ACT Neuroimaging Core
The First 5 Years

Christine Mac Donald, PhD
Professor & Vice Chair of Research
Department of Neurological Surgery
James and Gaye Pigott Endowed Chair
University of Washington School of Medicine
Harborview Medical Center

In the Beginning....

- Born out of a R01 focused on retrospective procurement of MRI scans on ACT participants
  - Clinically Ordered MRI
  - Research MRI from ACT participants co-enrolled in other Aging Studies
  - **Primary Objective: To develop an ACT Imaging Repository for Data Sharing**

Initial Motivation for Reclaiming MRI Scans:
An Economical Approach to Imaging Data

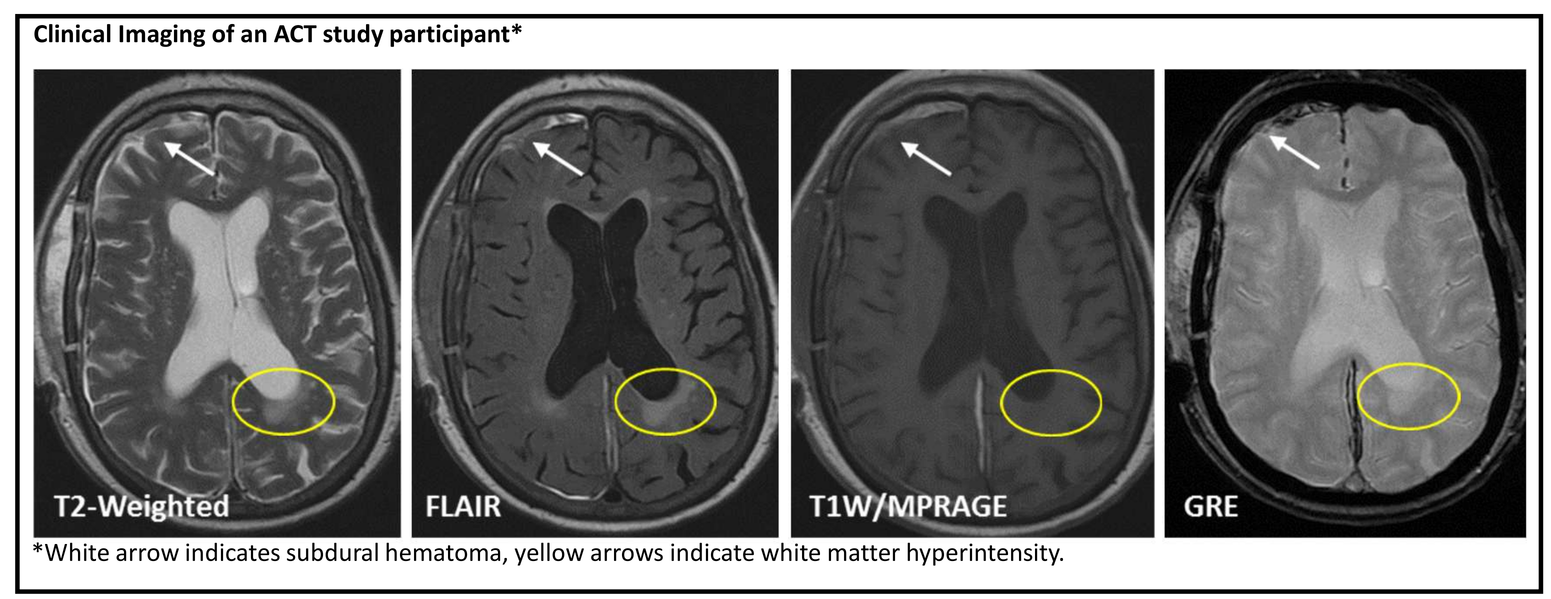
- Average research MRI scan - $800-1000

- Average Cost to reclaim ACT MRI scan - $40

- Total cost <u>savings</u> on 2000 scans - ~96%!
  - Reclaim: $80,000
  - New Research Scans: $1,600,000 - $2,000,000
    - Assuming participants were even able and willing to be scanned and assuming they were still alive

Radiology Rationale for Research

- Clinically-ordered neuroimaging scans can produce valuable data that can enhance understanding of brain-related outcomes and supplement information from research neuroimaging scans acquired in a more select population at considerable cost.
- Non-invasive diagnostic brain imaging has high sensitivity to aging- and dementia-related changes.
- Changes in brain volume, WM lesions, even subtle cortical thinning can be not only be visualized but also <u>counted</u> and <u>measured</u>.



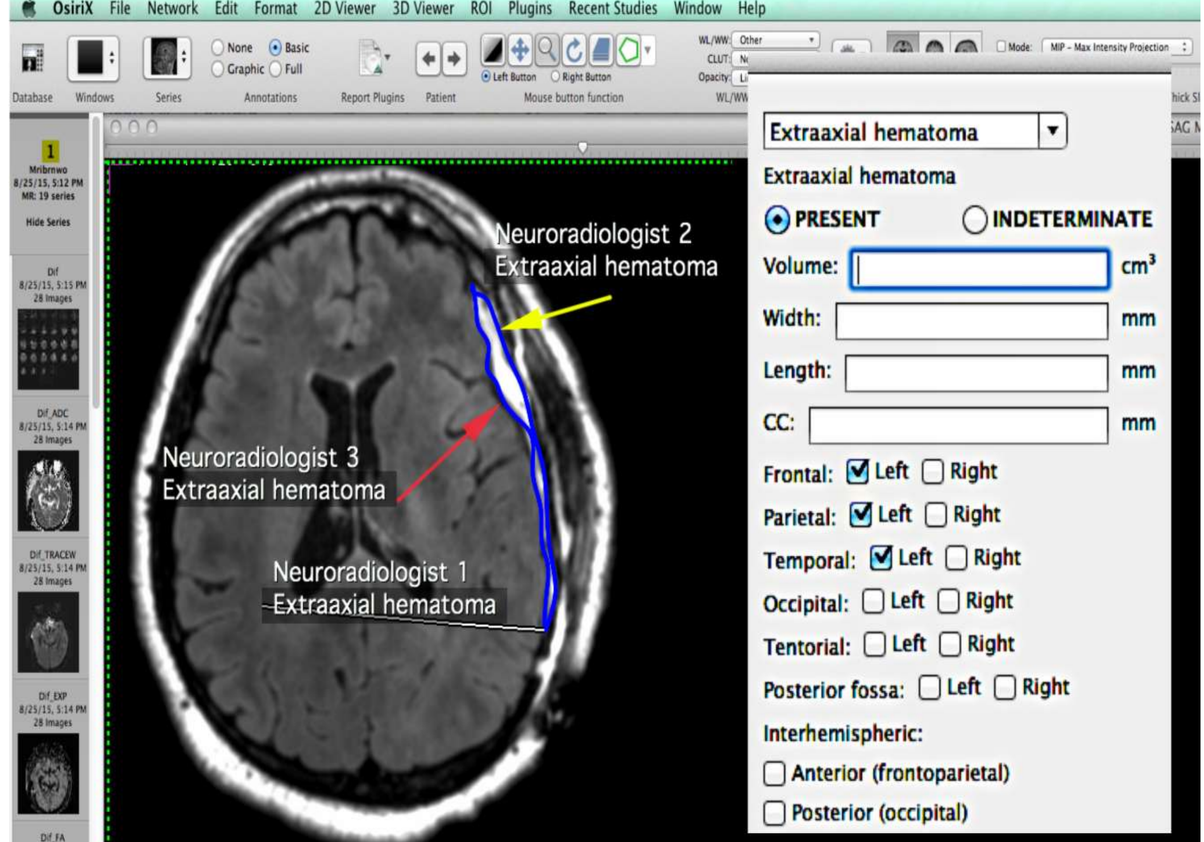
Clinical Imaging of an ACT study participant*

*White arrow indicates subdural hematoma, yellow arrows indicate white matter hyperintensity.

