NEUROPATHOLOGY CORE SESSION

2023 Hybrid Fall ADRC Meeting
Friday, October 20

10:15 - 10:25am PT		*10min*
Welcome, Vascular Pathology Survey Results and Other Updates	Thomas Wisniewski, MD NYU ADRC	
10:25 - 10:45am PT		*15min Presentation, 5min Q&A*
The Alzheimer's Disease Pathologic Work-up: Are We Missing Significant Vascular Pathology?	Julie Schneider, MD, MS Rush University ADRC	
10:45 - 11:00am PT		*10min Presentation, 5min Q&A*
Neuropathological Correlates of MRI-Visible Small Vessel Disease Lesions	Susanne Van Veluw, PhD Massachusetts General Hospital	
11:00 - 11:15am PT		*10min Presentation, 5min Q&A*
Neuropathology of Cerebrovascular Disease at UCLA	Shino Magaki, MD, PhD UCLA	
11:15 - 11:30am PT		*10min Presentation, 5min Q&A*
Proteomic Studies of Vascular Pathology in Alzheimer's Disease and COVID-19	Dominique Leitner, PhD NYU ADRC	
11:30 - 11:45am PT		*10min Presentation, 5min Q&A*
A Workflow for Automated Segmentation of Arteriolosclerotic Blood Vessels on Digitized H&E Stained Brain Tissues Using Deep Learning	Jerry Lou, MD UC Irvine ADRC	

2023 FALL ADRC MEETING

October 18th - 20th, 2023
Hybrid Event
The Westin San Diego Gaslamp Quarter, San Diego

Network Wifi: Westin_CONFERENCE
Password: ADRC2023

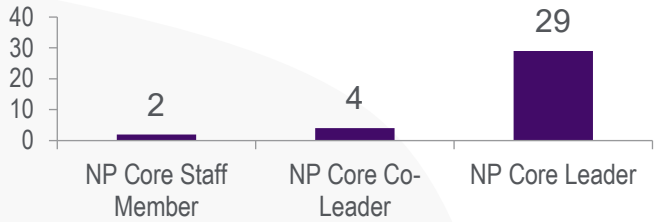
Welcome, Vascular Pathology Survey Results and Other Updates:

- **Results of vascular pathology survey among NPCs**
- **Digital Pathology Working Group Updates**
- **Modernizing Neuropathology Working Group Updates**
- **NeuroBiobank Working Group to Advance Brain Donation and Utilization for ADRD Research: Progress Update**
- **CLARiTI Neuropathology Core Update**

Neuropathology Core Vascular Pathology Survey Results

95%
NP Survey Response

35/37
Centers



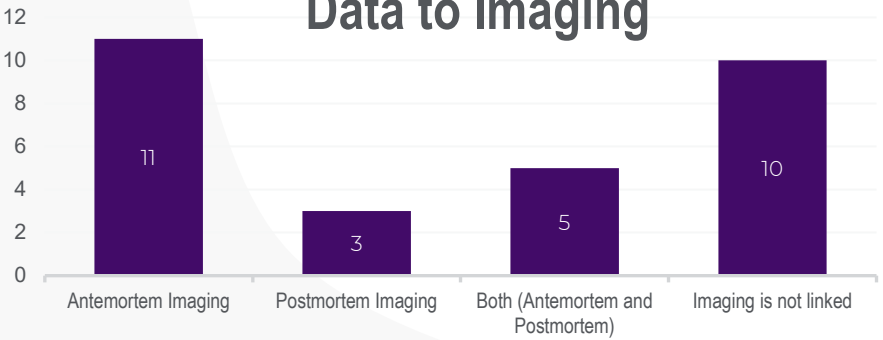
Use NP Form v.11 for CVD Documentation

89% 31 Centers

Inclusion of Subjects with Stroke History or Stroke on Imaging

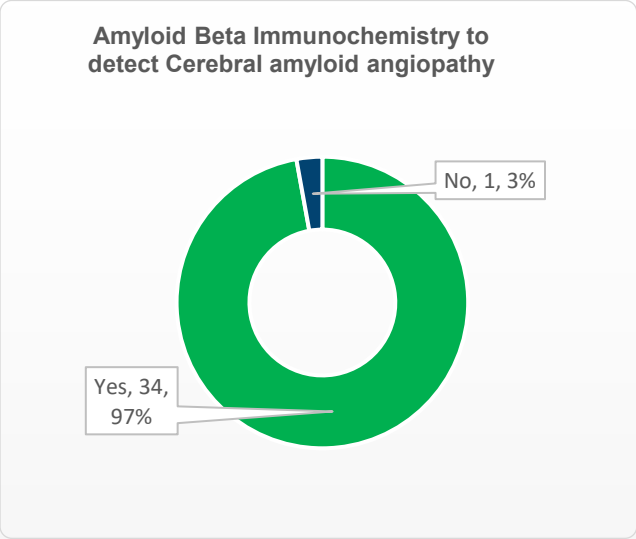
83% 29 Centers

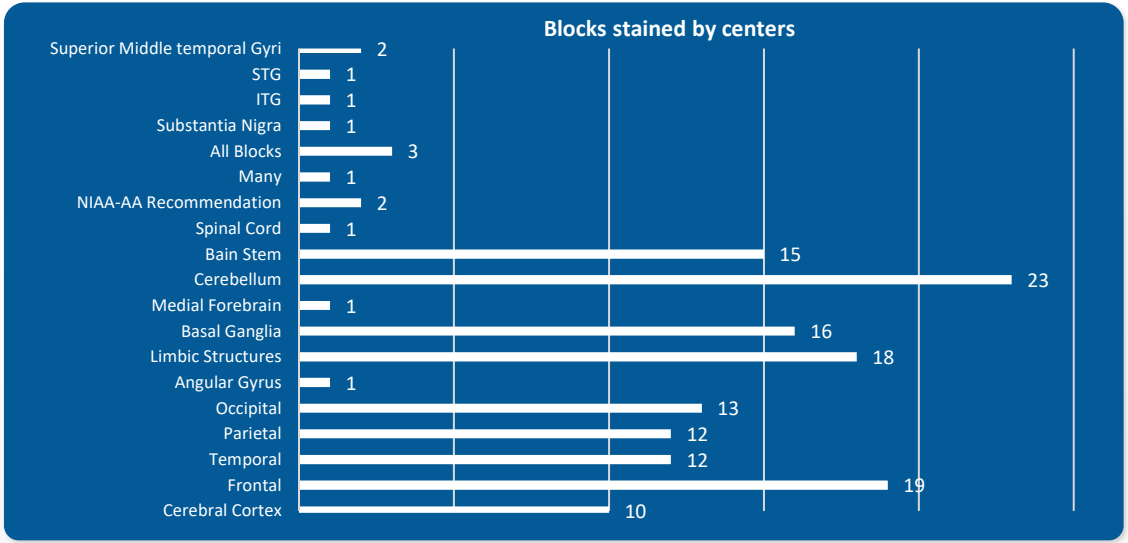
Linkage of NP11 form CVD Data to Imaging

