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Feinberg School of Medicine

# AI for Healthy Aging

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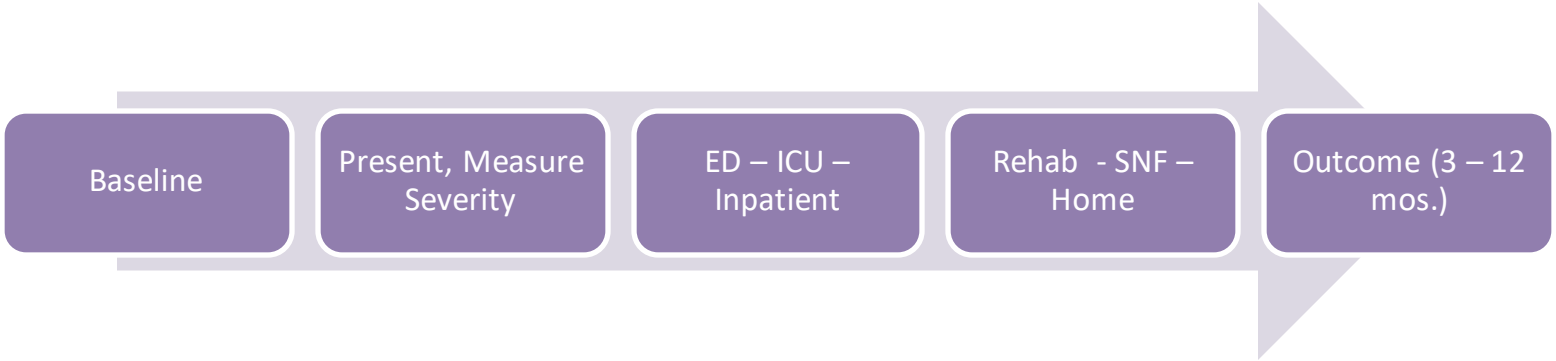
# An Aging America

- Background about ICH and an Aging America
- Outcomes Assessment – What does “healthy aging” mean?
- An aging America will be at higher risk for more diseases
- Using ML to predict discrete events:
  - Hematoma expansion
  - Seizures
- Using ML to predict multiple domains of HRQoL

# Models for Improving Outcomes in Acute Disease




**Therapies that improve outcomes in acute neurological disease in RCTs**:

tPA (alteplase) for acute ischemic stroke

Clot retraction (variable methods) for proximal stroke (vessel occlusion)

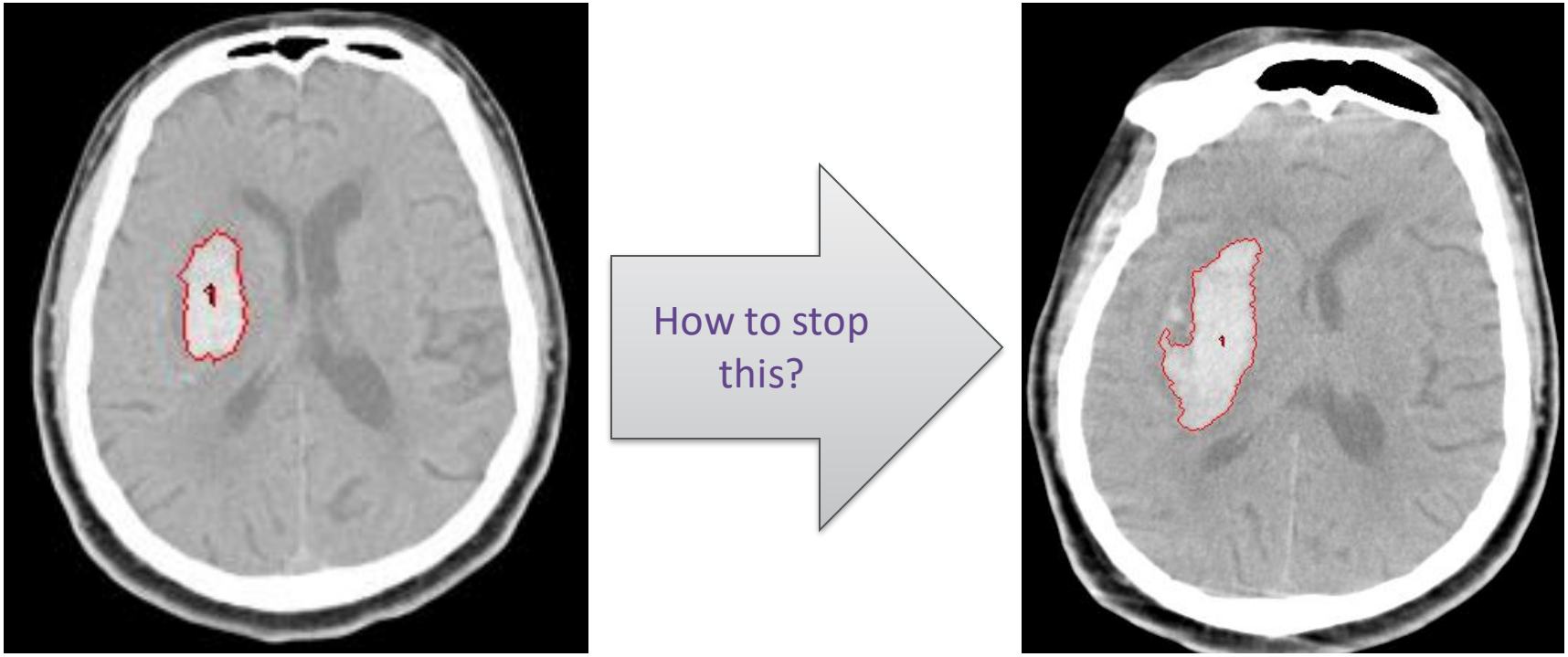
Blood pressure in acute ICH (a little, a few caveats)

