P.LS, Natural History, Study (PLS NHS) Update

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Wesley, J Howe, Professor of Neurology (at CUIMC)
And Grace E. Jang, BA, PLSNHS Study Coordinator.
Columbia University Irving Medical Center

Dr. Mitsumoto thanked the audience for this opportunity to update everyone on his PLS research and expressed his appreciation and delight with how the Spastic Paraplegia Foundation research is progressing so rapidly.

He began by displaying a chart entitled: “What Do We Know About PLS?

- Incidence and prevalence: extrapolated from ALS cases in the United States, we estimate that there are approximately 75 to 125 new PLS cases per year; if these patients survive for 20 years, the. Prevalence would be ~ 2,000 cases.
- Cause and pathogenesis: unknown.
- Nosology (Disease classification.): unsettled.
- Natural history: limited knowledge for long-term prognosis and outcome.
- Clinical features: variable; clinical description, dominates the literature.
- Diagnosis: still uncertain, particularly in the early stages.
- Assessment: UMN, scale and the PLSFRS Dash yet to be tested in the real world.
- Neural imaging: most progressed in relation to ALS studies to date.
- Neurophysiology: an important tool for diagnosis.
- Biomarker: iffy at best.
- Genetics: just beginning!
- Clinical trials: never done.

PLS and its current perspective.

- PLS has been a very rare, puzzling, and obscured disease.
- PLS is considered as an extreme end of the ALS spectrum.
- We conducted a prospective five multi site PLSCOSMOS study several years ago (supported by SPF, and NIH.)
- PLSFRS (21 multisite study) has been developed for the PLS, natural history study (NHS) and future clinical trials.
- International PLS conference was held in 2019

1. The PLS diagnostic criteria has been renewed and published.
2. PLS conference supplement has been published.

Dr. Mitsumoto displayed a illustration of the brain and spinal column, along with identification of the upper motor neurons (UMN). The illustration identified how the upper motor neuron travels from the cerebral motor cortex, through the brain, stem, through the PYRAMIDAL space DOCUSSATION, lateral corticospinal tract (para middle tract) Ventral corticospinal tract (pyramidal tract), to the anterior horn cells and skeletal muscles.

Dr. Mitsumoto then displayed his diagram comparing PLS with HSP that looked as follows:

PLS and HSP

	PLS	HSP
Clinical signs	PUMN syndrome. Legs, arms, speech / swallowing	PUMN syndrome Predominantly legs
Pathology	UMNs & their tracts	UMN and long axon disease, ascending sensory tracts
Inheritance	Mostly sporadic	AD and AR, ?Sporadic
Disease Course	Slowly progressive	Slowly progressive
Treatment	Symptomatic and supportive	Symptomatic and supportive

A lot of progress has been made with PLS in recent years. He displayed a scientific publication, published a few years ago, the measurement scale for a LS called the ALSFRS was too insensitive for measurement of people with PLS so they created the PLSFRS measurement scale. This study was also supported by the Spastic Paraplegia Foundation.supported by the Spastic Paraplegia Foundation, entitled phenotypic and molecular analysis of primary lateral sclerosis. The ALSFRS measurement scale has 48 parameters while the PLSFRS has 68 parameters. They also discovered that clear changes can be found within a six month period in the PLSFRS rating system. He showed a photograph of people in attendance at the 2019 international scientific PLS medical conference in Philadelphia PA. 75 world experts on PLS attended along with the former Spastic Paraplegia Foundation president.

