ADRC consortium for CLarity in ADRD Research Through Imaging (CLARiTI)

Sterling Johnson, Beth Mormino, Tatiana Foroud, Gil Rabinovici, Ozioma Okonkwo, Monica Rivera-Mindt, Brad Dickerson, Dave Wolk, Bud Kukull

Workgroup Lead investigators
Dirk Keene: Neuropath
Gil Rabinovici: image reads
Annalise Rahman-Filipiak: Disclosure
John Detre: Advanced MRI methods
Monica Rivera-Mindt: Diversity
Jeff Dage: Biofluid
Paul Thompson: Analyses

Synopsis:

- An ATN imaging and plasma study superimposed on existing longitudinal clinical cores already collecting UDS
- 2000 clinical core participants; 60% impaired, 40% unimpaired with risk factors
- Two time points
- *Heterogeneity* is the focus: syndromes, pathologies
- Create Etiologic Profile per patient

What will it consist of? – guiding principles

- More resources to the Centers to accomplish ATN imaging using SCAN protocol
- An opportunity to pursue joint scientific goals

Focus on ATN as a ***foundational*** component	Funding for the scans *and* the needed staff	Images are yours	Shared to NACC	**Flexible** protocol	**Keep it simple**
Diverse participants	Image interpretation	Disclosure toolkit	Blood Biomarkers	Optional FDG	Optional Research MRI

Some gaps in the ADRD field

- AD doesn't typically occur by itself
  - Vascular, DLB, LATE, FTLD, atypical
  - Mixture of etiologies; onset ages
- Most cohort studies are designed around 1 etiologic pathway
- Need an etiologic profile that spans common possible causes
  - Person-level prognosis is vague
  - Unified joint biomarker models that account for more than AD
- Neuropath to imaging relationships
- Blood markers in the context of latent or unknown heterogeneity
- Need a way of rapidly evaluating other MRI sequences that inform on the biology of ADRD

This consortium will:

- establish a comprehensive resource spanning the etiologic spectrum
- diverse ethnocultural representation
- includes the best available expertise in diagnosing the clinical syndromes
- encompasses the best available biomarkers for deep phenotyping

- populates SCAN enabling future discovery
- links to NACC longitudinal cognitive and clinical characterization
- link to genome-wide panels
- link with ultimate confirmation from quantitative neuropathology

The ADRCs can address these gaps quickly

- 37 centers of excellence in ADRD; various specialization
- 27% URP
- Recruitable pool of > 11,600
- 63% are enrolled brain donors
- 62% successful autopsy rate
- Established local infrastructure and workforce
- National infrastructure: NACC, NCRAD, SCAN, LONI, ADGSP
- There is strong interest in collaborating as a consortium!

This project uniquely covers the etiologic spectrum

Table 1. Prominent active cohort studies related to ADRD and their primary enrolling diagnosis

Cohort*	Size (Goal)	AD	VCID	LBD	FTLD	Atypical	LATE	Imaging A/T PET	purpose
CLARiTI	(2,000)	Y	Y	Y	Y	Y	nk	Y	Etiologic characterization of ADRD mixture
DVCID**	(2,250)	n	Y	n	n	n	nk	N	vascular risk for cognitive decline* will partner
ADNI4	(1,100)	Y	n	n	n	n	nk	Y	Clinical trial planning for AD with biomarkers
LEADS	(700)	Y	n	n	n	n	nk	Y	Clinical trial planning in early onset AD
ALLFTD	1,479	n	n	n	Y	n	nk	N	Clinical and biomarker progression
PPMI	(4500)	n	n	Y	n	n	nk	N	Biomarker progression in PD
DLBC	200	n	n	Y	n	n	nk	N	Dementia with Lewy bodies
DIAN	(600)	Y	n	n	n	n	nk	Y	Cohort of autosomal mutation carriers

Notes: *Single-site aging and AD-risk cohorts are not listed.
Nk= not known
LATE is a neuropath entity—clinical criteria are not defined and it is assumed all older cohorts contain some as yet unknown burden of LATE-NC; LBD includes Dementia with Lewy Bodies and Parkinson's disease dementia and their prodromes. Other abbreviations: VCID vascular cognitive impairment. LEADS Longitudinal early onset AD study; PPMI Parkinsons Progression marker initiative; DLBC Lewy Body consortium;

**DVCID Diverse VCID study: Participants may co-enroll because DVCID does not do PET and the core MRI is the same and will be at SCAN