Anticoagulant reversal for warfarin-related ICH

Early aneurysm clipping for ruptured brain aneurysms

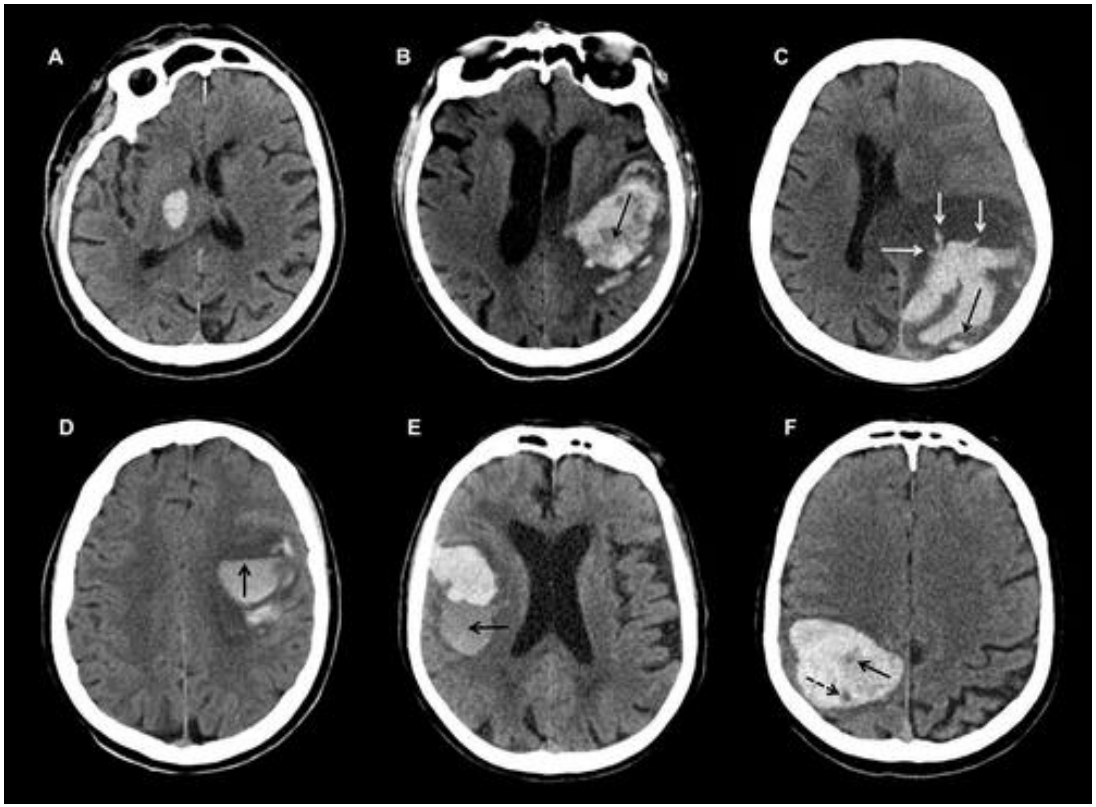
(2023) Surgery for superficial hematomas, but not deep hematomas

# Hematoma Growth Worsens Outcome




Hematoma Expansion by tested definition (e.g., >3 mL, >25% from initial volume) is predictive of worse patient outcome, by any definition

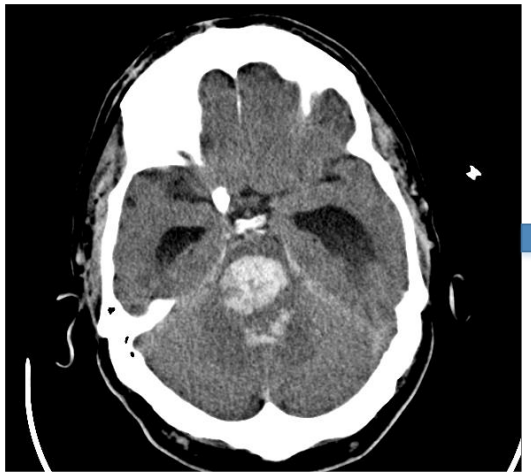
Standards for Detecting, Interpreting, and Reporting Noncontrast Computed Tomographic Markers of Intracerebral Hemorrhage Expansion




Representative examples of noncontrast computed tomographic markers of intracerebral hemorrhage expansion. (A) Regular shape (grade I) and homogeneous density (grade I). (B) Irregular shape (grade V) and heterogeneous density (grade V). Arrow indicates swirl sign. (C) Island sign (all arrows) and satellite sign (black arrow only). (D) Fluid level (arrow). (E) Blend sign (arrow). (F) Hypodensities (both arrows), swirl sign (both arrows), and black hole sign (dashed arrow only).