Out of that conference, they published a supplement going over the clinical spectrum, neurophysiology, neuroimaging, genetics, neurobiology, neuropathology, disease, progression, as well as clinical care and therapeutics. Free access to these publications can be found on Pubmed. After this conference, they established diagnostic criteria and this was written by Martin R. Turner, Richard J. Barjohn, Philippe Corcia, John K. Fink, Matthew B. Harms, Matthew C. Keenan, John Ravits, Vincenzo Milani, Zachary Simmons, Jefferey Stanland, and Leonard H. Van den Berg,

So, PLS is no longer a rare, enigmatic and neglected motor disease. International investigators and disease organizations have started paying serious attention to PLS:

- The fact that disease organizations other than Spastic Paraplegia Foundation fund PLS. Study/conference indicates their increasing interest in PLS.
- HSP/PLS Canada has been just recently established.
- NEALS UMN committee and more advanced neural imaging studies.
- Biennial PLS Conference in 2021 (Dr. Paganoni)

- The first disease modifying clinical trial in PLS is no longer unrealistic or far-fetched. In fact, potential medications are potentially available or are being developed.

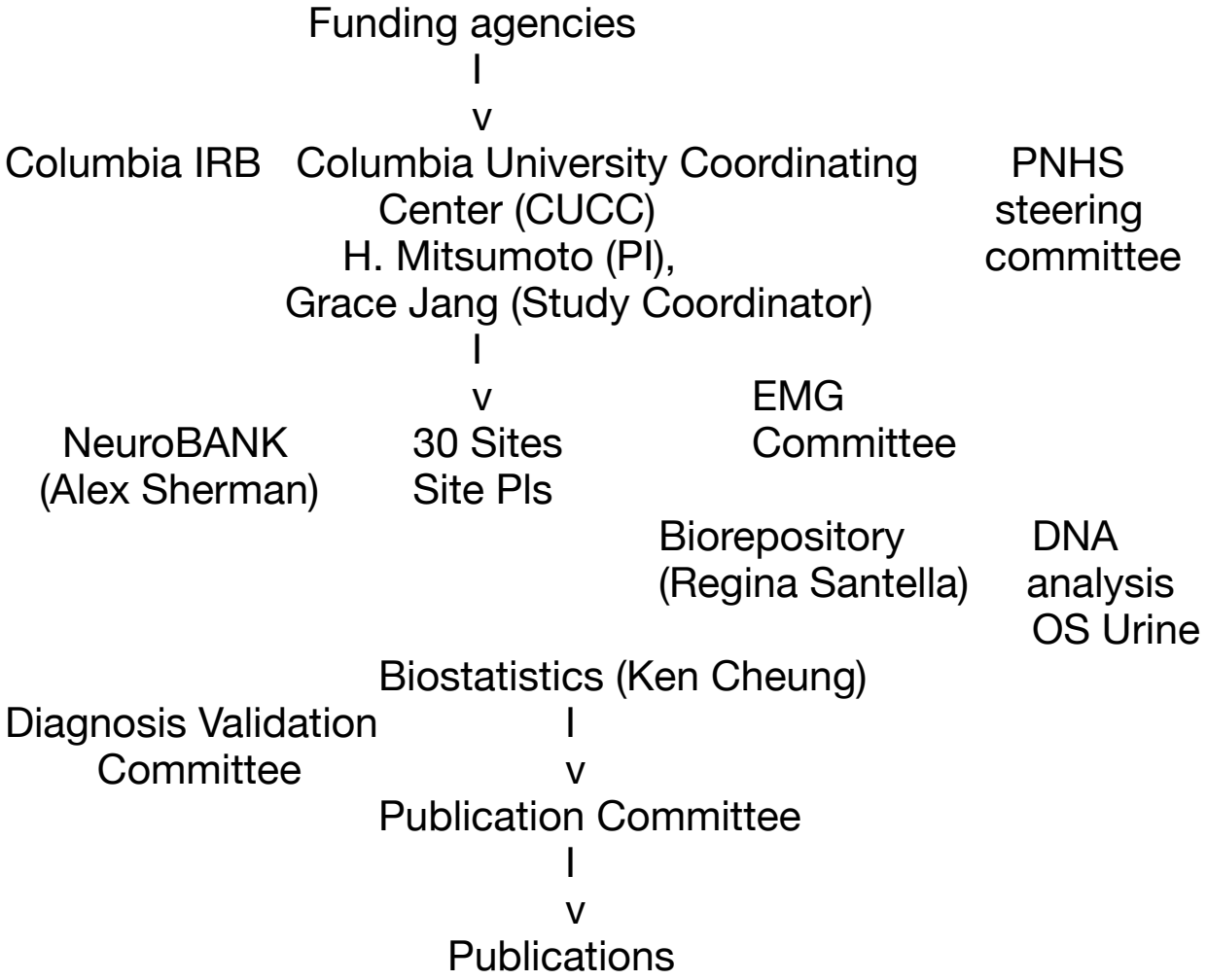
Why do we need a PLS? Natural history study (PLS NHS)?