NIH Neuroimaging Common Data Elements

(A systematic way to Characterize & Count)

- A historical critique of clinical scan data was the lack of a standardized approach to ‘score’ and/or evaluate the images in a way that would be robust and meaningful to research studies.
- The NIH Common Data Elements for neuroimaging addresses this limitation.
- The NIH neuroimaging Common Data Elements (CDEs) facilitate standardized collection of diagnostic imaging data (https://commondataelements.ninds.nih.gov).
- NIH-funded investigators have developed tools to facilitate comparison and pooling data across studies and across MRI scanner platforms for a variety of neurodegenerative disease states.



Neuroimaging CDEs for ACT Imaging Records

- Feasibility of Approach: 3 neuroradiologists reviewed 9 clinical and 7 research MRI scans from ACT participants. The 16 scans were obtained from 6 different machines, built by all 3 major MRI vendors (Siemens, Philips, GE), using 5 different operating system platforms.
- The Original Team:
- Esther Yuh, MD PhD (UCSF), Jalal Andre, MD & Mahmud Mossa-Basha, MD (UW)

- Our neuroradiologists used the "Stroke CDEs" which contain 99 Data Elements primarily focused on stroke pathoanatomic lesions, white matter hyperintensities, age-related changes, and a variety of vascular specific findings in addition to general injury lesions.
- Initial Data Generated: 16 scans x 99 CDEs x 3 reviewers = **4,752 total CDEs**.
- And they extracted the Stroke CDEs with excellent agreement!
    - 87% of CDEs had perfect agreement (kappa=1.0),
    - 5% had good agreement beyond that expected by chance (kappa=0.6-0.8),
    - 5% moderate (kappa=0.4-0.6),
    - 3% fair (kappa= 0.2-0.4).
- 92% of CDEs had at least good agreement beyond that expected by chance

CDEs facilitate highly reliable data extraction from research and clinical MRI scans.

And generate a ton of high-quality data useful for aging research

Comparison of brain imaging and physical health between research and clinical neuroimaging cohorts of ageing

	Research MRI only ($n=77$)	Research and clinical MRI (n = 46)	Clinical MRI only ($n=1043$)	Adjusted P-value[a]
Infarct present, *n*;% (95% CI)				
Acute infarct	0; 0.0% (0.0%-3.9%)	0; 0.0% (0.0%-6.5%)	134; 12.8% (10.8%-14.9%)	<.001
Chronic infarct	5; 6.5% (1.0%-12.0%)	5; 10.9% (1.9%-19.9%)	158; 15.1% (13.0%-17.3%)	.136
Leukoencephalopathy scores, mean (95% CI)				
Fazekas scale total	3.5 (3.2-3.9)	4.0 (3.5-4.4)	3.8 (3.7-3.9)	.758
Modified Scheltens total	14.1 (12.8-15.3)	15.7 (14.0-17.5)	13.6 (13.3-14.0)	.009
Age-related white matter changes total	5.5 (5.0-6.0)	6.1 (5.4-6.9)	5.4 (5.3-5.6)	.032
Haemorrhage presence, *n*;% (95% CI)				
Haematoma or haemorrhage	22; 28.6% (18.5%-38.7%)	9; 19.6% (8.1%-31.0%)	189; 18.1% (15.8%-20.5%)	.078
Chronic haematoma	1; 1.3% (0%-3.8%)	0; 0.0% (0.0%-6.5%)	31; 3.0% (1.9%-4.0%)	<.001
Microbleeds	20; 26.0% (16.2%-35.8%)	8; 17.4% (6.4%-28.3%)	146; 14.0% (11.9%-16.1%)	.030
Intraventricular haemorrhage	0; 0.0% (0.0%-3.9%)	1; 2.2% (0.0%-6.4%)	12; 1.2% (0.5%-1.8%)	.006
Subarachnoid haemorrhage	2; 2.6% (0%-6.2%)	0; 0.0% (0.0%-6.5%)	21; 2.0% (1.2%-2.9%)	<.001
Subdural haematoma	0; 0.0% (0.0%-3.9%)	1; 2.2% (0.0%-6.4%)	17; 1.6% (0.9%-2.4%)	<.001
Epidural haematoma	0; 0.0% (0.0%-3.9%)	0; 0.0% (0.0%-6.5%)	1; 0.1% (0.0%-0.3%)	.324
Haemorrhagic transformation	0; 0.0% (0.0%-3.9%)	0; 0.0% (0.0%-6.5%)	19; 1.8% (1.0%-2.6%)	<.001
Other findings, *n*;% (95% CI)				
Midline shift	0; 0.0% (0.0%-3.9%)	1; 2.2% (0.0%-6.4%)	12; 1.2% (0.5%-1.8%)	.006
Hydrocephalus	0; 0.0% (0.0%-3.9%)	1; 2.2% (0.0%-6.4%)	40; 3.8% (2.7%-5.0%)	<.001
Arteriovenous malformation	0; 0.0% (0.0%-3.9%)	0; 0.0% (0.0%-6.5%)	0; 0.0% (0.0%-0.3%)	NA
Tumour	3; 3.9% (0.0%-8.2%)	4; 8.7% (0.6%-16.8%)	59; 5.7% (4.3%-7.1%)	.619
Abscess	0; 0.0% (0.0%-3.9%)	0; 0.0% (0.0%-6.5%)	0; 0.0% (0.0%-0.3%)	NA
Other malformations	1; 1.3% (0.0%-3.8%)	1; 2.2% (0.0%-6.4%)	45; 4.3% (3.1%-5.5%)	.145
Quantitative thresholding, mean (95% CI)				
Total brain volume (mL)	1184.0 (1158.3-1209.7)	1149.5 (1110.0-1189.0)	1099.9 (1091.8-1108.1)	<.001
Percent white matter hyperintensity volume of total brain volume, mean (95% CI)	1.9 (1.6-2.2)	4.0 (3.1-4.8)	5.3 (5.1-5.5)	<.001

