Validation of Early Prognostic Data for Recovery after Stroke for Future, Higher Yield Trials: A Biomarker Validation Study (VERIFY)

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Objective

- Primary: To validate the most promising biomarkers of motor recovery after ischemic stroke in this first large-scale, prospective, generalizable dataset.
- Exploratory: To explore these biomarkers in a convenience sample of concurrently collected patients with intracerebral hemorrhagic stroke, for whom preliminary data are very limited.

Deliverables

Our study will immediately allow reliable prediction of patient outcomes after ischemic stroke to:

(a) improve stratification and inform entry criteria in clinical trials

(b) improve patient triage and inform therapy goals in clinical practice

Primary Aims

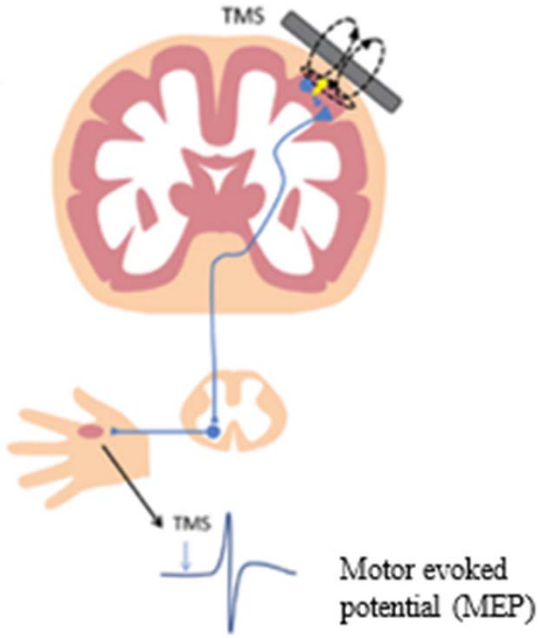
- **Aim 1:** To validate early (<1 wk) neuroimaging and neurophysiological biomarkers that distinguish subgroups of patients with differing 90-day motor impairment outcome after controlling for clinical variables
  - Motor impairment outcome = UE Fugl-Meyer (FM) scale score
- **Aim 2:** To validate the Predict Recovery Potential 2 (PREP2) algorithm to predict UE 90-day motor functional outcome in individual patients
  - Motor functional outcome = Action Research Arm Test (ARAT) score.
- **Aim 3:** To create and internally validate a prediction model of 90-day global functional outcome in individual patients, incorporating biomarkers and using state-of-the-art modeling approaches.
  - Global functional outcome = modified Rankin Scale score (mRS)

Rationale

- No major breakthroughs in stroke rehabilitation
  - Most trials are conducted with patients at the chronic stage Stinear 2013
  - Trials conducted at the early sub-acute stage are very challenging, and usually neutral Stinear 2020
- How do we increase our ability to detect intervention effects above early recovery?
- Biomarkers can be useful Boyd 2017, Kim & Weinstein 2017, Stinear 2010
- Focus on the upper extremity (UE)
  - Recovery of upper limb function is critical for independence Weinstein 2013
  - Most biomarkers relate to the upper limb Boyd 2017, Kim & Weinstein 2017

Neurophysiology Biomarker

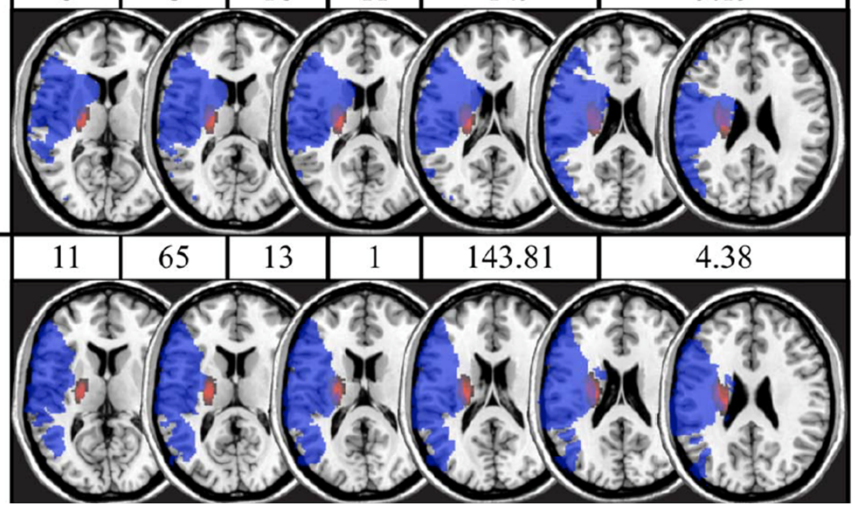
- Transcranial magnetic stimulation (TMS) of ipsilesional motor cortex
- Assess for motor evoked potentials (MEP) in either the extensor carpi radialis and/or first dorsal interosseous
- Presence of MEPs (MEP+) indicates **functionally intact** ipsilesional corticospinal system



