

# **Optimization of the Neuropathologic Assessment of AD**

NACC Project 2012

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# Contributors

## Central Sites/Central Evaluators

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## Participating Sites/Participating Evaluators

- 1. Massachusetts General Hospital/Frosch
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- 4. University of Kentucky/Nelson
- 5. Rush University/Schneider
- 6. Northwestern University/Bigio
- 7. Washington University/Cairns
- 8. Banner Health/Beach
- 9. University of California, Los Angeles/Vinters
- 10. University of Washington (now Utah)/Sonnen

**NACC: Sarah Monsell, Andrew Zhou, and Bud Kukull**

**UW: Aimee Schantz**

# NACC Project 2012

- “As part of fulfilling this charge from the NIA, we realized that we had no consensus on optimal methods for tissue staining and evaluation of AD neuropathologic changes ... this lack of consensus is a potentially serious limitation ...”
- “The goal of the proposed research is to fill this important gap in our knowledge by undertaking a collaborative study of neuropathologic assessment among 10 AD Centers.”

# Aims

1. Assess agreement among neuropathologists using the new NIA-AA criteria by current practice (local staining protocol and local reader)
2. Estimate source (staining protocol and/or reader) and magnitude of variation
3. Assess agreement for a scanned slide set with current practice

# Statistical analysis

- Outcomes of interest
  - A, B, & C scores
  - ABC score
- Measuring agreement
  - Weighted kappa
    - Accounts for agreement by chance
    - Ordinal data
    - Squared distance weights
    - Agreement between any two readers (paired kappa)
  - Average of the weighted kappas

# Statistical analysis

- Interpreting Kappa

  - .21 ≤ k ≤ .40 : fair

  - .41 ≤ k ≤ .60 : moderate

  - .61 ≤ k ≤ .80 : substantial

  - .81 ≤ k ≤ 1.00: almost perfect

- Measure of spread/variation

  - 95% CIs cannot be calculated under the alt. hypothesis

  - Complicated correlation structure

  - Histograms of paired k

# Aim 1

- **Variation:** Reader & staining protocol
- **Readers:** Sites (1 NP at each of 10 ADCs)
- **Slides:** Individually stained slides from own site (1 set of 14 subjects/ADC)

