CLARiTI

ADRC Consortium for Clarity in ADRD Research Through Imaging

NACC Spring Meeting
Imaging Core Session
May 6, 2024

Study Aims

mPI team: Johnson, Mormino, Foroud, Rabinovici, Okonkwo, Rivera-Mindt, Dickerson, Wolk, Kukull

Synopsis

Vision: Accurate and comprehensive biologic diagnoses and staging to treat the multiple intersecting causes of cognitive impairment within ADRD

GOAL: Create individual etiologic profiles from imaging and plasma

- ATN imaging and plasma study superimposed on existing longitudinal UDS
- 2,000 clinical core participants; 60% impaired, 40% unimpaired with risk factors
- Diverse representation for generalizable science
- Two time points [2-3 years apart]
- *Heterogeneity* is the focus: syndromes and multi-pathologies

CLARiTI

Component Lead Investigators (partial list of 47 investigators)

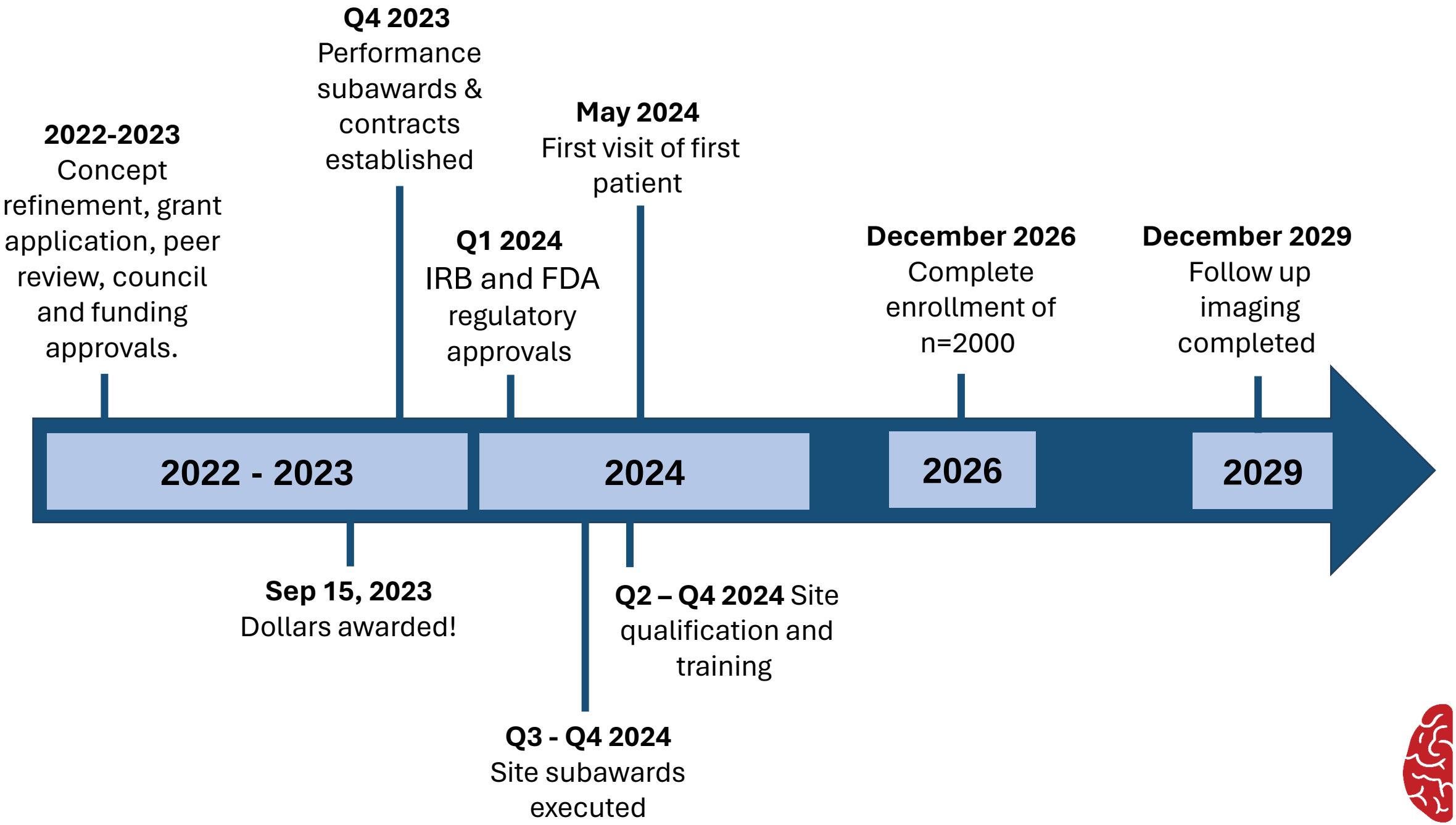
Johnson/Mormino/Biber: Admin
Rivera-Mindt/Okonkwo: Inclusion
Biber/Kukull/Toga: Image-Data informatics
Keene: Neuropath
Rabinovici: PET image reads
Shibata: MRI scoring