Neuroimaging Biomarker

- MRI-DWI
- Assess DWI lesion load along the ipsilesional corticospinal pathways
- Greater lesion load indicates greater structural damage

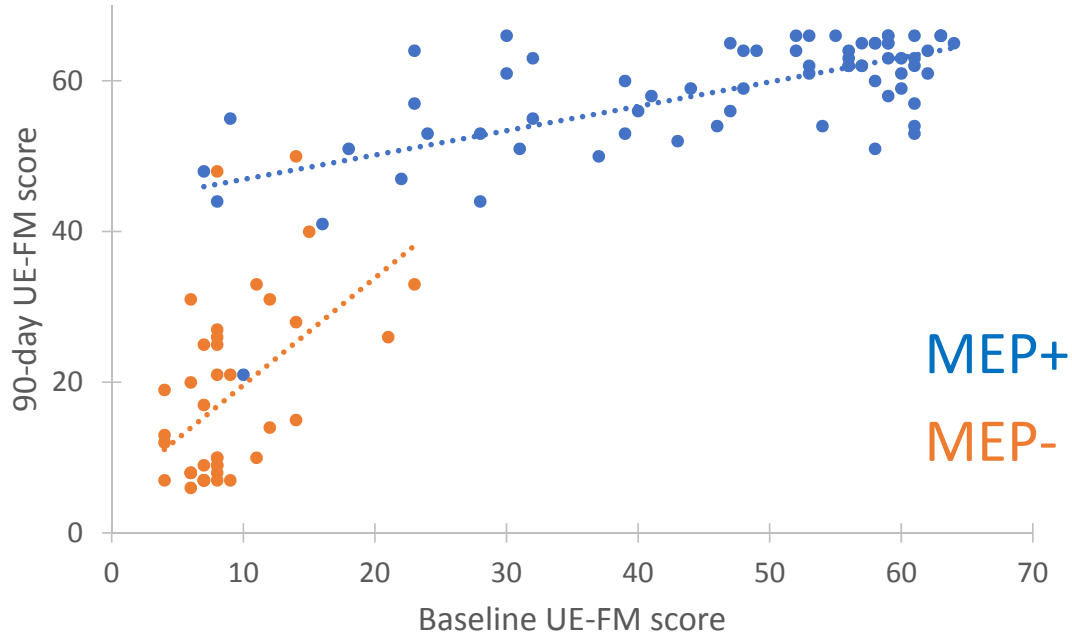
Patients	FM-UE		NIHSS		Lesion Size (cc)	Weighted Lesion Load (cc)
	Acute	3 mo.	Acute	3 mo.		
A	8	8	18	11	149	9.19
B	11	65	13	1	143.81	4.38