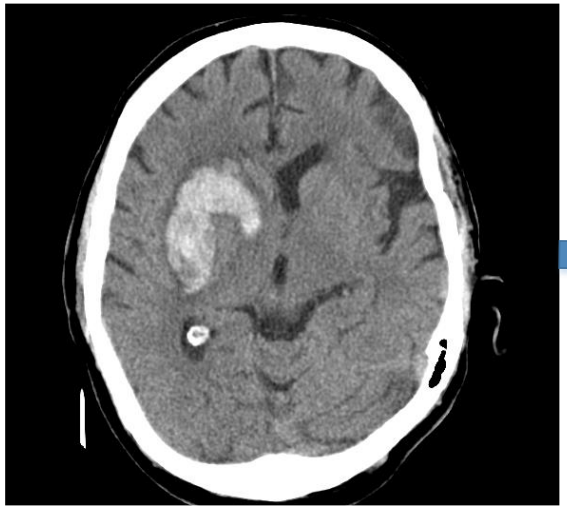


Annals of Neurology, Volume: 86, Issue: 4, Pages: 480-492, First published: 31 July 2019, DOI: (10.1002/ana.25563)

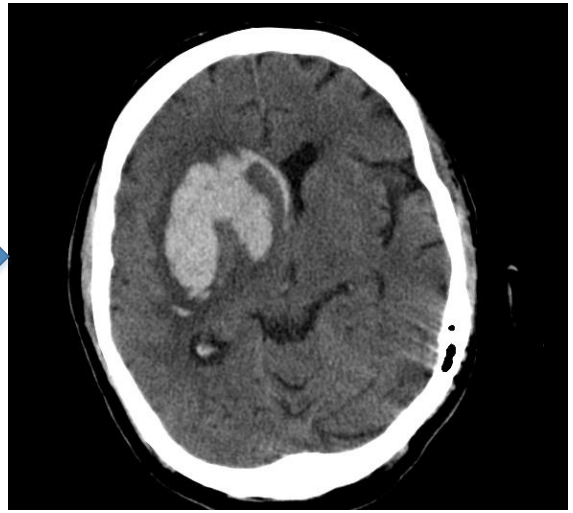


ICH070 presents with hypodensities in a 18.5 mL hematoma (“black hole ”). There is reduced platelet activity (427 aspirin reaction units, indicating an aspirin effect).

Hematoma Expansion (to 47.5 mL) is plainly visible 16 hours later.

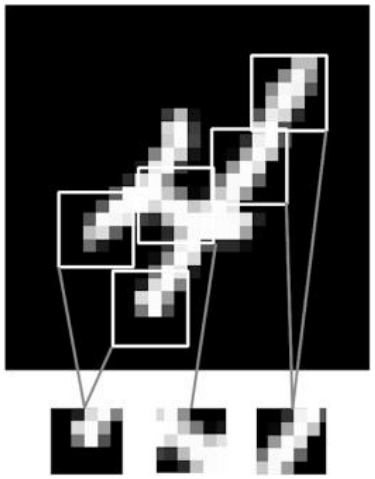


Patient ICH031 presents with hypodensities (“black hole”) in a 28 mL irregularly shaped hematoma. There is abnormal hemostasis (INR 2.4, 526 aspirin reaction units).



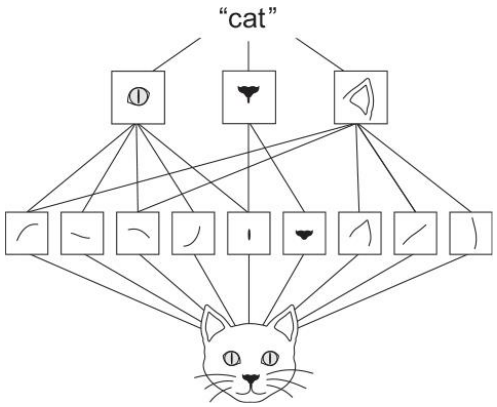
Follow-up CT shows hematoma growth to 44 mL.

# Convolutional Neural Networks



Form of deep learning that samples progressively more abstract information from image data.

Here, example of details from “4”.