Rahman-Filipiak/Clark/Chin: Disclosure
Rosen/Thompson: neuropath MRI templates; AI classification
Jagust/Jack: SCAN
Villemagne: PET harmonization
Detre: Advanced MRI methods
Dage/Foroud: Biofluid mgmnt, assays

Donohue: Stats
Betthauser: Biomarker time
Jones: FDG analysis
Hohman: Data harmonization integration
Kantarci: LBD image analysis

Industry collaborators

- LMI
- Lantheus/Cerveau
- Enigma
- Lilly
- Flywheel
- GE
- Siemens
- Philips


2022-2023
Concept refinement, grant application, peer review, council and funding approvals.
Q4 2023
Performance subawards & contracts established
Q1 2024
IRB and FDA regulatory approvals
May 2024
First visit of first patient
December 2026
Complete enrollment of n=2000
December 2029
Follow up imaging completed
2022 - 2023
2024
2026
2029
Sep 15, 2023
Dollars awarded!
Q3 - Q4 2024
Site subawards executed
Q2 – Q4 2024 Site qualification and training

Study status

- IRB approval (V2) and FDA IND permission to proceed
- Site sub-contracting underway in May 2024 (two phases)
- Site training (please don't start until your site is fully trained)
- NACC is building the database
- Tools being created to facilitate uploads

Cores/components:

- Inclusion Core: presenting today during CLARiTI breakout session
- Disclosure core: presenting today during CLARiTI breakout session and during Clinical Core session tomorrow

Update in the next few slides

- Advanced MRI
- FDG
- Biofluids
- Neuropath (fall 2024 ADC meeting)

CLARiTI MRI protocol

- All CLARiTI MRI studies:
  - **SCAN T1w**
  - **SCAN FLAIR**
- OPTIONAL neurodegeneration-focused ‘advanced’ MRI platform
  - QSM and SWI aligned with the new ISMRM guidelines (product sequences)
    - *Quantify microhemorrhages (cSVD/amyloid angiopathy) and iron deposition (DLB, etc.)*
  - **Motion corrected T1w** (research* sequences)
    - *Assess the impact of participant motion and its correction on morphometry metrics*
  - Long-label, long-PLD background-suppressed **3D ASL** (product or research* sequences)
    - *High quality CBF maps to evaluate ADRD-related patterns of hypoperfusion*
    - *Evaluate synthetic FDG-PET based on ASL+T1w-MRI*
  - **Multi-PLD ASL**
    - *Evaluate potential for improved accuracy of CBF quantification*
  - **Sites may choose to do one or more or none of the advanced sequences**
  - **Additional ‘advanced’ sequences can be considered for future evaluation**

*some research sequences will require an MTA for distribution

CLARiTI MRI protocol

1. SCAN T1-w (~5 min)
2. SCAN FLAIR (~5 min)

*Remainder of the session is at site discretion

*Optional

Neurodegeneration focused "advanced MRI"
One or more of these menu options:

