Short Report:
NACC CSF $A\beta_{42}$, p-Tau_{181}, t-Tau

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Overall Goal of this Presentation

- Give a short summary of the NACC CSF $A\beta_{42}$, p-Tau_{181},and t-Tau data as it stands now.

Objectives

1. Brief overview of CSF $A\beta_{42}$, p-Tau_{181} and t-Tau measures in Alzheimer's disease (AD).

2. Determine how many ADRC sites have contributed CSF $A\beta_{42}$, p-Tau_{181} and t-Tau biomarker data to NACC, which platforms were used, and the demographics of the participants.

3. Characterize NACC CSF $A\beta_{42}$, p-Tau_{181} and t-Tau biomarker differences between sites.

4. Examine the sensitivity, specificity and cut-points of the NACC CSF $A\beta_{42}$, p-Tau_{181} and t-Tau data so far.

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CSF Aβ and tau levels are abnormal in AD with some variability in levels across studies

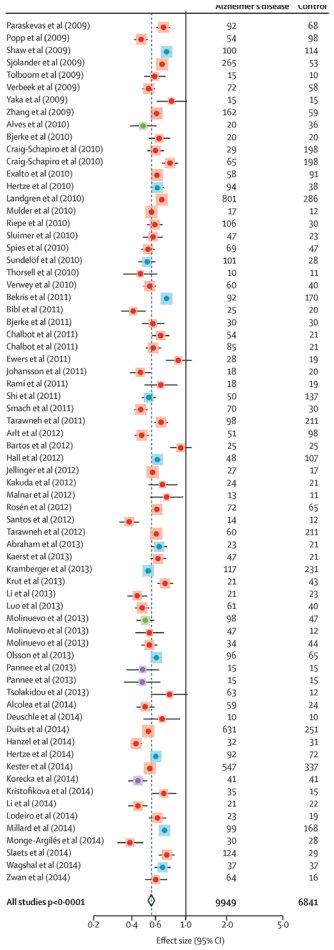
THE LANCET
Neurology
Volume 15, Issue 7, June 2016, Pages 673-684

Articles

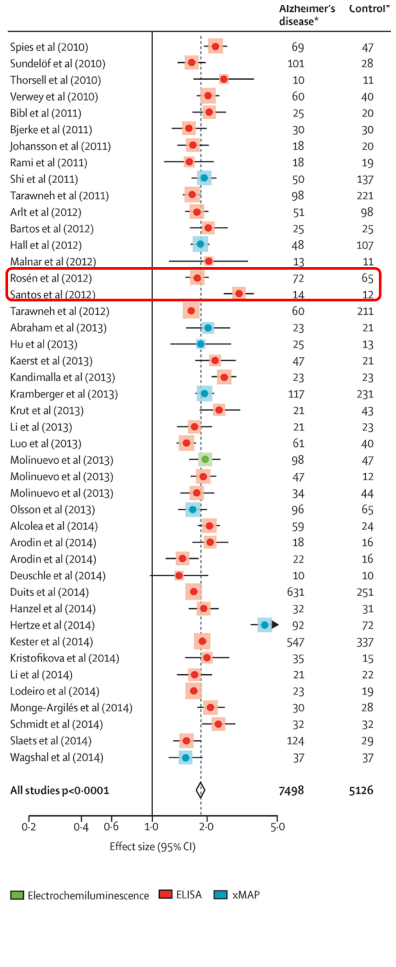
CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis

Dr Bob Olsson PhD [a], Ronald Lautner MD [a], Ulf Andreasson PhD [a], Annika Öhrfelt PhD [a], Erik Portelius PhD [a], Maria Bjerke PhD [a, b], Mikko Hölttä PhD [a], Christoffer Rosén MD [a], Caroline Olsson PhD [c], Gabrielle Strobel MSc [d], Elizabeth Wu MLIS [d], Kelly Dakin PhD [d], Prof Max Petzold PhD [e, f], Prof Kaj Blennow MD [a], Prof Henrik Zetterberg MD [a, g]