Sampling of features of a cat allow abstraction

# Updated Framework

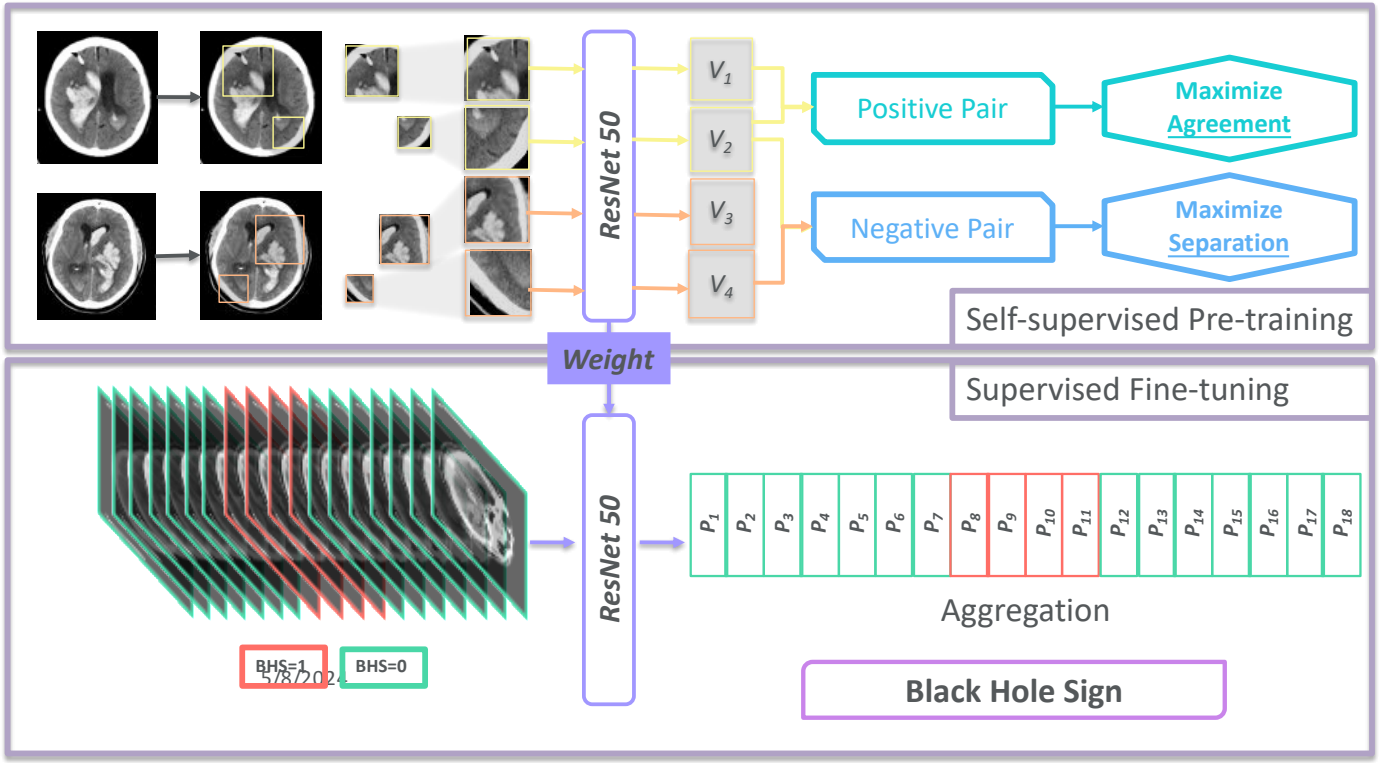



**Figure 10** Updated framework

# Results -- GradCAM++

## Gradient-weighted Class Activation Mapping++

- NUBAR -- ICH259

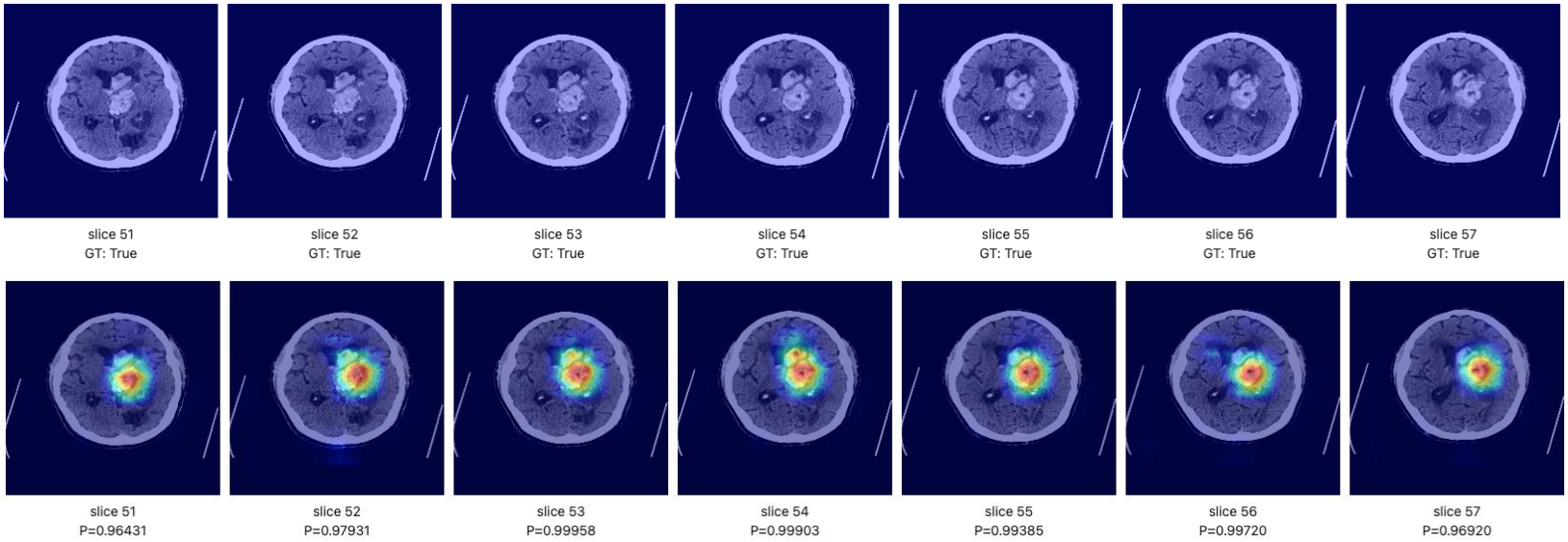



**Figure 13** A true positive case from NUBAR with GradCAM++ visualization

Chattopadhay, Aditya, et al. "Grad-cam++: Generalized gradient-based visual explanations for deep convolutional netw orks." *2018 IEEE winter conference on applications of computer vision (WACV)*. IEEE, 2018.

# Predicting Common Chronic Conditions

- Dementias will increasingly common in an aging America, 5.8m to 13.8 by 2050.
- Risk models, including ML/AI, might predict dementias.
- The actual incidence in the population is still (~5%) for prediction models
- Ongoing data harmonization project (R33 NS120245) will harmonize and curate 12 observational cohorts to improve dementia prediction

| Scale | Advantages | Disadvantages |
|---|---|---|
| **Modified Rankin Scale**, Glasgow Outcome Scale (and Extended) | High inter-rater reliability<br>Measures independence<br>Easy to obtain | Min. cognitive assessment<br>Not specific |
| Mortality | Easy to obtain in house, may be obtainable after discharge with search | Crude |
| NIH Stroke Scale | High inter-rater reliability<br>Clinically Useful<br>Quick examination | In-person only<br>Insensitive in coma<br>Min. cognitive assessment |
| Sickness Impact Profile | 136 questions | Long, subjective |
| Barthel Index | Comprehensive assessment of independence | More tedious |
| Tel. Interview Cognitive Status | Given remotely<br>Sensitive | Not specific |
| **Montreal Cognitive Assessment (MoCA)** | "Blind version" can be given remotely, new standard for PETAL Network | Not specific |
| **Euro-QOL 5D** | Many countries,<br>5 domains (mobility, pain, depression, self care, usual activities) | Only 3 categories for each domain |
| **NIH PROMIS and Neuro-QOL** | Web based (can be paper), validated for proxy entry, NIH imprimatur, numeric T score | Need someone to report outcomes |
| **NIH Toolbox** | Normed ages 3-85, comprehensive, validated | In-person assessment. Needs iPad and $500 app. |

# Patient Reported vs. Assessed


Labor intensive to input answers
Mostly patient reported

More labor intensive
Examination space

Validation studies may link specific instruments

# Modified Rankin Scale

0. No symptoms.

1. No significant disability; symptoms present but no limitations.

2. Slight disability, limitations in participation in usual social roles, but independent for daily living.

3. Moderate disability, need for assistance with some instrumental but not basic activities; able to walk independently with a device.