https://doi.org/10.1093/bjr/tqae004

	Research MRI only ($n = 77$)	Research and clinical MRI ($n = 46$)	Clinical MRI only ($n = 1043$)	No MRI ($N = 3146$)	Adjusted P-value[a]
Blood pressure and hypertension					
Systolic blood pressure, mean (95% CI)	132.9 (128.9-136.9)	135.3 (131.0-139.6)	135.5 (134.2-136.8)	136.2 (135.5-136.9)	.498
Diastolic blood pressure, mean (95% CI)	72.1 (69.9-74.3)	72.3 (69.6-74.9)	71.8 (71.2-72.5)	72.1 (71.7-72.5)	.952
Blood pressure over 140/90; *n*;% (95% CI)	27; 35.5% (24.8%-46.3%)	18; 40.0% (25.7%-54.3%)	351; 38.3% (35.2%-41.5%)	1062; 37.8% (36.0%-39.6%)	.968
Essential hypertension diagnosis past year; *n*;% (95% CI)	20; 28.6% (18.0%-39.2%)	22; 47.8% (33.4%-62.3%)	541; 52.0% (48.9%-55.0%)	1212; 40.6% (38.8%-42.3%)	<.001
Cardiovascular conditions; *n*;% (95% CI)					
Heart disease (self-reported)	14; 18.2% (9.6%-26.8%)	5; 10.9% (1.9%-19.9%)	218; 21.7% (19.2%-24.3%)	706; 23.0% (21.5%-24.5%)	.069
Cerebrovascular disease (self-reported)	3; 3.9% (0.0%-8.2%)	8; 17.4% (6.4%-28.3%)	255; 25.4% (22.8%-28.1%)	392; 12.8% (11.6%-14.0%)	<.001
Congestive heart failure (self-reported)	1; 1.3% (0.0%-3.8%)	2; 4.3% (0.0%-10.2%)	60; 6.0% (4.5%-7.5%)	258; 8.5% (7.5%-9.5%)	<.001
Atrial fibrillation past year	5; 7.1% (1.1%-13.2%)	7; 15.2% (4.8%-25.6%)	186; 17.9% (15.5%-20.2%)	405; 13.6% (12.3%-14.8%)	.009
Stroke past year	1; 1.4% (0.0%-4.2%)	2; 4.3% (0.0%-10.2%)	96; 9.2% (7.5%-11.0%)	26; 0.9% (0.5%-1.2%)	<.001
Diabetes past year; *n*; % (95% CI)	6; 8.6% (2.0%-15.1%)	4; 8.7% (0.6%-16.8%)	187; 18.0% (15.6%-20.3%)	401; 13.4% (12.2%-14.6%)	.002
Depression					
Depression (CES-D score 17 or greater), *n*;% (95% CI)	4; 5.2% (0.2%-10.2%)	6; 13.0% (3.3%-22.8%)	101; 10.7% (8.7%-12.6%)	269; 9.2% (8.1%-10.2%)	.288
CES-D score, mean (95% CI)	2.4 (1.8-3.1)	4.0 (2.8-5.2)	4.0(3.7-4.3)	3.6 (3.4-3.7)	.003
Cognitive functioning					
Dementia diagnosis; *n*;% (95% CI)	1; 1.3% (0.0%-3.8%)	2; 4.3% (0.0%-10.2%)	228; 21.9% (19.4%-24.4%)	245; 7.8% (6.9%-8.7%)	<.001
CASI score (only using "valid" scores), mean (95% CI)	0.6 (0.5-0.8)	0.5 (0.3-0.8)	0.0 (-0.1-0.0)	0.2 (0.2-0.3)	<.001
Charlson comorbidity index past year, mean (95% CI)	0.8 (0.6-1.1)	1.3 (0.7-1.9)	1.9 (1.7-2.0)	1.1 (1.1-1.2)	<.001
Inpatient hospitalization past 2 years, *n*;% (95% CI)	5; 7.1% (1.1%-13.2%)	7; 15.2% (4.8%-25.6%)	323; 31.1% (28.3%-33.9%)	571; 19.1% (17.7%-20.6%)	<.001
Regular exercise, *n*;% (95% CI)	62; 80.5% (71.7%-89.4%)	38; 82.6% (71.7%-93.6%)	588; 58.5% (55.5%-61.6%)	1925; 62.9% (61.2%-64.6%)	<.001
Physical functioning score, mean (95% CI)	12.7 (11.9-13.5)	11.5 (10.3-12.7)	11.5 (11.2-11.8)	12.0 (11.8-12.1)	.030
Body mass index, mean (95% CI)	25.9 (25.0-26.8)	26.8 (25.6-28.0)	26.4 (26.1-26.7)	27.0 (26.8-27.2)	.081
Self-rated health of "good" or better, *n*;% (95% CI)	76; 98.7% (96.2%-100.0%)	40; 87.0% (77.2%-96.7%)	804; 79.9% (77.4%-82.4%)	2617; 85.4% (84.1%-86.6%)	<.001
Smoking					
Ever smoked, *n*;% (95% CI)	39; 52.7% (41.3%-64.1%)	22; 47.8% (33.4%-62.3%)	485; 51.2% (48.0%-54.4%)	1445; 49.5% (47.7%-51.3%)	.591
Pack-years, mean (95% CI)	15.2 (10.5-20.0)	17.0 (8.0-26.1)	17.9 (14.6-21.2)	18.2 (16.3-20.0)	.872
APOE Epsilon 4 Allele (at least one copy), *n*;% (95% CI)	20; 28.6% (18.0%-39.2%)	9; 20.0% (8.3%-31.7%)	236; 27.2% (24.2%-30.1%)	646; 26.1% (24.4%-27.8%)	.478

Enter In the ACT U19 Neuroimaging Core!

(Past and Present)

Core Lead: Christine Mac Donald, PhD

Core Team:

Jalal Andre, MD
Patti Curl, MD
Mahmud Mossa-Basha, MD
Cecilia Lee, MD
Niranjan Balu, PhD
Ariel Rokem, PhD

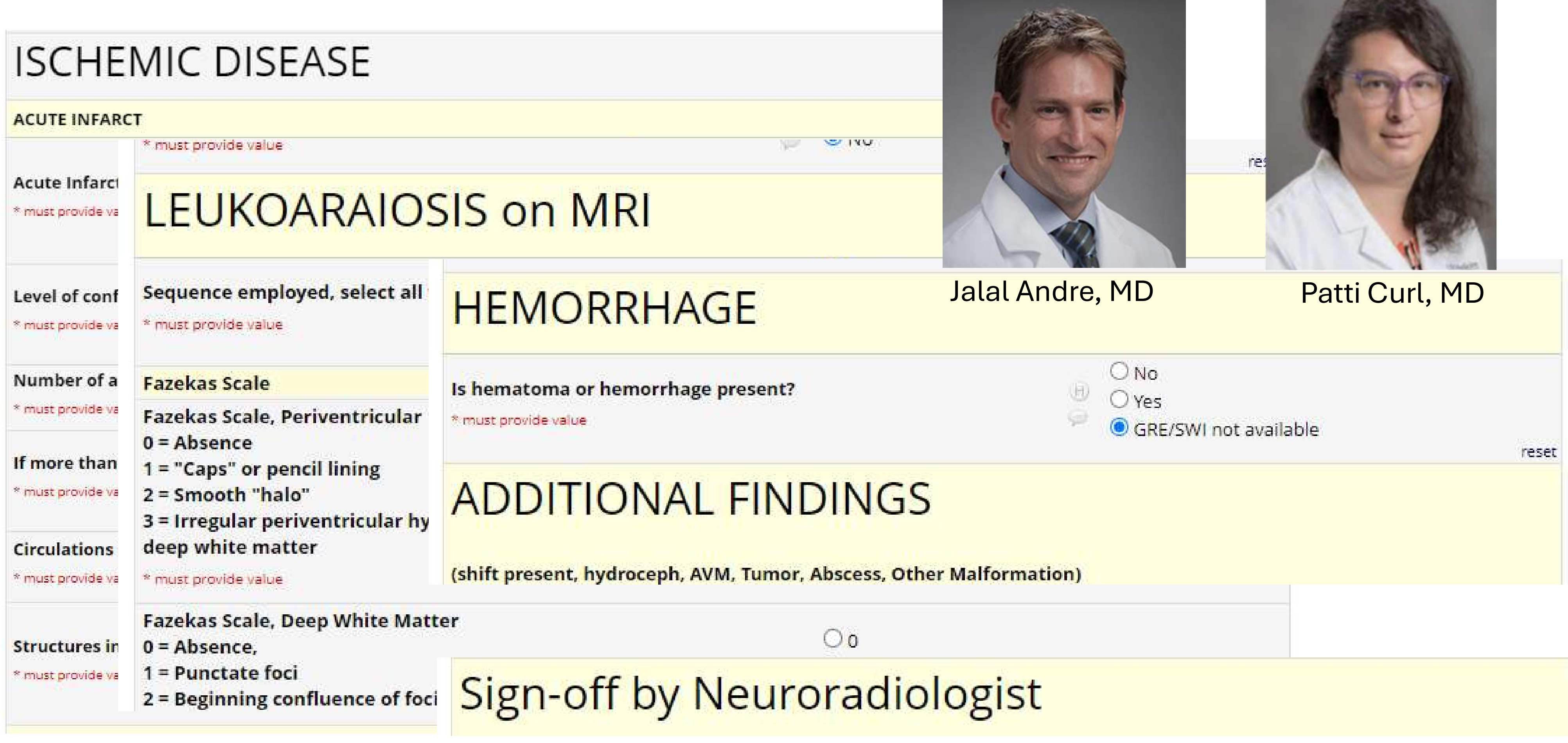
Gador Canton, PhD
Kelly Chang, PhD
David Hunt, PhD
Bradley Howlett, BS
Nina LaPiana, BS
Samantha Murray Tuesta, BS