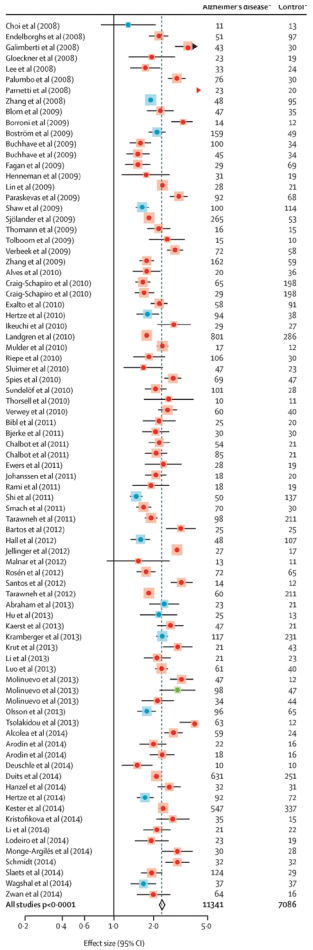
CSF Aβ42



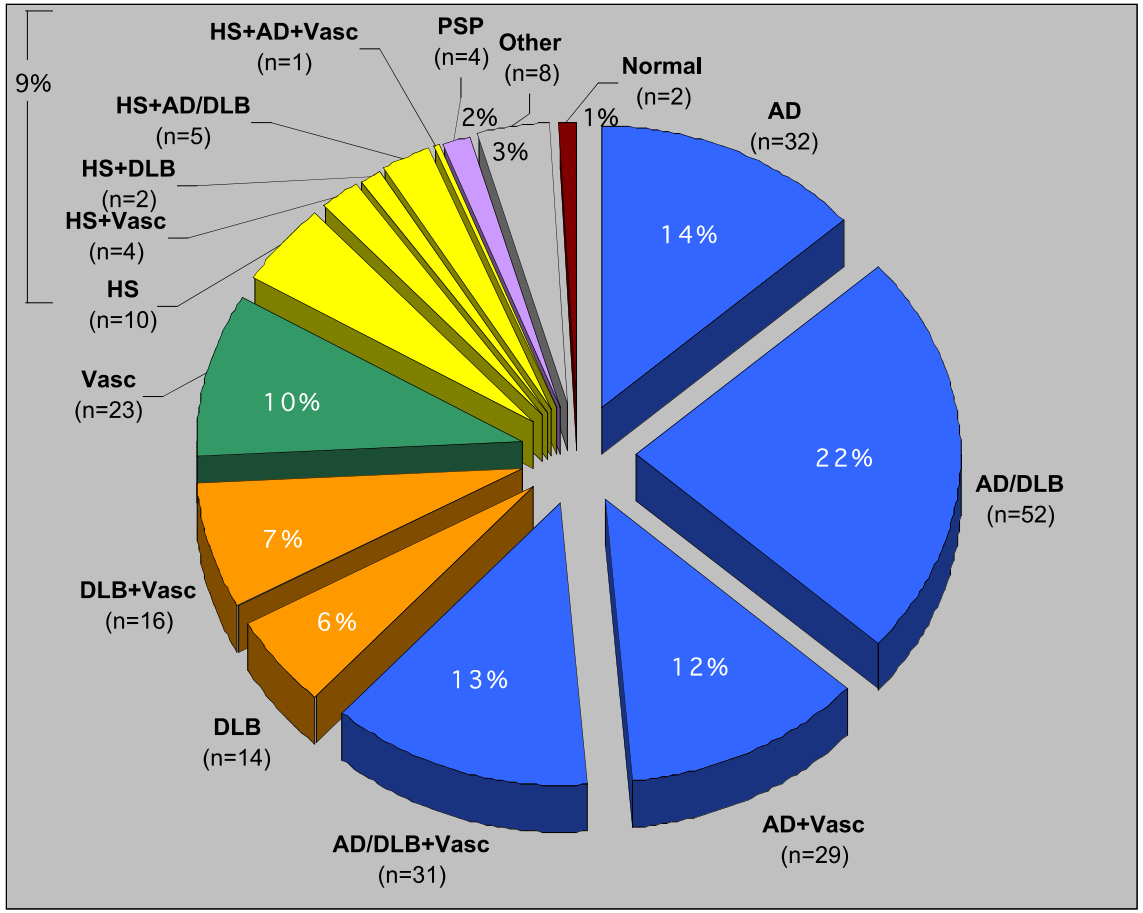
CSF p-Tau



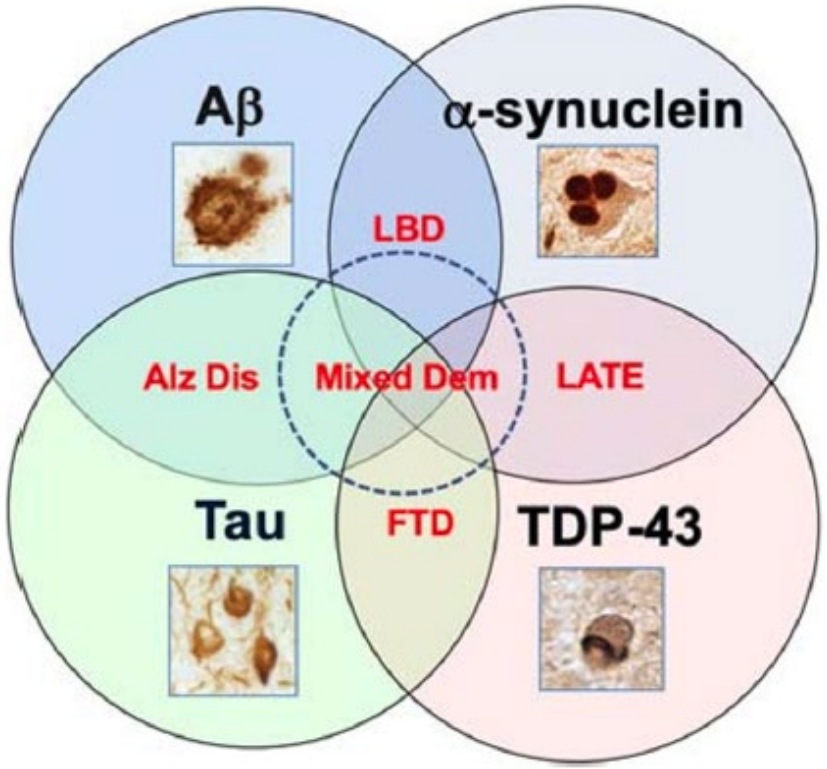
CSF t-Tau



CSF Aβ and tau data are necessary to sub-type AD/ADRD



Leverenz et al, JAMA Neurol, 2002; Riekse et al JAGS, 2004; Leverenz et al, Brain Path, 2008; Boyle PA et al. 2018



Kwon S, Iba M, Kim C, Masliah E, Review, Immunotherapeutics, 2020

CSF Aβ (A), p-Tau (T) and neurodegeneration (N) identifies AD pathology and supports biomarker discovery hypotheses

ELSEVIER
CrossMark
Alzheimer's & Dementia 14 (2018) 535-562
Alzheimer's & Dementia

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

Clifford R. Jack, Jr.,[a,*], David A. Bennett[b], Kaj Blennow[c], Maria C. Carrillo[d], Billy Dunn[e], Samantha Budd Haeberlein[f], David M. Holtzman[g], William Jagust[h], Frank Jessen[i], Jason Karlawish[j], Enchi Liu[k], Jose Luis Molinuevo[l], Thomas Montine[m], Creighton Phelps[n], Katherine P. Rankin[o], Christopher C. Rowe[p], Philip Scheltens[q], Eric Siemers[r], Heather M. Snyder[d], Reisa Sperling[s]
Contributors[†]: Cerise Elliott, Eliezer Masliah, Laurie Ryan, and Nina Silverberg