3. QSM with new ISMRM recs
4. Motion corrected T1w (~7 min)
5a. LL BS 3D ASL (~5 min)
5b. Multi-PLD ASL (~3.5 min)

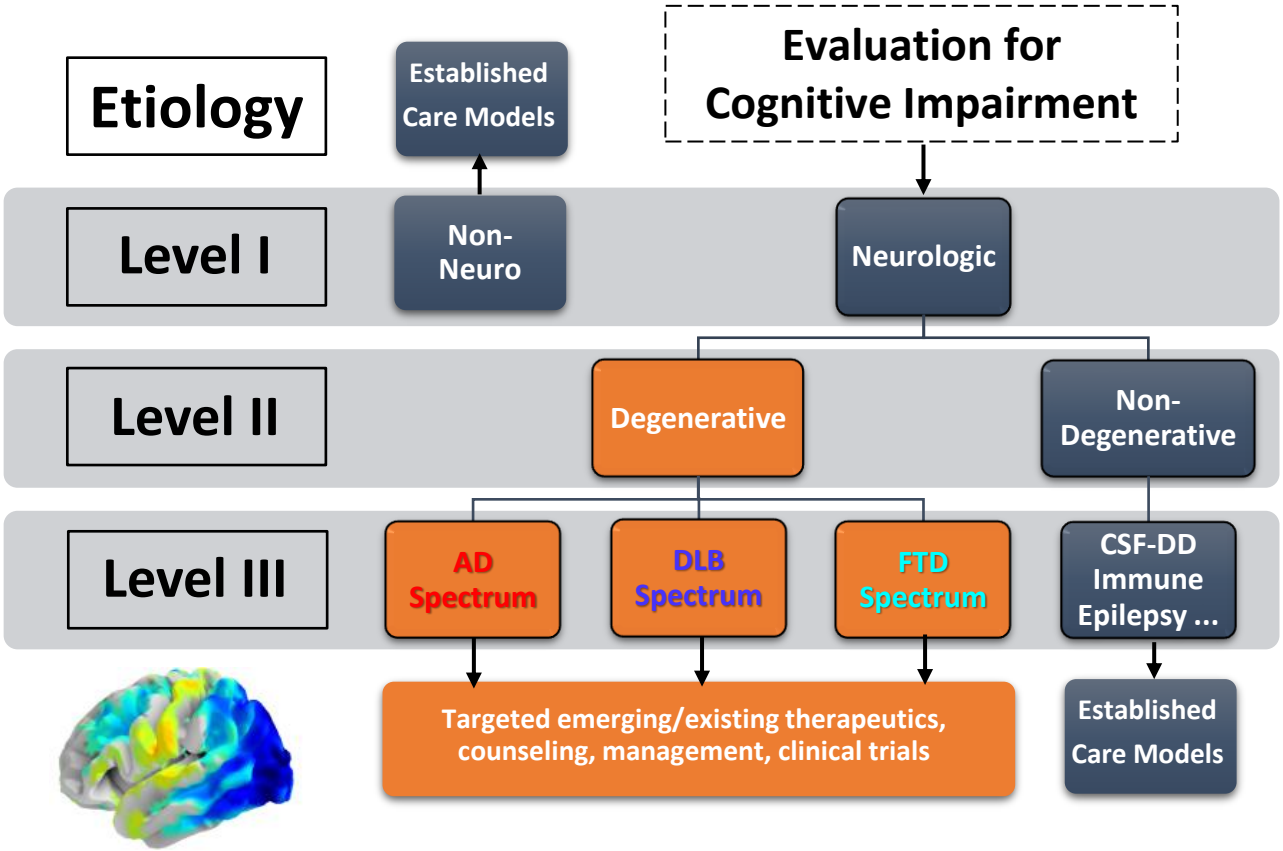
*Optional

Site Preference for additional sequences

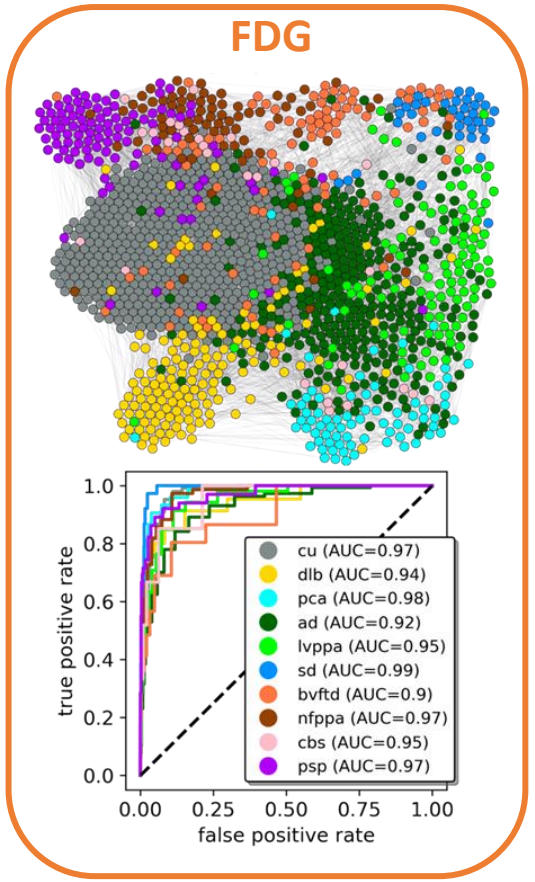
- Other SCAN MRI sequences
- Other local sequences

FDG can answer clinically relevant questions across AD/ADRD