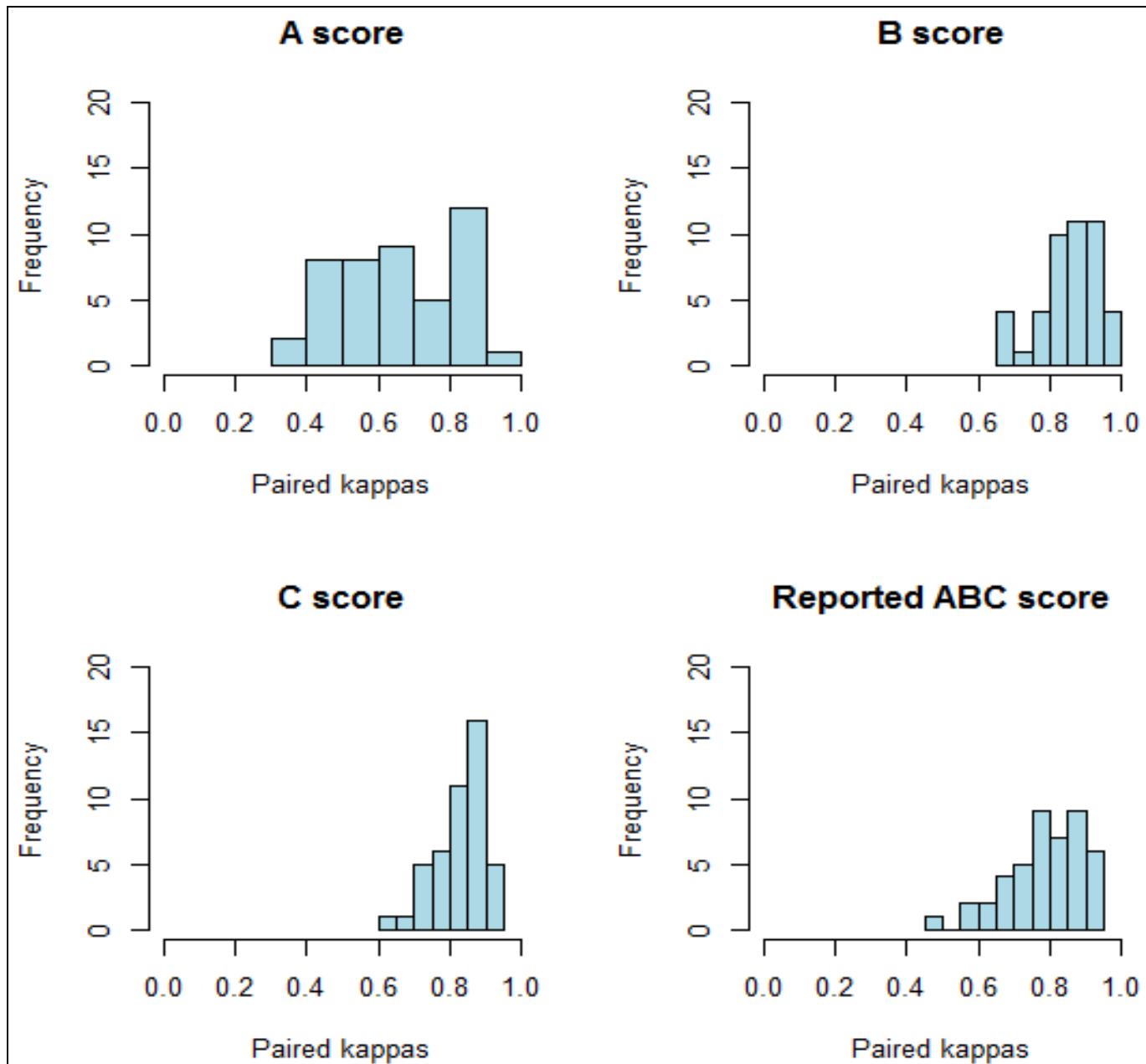
# Aim 1

- **Variation:** Reader & staining protocol
- **Readers:** Sites (1 NP at each of 10 ADCs)
- **Slides:** Each site stained of a set of 14 cases of unstained slides

	Average of paired k
Reported ABC score	0.88
A score	0.84
B score	0.70
C score	0.77

NOTE: One typo in the reported ABC score and one typo in the B score were corrected





# Aim2

- Variation: Reader
- Readers: Sites (1 NP at each of 10 ADCs)
- Slides: Single set of stained slides from 4 cases shipped around US to each site

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- **Readers:** Sites (1 NP at each of 10 ADCs)
- **Slides:** Single set of stained slides from 4 cases shipped around US to each site