ATN Biomarkers

Table 1
AT(N) biomarker grouping

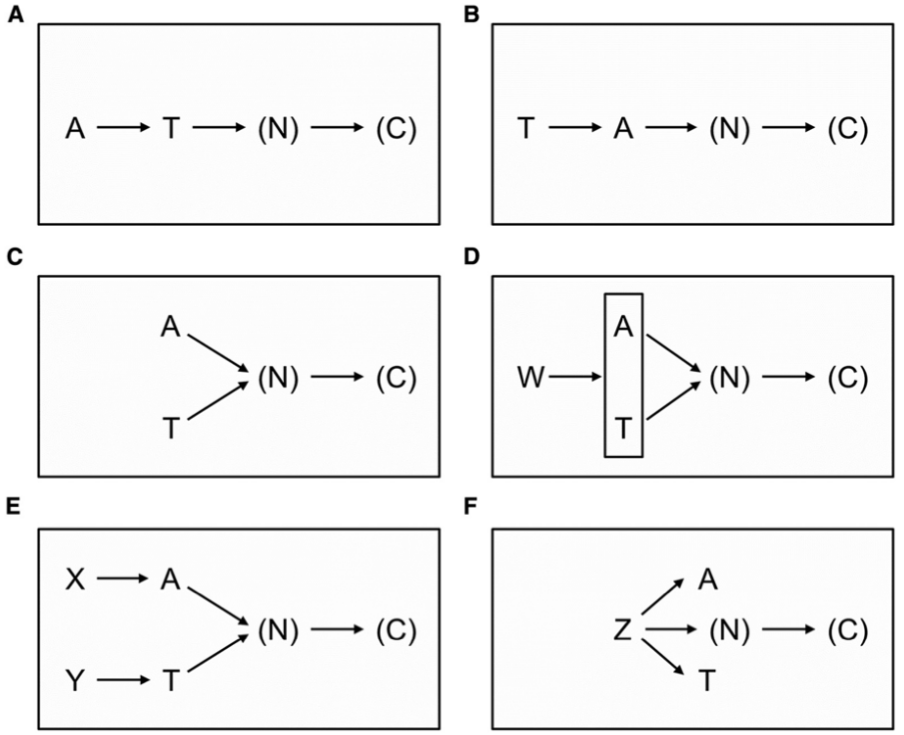
A: Aggregated Aβ or associated pathologic state
CSF $A\beta_{42}$, or $A\beta_{42}/A\beta_{40}$ ratio
Amyloid PET
T: Aggregated tau (neurofibrillary tangles) or associated pathologic state
CSF phosphorylated tau
Tau PET
(N): Neurodegeneration or neuronal injury
Anatomic MRI
FDG PET
CSF total tau

Biomarker categories

Table 2
Biomarker profiles and categories

AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)-	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

Hypothesis testing



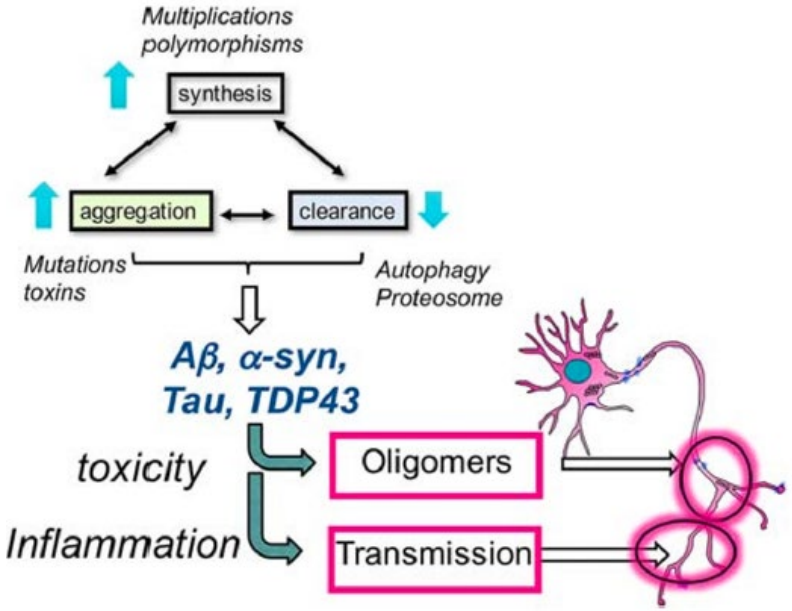
ATN categorization supports studies of novel biomarkers and drug targets that are a critical unmet medical need in AD/ADRD

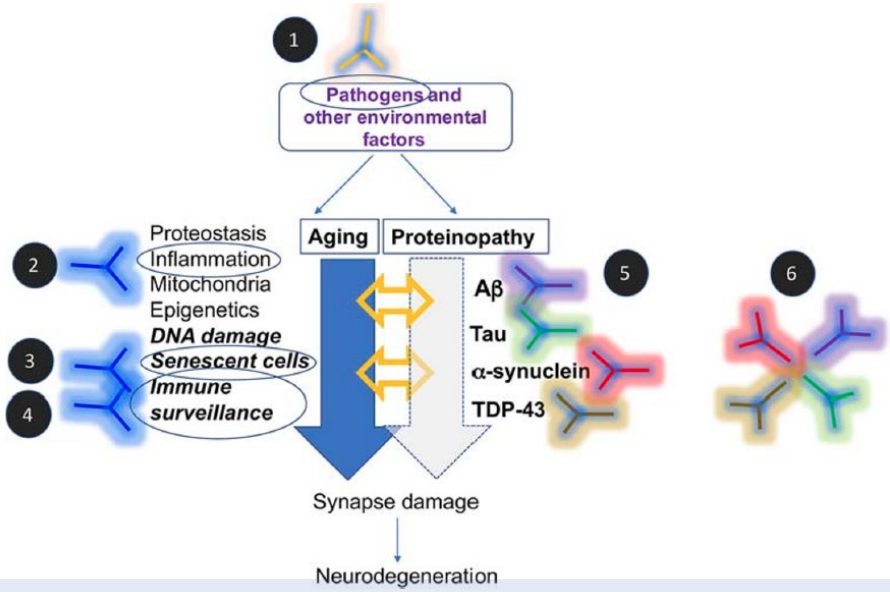
Neurotherapeutics (2020) 17:935–954
https://doi.org/10.1007/s13311-020-00853-2

CURRENT PERSPECTIVES

Immunotherapies for Aging-Related Neurodegenerative Diseases—Emerging Perspectives and New Targets

Somin Kwon [1] · Michiyo Iba [1] · Changyoun Kim [1] · Eliezer Masliah [1,2]





FDA approval of Fujirebio/Lumipulse CSF Aβ test

- On May 4th 2022 the FDA permitted marketing for the first in vitro diagnostic test for early detection of amyloid plaques associated with Alzheimer's disease.
- "The Lumipulse G β-amyloid Ratio (1-42/1-40) was granted Breakthrough Device designation, a process designed to expedite the development and review of devices that may provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or condition."

https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-new-test-improve-diagnosis-alzheimers-disease

Summary: Overview of CSF $A\beta_{42}$, p-Tau_{181} and tau in AD

- CSF Aβ and tau levels are abnormal in AD with some variability in levels across sites/studies
- CSF Aβ and tau data are necessary to sub-type AD/ADRD
- CSF Aβ (A), p-Tau (T) and neurodegeneration (N) identifies AD pathology and supports biomarker discovery hypotheses
- ATN categorization supports studies of novel biomarkers and drug targets that are a critical unmet medical need in AD/ADRD
- FDA approval has ramifications for use of the Lumipulse CSF Aβ ratio in AD research

Objectives

1. Brief overview of CSF $A\beta_{42}$, p-Tau_{181} and t-Tau measures in Alzheimer's disease (AD).
2. Determine how many ADRC sites have contributed CSF $A\beta_{42}$, p-Tau_{181} and t-Tau biomarker data to NACC, which platforms were used, and the demographics of the participants.
3. Characterize NACC CSF $A\beta_{42}$, p-Tau_{181} and t-Tau biomarker differences between sites.
4. Examine the sensitivity, specificity and cut-points of the NACC CSF Aβ42, p-Tau181 and t-Tau data so far.