4. Moderate disability, need for assistance with some basic activities, but not requiring constant care.

5. Severe disability, bed bound.

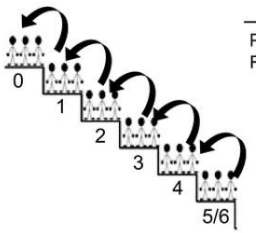
6. Dead.

Not independent
Rankin = 4


Social roles limited but able to ambulate
Rankin = 3

# Dichotomous Outcomes Have Low Power

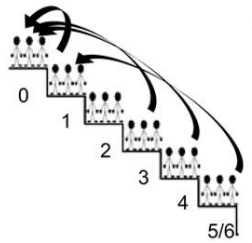
Model 1: Neuroprotective effect




| | 0 | 1 | 2 | 3 | 4 | 5/6 |
|---|---|---|---|---|---|---|
| Placebo | 16.7 | 16.7 | 16.7 | 16.7 | 16.7 | 16.7 |
| Rx | 22.1 | 16.7 | 16.7 | 16.7 | 16.7 | 11.2 |

| Analysis Technique | Sample Size |
|---|---|
| Shift analysis | 1200 |
| Dichotomized 0-1 v 2-6 | 2508 |
| Dichotomized 0-2 v 3-6 | 3956 |

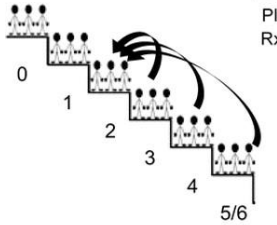
Model 2: Early recanalization effect




| | 0 | 1 | 2 | 3 | 4 | 5/6 |
|---|---|---|---|---|---|---|
| Placebo | 16.7 | 16.7 | 16.7 | 16.7 | 16.7 | 16.7 |
| Rx | 24.7 | 16.7 | 14.7 | 14.7 | 14.7 | 14.7 |

| Analysis Technique | Sample Size |
|---|---|
| Shift analysis | 1364 |
| Dichotomized 0-1 v 2-6 | 1200 |
| Dichotomized 0-2 v 3-6 | 2246 |

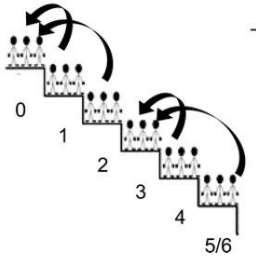
Model 3: Late recanalization effect




| | 0 | 1 | 2 | 3 | 4 | 5/6 |
|---|---|---|---|---|---|---|
| Placebo | 16.7 | 16.7 | 16.7 | 16.7 | 16.7 | 16.7 |
| Rx | 16.7 | 16.7 | 24.9 | 13.9 | 13.9 | 13.9 |

| Analysis Technique | Sample Size |
|---|---|
| Shift analysis | 3342 |
| Dichotomized 0-1 v 2-6 | Infinity |
| Dichotomized 0-2 v 3-6 | 1200 |

Model 4: Benefits cluster at unexpected transitions




| | 0 | 1 | 2 | 3 | 4 | 5/6 |
|---|---|---|---|---|---|---|
| Placebo | 16.7 | 16.7 | 16.7 | 16.7 | 16.7 | 16.7 |
| Rx | 27.4 | 9.5 | 13.1 | 27.4 | 9.5 | 13.1 |

| Analysis Technique | Sample Size |
|---|---|
| Shift analysis | 1200 |
| Dichotomized 0-1 v 2-6 | 5660 |
| Dichotomized 0-2 v 3-6 | Infinity |

The four analyzed treatment effect models.

For each, the staircase schematic shows the pattern of the treatment effect, the upper table shows the percentile distribution of outcomes among the six Rankin levels in the treatment and control groups, and the bottom table shows the sample size required by each of the endpoint analytic techniques.

In FASTEST, the FDA insisted on an ordinal analysis of mRS 0-2, 3, 4-6.

