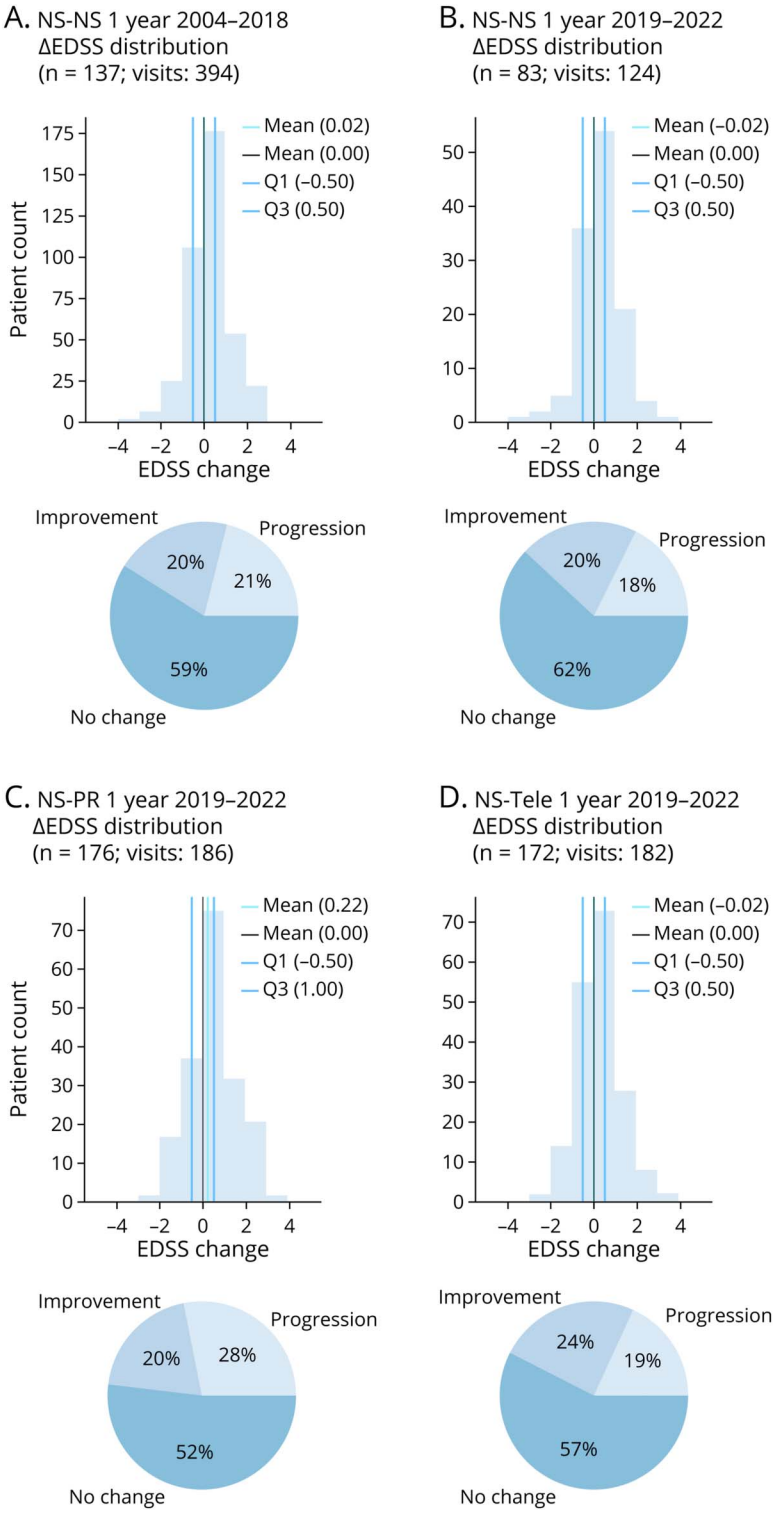
Figure 5 Distribution of Changes in Participants' Scores Between Annual Visits



Panel A represents annual changes in NS-EDSS for all visits from these participants, 2004–2018, and Panel B between 2019-2022. Panel C represents annual changes during the 2019–2022 epoch when switching from NS-EDSS at 1 time point to tele-EDSS at the next annual evaluation. Panel D represents annual changes during the 2019–2022 epoch when switching from NS-EDSS at 1 time point to ePR-EDSS at the next annual evaluation. For each comparison, the bar chart depicts absolute change and the pie chart represents the % of participants with EDSS stability, worsening or improvement between the annual visits as defined above, and using the 1-year NS-NS EDSS change from participants during the 2004–2018 timeframe as reference. Statistical equivalence was valid for 1-year NS-NS, NS-tele, and NS-PR 2018–2022 (p = 0.000006, 0.000017, 0.0196, respectively). ePR-EDSS = electronic patient-reported EDSS.

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Continued

Appendix 1 *(continued)*

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Eduardo Caverzasi, PhDi	University of California San Francisco	Additional Investigator	Ran image processing pipelines
Ari Green, MD	University of California San Francisco	Co-investigator	Clinical supervision
Roland Henry, PhD	University of California San Francisco	Additional Investigator	Directed image acquisition and processing pipelines
Jill Hollenbach, PhD	University of California San Francisco	Co-investigator	Oversaw data analysis
Jorge Oksenberg, PhD	University of California San Francisco	Co-investigator	Biosamples acquisition and analysis
Nico Papinutto, PhD	University of California San Francisco	Co-investigator	Ran image processing pipelines
Sam Pleasure, MD	University of California San Francisco	Co-investigator	Clinical supervision
Simone Sacco, MD	University of California San Francisco	Additional Investigator	Ran image processing pipelines
Emmanuelle Waubant, MD	University of California San Francisco	Co-investigator	Clinical supervision
Michael Wilson, MD	University of California San Francisco	Co-investigator	Clinical supervision, biosamples analysis
Scott Zamvil, MD	University of California San Francisco	Co-investigator	Biosamples analysis for immunology
Stacy Caillier, BA	University of California San Francisco	Co-investigator	Managed biorepository
Myra Mendoza, BA	University of California San Francisco	Research Coordination	Enrolled participants, ran study visits
William Stern, BA	University of California San Francisco	MRI acquisition	Acquired MRIs
Asritha Tubati, BA	University of California San Francisco	Research Coordination	Enrolled participants, ran study visits

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Remote Observational Research for Multiple Sclerosis: A Natural Experiment

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