NIH ADRC 2021 CSF biomarker inventory indicates the majority of centers collect and quantitate CSF Aβ and tau

Plasma	Serum	Buffy Coat	CSF	DNA	DNA at NCRAD	Frozen Tissue	Fixed Tissue	Dermal Fibroblast	IPSCs
25,567	17,449	8,980	6,963	24,050	17,560	11,284	14,014	885	146

Category	# Centers Yes	# Centers No
Collects CSF	26	5
Quantitate CSF AB40	21	10
Quantitate CSF AB42	22	9
Quantitate CSF Ttau	22	9
Quantitate CSF ptau	22	9

As of 11/1/21 (courtesy of Cerise Elliott)

Ten ADRC sites have contributed CSF Aβ and tau biomarker data from Luminex, ELISA and "other" platforms to NACC

	Luminex				ELISA				Other	
Site ID	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
									Lumipulse	ELISA Aβ & Luminex t-Tau
Total n=	48	108	234	367	88	70	12	181	773	170
Baseline Visit Year Dates	2006-2021	2017-2022	2005-2021	2005-2021	2015-2021	2015-2021	2014-2022	2009-2021	2005-2021	2005-2022
Case/Control	11/37	18/90	84/150	197/170	56/32	36/34	7/5	45/136	297/476	38/132
APOE4+ : Case/Control	4/11	5/25	53/45	117/49	42/18	10/1	5/4	31/51	172/163	21/41
Proportion Female	0.50	0.43	0.44	0.55	0.41	0.46	0.46	0.59	0.51	0.60
Mean Age	66.9	70.2	67.9	71.4	72.8	64.6	65.1	65.5	72.8	71.2
Hispanic	0.04	0.04	0.01	0.10	0.02	0.10	0.00	0.00	0.01	0.02
White	0.75	0.87	0.94	0.74	0.89	0.77	1.00	0.99	0.90	0.89
Black or African American	0.13	0.07	0.01	0.09	0.05	0.03	0.00	0.01	0.08	0.00
American Indian or Alaska Native	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Native Hawaiian	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Asian	0.04	0.01	0.03	0.01	0.01	0.03	0.00	0.00	0.01	0.09
Other	0.04	0.01	0.00	0.07	0.02	0.08	0.00	0.00	0.00	0.00

All ten sites: n=2051

Summary: ADRC sites that have contributed CSF $A\beta_{42}$, p-Tau_{181} and t-Tau biomarker data to NACC

- NIH ADRC 2021 CSF biomarker inventory indicates the 22 centers collect and quantitate CSF Aβ and tau with a total of 6963 samples
- Ten ADRC sites have contributed CSF Aβ and tau biomarker data from Luminex, ELISA and “other” platforms to NACC
- Nine out of ten sites contributed CSF $A\beta_{42}$, p-Tau_{181} and tau utilizing one platform for all three analytes.

Objectives

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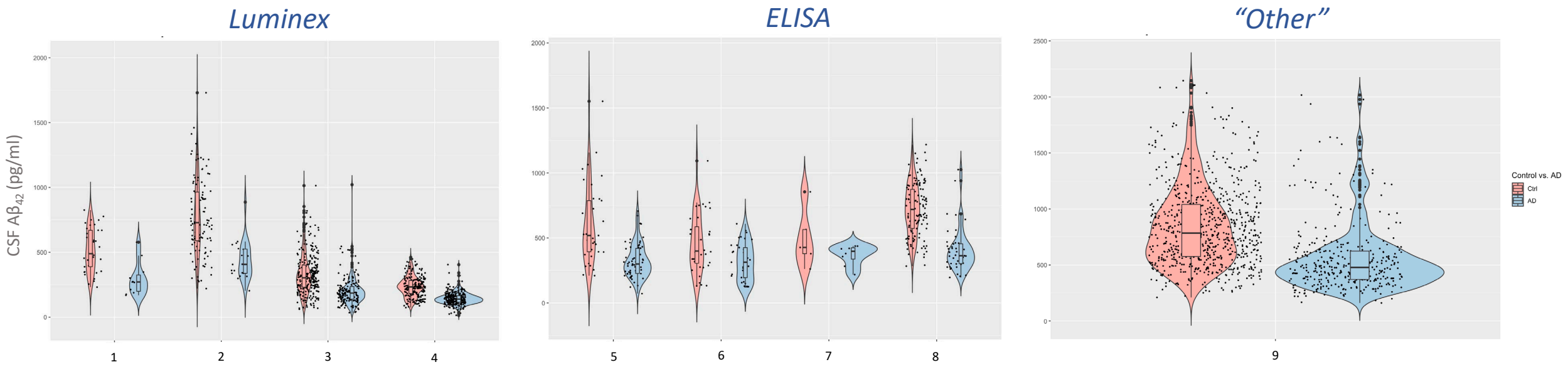
4. Examine the sensitivity, specificity and cut-points of the NACC CSF $A\beta_{42}$, p-Tau_{181} and t-Tau data so far.

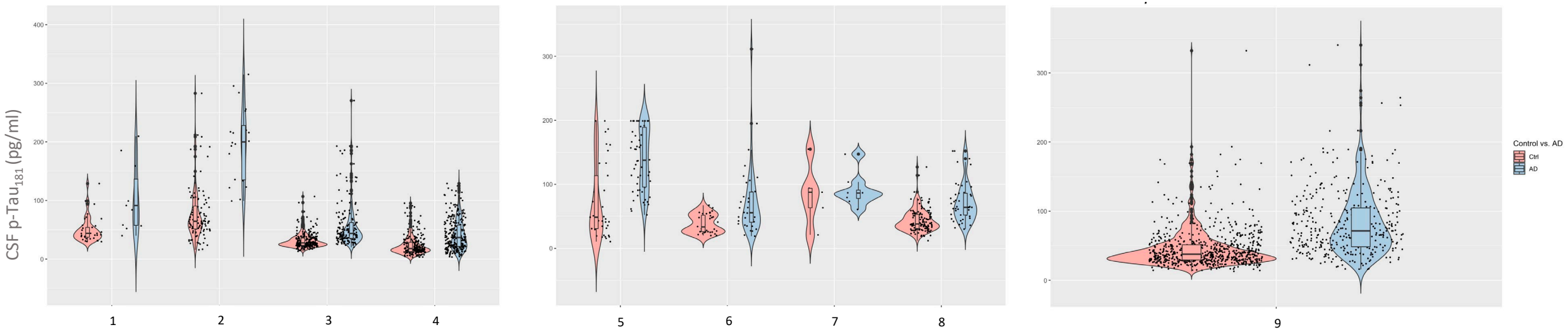
CSF $A\beta_{42}$ is significantly different between controls and AD for all but one site