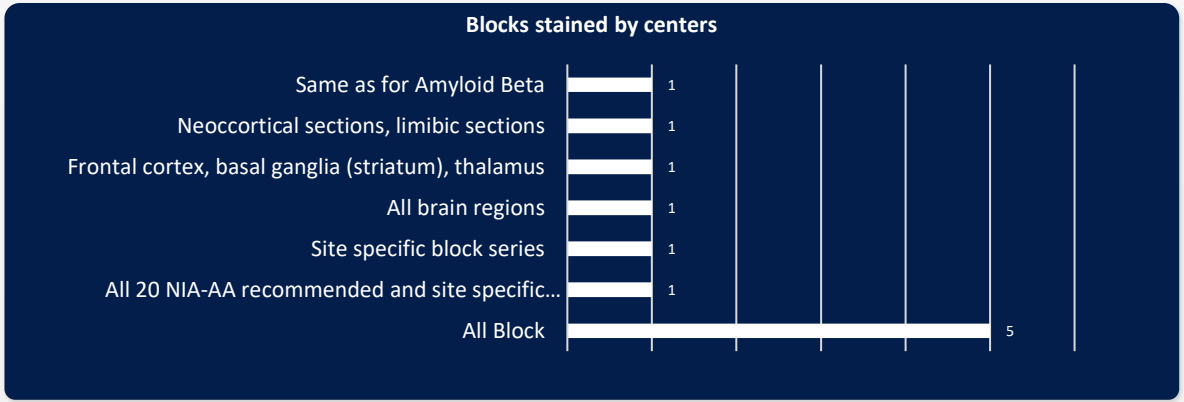


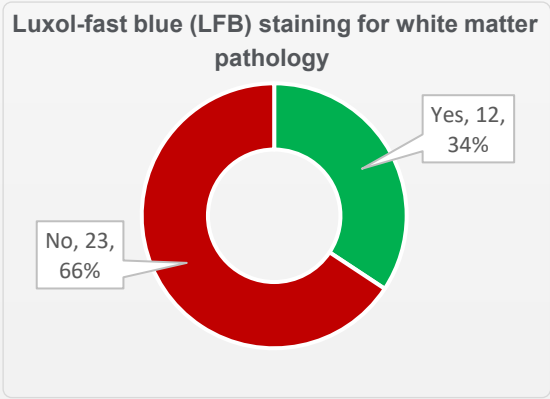
NYU Langone Health

Stains Used to Assess Cerebrovascular Disease

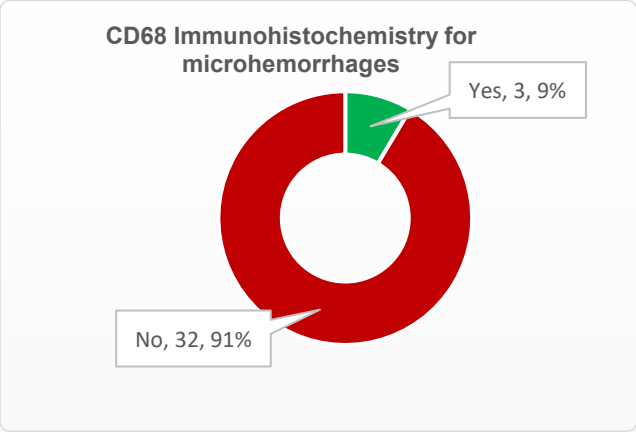


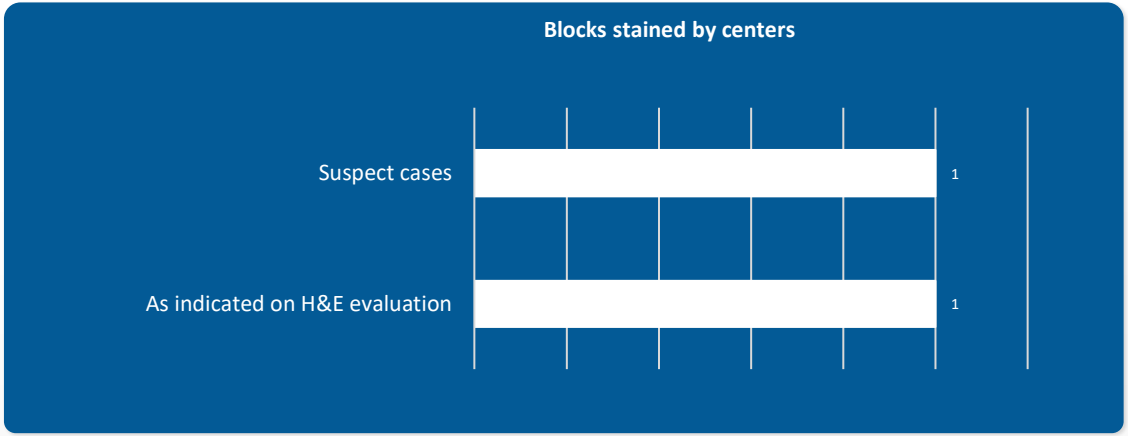


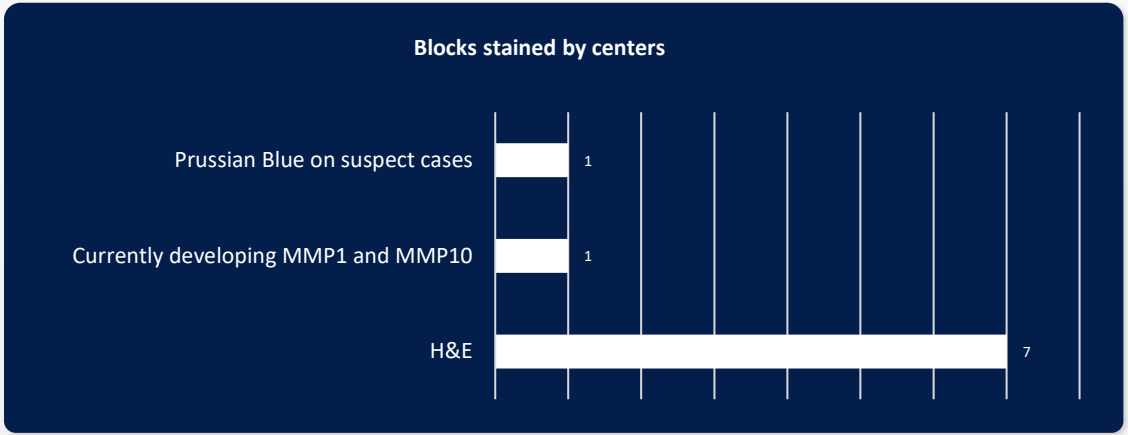


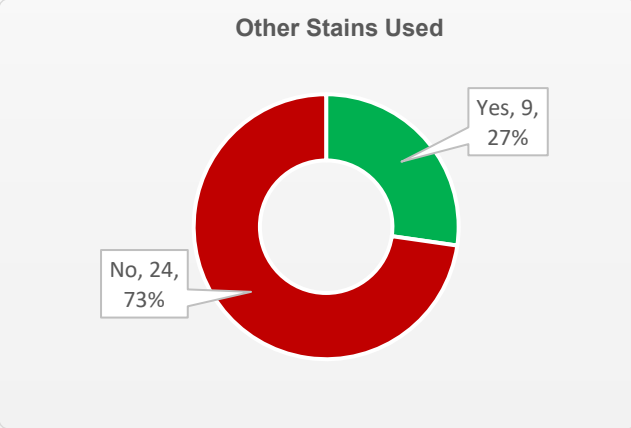


Stains Used to Assess Cerebrovascular Disease

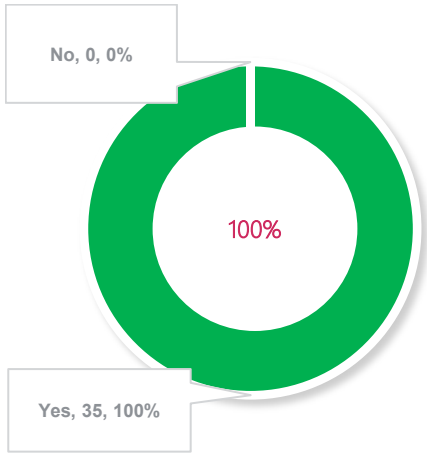