Jones, D., Lowe, V., Graff-Radford, J. *et al.* A computational model of neurodegeneration in Alzheimer's disease. *Nat Commun* **13**, 1643 (2022).

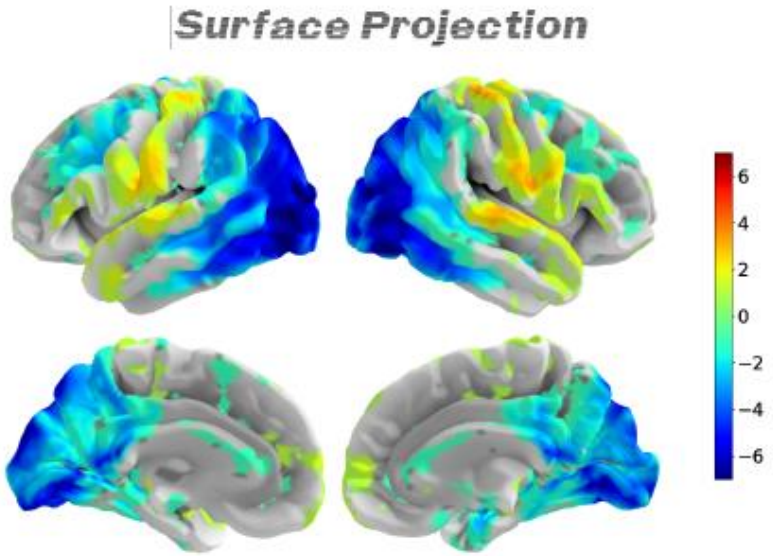


AD or DLB?



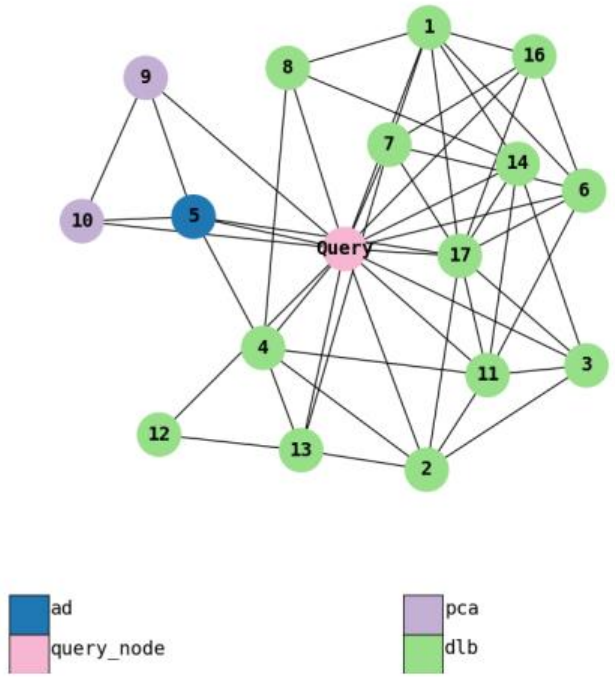
Automated vs. Visual Reading of Pathology Confirmed Cases