	Luminex				ELISA				Other
	1	2	3	4	5	6	7	8	9
CSF $A\beta_{42}$									
mean AD	296.70	439.02	203.35	143.51	322.92	316.25	368.36	407.91	557.60
mean Ctrl	517.74	775.44	330.76	235.64	599.03	460.59	497.33	718.88	843.89
p-value	0.000132	3.92E-10	< 2.2e-16	< 2.2e-16	3.15E-06	0.001803	0.2804	< 2.2e-16	< 2.2e-16

CSF p-Tau$_{181}$ is significantly different between controls and AD for all but one site

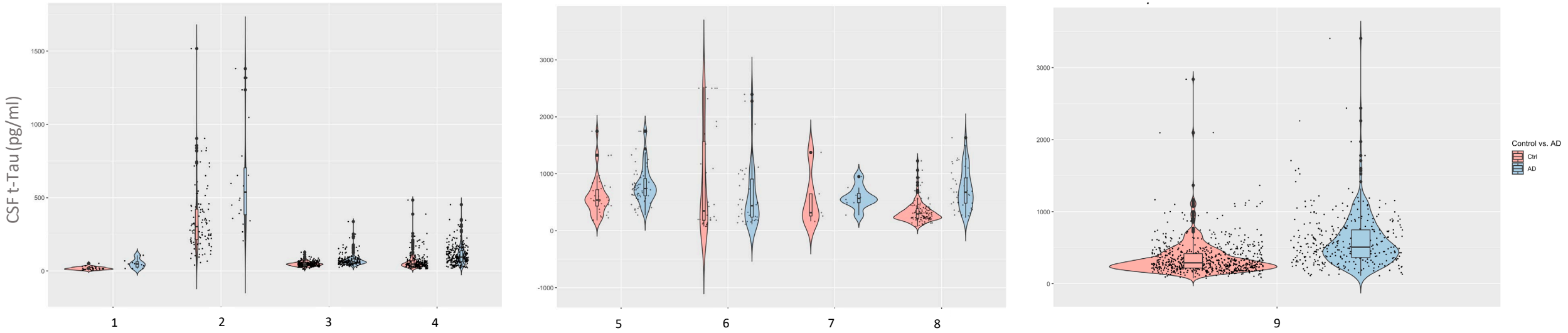
Luminex *ELISA* *"Other"*



	Luminex				ELISA				Other
	1	2	3	4	5	6	7	8	9
p-Tau									
mean AD	104.52	197.83	58.85	42.11	138.21	73.81	90.46	73.02	83.88
mean Ctrl	50.40	76.77	31.80	23.62	73.18	38.49	84.10	43.32	45.50
p-value	0.0106	3.86E-08	7.95E-15	< 2.2e-16	4.57E-07	0.0007531	0.798	1.44E-07	< 2.2e-16

CSF t-Tau is significantly different between controls and AD for all but two sites

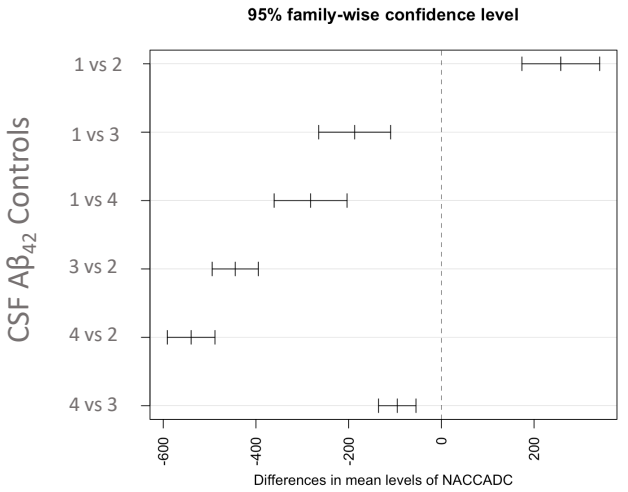
Luminex *ELISA* *"Other"*

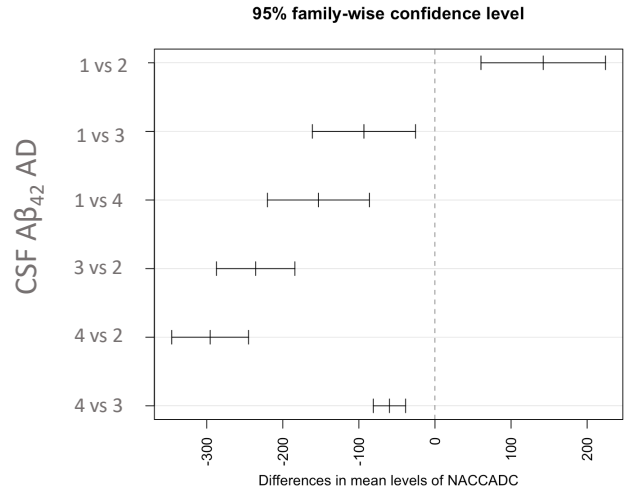


	Luminex				ELISA				Other
	1	2	3	4	5	6	7	8	9
t-Tau									
mean AD	51.59	632.70	75.71	107.05	800.67	614.25	589.10	740.87	596.87
mean Ctrl	18.34	347.11	48.16	63.63	600.42	873.99	551.35	324.82	351.21
p-value	0.006632	0.00198	1.20E-14	2.35E-15	0.004704	0.1468	0.8775	6.67E-10	< 2.2e-16

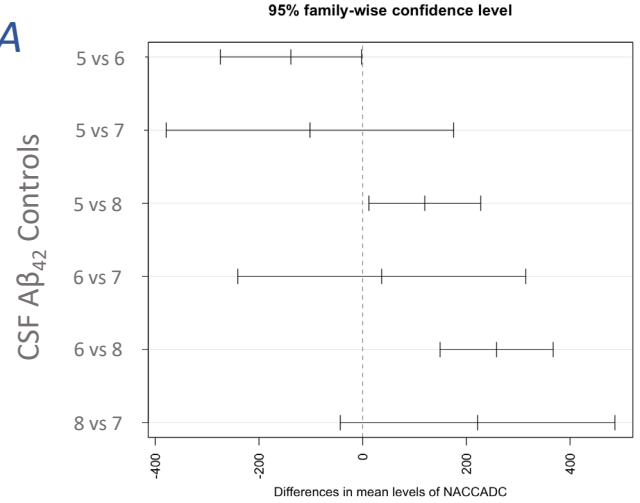
CSF $A\beta_{42}$ is significantly different between all sites for Luminex, but not all sites for ELISA.