Feng, Annals of Neurology, 2015

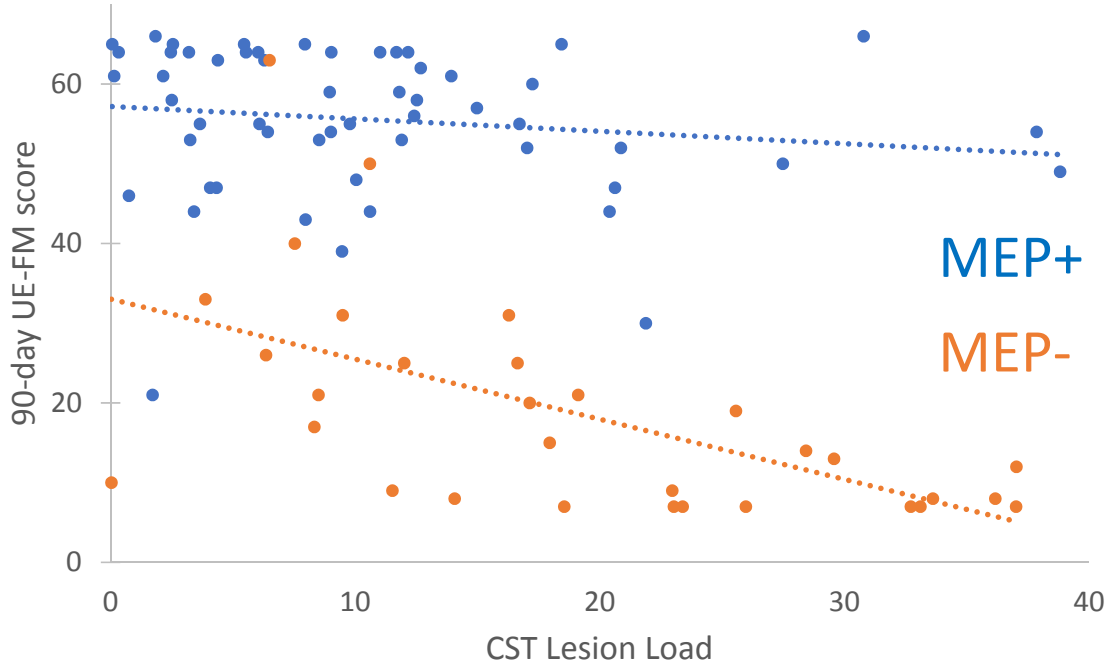
Aim 1 Hypotheses

- Hypothesis 1a*:* The relationship between baseline impairment and 90-day motor impairment outcome (FM score) will differ according to baseline MEP status



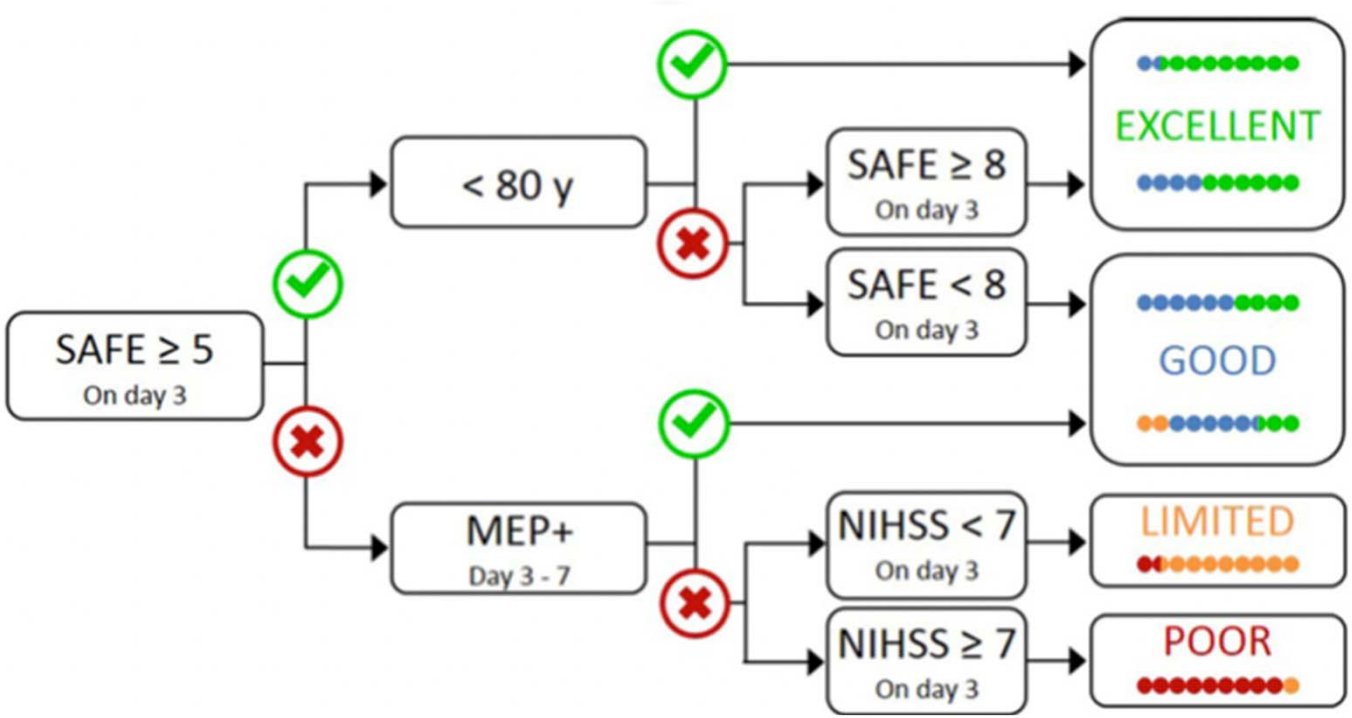
Aim 1 Hypotheses

- Hypothesis 1b: The relationship between 90-day motor impairment outcome and baseline *structural* integrity of the ipsilesional corticospinal tract will differ according to baseline MEP status