Path: AD
Clinical: PCA



Automated vs. Visual Reading of Pathology Confirmed Cases

Neighborhood Graph

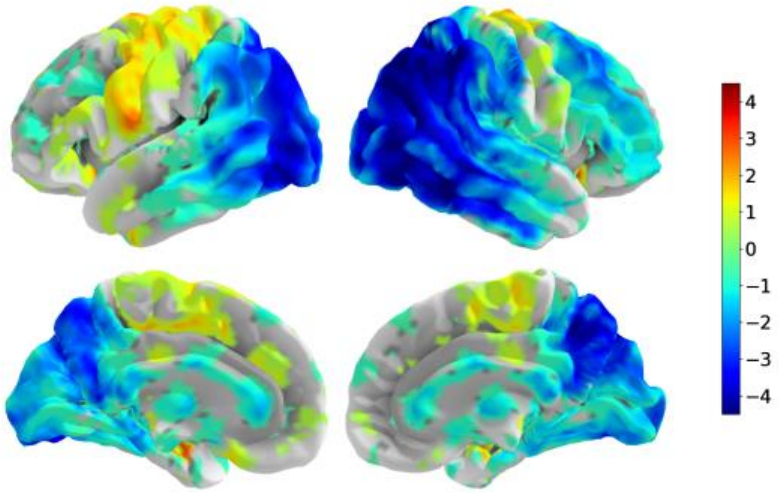


Node Label Associations

label	neighborhood	database	log_odds	p-value	direction
dlb	0.81	0.09	3.7	<0.0001	enriched
cu	0.0	0.33	-2.78	<0.01	depleted