- PLS NHS is the logical next step after our early PLS studies!
- Establishing the natural history is a prerequisite for designing future clinical trials in PLS
- We need to determine the best outcome measure for PLS clinical trials.
- We should be able to validate the reliability of the new diagnostic criteria.
- To develop bio markers for the future.
- To improve understanding of PLS

The funding for the PLS Natural History Study was made by:

- The Spastic Paraplegia Foundation
- The ALS Association
- Mitsubishi-Tanabe Pharma (MTP)
- David Marren and Family
- MDA Wings
- MGH NeuroBank

Study Structure:



Inclusion Criteria:

- Adult participants (≥ 25 years of age)
- PLS diagnosis based on the new PLS diagnostic criteria.
- Symptom onset was no more than 15 years prior to baseline.
- Ability to independently walk with or without an assistive device (e.g., Walker) at the baseline evaluation.
- In cases where a molecular test has been done prior to enrollment in this study, HSP or HSP related mutations are negative.
- Expected to have at least some bulbar symptoms (dysarthria, dysphasia, drooling, or pseudo bulbar affect); however, the

absence of these symptoms will not exclude participants when molecular testing is negative for known HSP.
- UMN symptoms and signs in a region other than the legs
- Normal brain and spinal cord neural imaging except for changes expected for PLS
- No active major neurological diseases other than PLS and no history of major neurological diseases.
- No major unstable medical diseases that require treatment (E. G., Active cancer, dialysis) in the past six months.
- Residing within a commutable distance to the study site and willing to visit the study site as required
- No history of a LS or PLS in immediate family and no family history of hereditary spastic paraplegia (HSP)
- If disease duration is less than four years, no significant lower motor neuron (LMN) degeneration upon the EMG examination within 12 months before enrollment (evident entrapment, Nuro, pathology or radical PY4E are acceptable). If disease duration, exceeds four years, at least one EMG post diagnosis.
- If an EMG test was not done in this period, an EMG should be obtained through regular patient (insurance) in order to make a diagnosis of PLS (this cost will not be covered by the research study)
- Participant understands the purpose of the study, has capacity to consent, and is willing to sign the informed consent form.

Exclusion Criteria:
- Unwilling or unable to give informed consent.
- UM in symptoms and signs only in the legs.
- Unwilling or unable to visit the study site as required.
- Clinically obvious cognitive impairment that precludes obtaining informed consent, as determined by the site PI
- Participating in clinical treatment trials.

Recruitment and enrollment. (early vs definite, PLS)
- 50 "early" PLS (less than 24 months after symptom onset.) including "probable" PLS? (Effective treatment should begin as

early as possible. This design makes it possible to investigate the early stages of the disease.)
- 50 "definite" PLS (4 years after symptom onset.) (existing or prevalent patients are mostly those who have definite PLS. We can study these patients as well.)