Design & Schedule of events

Scan.naccdata.org

N=2000 x 2 timepoints
MCI/dementia ~1200
CU with risk ~800

Radiotracers: SCAN menu
FDG: SCAN protocol

Schedule of events	Baseline	~2 yr follow up	Comment
Screening for eligibility	X		
Consent	X		Enable wide sharing and combining with UDS and other data
SCAN Amyloid PET (site choice)	X	X	Use consistent tracers and scanners
SCAN Tau PET (site choice)	X	X	Use consistent tracers and scanners (optional if A-)
SCAN MRI (site choice); DVCID	X	X	Use consistent scanners (minimum protocol); compatible with DVCID
Plasma NCRAD protocol	X	X	Uniform preanalytic; waived if done within 12 m
Advanced MRI add on	(o)	(o)	Optional; 35 sites agreed
SCAN FDG (N)	(o)	(o)	Optional; valuable for assessing heterogeneity

CLARiTI ATN - RO1

Admin
- Wisconsin; NACC; Stanford

$

data

NACC

Data coordination, collection, sharing and integration

$

results

ADRC sites (37)

Image and Plasma acquisition
- Funding to recruit **2000** x 2 timepoints
- 1 FTE coordinator
- 1 FTE outreach specialist

Diversity recruitment
- Rivera Mindt, others
- Coordinate with ORE cores
- Outreach staff at each site

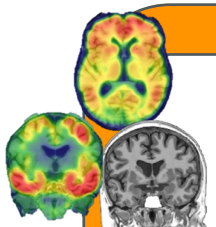
Clinical ops
- ATNV clinical interpretation
- Support for disclosure

Stats and Analysis
- Stats plan and hypothesis testing
- Ancillary img analysis beyond SCAN

Research MRI
- Detre, others
- Cross-platform sequences for N
- Evaluate new sequences
- collaborate

Plasma biomarkers
- Foroud, Dage
- NCRAD central infrastructure
- Standard collection kits

Neuropathology
- Dirk Keene
- Central standard assays; digital



Flywheel
MRI

NCRAD

Image repository

LONI

Raw images

Curated files

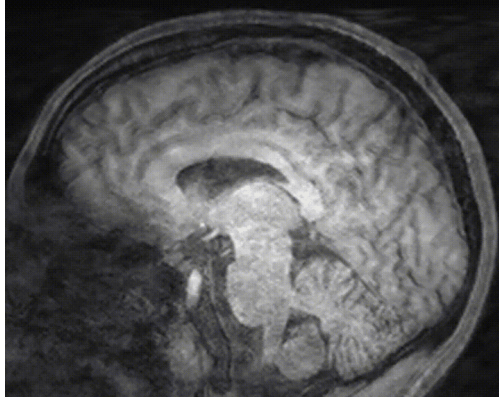
scan

SCAN analysis
- Site qualification
- QC
- Standard analyses

Workgroups (cores)

Workgroup	
Advanced MRI	Detre, Tisdall, Kecskemeti, Levendovszky, Qiu, Arfanakis, Johnson
Diversity	Rivera-Mindt, Okonkwo, Bird, Windon, Carter, Mormino
Data Analysis	Donohue, P. Thompson, Rosen, Hohman, Grabowski, Bud Kukull, Gary Chan, Yen-Chi Chen
Image interpretation	Rabinovici, Villemagne, Dickerson, Wolk, La Joie, others
PET disclosure	Rahman-Filipiak, Agrawal, Chin, Clark
Neuropathology	Dirk Keene
Blood Biomarkers	Dage, Foroud

Advanced MRI (in addition to SCAN MRI)



- MRI protocol
- SCAN T1w
- SCAN FLAIR
- 12 min additional
  - vNAV or MPnRAGE motion corrected T1w
  - Multi-delay ASL
- Goal: improve understanding of biology of neurodegeneration-cor. thickness patterns; pseudometabolic
- Rationale for limited focus on MRI measures of ‘N’:
  - Maximize consistency with overall ATN theme
- Advanced MRI infrastructure can be expanded to other MRI methods and exploratory analyses
- Plan: ~12-min protocol added to standard protocol at participating Advanced MRI sites
  - Protocols will be available for GE, Siemens, and Phillips MRI platforms
  - Central processing of MRI data with results returned to sites
  - Platform for more automated image uploads and mutual access

Survey results

Neuropath survey: 33/34 agreed to support CLARiTI

- Sites that responded: 37/37
- How big is our collective recruitable pool?