James Ralston, MD
Kelly Ehrlich, MS
Margaret Dezelar, MS
Luke Burke, BS
Brandie Sevey, BS
John Ewing, BS

ACT U19 NeuroImaging Core (NIC) Aims

- Specific Aim 1: Collect, analyze, and archive new MRI scans to support the Projects.
- Specific Aim 2: Analyze research and clinical MRI scans in support of the Projects.
- Specific Aim 3: Collect, process, and analyze post-mortem neuroimaging.
- Specific Aim 4: Apply state-of-the-art machine learning techniques to expand utility of neuroimaging data.

Neuroimaging CDEs Report out 99 CDEs across 4 Main Domains



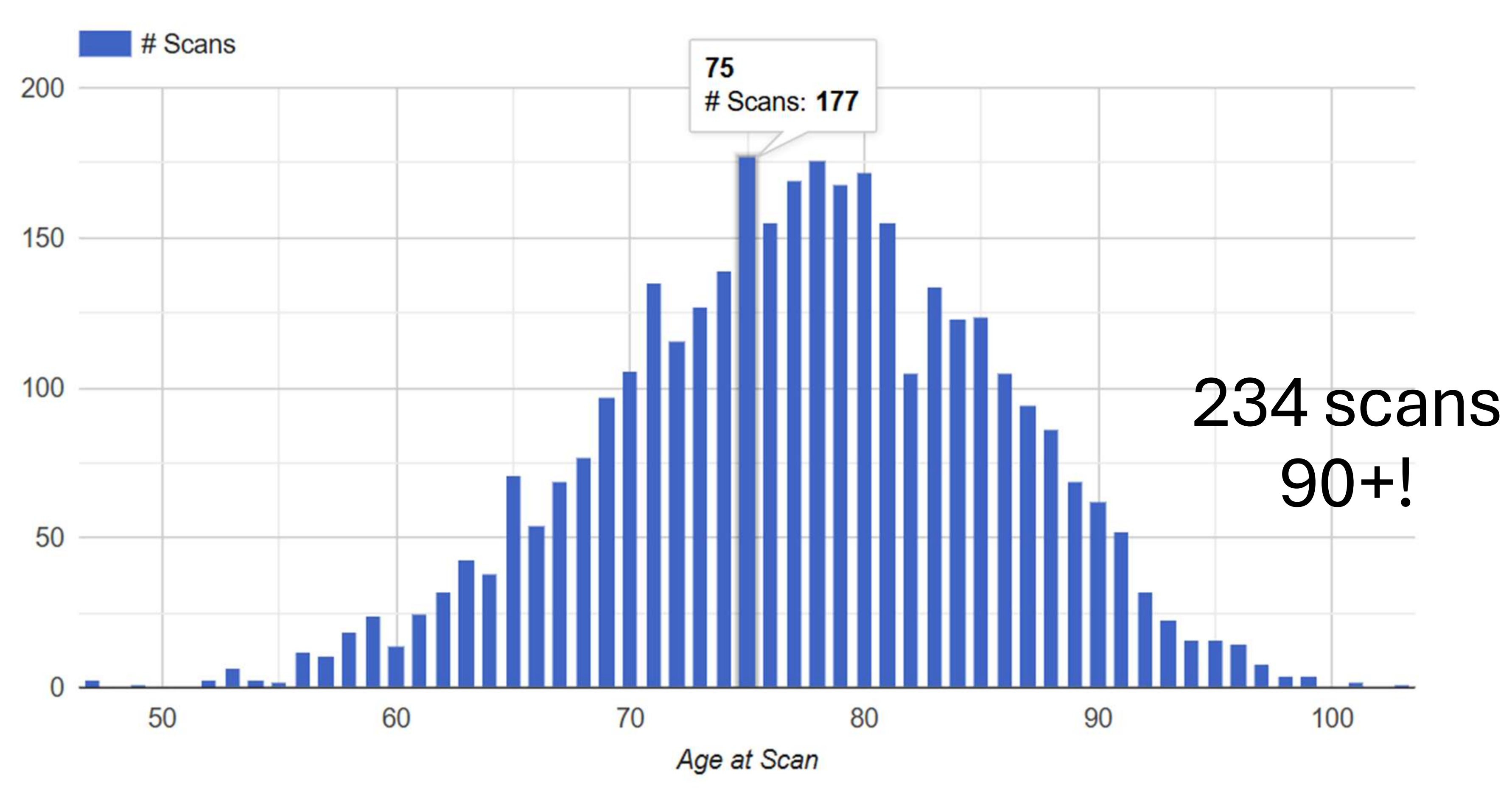
Busy Bees in the NIC! ☺

- Ante-Mortem Imaging – MRI scans while patients are Alive
  - 3477 MRI scans procured on 2069 ACT participants
    - 708 who have more than 1 MRI Scan
  - 56% Female, 44% Male
  - 210 ACT Participants with both a Clinically-Ordered Exam and a Research Scan
  - 602 Research-Grade MRI scans, CLARiTI & SCAN compliant
- Analysis of these MRI Scans
  - 3292 Scans with Neuroimaging CDEs Complete
    - 143 Unusable
  - 2514 Scans with Freesurfer Quantitative Volumetrics Complete
    - 40 Unusable
  - 2322 Scans with Quantitative White Matter Hyperintensity Analysis Complete
    - 113 Unusable

Across All ACT Cohorts

ACT Ante-Mortem Cohorts

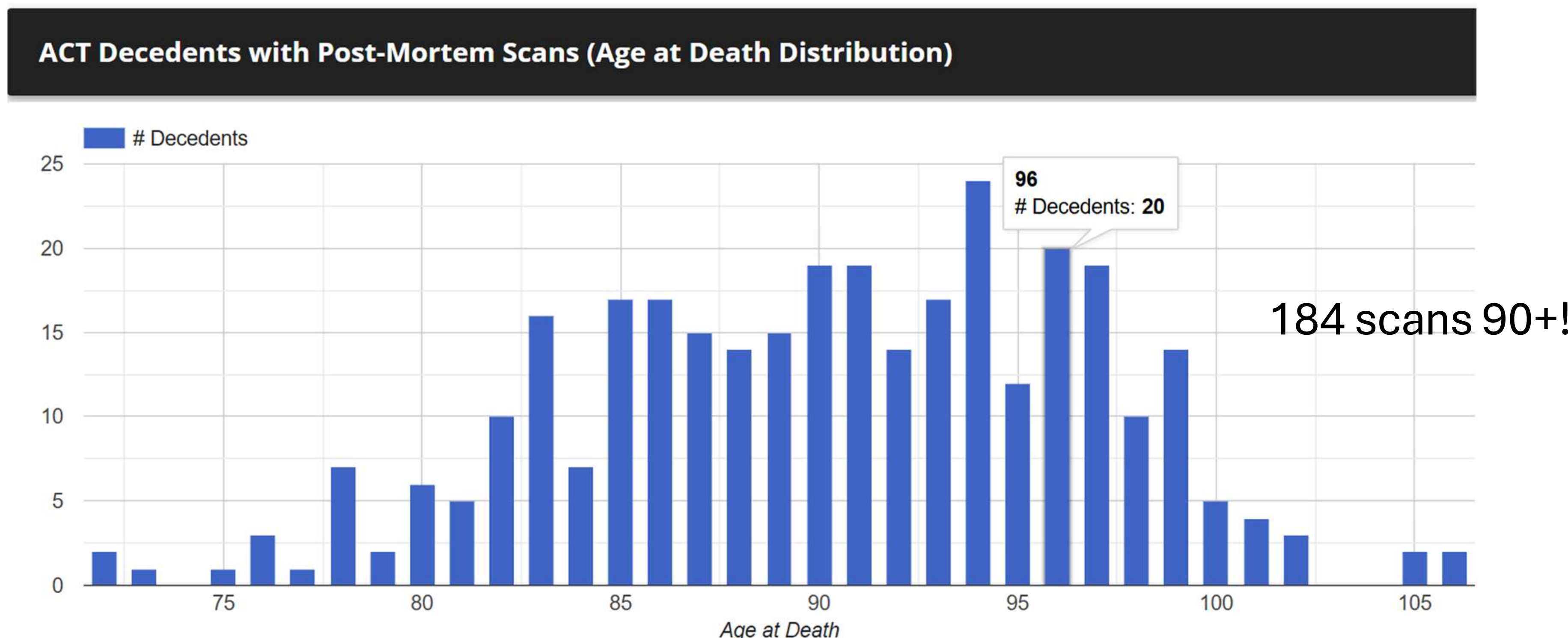
Cohort Name And ID Range	Number Of Participants With Scans In The NIC	Number Of Scans On These Participants In The NIC	Clinical	Research
Original Cohort:	321	457	443	14
Expansion Cohort:	234	397	366	31
U01 Continuous:	1151	2027	1540	487
Post-Covid Diversity:	363	596	526	70