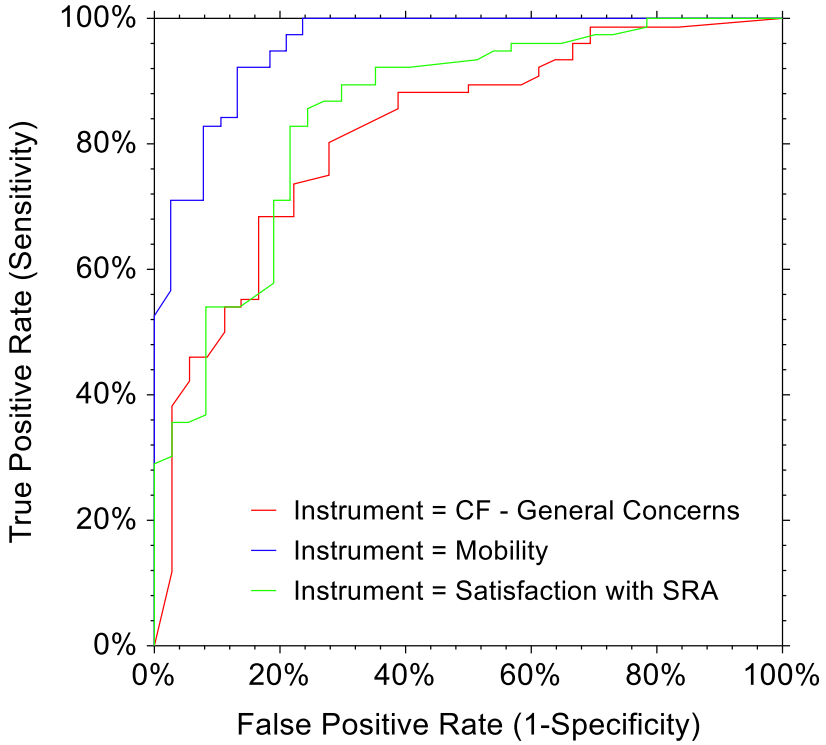
Saver J, Gornbein J. Neurology 2009;72:1310-1315

# Analysis of Neuro-QOL/PROMIS/Toolbox

- Results presented in continuous, numeric scores
- Appropriate for usual parametric or non-parametric analyses
- For data over time, mixed models or repeated measures may be used

- Cross-walked to other standard outcomes (PROsettastone website)

# “Good outcome” is domain specific



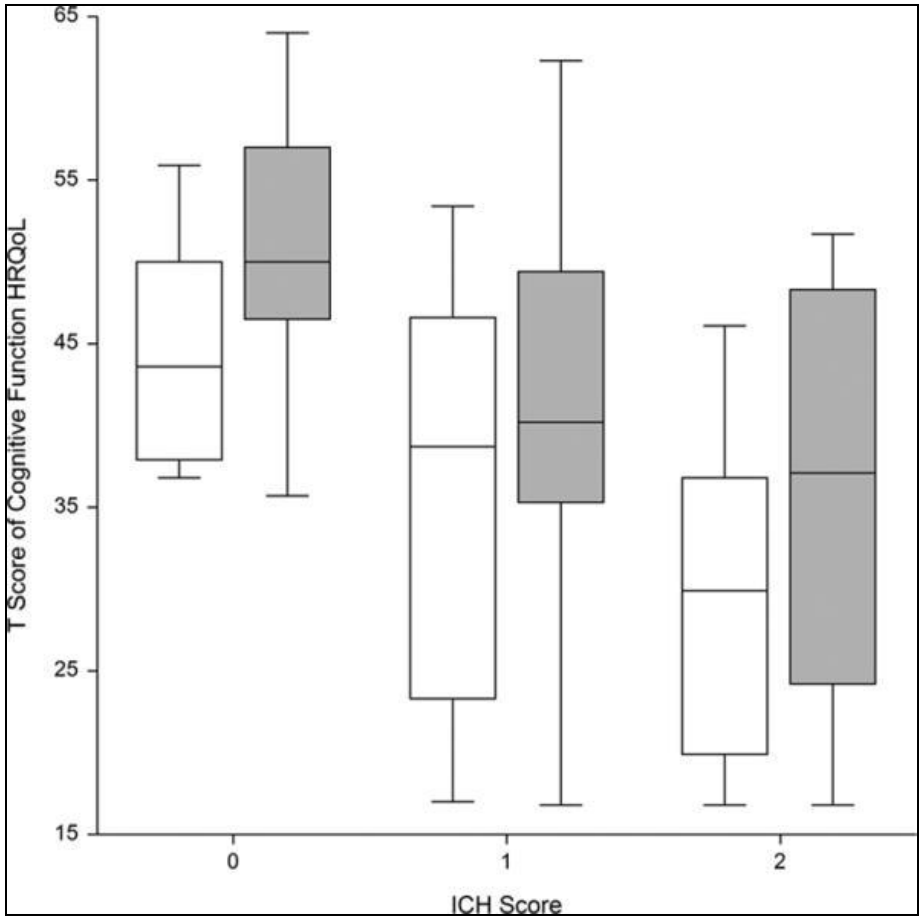

Receiver Operating Characteristic Curves of specific domains of Neuro-QOL vs. “good outcome” for survivors of ICH and SAH at one month.

Area under the curve for mobility (blue, 0.957) is greater than for satisfaction with social roles and activities (SRA, green line, 0.850) and cognitive function (CF, red line, 0.819).

“Good outcome” is less informative of cognitive function or social function. N=63.

SRA – social roles and activities
CF – cognitive function

# Prophylactic Levetiracetam Specifically Predict Worse Cognitive HRQoL




If you only study mRS or motor function, there is no difference. (Of course there isn't.)

**Prophylactic Seizure Medication and Health-Related Quality of Life After Intracerebral Hemorrhage.**
Naidech, Andrew; MD, MSPH; Beaumont, Jennifer; Muldoon, Kathryn; Liotta, Eric; Maas, Matthew; Potts, Matthew; Jahromi, Babak; MD, PhD; Cella, David; Prabhakaran, Shyam; MD, MS; Holl, Jane; MD, MPH

Critical Care Medicine. 46(9):1480-1485, September 2018.
DOI: 10.1097/CCM.0000000000003272

Figure 1 . Box plot of T-score for cognitive function health-related quality of life (HRQoL) at 3 mo, stratified by prophylactic levetiracetam (white) or no prophylactic levetiracetam (shaded).

Prophylactic levetiracetam was associated with lower HRQoL, regardless of severity of injury (Intracerebral Hemorrhage [ICH] Score).