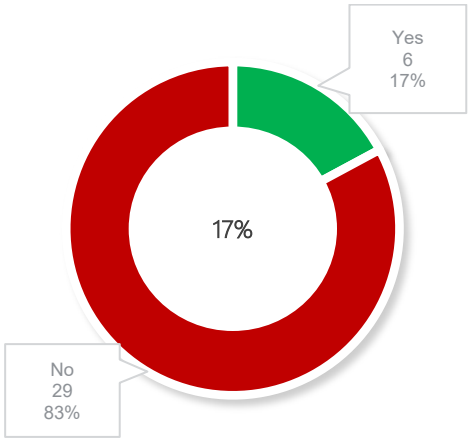




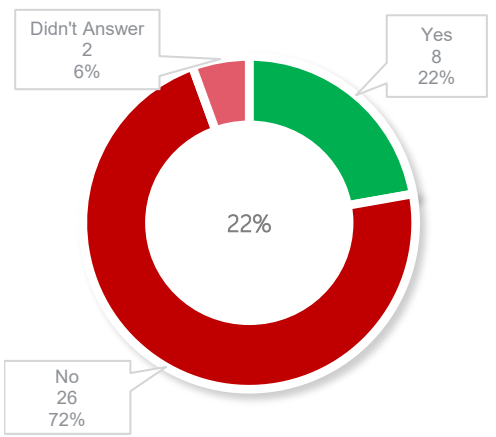
Which vessels do you assess gross atherosclerosis?



Circle of Willis



Sections taken from circle of Willis?



Sections taken from other major vessels

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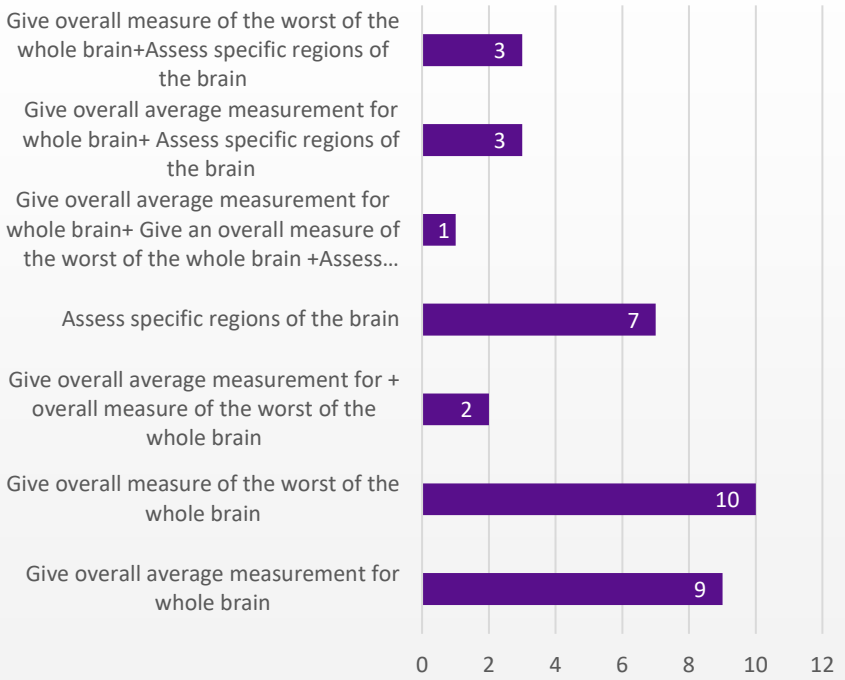
Your Logo Here

How do you assess arteriolosclerosis?