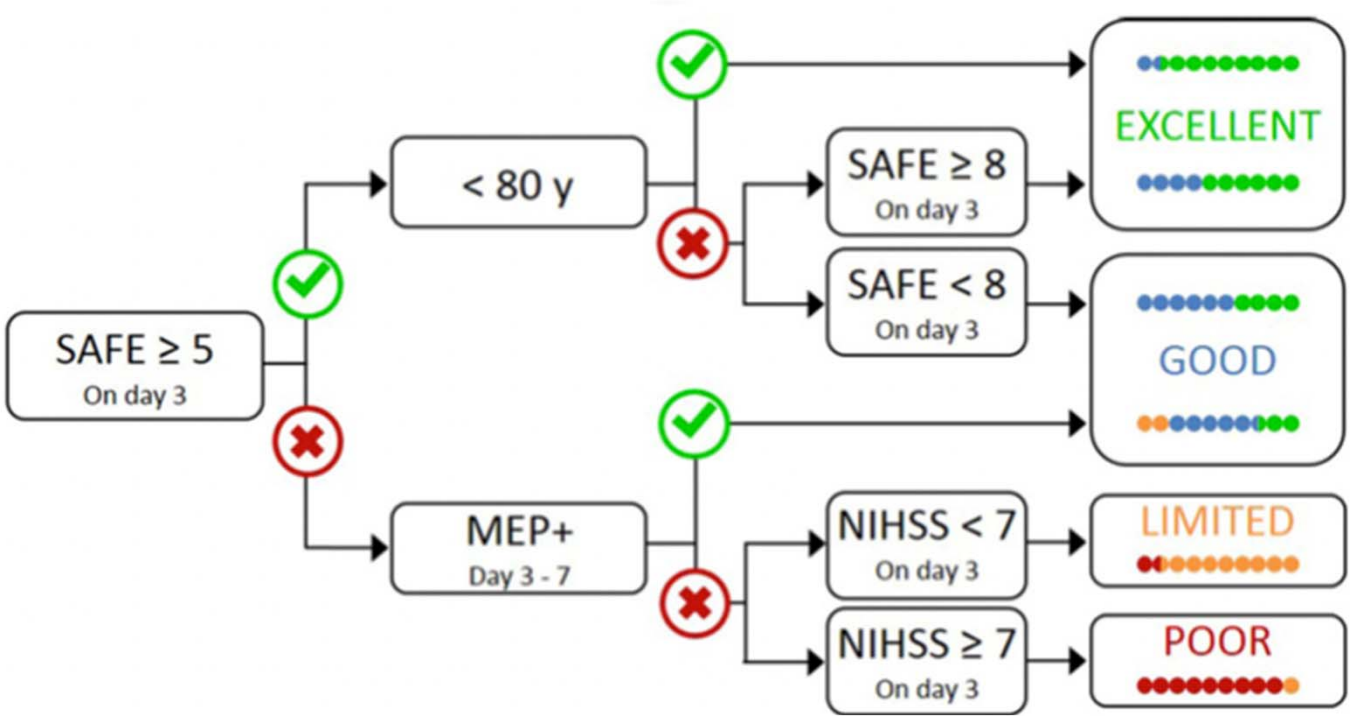
Aim 2 Hypotheses

- Hypothesis 2a: The PREP2 algorithm will correctly predict UE motor functional outcome (ARAT score) for at least 70% of ischemic stroke patients



Aim 2 Hypotheses

- Hypothesis 2b: Incorporating MRI-measured lesion load will improve the accuracy of the PREP2 algorithm beyond the accuracy of prior models to > 80%



Aim 3 Hypothesis

- Hypothesis 3: Global functional independence of individual patients (mRS 0-2) with UE motor deficits due to ischemic stroke will be better predicted early after stroke (<1 week) by combining MEP status and imaging biomarkers with clinical factors, as compared to clinical factors alone.