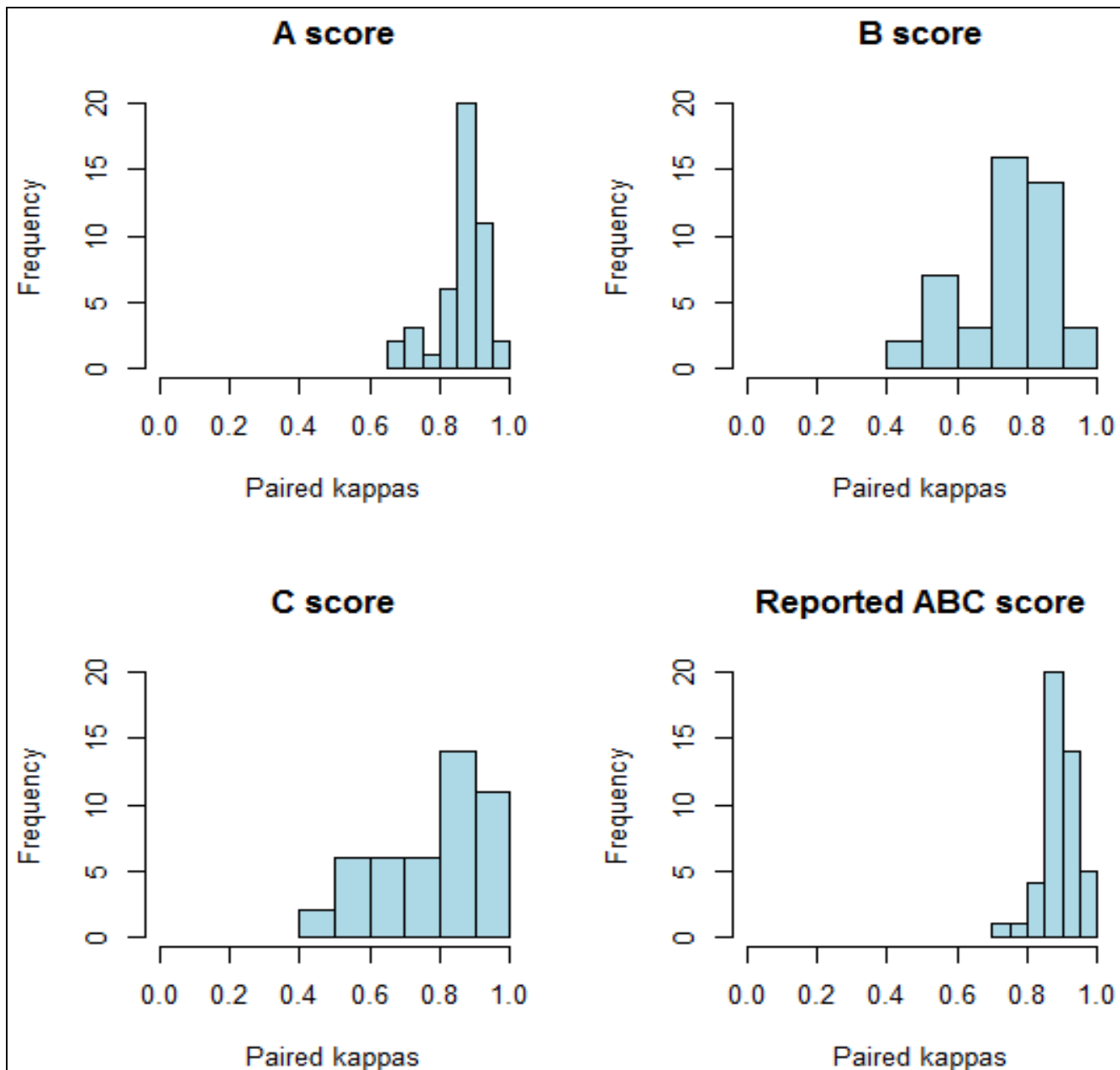
	Single set of slides
	Average of paired k
Reported ABC score	0.67
A score	0.61
B score	0.71
C score	0.78

# Aim2

- **Variation:** Reader
- **Readers:** Sites (1 NP at each of 10 ADCs)
- **Slides:** Single set of stained slides from 4 cases shipped around US to each site

	Single set of slides	Individually stained slides <sup>†</sup>
	Average of paired k	Average of paired k
Reported ABC score	0.67	0.89
A score	0.61	0.87
B score	0.71	0.85
C score	0.78	0.80

<sup>†</sup>Read by sites; restricted to those subjects in the single-slide set



# Aim 2

- Variation: Stain protocol
- Readers: Central
- Slides: Site stained slides from each of 10 ADCs for 4 cases (40 reads)

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- **Variation:** Stain protocol
- **Readers:** Central
- **Slides:** Site stained slides from each of 10 ADCs for 4 cases (40 reads)