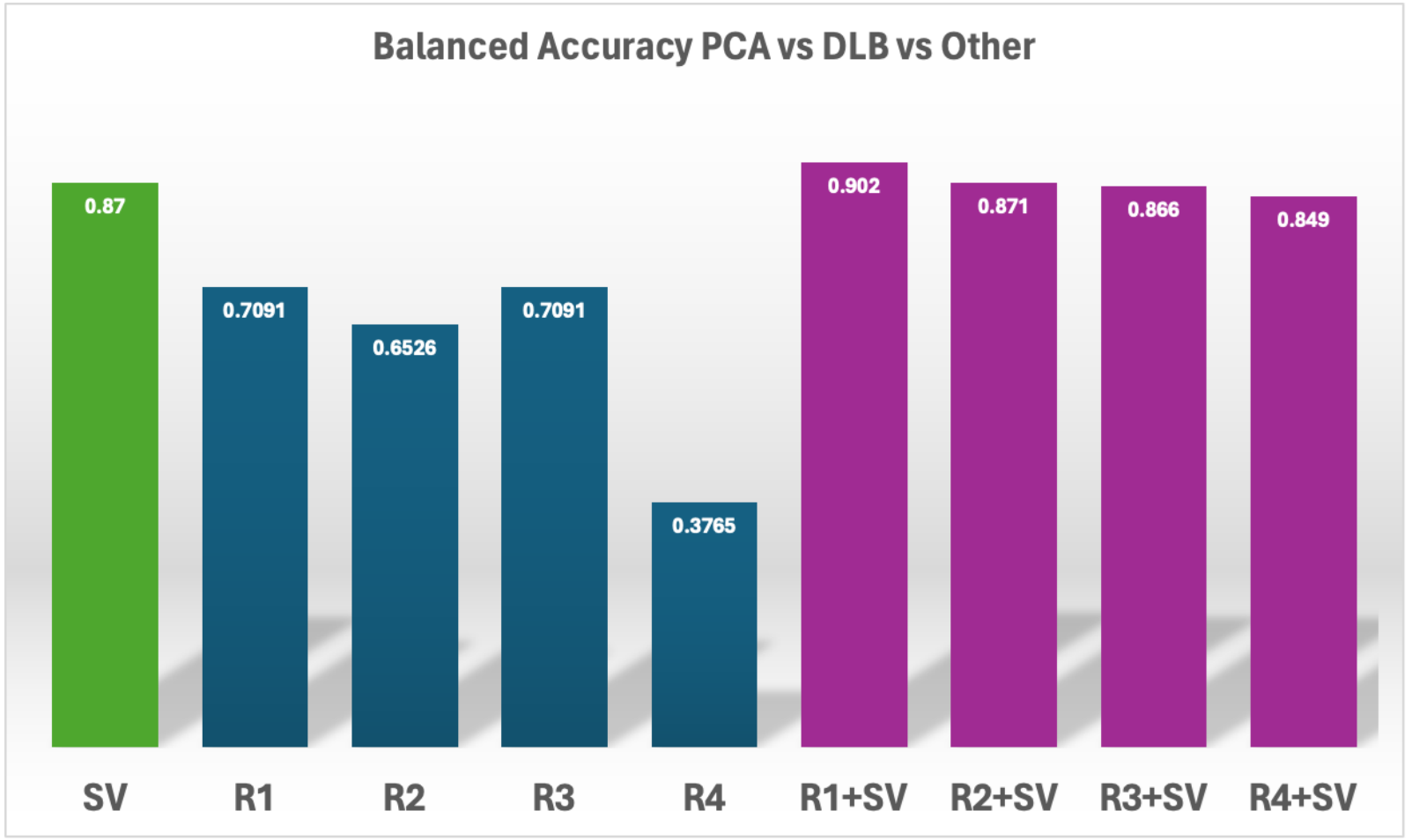
Path: LBD
Clinical: DLB

Surface Projection



Automated vs. Visual Reading of Pathology Confirmed Cases

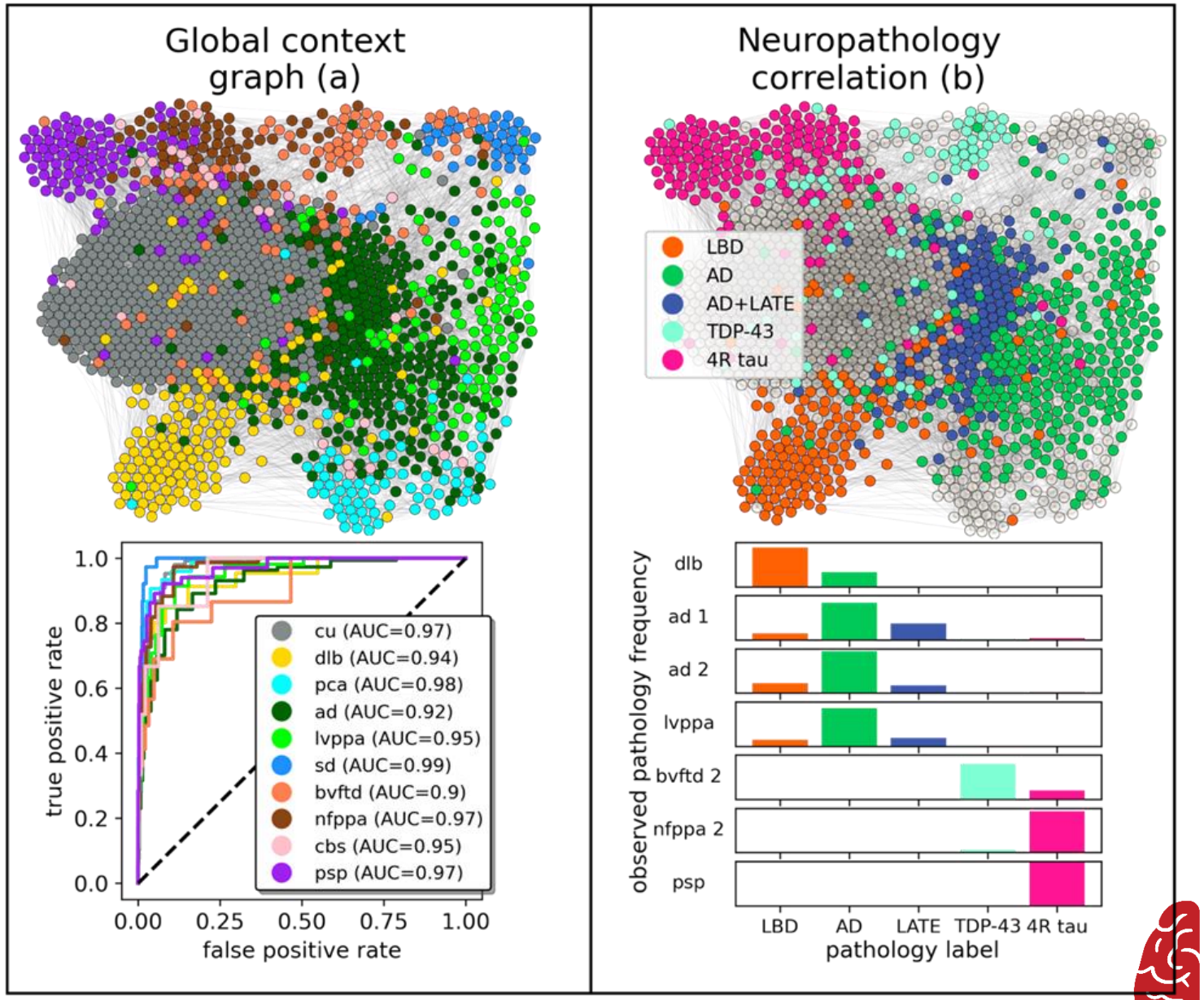
Readings of N = 67 Autopsy Confirmed Cases