Study Outline and 24 month follow up

Evaluations	0	3	6	9	12	24
Eligibility assessment	X					
Consent/Enrollment	X					
Physical Exam	X					
Neurological Exam	X					
Cognitive Testing	X					
Equipment and Medication Review	X	X	X	X	X	
Penn UMN Score & FVC	X		X		X	
PLSFRS*	X	X	X	X	X	X
Pa-ta-ka Test*	X	X	X	X	X	X
Finger & Foot Tapping*	X	X	X	X	X	X
ALSAQ-5 & Neuro-QoL*	X	X	X	X	X	X
ROADS*	X	X	X	X	X	X
Timed Up and Go (TUG)	X		X		X	
DNA	X					
Blood	X				X	
Urine	X				X	
EMG (Needle Electrode)	X				X	

(*)To be completed remotely by Columbia University.

Standing Committees and Objectives

1. Steering committee (Cheung, Dave, Davis, Floater, Jang, Marren, Mitsumoto, Paganoni, Sherman, Simmons)

- Steer the entire project.
- Solve any unforeseeable issues
- Approve data and bio sample sharing
- Interpret results and guide publications

2. EMG Committee
3. Diagnosis Validation Committee
4. Publication Committee

EMG Committee
Members: Daragh Heitzman*, Eric Sorenson*, Mary Kay Floeter, Stephen Outman, Ali A. Habib, Ghazala Hayat, James Wyler
*Co-Chairs

- For all sites, EMGs performed for enrollment requirement will be reviewed: no LMN involvement/dysfunction
- EMG completed at one-year time point: to classify the diagnosis as PLS vs. UMN – predominant ALS
- To decide which muscles to be tested
- A full interpretation of one year EMG changes

Diagnosis Validation Committee.
Members: Lauren Elman*, J. Americo M. Fernandes*, Senda Ajroud-Driss, Kelly Gwathmey, Ed Kasarskis, Yaz Kisanuki, Catherine Lomen-Hoerth, David Walk
*Co-Chairs

- Goal: to determine the specificity of the PLS diagnostic criteria.
- Method: after each enrolled subject completes one year of data collection, their charts will be assigned to two members of the committee who will be blinded to the length of disease. They will independently determine if PLS criteria are met. If they agree, that is the answer. If not, then a third person will referee. We will be largely relying on the one-year EMG data, and the regions of involvement documented.
- This information will be used by the biostatistician, Ken, Cheung, to calculate the sensitivity of the criteria.

Publication committee.

Members: Christina N. Fournier*, Sabrina Paganoni*, Steven, Goldman, Terri, Heiman-Patterson, Yaz Kisanuki, David Walk.

*Co-Chairs

- Draft publication agreement created by the committee, will be circulated to the study team for review and comment before approval.
- PLS, natural history, study, primary manuscript (to be written and approved by the publication committee. Author order: primary author (s) to be determined by the PLS, natural history, study publication committee, and study PI, primary biostatistician, coordinating center and key staff, and site PI's or designates (in descending order based on the number of participants enrolled per site), as appropriate, with the study, PI, Dr. Hiroshi, Mitsumoto, as senior author.
- Secondary publications/abstracts/presentations (to be reviewed and approved by the publication committee).

Data Management
NeuroBANK
Mass General Hospital and NEALS
Alex Sherman

Biostatistical Analysis
Dr. Ken Cheung
Columbia University Irving Medical Center

- Analysis, goals: 1. Characterize the natural history of the two patient cohorts. 2. Provide information for future RCT
- Primary outcome: PLSFRS
- Longitudinal outcomes: Pa-Ta-Ka test, Neuro–Qol, ROADS, finger, tapping, etc.
- 3 visits (site) or 6 visits (CUCC), including baseline
- Analysis using generalized linear mixed affects model: 1. To estimate decline rate (linear and non-linear). 2. To examine differences between the two patient cohorts. 3. To account for participant characteristics (e.g. age, onset, cognitive test, etc.)

Communication between CUCC and Study Sites

- PLS, natural history study (PNHS): steady, initiation, and training, zoom conference call, May 2021 (repeat x3)
- Monthly Zoom conference calls with all sites on the first Monday of each month at noon
- Frequent email exchanges.