234 scans
90+!

Postmortem Imaging and Analysis

- 323 ACT Brain Donors with Postmortem MRI (309 we have scans in life!)
  - 63% Female, 37% Male
  - 304 Freesurfer Quantitative Volumetrics Complete
  - 172 of 173 Cadaveric Quantitative White Matter Hyperintensity Complete



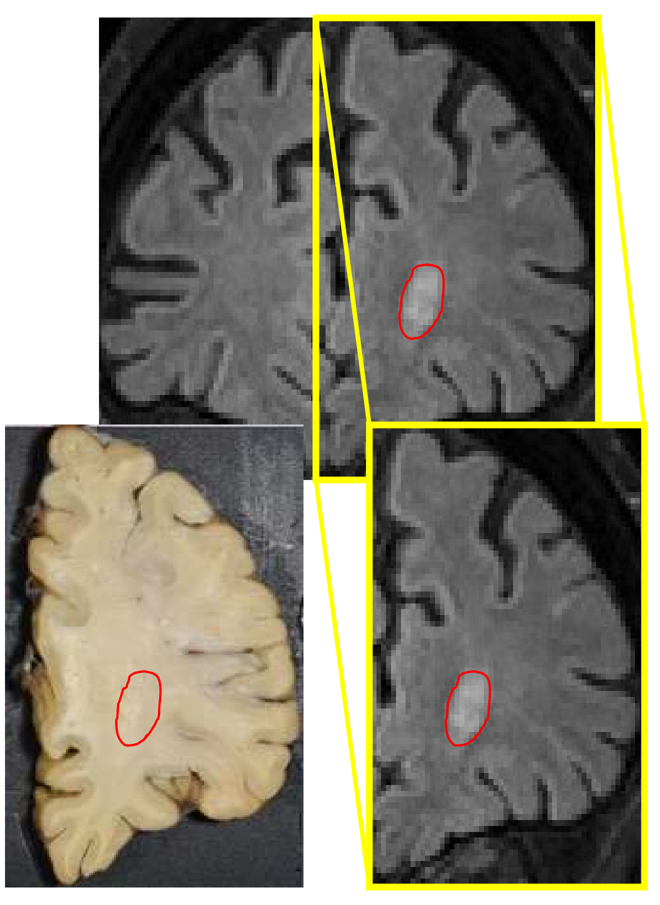
184 scans 90+!