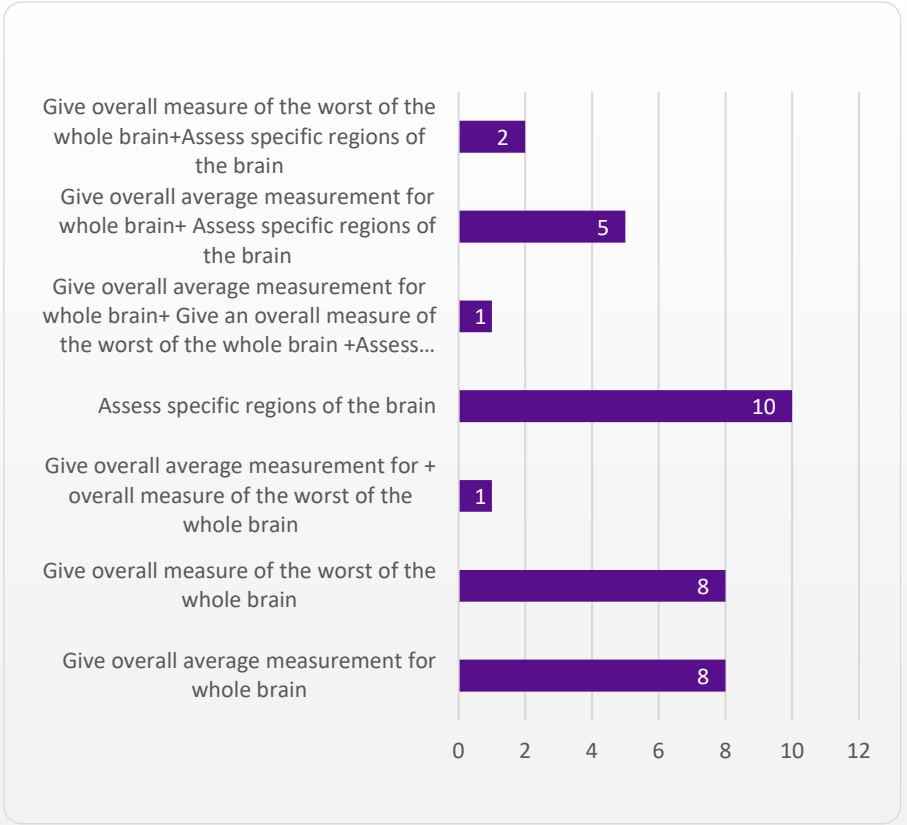
Specific brain regions assessed by centers

- ACC, MFG, IFG, ITG, amygdala, thalamus, insula and basal ganglia, angular gyrus
- All brain regions sampled (usually around 20 blocks) are screened. When arteriosclerosis is present in a given brain region, presence and severity noted in the neuropathology report.
- All regions assessed with more detailed assessment performed on cortical, thalamic, and basal ganglia sections.
- Basal ganglia (caudate, putamen, internal capsule), subcortical frontal white matter, and subcortical parietal white matter
- Cerebral cortex, striatum, thalamus
- Cortical areas, striatum, thalamus, brainstem & cerebellum
- Deep cerebral white matter
- Dorsolateral frontal and superior temporal
- Essentially all
- Every sampled brain region is assessed for arteriolosclerosis, including, mid frontal, inferior parietal, superior temporal, occipital, hippocampus, amygdala, basal ganglia, thalamus, midbrain, pons, medulla, cerebellum
- Have specific semi-quantitative measures of arteriolosclerosis within periventricular white matter for frontal, parietal, and occipital- and in NACC report avg of these
- MFG, ACG, PreCG, STG/MTG, IPL, Precuneus, Occ, Amy, Hippo, Striatum, Pallidum, Thal, MB, Pons, Med, Cblm, SC
- Occipital white matter per VCING criteria
- Arteriolosclerosis described in any block where it is noticeable

How do you assess cerebral amyloid angiopathy?

Specific brain regions assessed by centers

- All (frontal, temporal, parietal, occipital, amygdala, hippocampus, basal ganglia, thalamus, midbrain, pons, medulla, spinal cord, cerebellum)
- All regions assessed with more detailed assessment also performed on occipital cortex
- Cerebral cortex and cerebellum (separately report leptomeningeal and parenchymal involvement; also comment on presence/absence of capillary involvement)
- Cortex, cerebellum generally using Vonsattel approach
- DLPFC, MTG-STG, IPL, Calcarine, cerebellum (overall classification of CAA is derived from Calcarine Ctx but CAA is recorded for each region separately
- Essentially all
- Four Cerebral cortical blocks, hippocampus, midbrain, cerebellum
- Frontal, hippocampus, basal ganglia, cerebellum
- Frontal, temporal, inferior parietal
- Frontal, temporal, parietal, occipital lobes and cerebellum.
- Hippocampus/entorhinal cortex, frontal, temporal, parietal and occipital lobes
- Leptomeninges vs parenchymal (capillary, etc.)
- MFG, ACG, PreCG, STG/MTG, IPL, Precuneus, Occ, Amy, Hippo, Striatum, Pallidum, Thal, MB, Pons, Med, Cblm, SC
- MFG, ITG, hippocampal formation, STG, angular gyrus, visual cortex
- Mid frontal, Inferior parietal, Superior temporal, Occipital lobe, Cerebellum
- Midfrontal, midtemporal, inferior parietal, calcarine cortex
- Superior/middle temporal, superior parietal, striatum, midbrain, middle frontal, cerebellum with dentate nucleus and give average of these utilizing NACC guidelines
- Severity of CAA in limbic structures, all neocortical regions sampled (usually 6-7 regions), and cerebellum



Which Lesions are Documented and what Cut-offs are Used?

Cerebral Microhaemorrhages	Cerebral Macrohaemorrhages	Cerebral Microinfarcts	Lacunar Infarcts	Large Infarcts
15 (43%)	12 (34%)	18 (51%)	21 (60%)	14 (40%)
• **Visible only on microscopic evaluation** • **< 0.5 cm** • **≤ 1 mm Visible only on microscopic evaluation**	• **≥ 0.5 cm** • **Visible (grossly visible to the naked eye)** • **Visible (with specification of acute vs. chronic)** • Small (1-27 cc); Large (>27 cc)	• **≤0.5 mm (invisible by the naked eye)** • **≤ 0.5mm (with specification of acute vs. chronic)** • **grossly invisible** • **Up to 1 mm but reactive changes are often larger**	• **≥0.5cm but less than 1.0cm** • **Visible grossly or in size range 0.5-1 cc** • 10 mm or 15 mm in greatest dimension • 2cm • Distribution of penetrating arteries • more than 15 mm	• **≥1 cm** • **Any visible ≥1 cm (with specification of acute vs. chronic)** • **Not lacunar; we give sizes but generally don't use descriptors such as 'large'** • Small (1-27 cc); Large (> 27 cc)

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How many NPCs link CVD Data to Brain Imaging?