ADRC-wide	Average per site
11,634 (of 14,800) *62% brain donor enrolled*	314

Only 21% of recruitable pool have had amyloid PET in last 3 years! (2,498)

- How many people do you want to enroll in CLARiTI for ATN imaging?

group	ADRC-wide	Average per site
CU	2,038	55
MCI	1,147	31
dementia	640	17
total	3,825	104
Goal	2,000	54

Feasible!
But, doesn't fully meet need

Survey summary

question	overall
Neuropath support	33/34 97%
Blood collection	34/37 92%
Advanced MRI	35/37 94%
FDG	28/37 75%
MRI scanner Install year: avg=2015	10 GE 22 Siemens 5 Phillips
MRI ADNI or SCAN qualified?	33, 89%

Barriers to PET	count, %
Funding for imaging	31, 92%
Funding for personnel	27, 75%
Radioligand relationship	10, 27%
Radioligand supply	13, 36%
Reliability of ligand delivery	11, 31%
Scanner access	13, 36%
Cyclotron availability	14, 39%
IND process	10, 28%
Already have ATN biomarkers	1, 3%
ATN not appropriate	2, 6%
Radiation concerns	9, 25%
Participant wants result	15, 42%

Funding	ligand Supply	Local constraints	alignment	Participant concerns
94%	44%	58%	8%	50%