	Central read
	Average of paired k
Reported ABC score	0.77
A score	0.72
B score	0.81
C score	0.86

†Read by sites; restricted to those subjects in the single-slide set

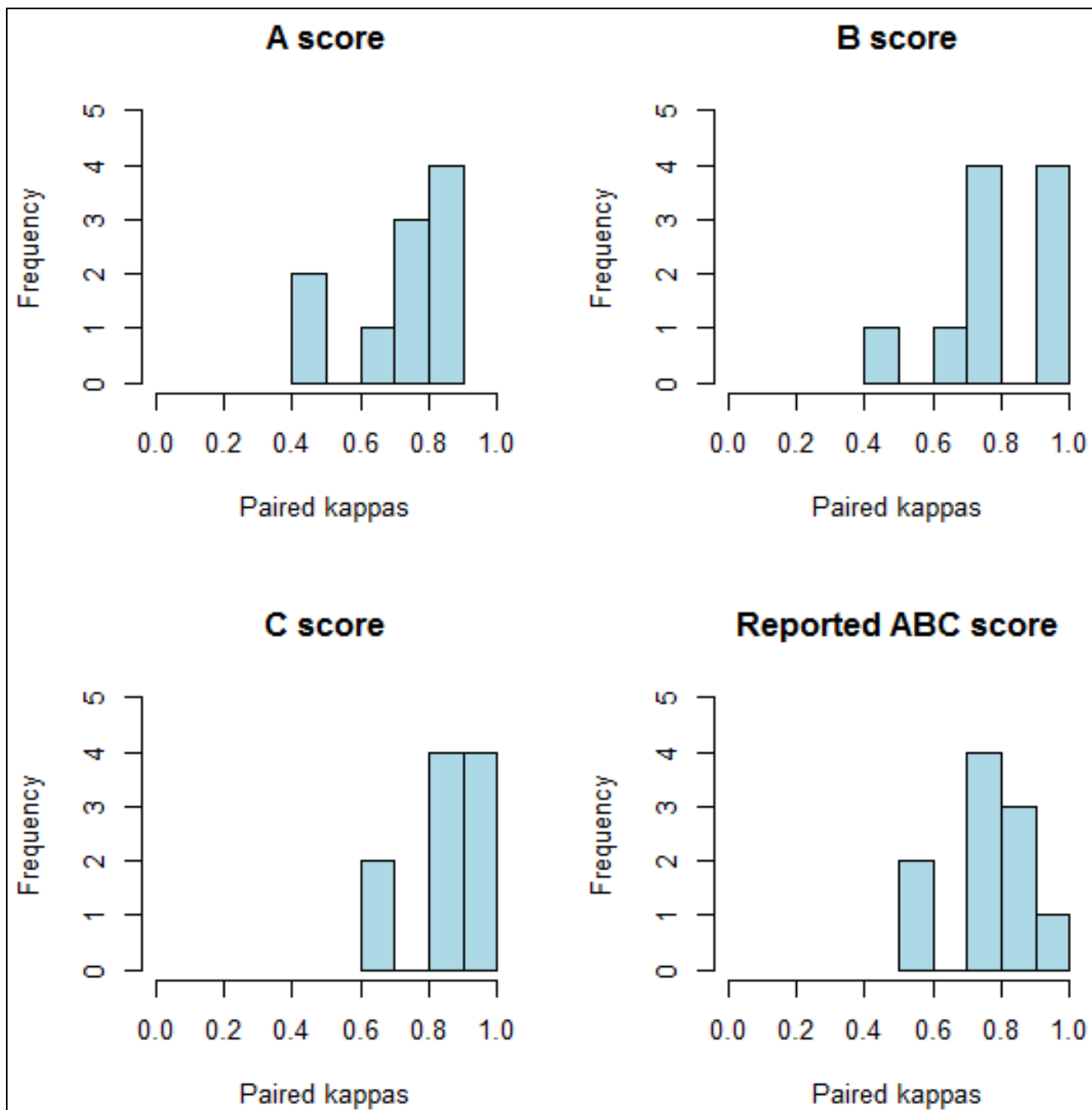
# Aim 2

- **Variation:** Stain protocol
- **Readers:** Central
- **Slides:** Site stained slides from each of 10 ADCs for 4 cases (40 reads))