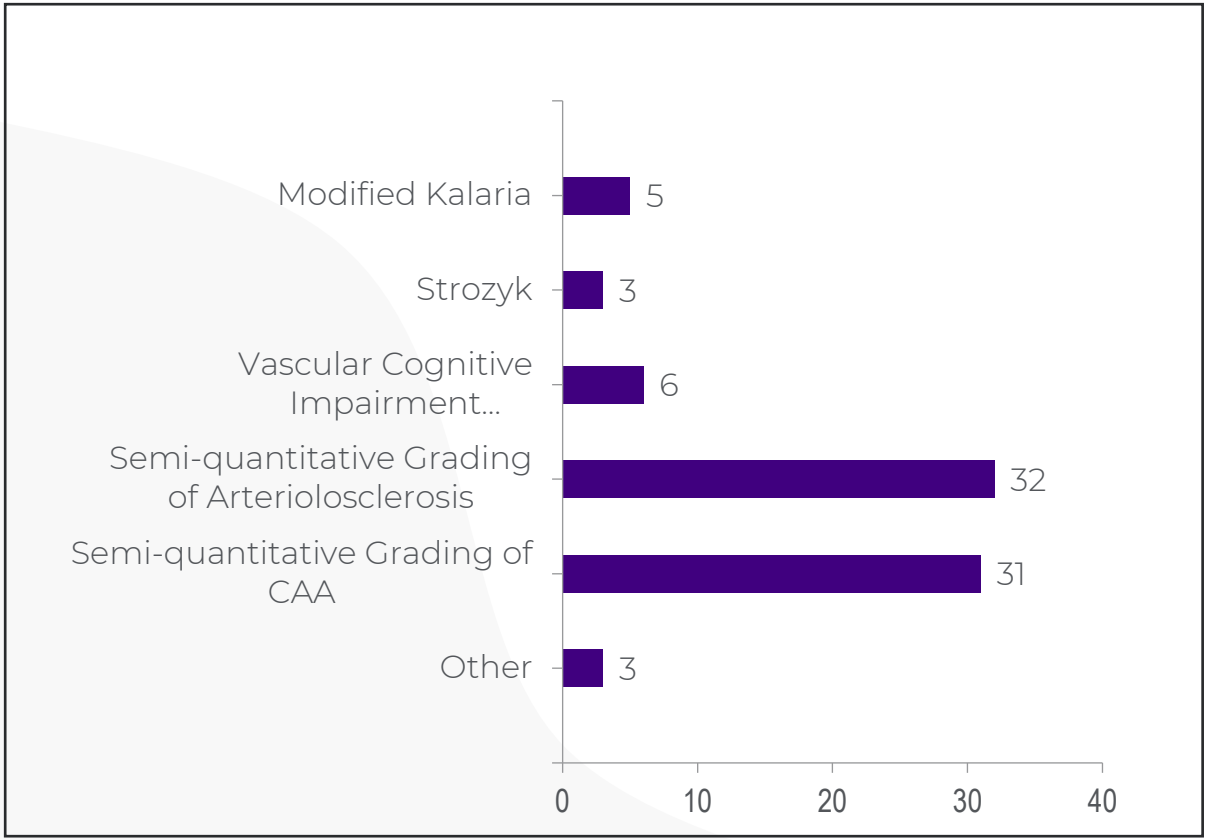
46% (16)

Match neuropathological CVD Data to pre-mortem brain imaging

31% (11)

Match neuropathological CVD data to both pre-mortem and post-mortem brain imaging

What Scales are Used to Assess CVD at Differing NPCs?



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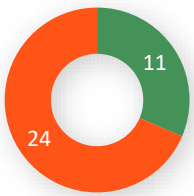
What is the Utilization of CVD data for Publications?

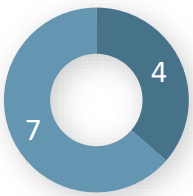
Utilization of vascular pathology data for publication



YES 31%

NO 69%

Data Source



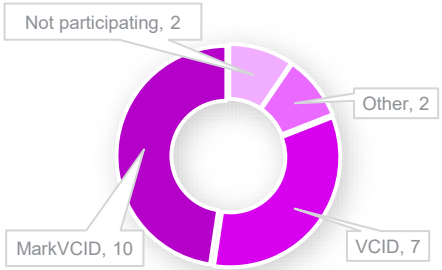
Individual Center 36%

Individual Center + NACC 64%

Publications

>350

Consortium Participation



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Examples of the Many Publications Using Vascular Pathology Data

Adeniyi, P. A., Gong, X., MacGregor, E., Degener-O'Brien, K., McClendon, E., Garcia, M., Romero, O., Russell, J., Srivastava, T., Miller, J., Keene, C. D., & Back, S. A. (2023). Ferroptosis of Microglia in Aging Human White Matter Injury. Ann Neurol. https://doi.org/10.1002/ana.26770

Lahna, D., Schwartz, D. L., Woltjer, R., Black, S. E., Roese, N., Dodge, H., Boespflug, E. L., Keith, J., Gao, F., Ramirez, J., & Silbert, L. C. (2022). Venous Collagenosis as Pathogenesis of White Matter Hyperintensity. Ann Neurol, 92(6), 992-1000. https://doi.org/10.1002/ana.26487

Lopez, O. L., Kofler, J., Chang, Y., Berman, S. B., Becker, J. T., Sweet, R. A., Nadkarni, N., Patira, R., Kamboh, M. I., Cohen, A. D., Snitz, B. E., Kuller, L. H., & Klunk, W. E. (2020). Hippocampal sclerosis, TDP-43, and the duration of the symptoms of dementia of AD patients. Ann Clin Transl Neurol, 7(9), 1546-1556. https://doi.org/10.1002/acn3.51135

Scalco, R., Saito, N., Beckett, L., Nguyen, M. L., Huie, E., Wang, H. P., Flaherty, D. A., Honig, L. S., DeCarli, C., Rissman, R. A., Teich, A. F., Jin, L. W., & Dugger, B. N. (2023). The neuropathological landscape of Hispanic and non-Hispanic White decedents with Alzheimer disease. Acta Neuropathol Commun, 11(1), 105. https://doi.org/10.1186/s40478-023-01574-1

Sepulveda-Falla, D., Villegas Lanau, C. A., White, C., Serrano, G. E., Acosta-Uribe, J., Mejía-Cupajita, B., Villalba-Moreno, N. D., Lu, P., Glatzel, M., Kofler, J. K., Ghetti, B., Frosch, M. P., Lopera Restrepo, F., Kosik, K. S., & Beach, T. G. (2023). Comorbidities in Early-Onset Sporadic versus Presenilin-1 Mutation-Associated Alzheimer's Disease Dementia: Evidence for Dependency on Alzheimer's Disease Neuropathological Changes. medRxiv. https://doi.org/10.1101/2023.08.14.23294081

Standring, O. J., Friedberg, J., Tripodis, Y., Chua, A. S., Cherry, J. D., Alvarez, V. E., Huber, B. R., Xia, W., Mez, J., Alosco, M. L., Nicks, R., Mahar, I., Pothast, M. J., Gardner, H. M., Meng, G., Palmisano, J. N., Martin, B. M., Dwyer, B., Kowall, N. W., . . . Stein, T. D. (2019). Contact sport participation and chronic traumatic encephalopathy are associated with altered severity and distribution of cerebral amyloid angiopathy. Acta Neuropathol, 138(3), 401-413. https://doi.org/10.1007/s00401-019-02031-x