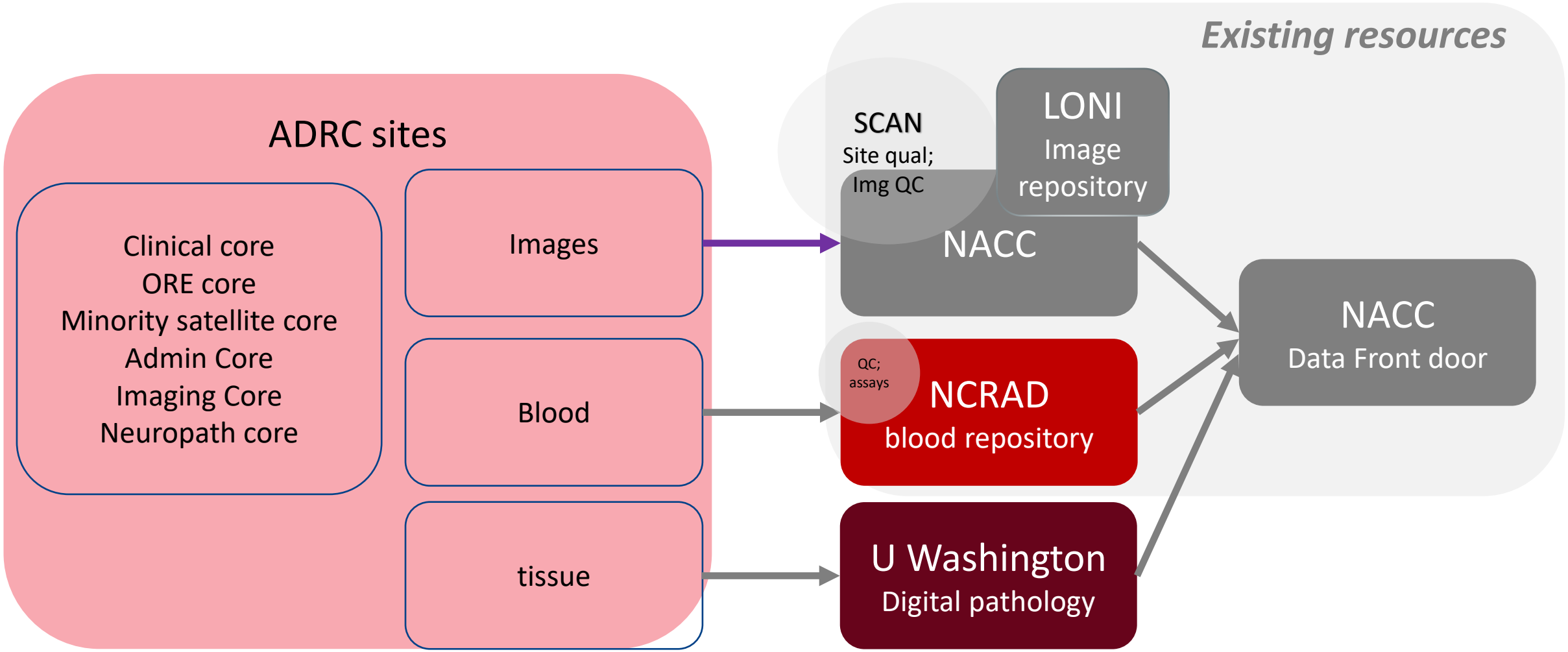
Ligand preference

Amyloid	1st choice
[11C]PiB*	38%
[18F]NAV*	21%
[18F]FBB	23%
[18F]FBP	30%

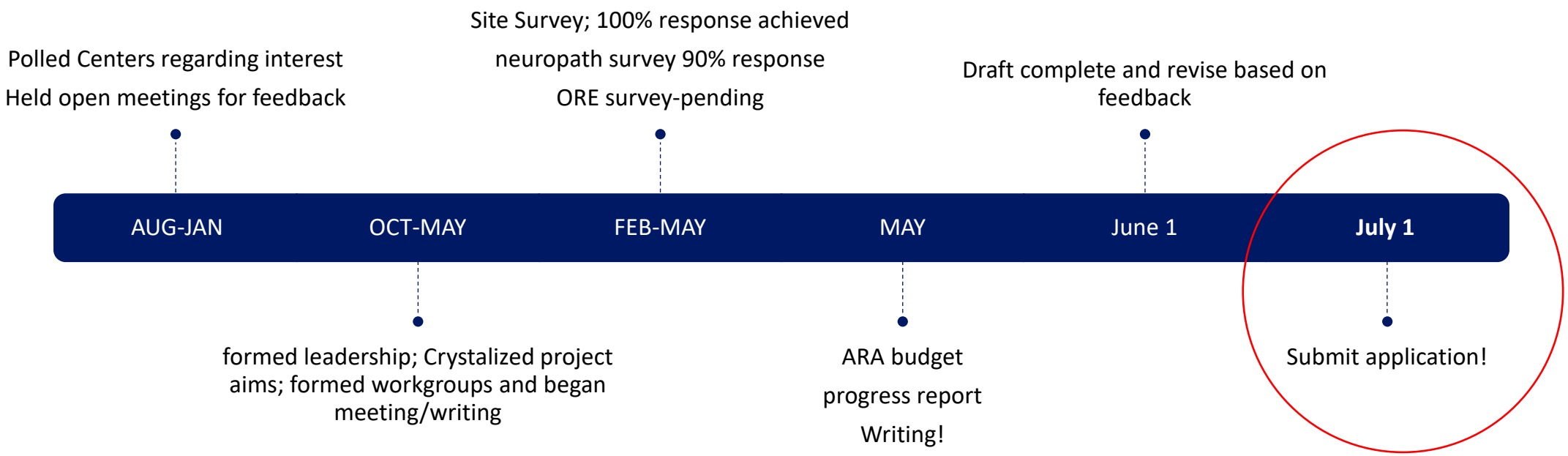
Tau	1st choice
[18F]MK6240*	51%
[18F]PI2620*	12%
[18F]FTP	44%
[18F]GTP1*	3%