Propylactic levetiracetam was not associated with mobility HRQoL or mRS

# Anti-Seizure Medication

## Ideal: Only give anti-seizure medication to patients who are definitely going to have a seizure

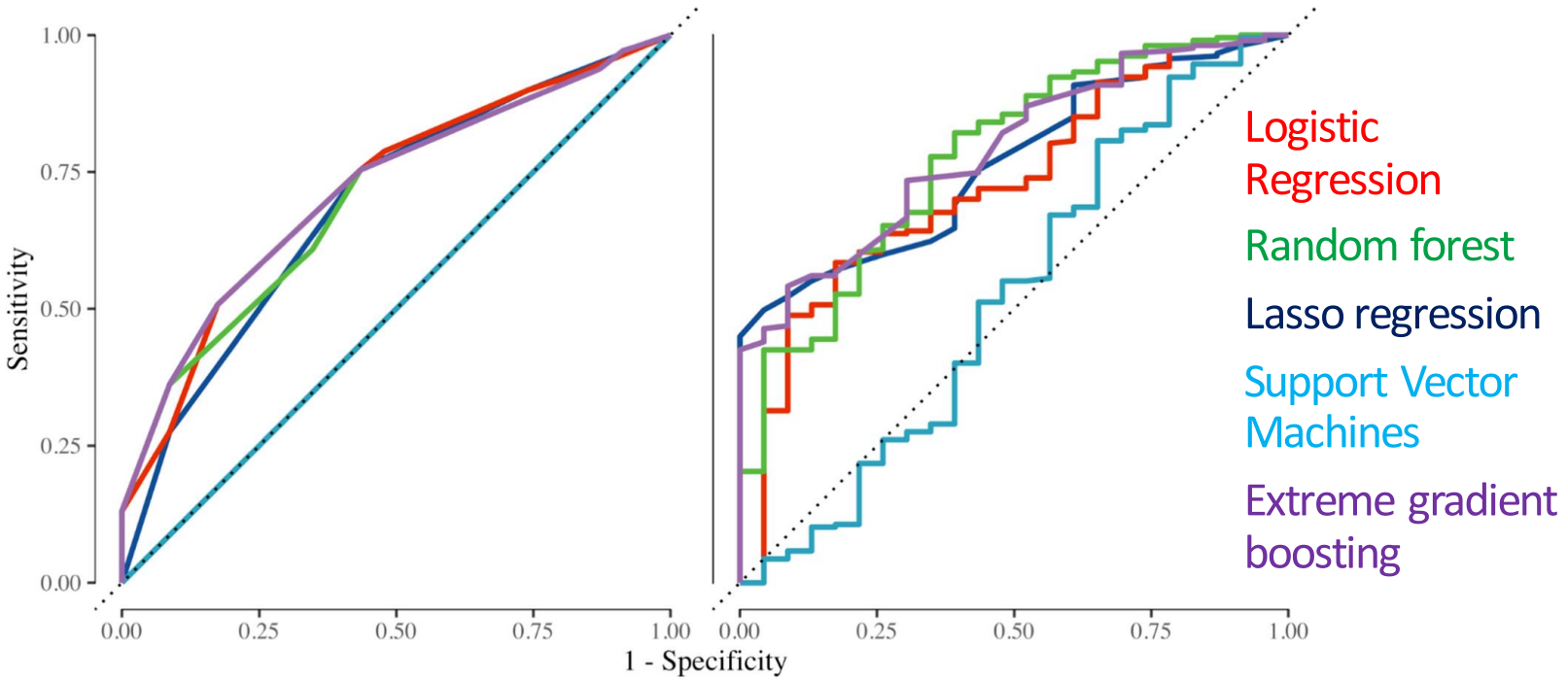
- Current prediction rules are only moderately predictive
- Machine learning of common predictors (hematoma location, age, hematoma volume) are a little better
- Electrocephalography (EEG) predictive