Investigational Research Within the PLS NHS

- Establish the natural history, data of PLS
- Validation for the current PLS diagnostic criteria.
- EMG changes in PLS
- DNA and molecular analysis to identify novel genes (Matt Harms)
- Validate increased OS in the urine (Regina Santella
- Novel biomarkers – Lipidomics (Ikjae Lee) – not budged.
- Establish a bio repository for future studies.

DNA Studies (Matt Harms)

- C9 determination by repeat-primed PCR
- Identify pathogenetic genes (fALS, HSP and PD) (exam or panel HaloPlex)
- Genome sequencing as a future study

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- NOTE: The results of the genetic test will be reported to the investigators – not the patients. If the investigators wish to report to their patients, they will have to obtain a formal diagnostic test at the available diagnostic lab. Our genetic tests are completely investigational; therefore, we are not responsible for reporting the results to the patients themselves.

Lipidome as Potential Biomarker for PLS

- Machine learning coupled with lipid Om data was able to differentiate PLS from ALS and controls with very high sensitivity and specificity (AUC of 0.96 and 0.9 respectively) (unpublished data from the ALS COSMOS)

- Most Discriminating variables were monoacylglycerol (MG) 18:1, MG 18:2 and MG:22:3
- Monoacylglycerol lipase that hydrolyzes above MGs has been studied for its role in neuroinflammation.
- A future study to validate these findings and examine the responsible metabolic pathway is warranted.

The current status of PLS space MHS: the IRB approval, subcontract and enrollment.

Year (May - June)	Total #IRB & Subcontract**s**	Average Enrollment per Month	Total Enrollment	# One Year Completion	# Two Year Completion
2021 - 2022 (May - June)	23	1.58	18 (E7/D11)	0	0
2022 - 2023 (May - June)	29	3	56 (E24/D32	14	0

Study Sites Enrollment

Site	**Site PI**	**Site Name**	**Enrolled #**
1	Daragh Heitzman	Texas Neurology Dallas	2
2	Omar Jawdat	U Kansas, Kansas City	1
3	Eric Sorenson	Mayo Clinic, Rochester, MN	0
4	Stephen Outman	U Michigan, Ann Arbor	1
5	Stephen Sceisa	Mt. Sinai/Beth Israel New York	2
6	Sabrina Paganoni	Mass General Hospital Boston	3
7	Terry Heiman-Patterson	Temple U, Philadelphia	3
8	Nick Maragakis	Johns Hopkins U Baltimore	3
9	David Walk	U Minnesota, Minneapolis	2
10	Christine N. Fournier	Emory U. Atlanta	2
11	Lauren Elman	U Penn, Philadelphia	0
12	Nanette Joyce	U California Davis / Davis CA	0

13	Jaimin Shah	Mayo Clinic Jacksonville FL	4
14	Zachary Simmons	Penn State U Hershey	0
15	Yasushi Kisanuki	Ohio State U. Columbus OH	2
16	J. Americo M. Fernandes	U Nebraska, Omaha	3
17	Ghazala Hayat	St. Louis U, St. Louis	0
18	Hiroshi Mitsumoto	Columbia U. New York	3
19	Lorne Zinman	U Toronto, Toronto	3
20	Ali A. Habib	U California Irvine / Irvine CA	3
21	Christian Shoesmith	Western U London, Ontario	1
22	Wendy S. Johnston	U Alberta, Alberta	4
23	Angela Genge	McGill U, Montreal	0
24	Catherine Lomen-Hoerth	U California, San Francisco	1
25	James Wymer	U Florida, Gainsville	3
26	Kelly Gwathmey	Virginia Commonwealth U., Richmond	2
27	Senda Ajroud-Driss	Northwestern U., Chicago	4
28	Michael Pulley	U Florida, Jacksonville	0
29	Edward Kasarkis	U Kentucky, Lexington	2
30	Richard A. Lewis	Cedars-Sinai Medical Center	2