	Central read	Site read <sup>†</sup>
	Average of paired k	Average of paired k
Reported ABC score	0.77	0.89
A score	0.72	0.87
B score	0.81	0.85
C score	0.86	0.80

<sup>†</sup>Read by sites; restricted to those subjects in the single-slide set





# Aim 3

- **Variation:** Image vs. slide
- **Reader:** Sites (1 NP at each of 10 ADCs)
- **Slides:** Whole slide imaging (Aperio) of stained slides from 8 cases

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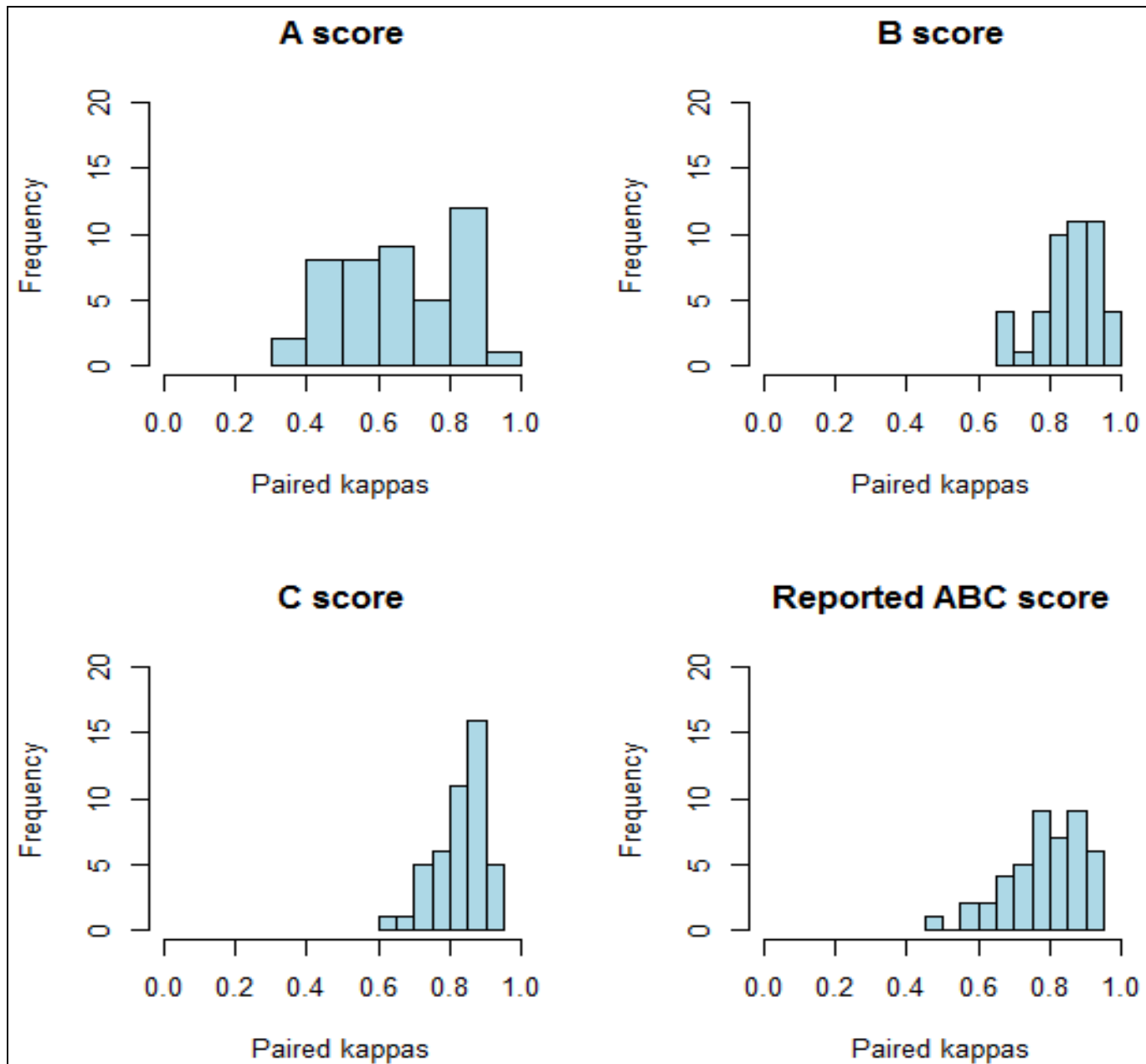
	Scanned slides
	Average of paired k
Reported ABC score	0.79
A score	0.66
B score	0.86
C score	0.83