# Predicting Seizures After ICH from Clinical Criteria

## Data from Northwestern and Hopkins (courtesy R Faigle)
## Lasso and Extreme Gradient Boosting were more predictive

CAV – Cortical hematoma
Age < 65,
Volume > 10 mL

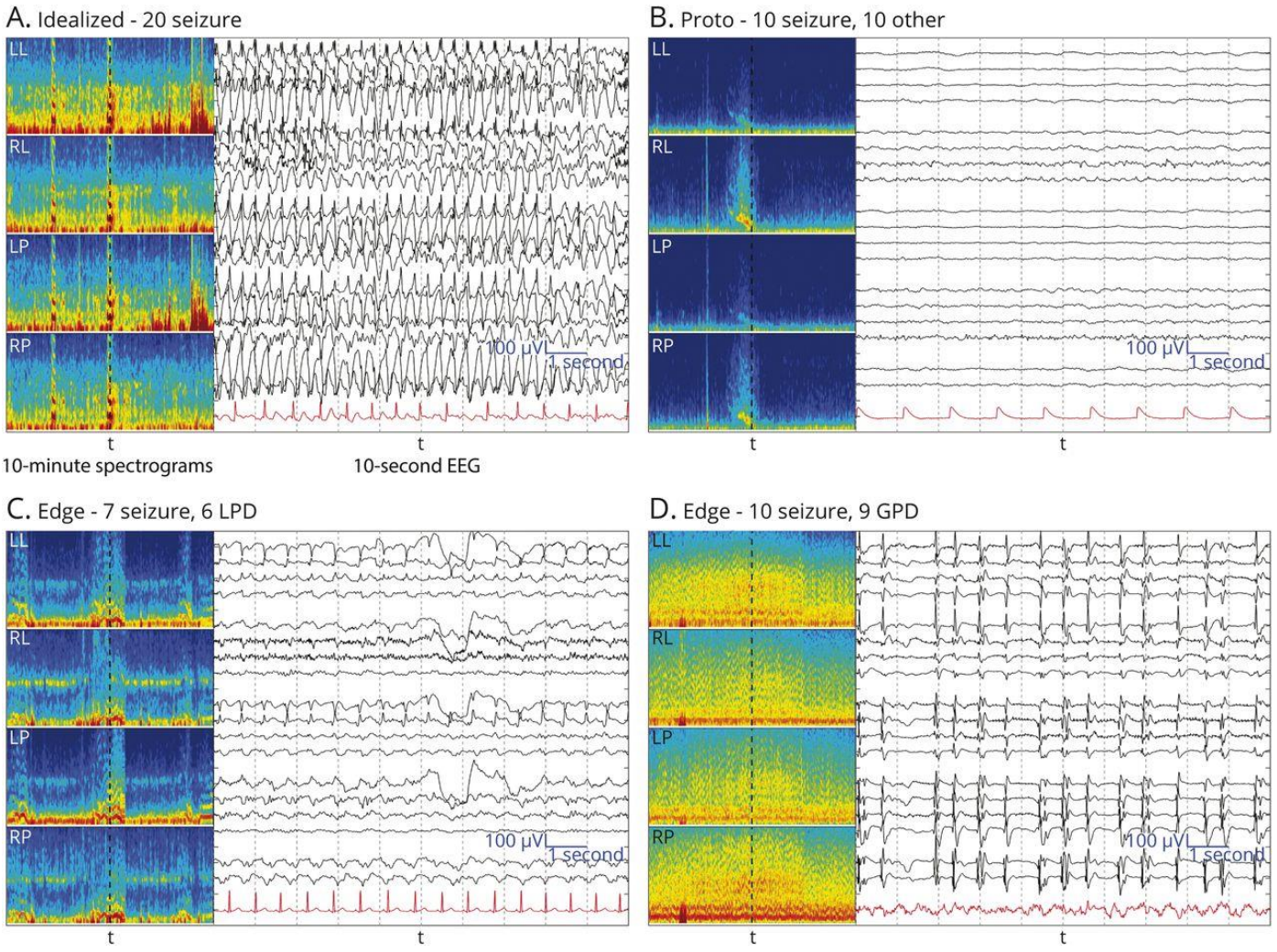
CAV + antiplatelet, anticoagulant,
GCS, INR, Systolic BP





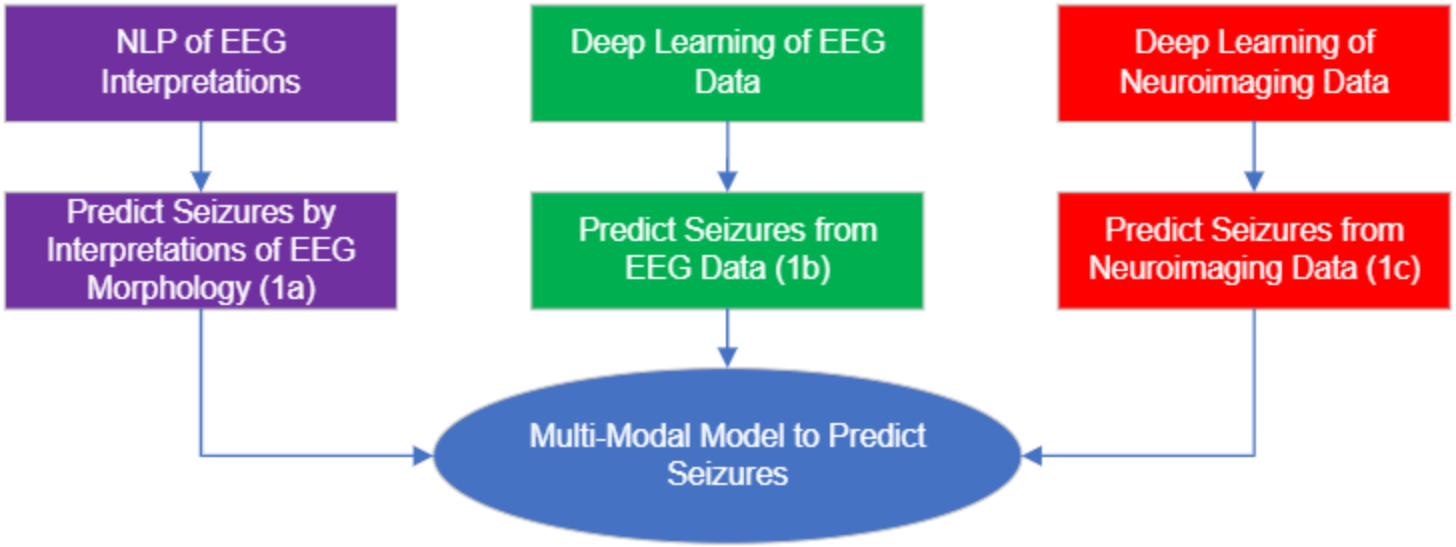

Neurocrit Care 2022 Aug;37(Suppl 2):322-327. doi: 10.1007/s12028-022-01470-x.

# Figure 2 Selected EEG Examples for Class Seizure




**Jin Jing et al. Neurology 2023;100:e1737-e1749**

# Ideal: Give Prophylactic Anti-Seizure Rx Iff (if and only if) the Patient Will Have a Seizure



# Health Neurological Aging

- "A healthy patient is one who has been inadequately studied"
- Defining "healthy" aging will need a lot of data from a variety of sources, several of which may not be routinely collected
  - EEG
  - Cognitive
  - Imaging
- Will need a paradigm shift from treating individual diseases to global outcomes
- Opportunity where parametric statistics leaves off