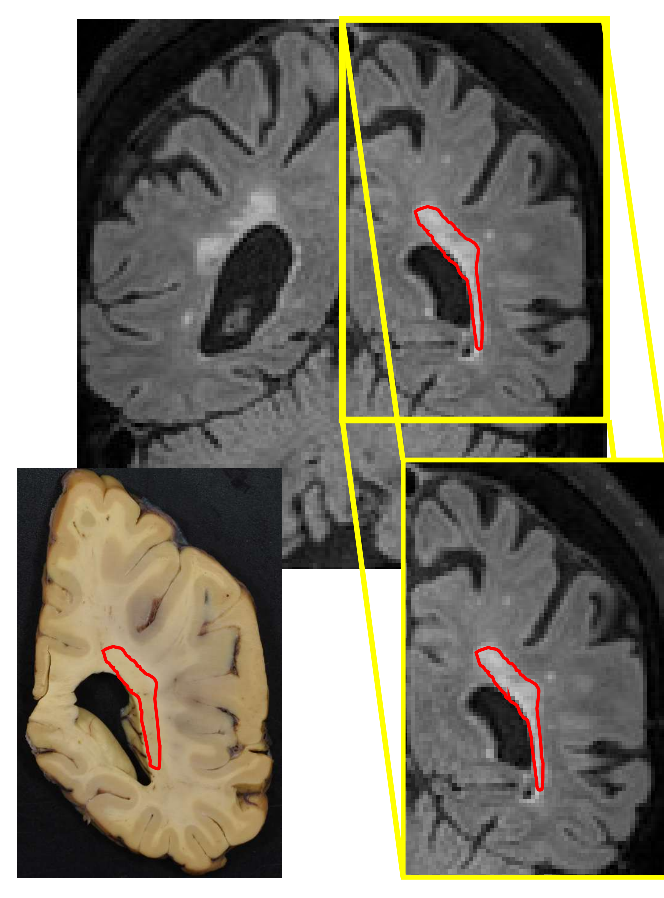
Again, Across All ACT Cohorts

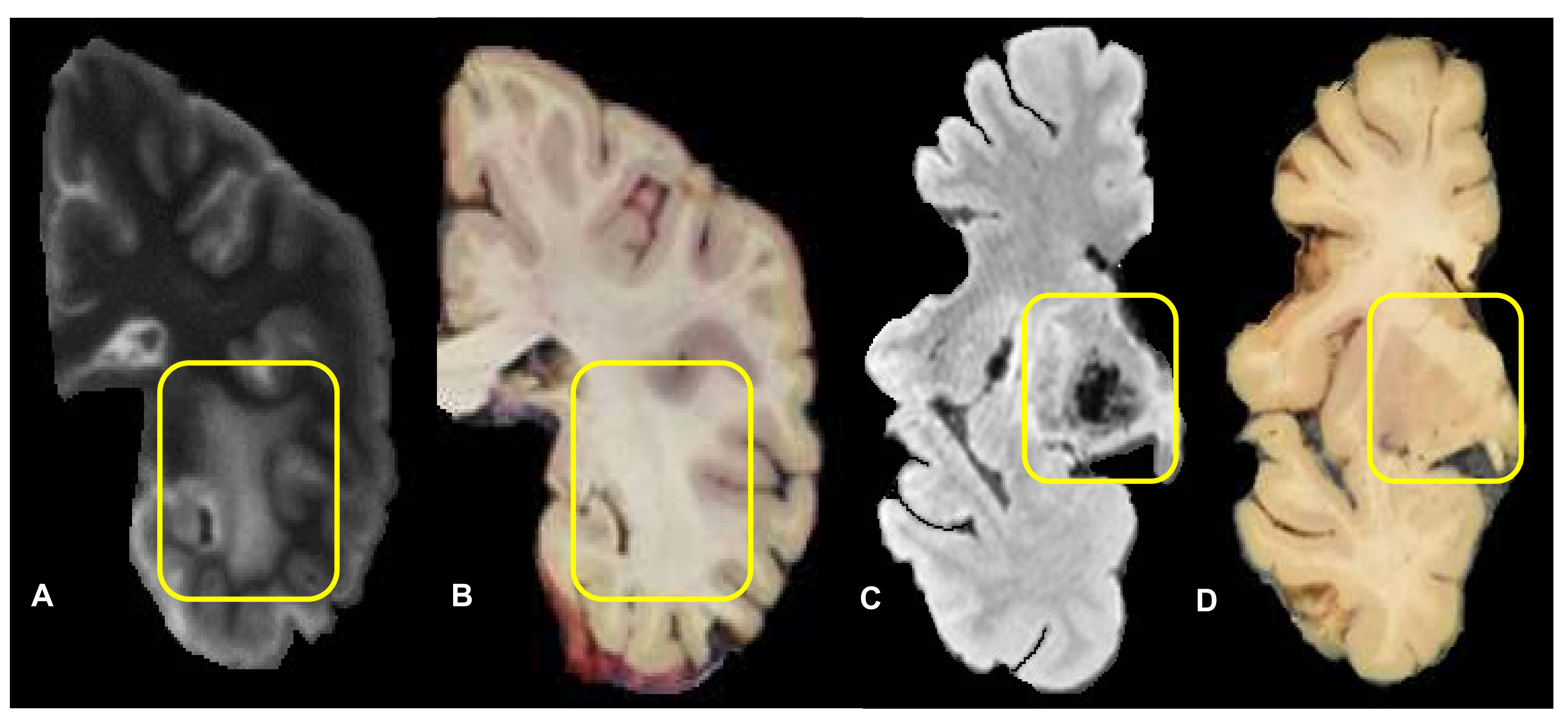
ACT Post-Mortem Cohorts

Cohort Name And ID Range	Number Of Decedents With Scans In The NIC	Number Of Scans On These Decedents In The NIC	Clinical	Research
Original Cohort:	106	161	153	8
Expansion Cohort:	75	126	117	9
U01 Continuous:	127	235	203	32
Post-Covid Diversity:	1	9	9	0

Image-Guided Tissue Selection of White Matter Hyperintense Lesions






A
B
C
D

Advancements Made for Rapid Autopsy Imaging (in collaboration with the Neuropath Core)

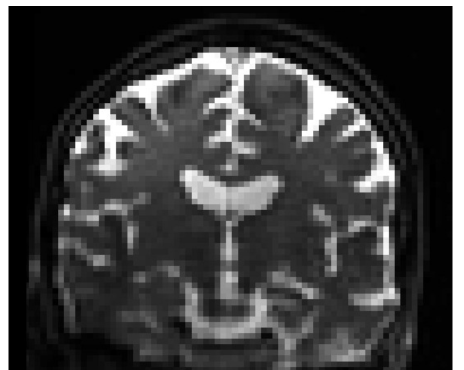
- Rationale – as we are able to get decedents more and more at shorter PMI making them viable for Rapid Autopsy – we lose the opportunity to image and examine the whole brain – both hemispheres
- Some conditions can be asymmetric and only occur on one side of the brain
  - What if you imaged the 'wrong' pathology side and completely missed key findings?!
- Is there a way to also do a fast and dirty scan at Brain Autopsy?
- Could it help address this challenge?

YES! - Hyperfine – Rapid MRI

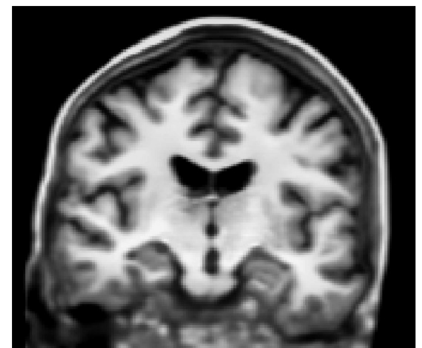
- 0.07 T Portable MRI
- Installed in HMC autopsy suite in 09/2021
- *Cadaveric* or *fresh* brain MRI
- Scan acquisition time is <60 min (~40 min target)

Hyperfine Imaging Protocol

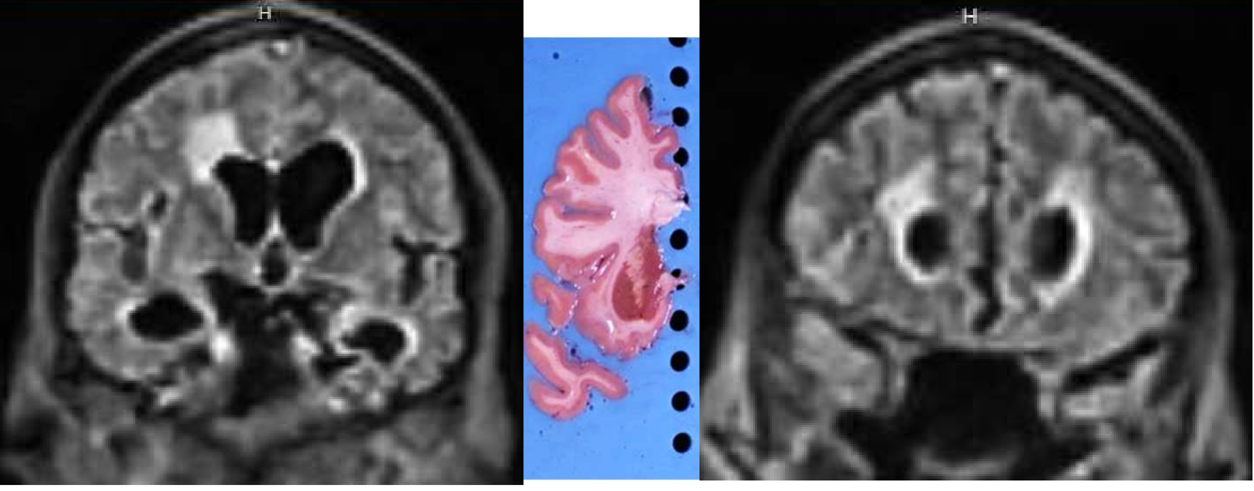
We collect 2 – 3D T2 Weighted Images



Synthetically Generated High Resolution T1 for Coregistration with ExVivo Imaging



We collect a 2D FLAIR to identify white matter lesions not visible on the fresh tissue at brain autopsy