# Aim 3

- **Variation:** Image vs. slide
- **Reader:** Sites (1 NP at each of 10 ADCs)
- **Slides:** Whole slide imaging (Aperio) of stained slides from 8 cases

	Scanned slides	Individually stained slides <sup>†</sup>
	Average of paired k	Average of paired k
Reported ABC score	0.79	0.83
A score	0.66	0.81
B score	0.86	0.79
C score	0.83	0.76

<sup>†</sup>Read by sites; restricted to those subjects in the scanned single-slide set



# Aim 3

- Web application which features the delivery of whole slide images
- Side-by-side online data collection
  - <https://staff.washington.edu/jhenrik/applications/ADAssessment/>

# Summary

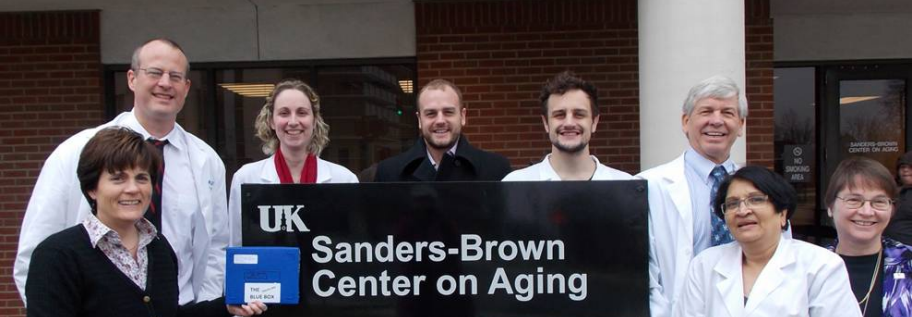
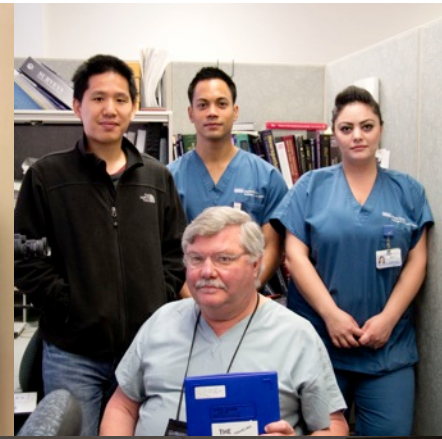
## From highest to lowest agreement

- **Best:** Individual pathologists reading slides stained at their own institution (**kappa 0.88**)
- **Worse:** Central read of slides stained at multiple institutions (**kappa 0.77**)
- **Worst:** Individual neuropathologists reading slides stained at multiple institutions (**kappa 0.67**)

# Summary (con't)

- **Comparable:** Reading glass slides (**kappa 0.83**) or WSI (**kappa 0.79**)
- **Last Step:** We are expanding the dataset for the least favorable approach from 4 cases read at each of 10 sites (kappa 0.67) to 8 cases at each of 10 sites.





***Thank you***