Radiologist Alone

Radiologist with StateViewer

The entire AD/ADRD Clinical and Pathologic Spectrum is Captured by FDG-PET

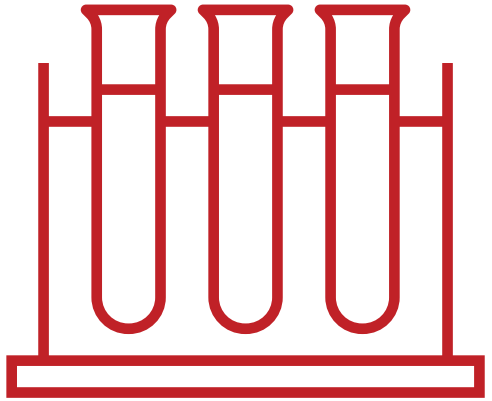


FDG

- Useful in people with symptoms
- Analyses are led by Dave Jones, MD and team at Mayo ADRC
  - Based on neuropathology ground truth
  - Image classification and probability of disease(s)
    - The intent is to make this output available to P30 sites via the dashboard.

Blood Collection

- **25/37 ADRC's** are collecting blood using the NCRAD ADCFB protocol
- Some sites commented they need to take **participant burden** into consideration
- **30mL** is ideal and requested
- Minimum accepted will be 10mL
- Blood is important for current and future assays
  - Ptau217, ab42/40, GFAP, NfL
  - TDP43
  - Alpha-synuclein
  - Other TBD assays
- **Dried blood spots are in our future**



Flortaucipir (FTP) and Florbetapir (FBP)

- A number of free doses from Lilly
- More sites are asking for FTP and FBP doses
- We likely will use free doses in year1
- Subsequent doses will be charged at commercial rate ~$3,800/dose
  - (the net cost balances out comparable to other tracers)

- Now asking sites to consider using other tracers
- Think also about your site's tracer continuity (after CLARiTI) and whether you will have a dependency that you can sustain

Thank you

- **Stop by our booth—We are here to answer your questions!**

- **Next webinar is on June 20, 10 AM CT**
  - Blood & Biomarkers/NCRAD
- **Stay in touch**
  - Email CLARiTI Administrative Team: clariti@medicine.wisc.edu
  - Email CLARiTI Inclusion Team: clariti-inclusion@medicine.wisc.edu
  - Website: https://naccdata.org/nacc-collaborations/clariti

THANK YOU!

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