* Requires IND

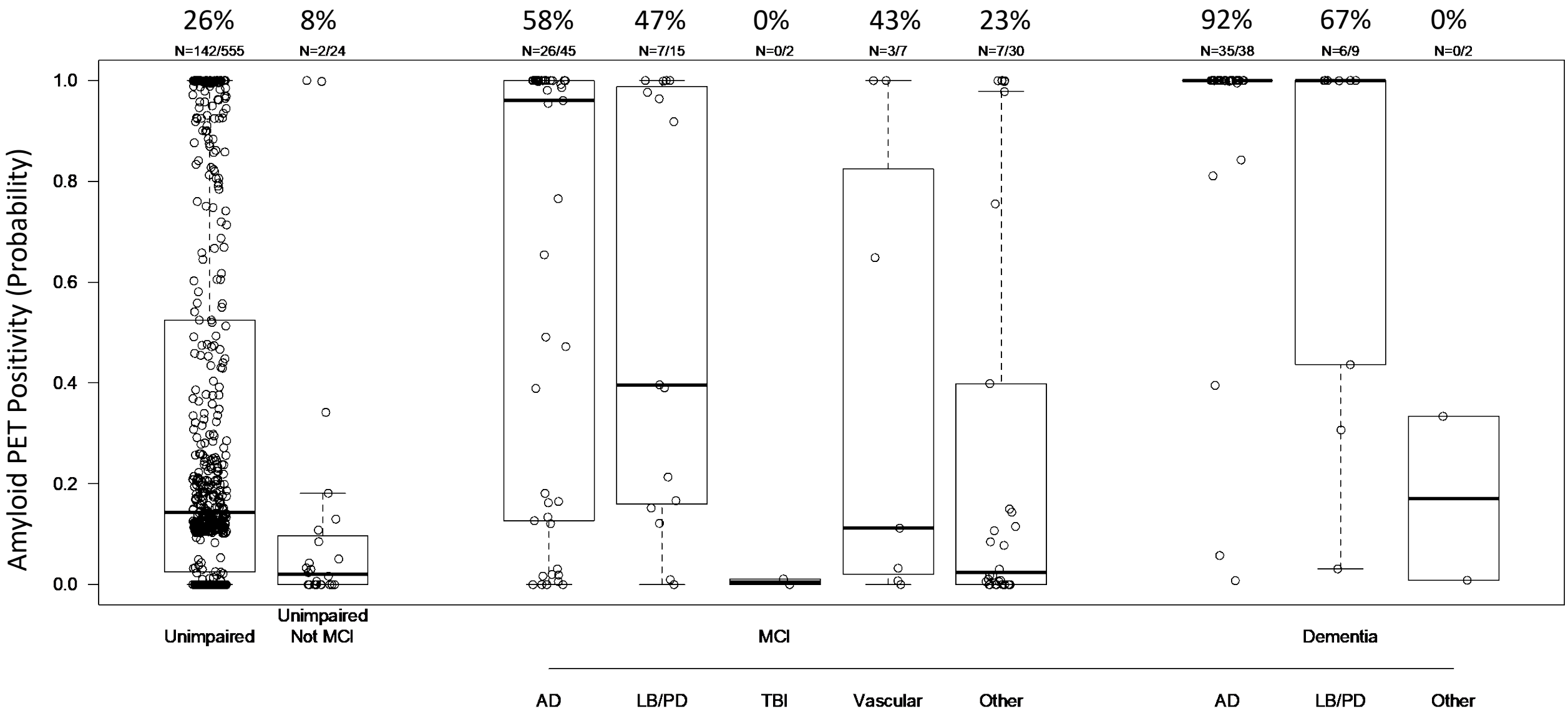
- Cerveau, LMI, Lilly on board to supply radiotracers
- Are you willing to collect FDG? 28 sites, 75%


Existing resources
ADRC sites
Clinical core
ORE core
Minority satellite core
Admin Core
Imaging Core
Neuropath core
Images
Blood
tissue
SCAN
Site qual;
Img QC
LONI
Image
repository
NACC
QC;
assays
NCRAD
blood repository
U Washington
Digital pathology
NACC
Data Front door

Timeline – July 1, 2022



Amyloid PET Positivity across clinical variables: primary etiology and cognitive status



Post mortem workups with prior in vivo MRI: 900+

n=238	Suspected AD (N, %)	Normal Cognition (N, %)
Absent Pathology		
T- / LB - / TDP43-	6 (2.5%)	28 (60%)
Single-Pathology		
T+ / LB - / TDP43-	86 (36%)	9 (19%)
T- / LB + / TDP43-	2 (0.8%)	1 (2.1%)
T- / LB - / TDP43+	5 (2.1%)	2 (4.3%)
Co-Pathology		
T+ / LB + /TDP43-	48 (20%)	3 (6.4%)
T+ / LB - / TDP43+	50 (21%)	3 (6.4%)
T- / LB + / TDP43+	2 (0.8%)	0
Poly-Pathology		
T+ / LB + / TDP43+	39 (16.4%)	1 (2.1%)
Total with all three postmortem measurements		
	238 (100%)	47 (100%)

Inclusion of "emergent" pathology.
Criteria are relaxed to include emergent pathologies.

Tangle+ (T+) was defined as the presence of Braak III and higher (NACCBRAA>2),

Lewy Body+ (LB+) was defined as having LB in limbic or diffuse neocortex (NACCLEWY==2 or NACCLEWY==3)

TDP43+ was defined as having TDP-43 in amygdala or EC/Inferior temporal (NPTDPB==1 or NPTDPD==1).

Two or more pathologies were present in over 58% of the suspected AD group.

Synergy with DVCID, ADNI4, LEADS

- Same base imaging protocol (SCAN T1w and FLAIR) will enable leveraging
- DVCID does not involve PET; may co-enroll in CLARITI (we will accept DVCID MRI and plasma)
- Fills a unique lane regarding etiologic heterogeneity
- No need to co-enroll clinical core participants in ADNI and CLARiTI
- Joint focus on diversity

Thank you for supporting this