UCLA
Health System

Study Design

- We will collect clinical, neuroimaging, and TMS data
- Enroll 657 with ischemic and intracerebral hemorrhagic stroke within 3 days of symptom onset.
  - 557 ischemic stroke
  - 100 intracerebral hemorrhagic stroke (convenience sample)

Other Key Design Features

- Screening and enrollment during the acute hospitalization.
- Enrollment ANYTIME within 3 days of onset of stroke.
- Study-related assessments at 3-7 days (after clinical stabilization, prior to discharge).
- Standardized methods for biomarker/imaging acquisition, collection, and analysis.
  - MRI acquisition calibrated across sites following the ADNI multicenter imaging trial model.
  - Site training for TMS, imaging, and outcome measure collection.
  - Standardized MRI and TMS collection approaches enables broad application of study findings.
- Will capture rehabilitation interventions provided as routine clinical care.
- Data collected at ≤ 7 days of onset (in person), 30 days (phone), and 90 days (in person).

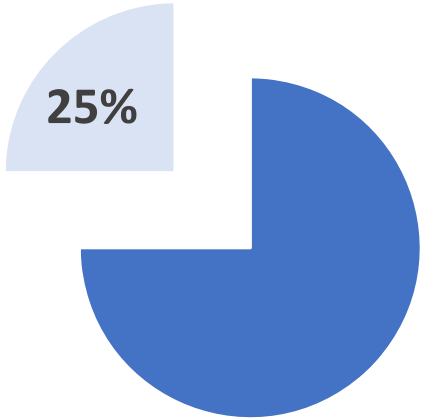
Key Eligibility Criteria

- Inclusion Criteria
  - Any upper extremity motor deficit with SAFE score ≤ 8
  - Ischemic or intracerebral hemorrhagic stroke
  - Ability to consent by patient or surrogate ANYTIME within 3 days from stroke onset
- Exclusion Criteria
  - Pre-stroke dependence (modified Rankin Score of 3 or more)
  - Cerebellar stroke
  - Unable to participate/contraindications to MRI or TMS
  - Unable to abduct shoulder or extend fingers of the non-paretic UE on command
  - Low likelihood of survival beyond the acute hospitalization.

Impact (1)

- Establish the most promising neuroimaging and neurophysiological biomarkers of motor recovery and functional outcome after ischemic stroke as validated, generalizable and feasible.

- Substantially reduce the sample size and monetary cost of future trials of motor recovery
  - We estimate that a clinically meaningful treatment effect could be detected with 75% fewer patients,, based on our preliminary data regarding the patient selection via the proposed biomarkers (Stinear, 2017a).



Impact (2)

- Inform clinical practice by helping patients, families, and physicians plan next steps and goals of care.
- Expand the capacity of the NIH StrokeNet infrastructure to perform recovery trials (largest funded recovery trial in StrokeNet to date consisted of 124 patients enrolled at 11 sites).
- Create a database to inform feasibility assessments for future StrokeNet trial proposals; ensures efficient recruitment.
- Encourage ancillary studies that test additional biomarkers and assess additional domains of recovery.
- Generate hypotheses for future independent validation studies of biomarkers for patients with hemorrhagic stroke.

Thank You

BACKUP SLIDES

Additional Exploratory Aims

- To explore feasibility of obtaining these biomarkers, and their predictive potential in a convenience sample of **ICH patients**, a very understudied subgroup.
- To explore UE motor functional outcome (ARAT score at 90 days) as a **mediator** of global functional independence (mRS score 0 – 2 at 90 days) and, in turn, quality of life (EQ-5D).
- To explore rehabilitation therapy (utilization, intensity, and the number of post-acute care settings) in the first three months after stroke, estimated by using Medicare Claims data (Skolarus, 2017), as a **mediator** of global functional independence (mRS 0-2 at 90 days).

These exploratory aims will generate hypotheses for future studies.

Outcome Measures

- Aim 1: 90-day motor recovery, measured as 90-day **UE-FM score**
- Aim 2: 90-day UE motor functional outcome, categorized as excellent, good, limited, or poor, using **the ARAT score**.

- Aim 3: 90-day global functional outcome, categorized as **mRS score** of 0-2 (functional independence) versus mRS 3-6 (functional dependence or death).

Note secondary outcome measures of Ambulation (10-meter walk test), Compensation for weakness (Reaching Performance Scale [RPS]), Quality of life (EQ5D), Cognition (MoCA), Language (Western Aphasia Battery Bedside Screen), Measurement of rehabilitation therapy utilization, intensity, and the number of post-acute care settings using Medicare Claims data (Skolarus, 2017), Depression (CES-D), Anxiety (NeuroQOL-Anxiety), Fatigue (NeuroQOL-Fatigue)