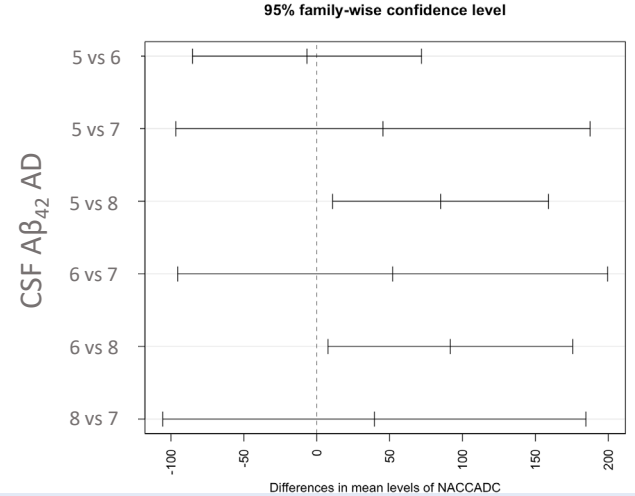
Luminex





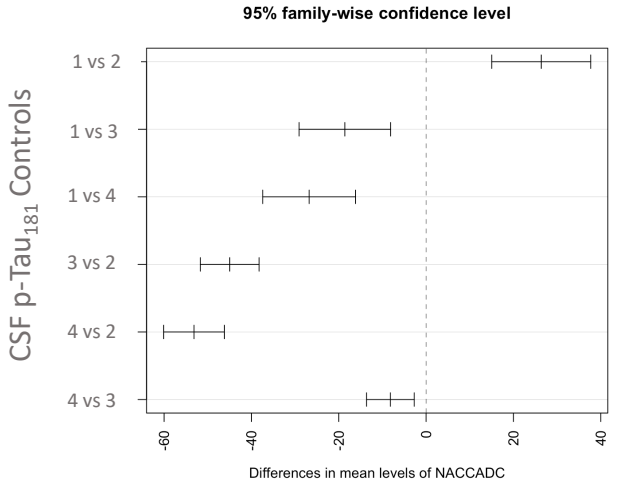
ELISA

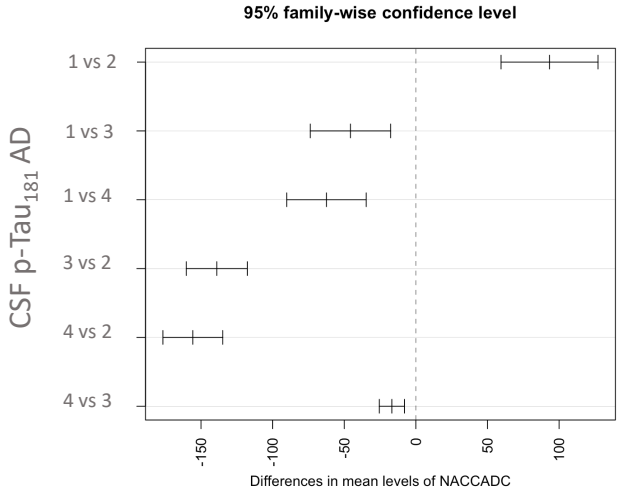




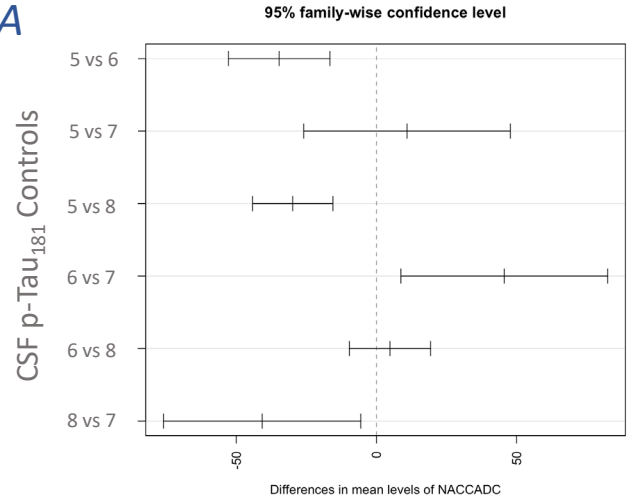
CSF p-Tau$_{181}$ is significantly different between all sites for Luminex, but not all sites for ELISA.