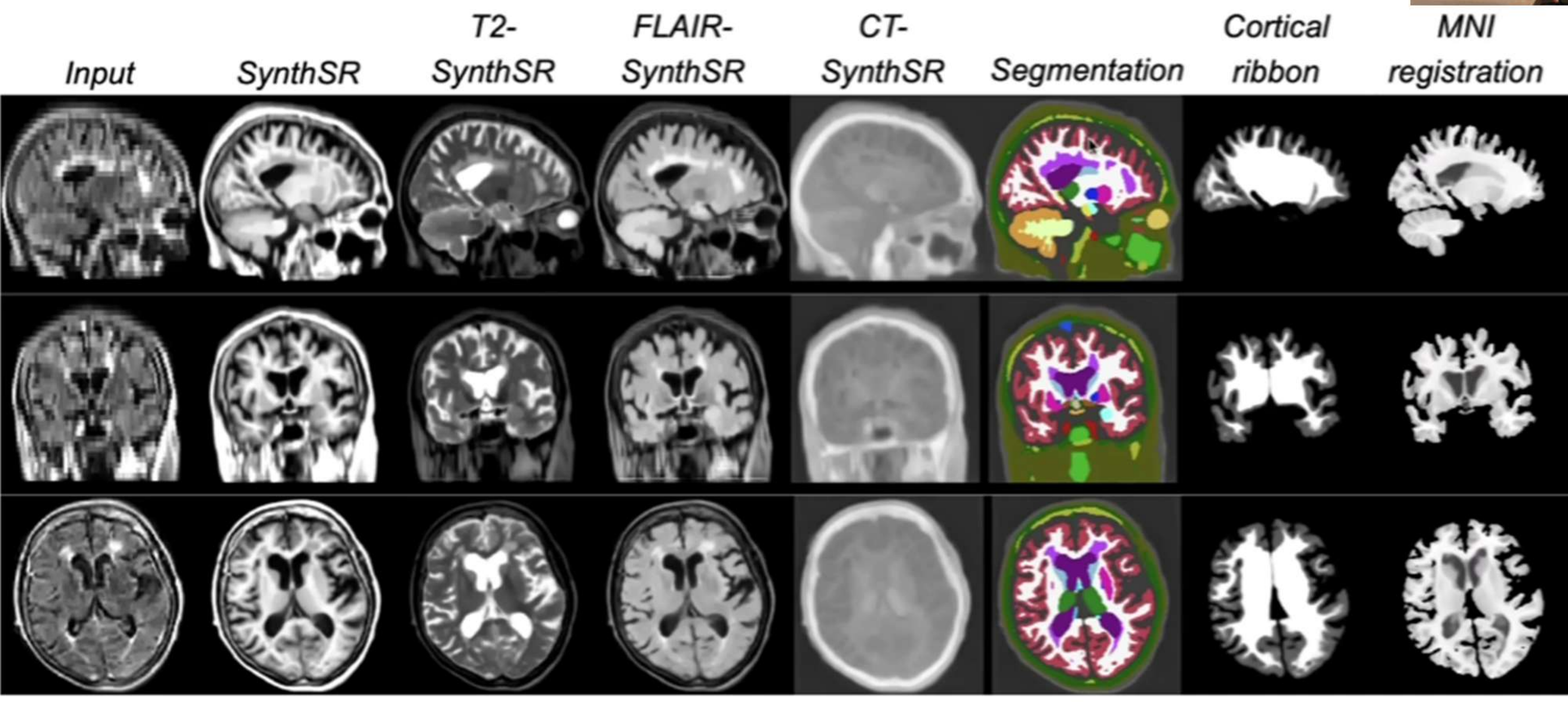


Examples of ACT decedents with white matter lesions Fresh Tissue from Case to Left with big WMH further forward but still was lesioned on imaging at this level and no apparent tissue change from fresh tissue

Could we do even better with advancements in Neuroimaging Machine Learning Algorithms? (Aim 4)

SuperSynth – Developed in Living Patients

Sample outputs (*in vivo*)

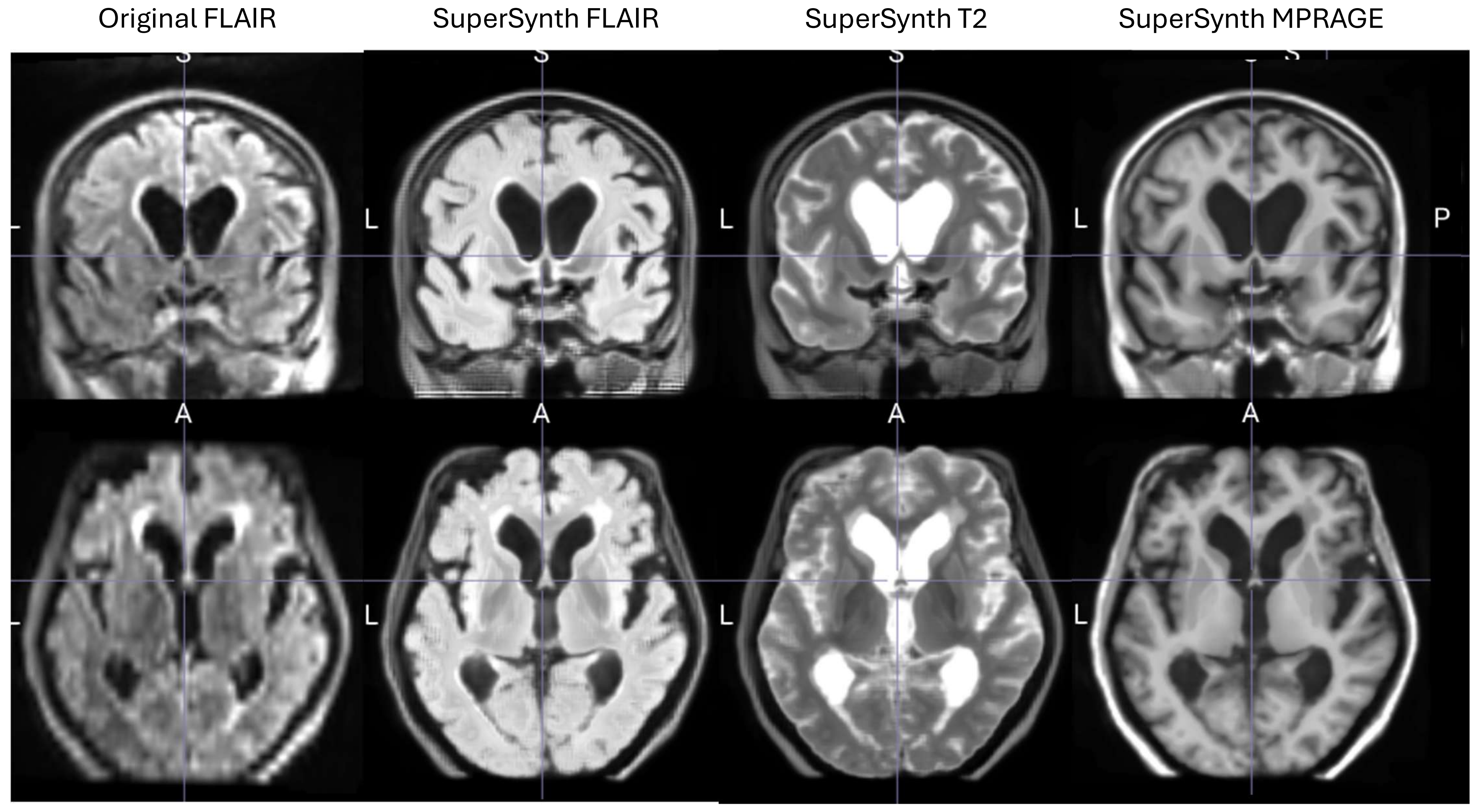


Complements of the Brilliance of Dr. Eugenio Iglesias, MGH

We are first to try Postmortem!

- Rapid MRI scan via low field Hyperfine MRI scanner
- Drum roll please.....

Rapid MRI at Brain Autopsy



And not only does it work
We can use it for quantitative analysis!!