Sun, Z., Jiang, D., Liu, P., Muccio, M., Li, C., Cao, Y., Wisniewski, T. M., Lu, H., & Ge, Y. (2022). Age-Related Tortuosity of Carotid and Vertebral Arteries: Quantitative Evaluation With MR Angiography. Front Neurol, 13, 858805. https://doi.org/10.3389/fneur.2022.858805

Wang, S. J., Guo, Y., Ervin, J. F., Lusk, J. B., & Luo, S. (2022). Neuropathological associations of limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC) differ between the oldest-old and younger-old. Acta Neuropathol, 144(1), 45-57. https://doi.org/10.1007/s00401-022-02432-5

Conclusions of the Neuropathology Core Cerebrovascular Disease Survey

- Neuropathology Core Leaders are very responsive to survey requests!
- Vast Majority of NPC use the NP form v.11 for CVD documentation.
- ~50% of NPCs link CVD data to imaging information.
- Almost all use Aβ immunohistochemistry for CAA detection.
- ~1/3 use Luxol-fast blue staining and 27% use H&E for detection of white matter pathology.
- There is broad agreement on how to assess arteriosclerosis and CAA.
- There is good agreement on the definition of CVD lesions identified and their cutoffs.
- The manuscript productivity related to the utilized CVD data by NPC is excellent (although only ~1/3 report using the data).

ADRC Digital Pathology Working Group Updates

Involvement of many institutions/centers!!!

And many others!!!!!

ADRC FALL MEETING

OCT 20 2023

Journal of Neuropathology & Experimental Neurology, 2023, **82**, 202–211
https://doi.org/10.1093/jnen/nlac127
Advance access publication 24 January 2023
Original Article

OXFORD

The status of digital pathology and associated infrastructure within Alzheimer's Disease Centers

Rebeca Scalco, DVM, MS,[1] Yamah Hamsafar, BS,[1] Charles L. White, III, MD,[2] Julie A. Schneider, MD, MS,[3] Robert Ross Reichard, MD,[4] Stefan Prokop, MD,[5] Richard J. Perrin, MD, PhD,[6,7,8] Peter T. Nelson, MD, PhD,[9] Sean Mooney, PhD,[10] Andrew P. Lieberman, MD, PhD,[11] Walter A. Kukull, PhD,[10] Julia Kofler, MD,[12] Christopher Dirk Keene, MD, PhD,[13] Alifiya Kapasi, PhD,[3] David J. Irwin, MD,[14] David A. Gutman, MD,[15] Margaret E. Flanagan, MD,[16,17] John F. Crary, MD, PhD,[18,19,20] Kwun C. Chan, PhD,[10] Melissa E. Murray, PhD,[21] Brittany N. Dugger, PhD[1*]

Benchmarks and helpful guides

Free Neuropathology 4:6 (2023)

Original Paper

Survey of Neuroanatomic Sampling and Staining Procedures in Alzheimer Disease Research Center Brain Banks

Juan C. Vizcarra[1], Andrew F. Teich[2], Brittany N. Dugger[3], David A. Gutman[4], and the Alzheimer's Disease Research Center Digital Pathology Working Group[5]

1 *Department of Biomedical Engineering, Emory University & Georgia Institute of Technology, Atlanta, USA*
2 *Department of Pathology and Cell Biology, Department of Neurology, The Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University, New York, New York, USA*
3 *Department of Pathology and Laboratory Medicine, University of California-Davis, Sacramento, California, USA*
4 *Department of Neuropathology, Emory University, Atlanta, Georgia, USA*
5 *Members of the group and their affiliations can be found in Supplementary material 2.*

2 funded projects!

Funding Opportunity Title	Connecting Machine Readable Digital Human AD/ADRD Neuropathological Library Platforms for Advanced Analytics (U24 Clinical Trial Not Allowed)
Activity Code	U24 Resource-Related Research Projects – Cooperative Agreements
Announcement Type	New
Related Notices	NOT-OD-22-190 - Adjustments to NIH and AHRQ Grant Application Due Dates Between September 22 and September 30, 2022
Funding Opportunity Announcement (FOA) Number	RFA-NS-22-062
Companion Funding Opportunity	None
Number of Applications	See Section III. 3. Additional Information on Eligibility.
Assistance Listing Number(s)	93.853, 93.866
Funding Opportunity Purpose	The purpose of this NINDS-led Alzheimer's Disease and Alzheimer's Disease Related Dementias (AD/ADRD) initiative is to 1) develop tools, standards, and an Open-source software platform that enables a federated (multiple data repository sites with a single access portal) approach for data sharing and analysis of human digital neuropathological slides and 2) perform software testing to validate and verify that the software and tools developed can be used to perform multisite neuropathological analyses using a federated approach. The federated approach requires a single access point of digital slides from multiple geographically distinct brain banks. The resources developed are expected to also enable cross-site annotation and computational image analysis, including advanced analytic approaches. A critical feature of this FOA includes the broad sharing of neuropathological data to further advance research in this area, including the development of a digital resource for distribution and sharing of assessed neuropathological tissue. Software and tools developed under this initiative are expected to be shared using Open Science principles, and the federated digital library

U24NS133949-01
PIs:
Dr. David Gutman, Emory
Dr. Thomas Pearce, Pittsburgh
Dr. Brittany Dugger, UC-Davis
Dr. Lee Cooper, Northwestern

U24NS133945-01
PIs:
Dr. Pete Nelson, Kentucky
Dr. Cody Bumgardner, Kentucky
Dr. Maggie Flanagan, UTHSA

Involvement of many other institutions too!!!!!