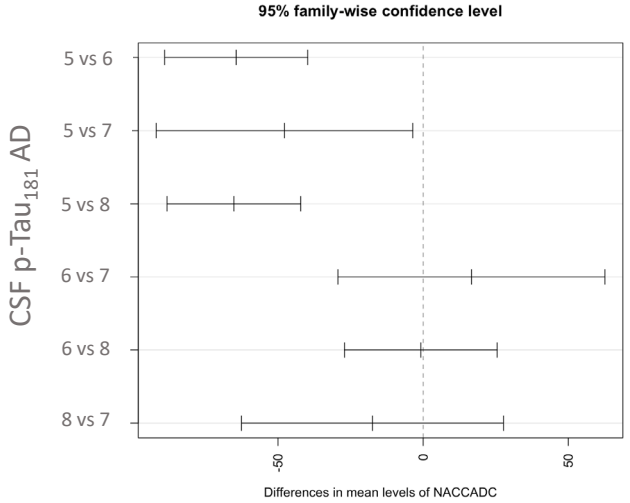
Luminex





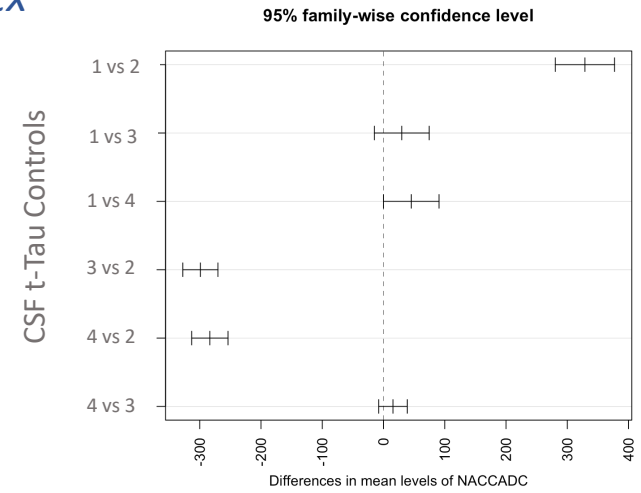
ELISA

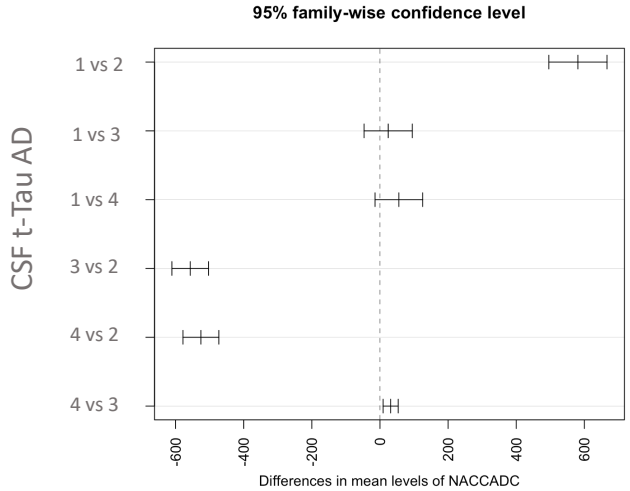




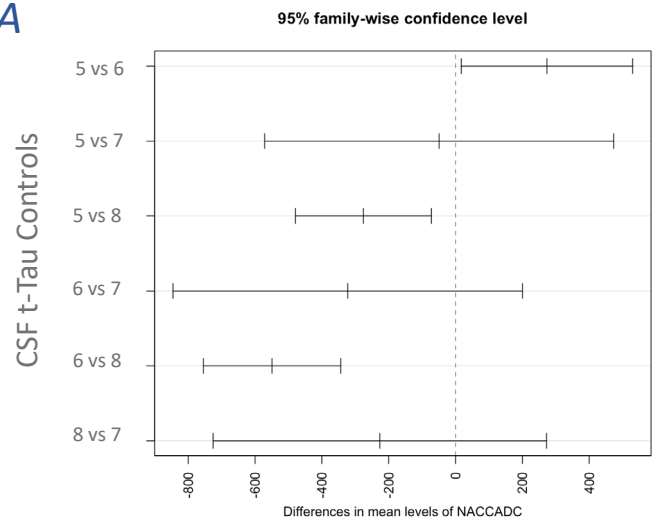
CSF t-Tau is significantly different between some sites for Luminex and ELISA.

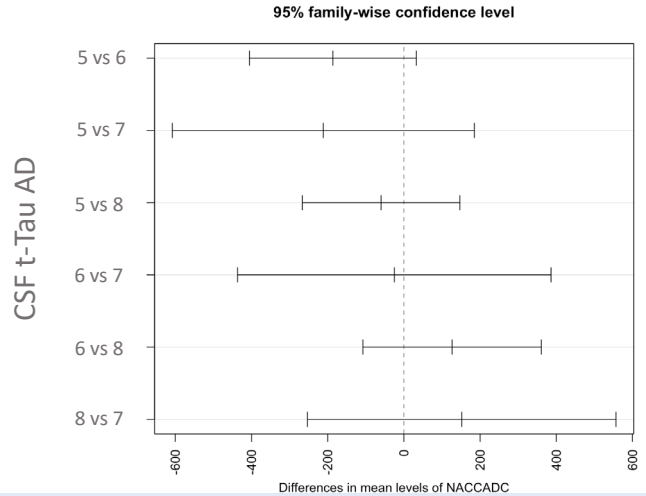
Luminex





ELISA





Summary: NACC CSF $A\beta_{42}$, p-Tau_{181} and t-Tau

- For the nine ADRC sites that contributed data, CSF $A\beta_{42}$, p-Tau_{181} and t-Tau are all significantly different between controls and AD, for all but one site with limited samples collected.
- CSF $A\beta_{42}$, p-Tau_{181} and t-Tau is significantly different between most sites for Luminex, but fewer sites for ELISA.