- Next is an ACT decedent run through Hypermapper for quantitative white matter hyperintensity analysis

Nina LaPiana

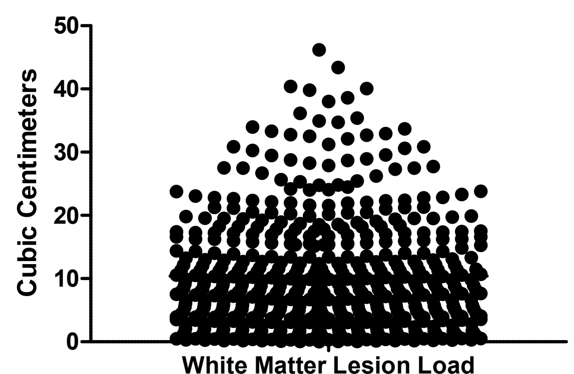
Bradley Howlett

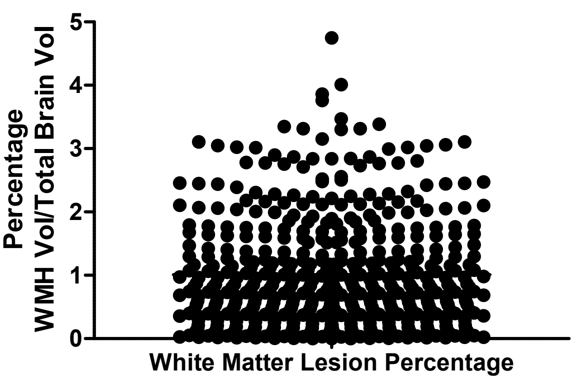
Sam Murray Tuesta

David Hunt, PhD

Postmortem Imaging Analyst Team

Quantitative Output of White Matter Lesioning Analysis in Cadaveric Rapid MRI





What have we found?

Comparative Leukoariosis Quantification Between 2 and 3-Dimensional Fluid Attenuated Inversion Recovery Brain MRI Sequences

Patti K. Curl[1] | Jalal B. Andre[1] | Wenxuan Xiong[2] | Nina LaPiana[2] | Bradley Howlett[2] | Samantha Murray Tuesta[2] | David Hunt[2] | Christine L. Mac Donald[2]

Diffusion MRI sheds light on FLAIR white matter hyperintensities in an aging cohort

Kelly Chang[1], Luke Burke[2], Nina LaPiana[2], Bradley Howlett[2], David Hunt[2], Margaret Dezelar[4], Jalal B. Andre[3], James Ralston[4], Ariel Rokem[1,5], and Christine Mac Donald[2,5]

Cumulative Anticholinergic Exposure and White Matter Hyperintensity Burden in Community Dwelling Older Adults

Kevin H. Li, PharmD[a], Chloe Krakauer, PhD[b], Jennifer C. Nelson, PhD[b], Paul K. Crane, MD, MPH[c], Jalal B. Andre, MD[d], Patti K. Curl, MD[d], Esther Yuh, MD, PhD[e], Mahmud Mossa-Basha, MD[d], James D. Ralston, MD, MPH[b], Christine L. Mac Donald, PhD[f,*], Shelly L. Gray, PharmD, MS, AGFS[a,*]

Free water elimination tractometry for aging brains

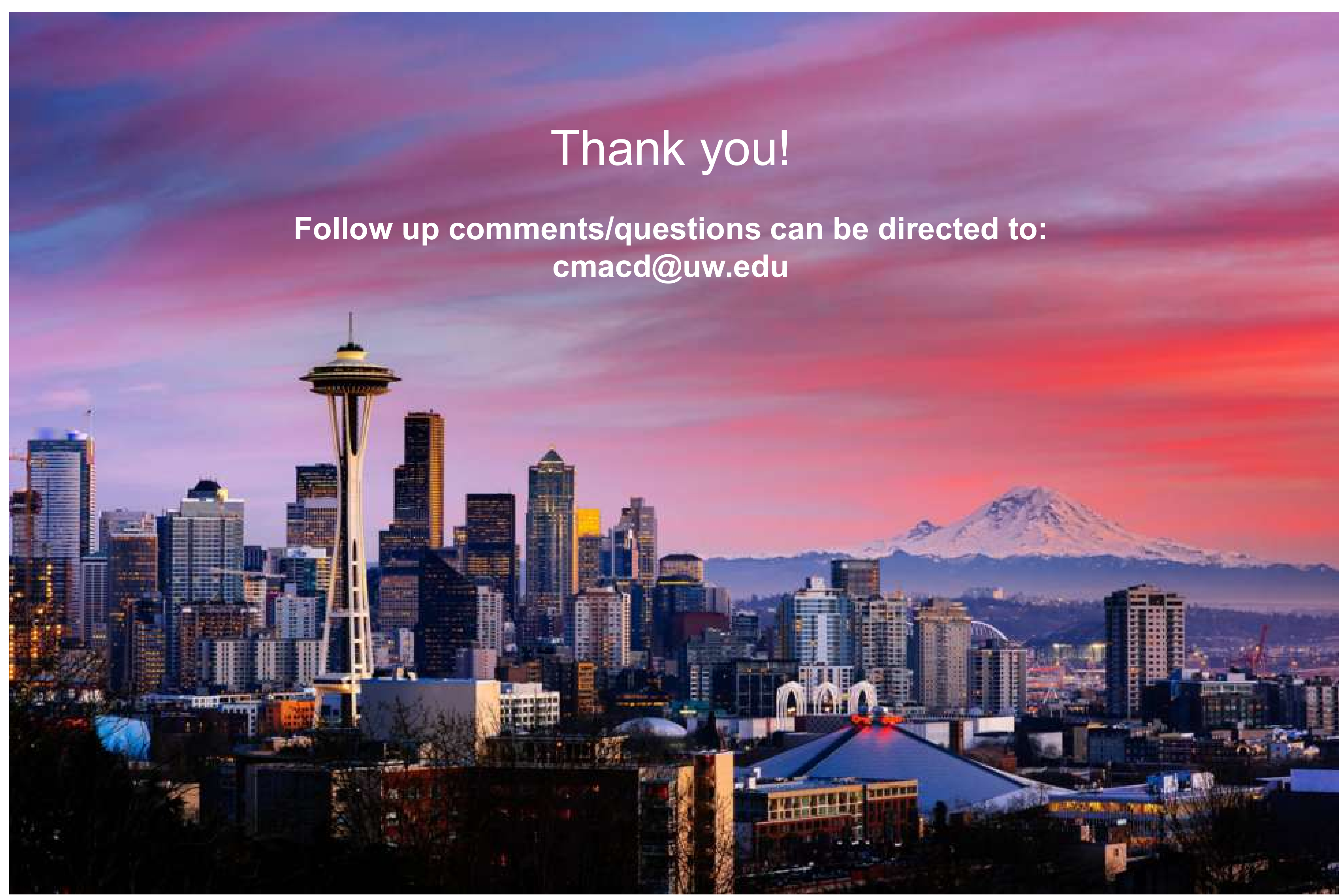
Kelly Chang[a], Luke Burke[b], Nina LaPiana[c], Bradley Howlett[c], David Hunt[c], Margaret Dezelar[b], Jalal B. Andre[d], Patti Curl[d], James D. Ralston[b], Ariel Rokem[a,*], Christine L. Mac Donald[c,*]

Comparison of brain imaging and physical health between research and clinical neuroimaging cohorts of ageing

Mahmud Mossa-Basha, MD[1], Jalal B. Andre, MD[1], Esther Yuh, MD, PhD[2], David Hunt, PhD[3], Nina LaPiana, BS[3], Bradley Howlett, BS[3], Chloe Krakauer, PhD[4], Paul Crane, MD[5], Jennifer Nelson, PhD[4], Margaret DeZelar, MS[4], Kelly Meyers, BA[4], Eric Larson, MD[4], James Ralston, MD[4], Christine L. Mac Donald, PhD[3,*]

Looking Ahead

- Robust Neuroimaging Repository aligned with other Rich ACT Data
- One of the largest combined antemortem/postmortem imaging repositories available in an aging cohort with brain autopsy endpoints.
- Well positioned to link and expand to other cohorts given strategic selection of CLARiTI/SCAN compliant sequences.
- Scalable processes for continued imaging data collection, flexible visualization tools for easier tracking and reporting, and a wealth of imaging Radiology knowledge to support new investigators and newcomers to ACT data.



http://www.myphotodump.com/seattle-washington-and-mt-rainier-oc-3680x2453/