When PLS NHS is successfully completed, it will be:

- The largest (the first) multi site study to establish PLS natural history.
- A large collaborative study funded by multiple funding sources: Spastic Paraplegia Foundation, ALS Association, MTP, private, donation, and NeuroBank Database Management (on gratis)
- The effective use of smart phone to obtain outcome data, giving less burden to participants with PLS
- PLS NHS will be succeeding appropriate clinical trials in PLS

- Providing a series of novel research data for 1. Understanding of disease mechanisms, 2. New biomarkers for PLS, and 3. Validating the current PLS diagnostic criteria.

Problems and Difficulties, and Potential Solutions.

- P.LS is simply so rare (1. SPF sent an email blast to its members to let them know of the study. 2. We will continue to publicize the study more.)
- Multisite study poses an administrative nightmare (No clear solution here: it is the best design to deal with such a rare disease.)
- Enrollment criteria are too strict (The EMG criteria have been modified to make it easier to recruit/enroll. The disease duration cutoff for definite PLS can be expanded if needed, being accepted so protocol exception.)
- COVID-19 has so greatly interfered the entire study (participant enrollment and study execution). At last COVID is now getting better.
- PLS NHS is likely to compete against ALS clinical trials for use of manpower at each site as it is on a shoestring budget (it is hard to prioritize the study. We need to keep emphasizing the importance of PLS NHS
- A donation made by Mr. Maren to encourage enrollment, cannot be easily used as some sites are not allowed to receive "any reward" for enrollment. (We will provide this as a budget adjustment to the sites (institutions), based on their enrollment effort.
- The budget allocated for patients study is still largely preserved. However, the coordinators salary is now exhausted. The current budget status would not allow us to continue the study. (SPF supplemented additional funding to let us continue the study.)

Current and Future Plans

- SPF's has given new support for 50% of the coordinators salary for the next two years (from 1/2023), so we can sustain the current study.
- We intend to add a few new sites.
- We have expanded the publicity of the study.
- If we continue the enrollment at the current pace, it would take another xx (12–18?) Months to complete the enrollment, that means it would take an additional 12 months to complete the 12 month follow-up visit.
- It may be more logical to stop the enrollment at some point, and analyze available results for the next clinical trial.

Is it Possible to Start a New Clinical Trial Immediately Following this PLS Natural History Study?

- If we enroll 66% of target enrollment, we may have a reasonably good data for the natural history of PLS. The goal set was 50 and 50 but a smaller number may very well be statistically significant.
- If the data is reasonable to apply for the next clinical trial, we should go ahead with a new clinical trial for PLS
- Are there any potential drugs to be tested for PLS? We know of two medications approved. One is oral Redicava (sp?) that was approved last summer for ALS clinical trials and xxxxx which was approved for ALS clinical trials earlier this year. Both of these drugs need to be tested for efficacy with PLS.
- Is the current study group enough for the next clinical trial consortium? Also, Dr. Ozdinler is trying to get her new drug for upper motor neurons approved for testing in the next few years.
- We need to add an international consortium to conduct a clinical trial to improve the recruitment for the trial. This coming December there will be a symposium in Europe that will allow them to explore this possibility.
- Realistically, we may need to move on from this difficult natural history study to the next practical and potentially more productive phase.

- He and his team plan to work diligently for the next few months with drug companies to get something working for PLS.

Dr. Mitsumoto closed by thanking the audience for their attention and offering to answer any questions. When he was asked what are the potential biomarkers for PLS, he answered that currently there are no known biomarkers but the list of potential PLS biomarkers include: lipidomic analysis, urinary oxidative stress, NFL, The SP-CERN biobank will be crucial for future biomarker development. Someone asked what drugs he would recommend for symptom modification for people with PLS and Dr. Mitsumoto mentioned baclofen, tizanidine and low doses of benzodiazepine.