Objectives

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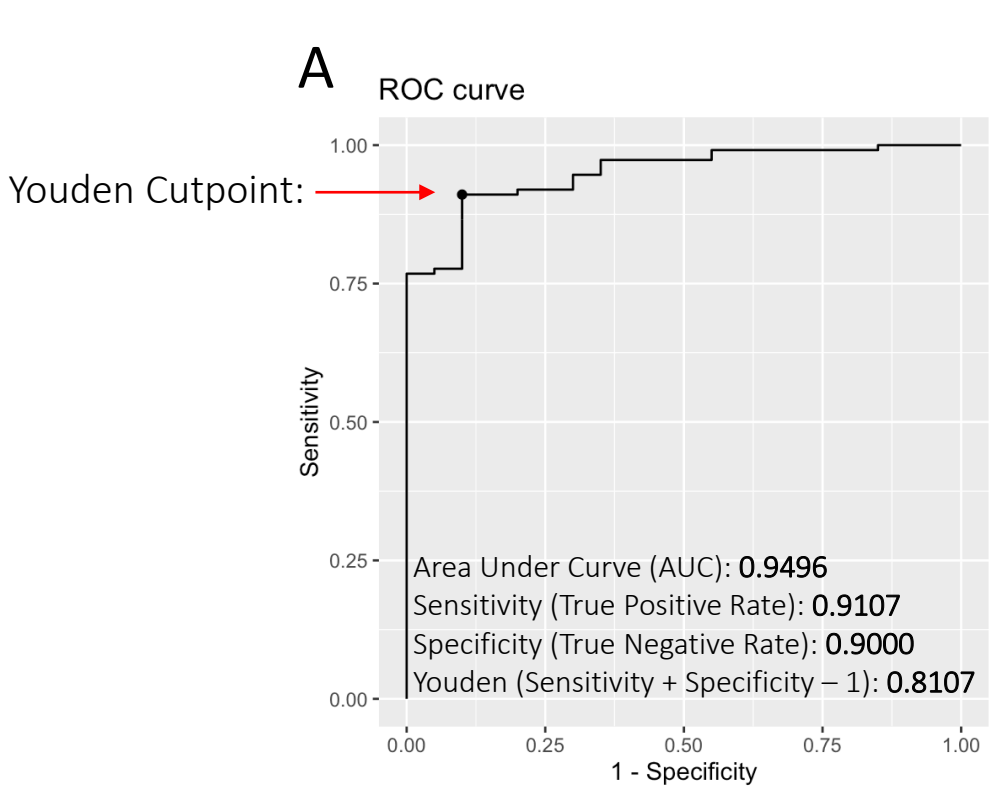
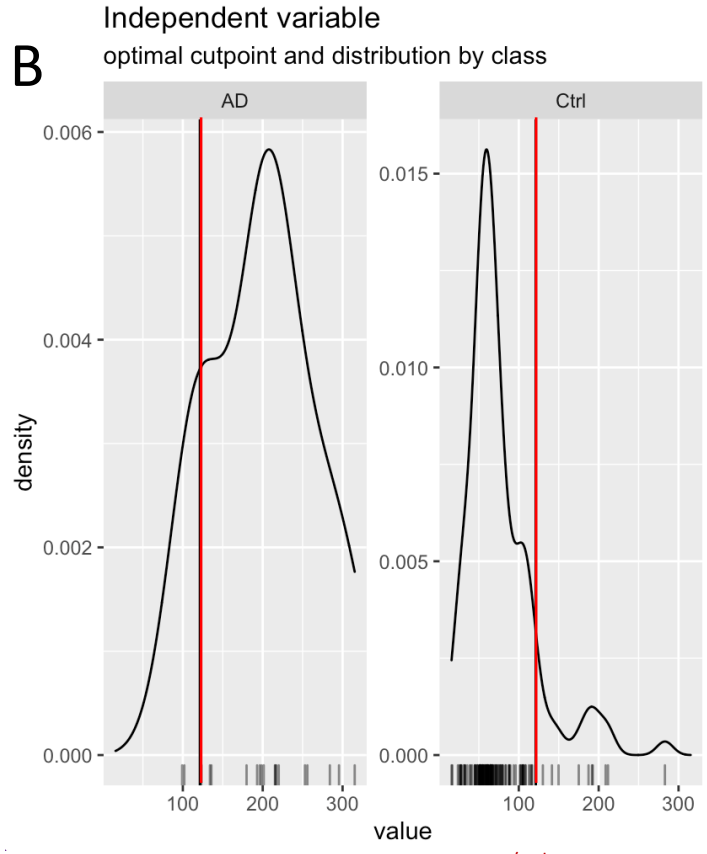
2. Determine how many ADRC sites have contributed CSF $A\beta_{42}$, p-Tau_{181} and t-Tau biomarker data to NACC, which platforms were used, and the demographics of the participants.

3. Characterize NACC CSF $A\beta_{42}$, p-Tau_{181} and t-Tau biomarker differences between sites.

4. Examine the sensitivity, specificity and cut-points of the NACC CSF $A\beta_{42}$, p-Tau_{181} and t-Tau data so far.

Receiver Operating Characteristic (ROC) defines the sensitivity and specificity and establishes cut-points of biomarker positivity





ROC analyses per NIH ADRC site suggest that the sensitivity, specificity and cut-points vary between sites

CSF $A\beta_{42}$

	CSF Aβ42								
	Luminex				ELISA				Other
	1	2	3	4	5	6	7	8	9
Area Under the Curve	0.8649	0.8549	0.7791	0.8437	0.8219	0.6914	0.6500	0.8891	0.7697
Sensitivity	0.8182	0.9500	0.7412	0.8804	0.7097	0.9189	1.0000	0.8222	0.7047
Specificity	0.8108	0.7589	0.7603	0.7327	0.8378	0.4167	0.4000	0.8750	0.7429
Youden	0.6290	0.7089	0.5015	0.6132	0.5475	0.3356	0.4000	0.6972	0.4476
Cutpoints	348.40	583.31	227.42	189.13	349.17	508.40	437.20	469.00	582.00

p-Tau_{181}

	CSF p-Tau181								
	Luminex				ELISA				Other
	1	2	3	4	5	6	7	8	9
Area Under the Curve	0.8550	0.9496	0.8221	0.7381	0.8130	0.7500	0.4750	0.8235	0.7949
Sensitivity	0.7027	0.9107	0.6742	0.6083	0.6216	0.9722	0.4000	0.8741	0.7823
Specificity	0.9091	0.9000	0.8235	0.7826	0.9839	0.4722	0.8750	0.6444	0.7019
Youden	0.6118	0.8107	0.4977	0.3909	0.6055	0.4444	0.2750	0.5185	0.4843
Cutpoints	51.00	121.30	33.44	20.55	53.80	63.22	63.35	59.00	54.00

t-Tau

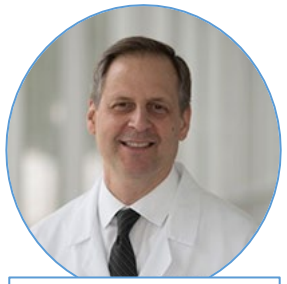
	CSF t-Tau								
	Luminex				ELISA				Other
	1	2	3	4	5	6	7	8	9
Area Under the Curve	0.8600	0.7873	0.7956	0.7690	0.7129	0.4962	0.6250	0.8814	0.7657
Sensitivity	0.9730	0.6696	0.7828	0.7143	0.7027	0.4722	0.6000	0.8593	0.6694
Specificity	0.7273	0.8000	0.6941	0.7935	0.7419	0.7297	0.8750	0.7778	0.7632
Youden	0.7002	0.4696	0.4769	0.5078	0.4446	0.2020	0.4750	0.6370	0.4326
Cutpoints	35.90	357.96	56.72	63.00	613.38	247.30	316.70	457.50	355.00

Summary: NACC CSF $A\beta_{42}$, p-Tau_{181} and t-Tau sensitivity, specificity and cut-points

- ROC analyses per NIH ADRC site suggest that the sensitivity, specificity and cut-points vary between sites within assay type

Conclusion

- Ten sites that contributed data to NACC allowed examination of site to site variability between nine sites within two assay types and reveals site to site differences.
- ROC analyses indicate potentially important site to site differences in sensitivity, specificity and cut-points.



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Discussion – Next Steps?

- Is the collection of the CSF Aβ and tau data in the current state helpful or not?
  - What are the barriers to uploading or sharing data?
  - Should more data fields be added to NACC (e.g. other assay types, pre-analytical methods)?
- How can we increase and improve NACC CSF Aβ and tau biomarker data?
- Will sharing CSF Aβ and tau data advance the field?