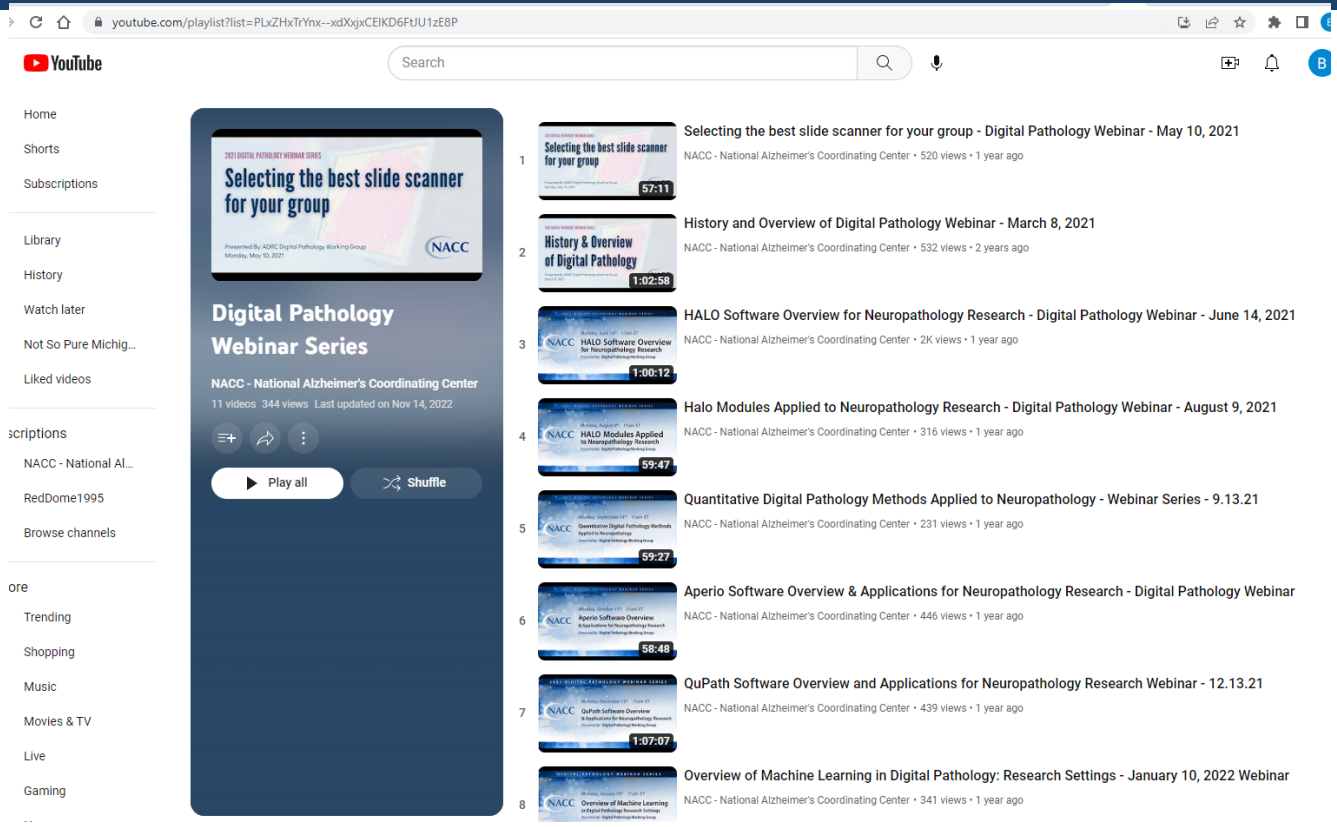
Digital pathology webinars on youtube!

Dr. Margaret Flanagan

UT Health San Antonio
The University of Texas Health Science Center at San Antonio

Hannah Rosentreter

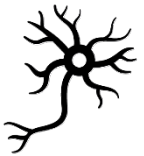
NACC National Alzheimer's Coordinating Center



Have a recent paper in digital pathology you'd like to share/present? Feel free to contact us!

Dr. Maggie Flanagan
margaret.flanagan@northwestern.edu
and/or
Dr. Brittany Dugger
bndugger@ucdavis.edu

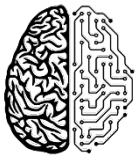
Brain Banking in the Modern Era of Digital Pathology, ’Omics, Biomarkers, and Artificial Intelligence Work Group



- Convened at Cold Spring Harbor Laboratory under co-chairs
  - Dr. Melissa E. Murray, Professor of Neuroscience, Mayo Clinic Florida
  - Dr. Hemali Phatnani, Assistant Professor of Neurology, Columbia University

- Brought together a wide-range of scientists studying neurodegeneration
  - Spectrum of tissue providers and tissue requestors
  - Individuals utilizing data derived from postmortem tissue
- Synthesized **actionable solutions** to enhance sustainability of brain banking to meet ever-increasing demands for tissue sharing

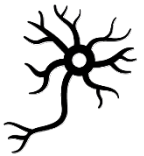
- Discussed upcoming plans to disseminate findings through a **Perspective** piece
  - Recommendations for critical unmet needs
  - Will include results from an upcoming survey of impact to be shared via listserv and social media for community feedback



Actionable solutions

Enhance brain bank framework

- Center of Excellence with strategic hire and training of tissue request team
- Neuropathologist-led program projects and R series MPI grants
- Cost-recovery models



Build out tissue sharing pipeline

- Slide sharing/hosting efforts
- Standardization in tissue preparation (fixative, freezing) and tissue storage
- Data harmonization for common data elements
- Codified brain library through an accessible portal
- Convergence of diverse data streams

Neurophenomics

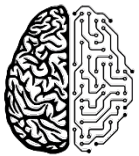
- Neuropathologic encyclopedia
- Phenotypic data provision
- Molecular Diagnostics past AIC (like cancer)

These critical unmet needs (and exciting avenues of research) require functioning brain bank resource with additional capacity for external requests and sufficient daily operations to not impact patient care

Training & Diversity

- Neuropathology training fellowships for MDs and PhDs
- Data science training and integration
- Enhanced socioeconomic and ethnoracial diversity of brain donors
- Enhanced efforts to bank neurotypical brains

Goal: Sustainability of brain banking to meet ever-increasing demands for tissue sharing



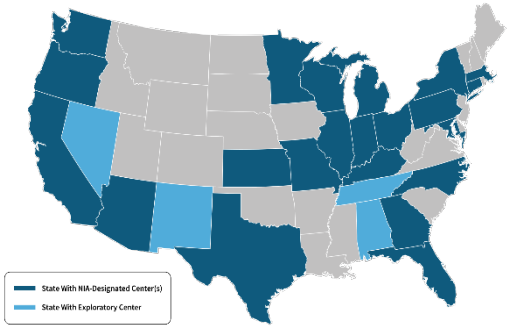
ADRC – NeuroBiobank Working Group to Advance Brain Donation and Utilization for ADRD Research: Progress Update

Julia Kofler, Nina Silverberg, Abigail Soyombo, Erika Tarver, Daniel Miller, Tish Hevel, Erica Melief, Harry Haroutunian, Bill Scott, Sabina Berretta, Anita Huttner, C. Dirk Keene

PILOT PROJECT GOALS (completed in red)

- Build a **collaborative network** (Brain Donor Project + Pitt, Yale, UW + NBB)
- Establish **coordination pipelines** between donors, coordinators (TBDP, NBB, LBDA, etc.) and NP sites (NBB, NP Cores)
- Develop **communication strategies** with donors and their families
- Determine **inclusion and exclusion criteria**, including minimum and optimum clinical/other characterization criteria for brain donors
- Develop central **protocols for site selection/donor referral**
- Establish **data and biospecimen sharing** and tracking protocols
- Successfully **share data/biospecimens** for research through NBB
- Determine **impact**
  - Frequency and utility of brain donation and tissue utilization across network
  - Identify areas for improvement
- Extend to the **broader research community**

NIH National Institute on Aging DESIGNATED Alzheimer's Disease Research Center



NIH NeuroBioBank
Facilitating Research and Creating Awareness

Progress: Pilot Donors (UW, Pitt, Yale ADRCs)

Pilot Consented and Brain Donors to date (n = 105)

	Total	M/F	Age	Dementia	Controls
Consented	144	59/85	54-101	88	48
Donations	68	28/40	60-101	46	1

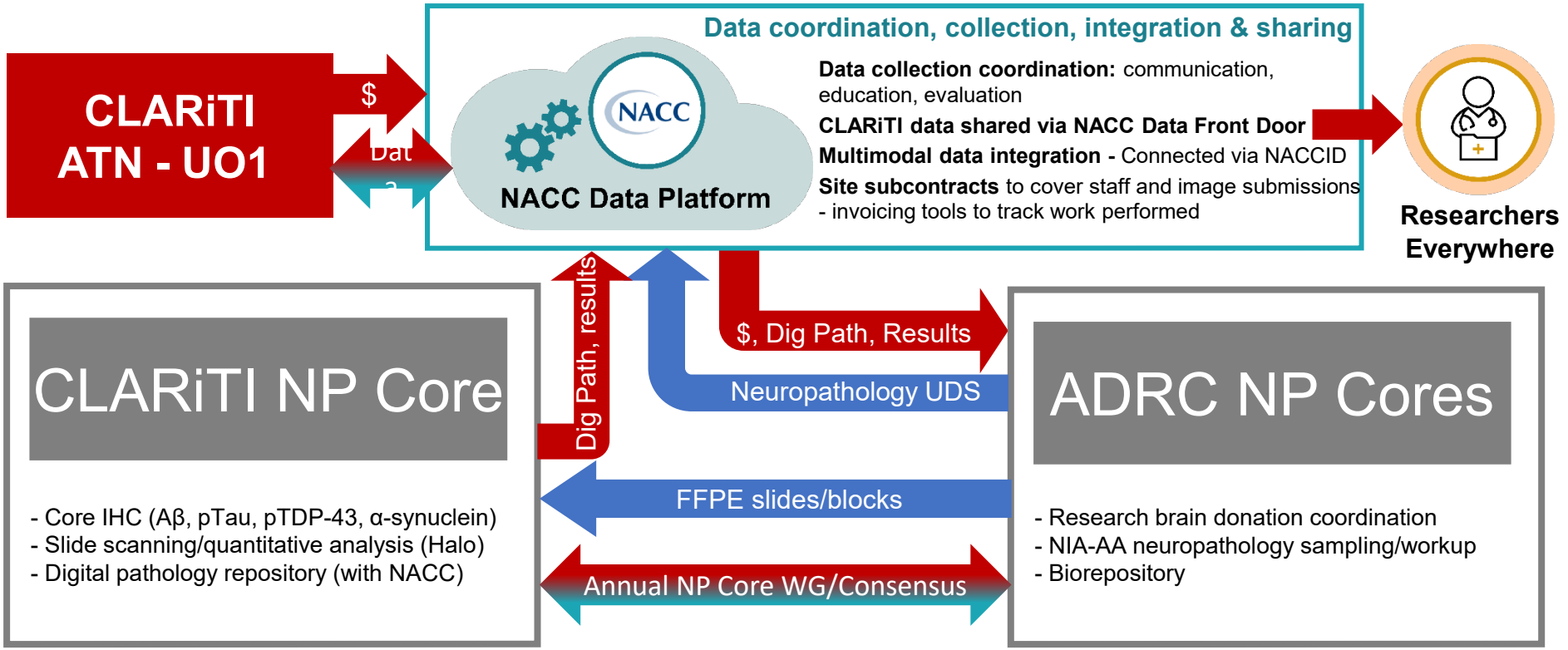
Neuropathology Summary of Pilot Donors (n=45)

	ADNC	n	Other NP Dx
Demented	High	40	FTLD, HS, LBD, uVBI, LATE, ARTAG, CAA, remote hem, dural Rosai-Dorfman
	Interm.	2	HS, LBD, uVBI, LATE, ARTAG
	Low	1	FTLD
	NA	1	PSP
Non-demented	None	1	LBD

Potential Benefits of Program

- **Promotes collaboration** across NBB, ADCs, BDN to set the foundation for enhanced national access for brain donation and brain research in AD, ADRD
- Allows both NBB and ADCs ability to accept **greater number and greater diversity of community-based AD** and control donations and make more biosamples and data available to the research community.
- Shared approaches/protocols can help **cross pollinate best practices** across programs
- **Improved and harmonized methods** to provide access to brain donors and scientists and for stakeholders to communicate with each other and donors/scientists.
- Increased ability for sites to retrieve registered cases outside of the pilot across programs (through NBB, NACC, local ADRC, etc.)
- Shared costs allow for greater collection of cases of interest to all parties
- Small catchment area and specific expertise of ADCs **allows for rapid autopsy and tissue processing for next generation research approaches**

Neuropathology Core Overview: CLARiTI
(CLarity in ADRD Research Through Imaging)



NEUROPATHOLOGY CORE SESSION

2023 Hybrid Fall ADRC Meeting
Friday, October 20

10:15 - 10:25am PT		*10min*
Welcome, Vascular Pathology Survey Results and Other Updates	Thomas Wisniewski, MD NYU ADRC	
10:25 - 10:45am PT		*15min Presentation, 5min Q&A*
The Alzheimer's Disease Pathologic Work-up: Are We Missing Significant Vascular Pathology?	Julie Schneider, MD, MS Rush University ADRC	
10:45 - 11:00am PT		*10min Presentation, 5min Q&A*
Neuropathological Correlates of MRI-Visible Small Vessel Disease Lesions	Susanne Van Veluw, PhD Massachusetts General Hospital	
11:00 - 11:15am PT		*10min Presentation, 5min Q&A*
Neuropathology of Cerebrovascular Disease at UCLA	Shino Magaki, MD, PhD UCLA	
11:15 - 11:30am PT		*10min Presentation, 5min Q&A*
Proteomic Studies of Vascular Pathology in Alzheimer's Disease and COVID-19	Dominique Leitner, PhD NYU ADRC	
11:30 - 11:45am PT		*10min Presentation, 5min Q&A*
A Workflow for Automated Segmentation of Arteriolosclerotic Blood Vessels on Digitized H&E Stained Brain Tissues Using Deep Learning	Jerry Lou, MD UC Irvine ADRC	

2023 FALL ADRC MEETING

October 18th - 20th, 2023
Hybrid Event
The Westin San Diego Gaslamp Quarter, San Diego

Network Wifi: Westin_CONFERENCE
Password: ADRC2023