SCAN MIXED PROTOCOL PET DATA DOCUMENTATION

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The SCAN Mixed Protocol (MP) Project curates and analyzes amyloid and tau PET data on ADRC Clinical Core research participants that were collected before standardized acquisitions and coordinated data sharing was implemented across ADRC sites in 2021 via the SCAN (Prospective) initiative (https://scan.naccdata.org/). The goal of the SCAN MP Project is to incorporate this unstandardized PET data into the NACC database so that it can be disseminated to the scientific community. Importantly, this data will be made available alongside standardized SCAN (Prospective) imaging data. Whereas (Prospective) PET and MRI data utilizes rigorous standardization methods during image acquisition and post-acquisition processing, the SCAN MP Project allows more flexibility to utilize PET data on as many unique ADRC Clinical Core participants as possible.

PET Processing

SCAN MP amyloid PET data has been processed with an MRI-free amyloid PET pipeline developed by Landau et al [1]. The process includes: (1) aligning summed late-frame PET data to an MNI152 T1 template linearly, (2) performing non-linear spatial adjustments to align the summed PET data to a "universal" amyloid PET template (an average across FBP, FBB, and PiB templates), (3) extracting signal intensities from cortical regions of interest (ROIs), and (4) generating standardized uptake value ratios (SUVRs) as well as centiloids (CLs). SUVRs are calculated as intensity in the cortical target region normalized to the whole cerebellum. SUVRs are provided for ROIs in both the GAAIN and NPDKA atlases, which have previously been described in **UCBerkeley_SCAN_Amyloid_MRIfree_Methods.pdf**. Amyloid PET SUVRs were normalized to the whole cerebellum associated with each atlas. For comparison of amyloid SUVR values derived from standardized and unstandardized protocols see Cody et al. [2].

Our local MRI-free tau PET pipeline was similar to the amyloid PET pipeline and included tracer-specific templates during the non-linear warping stage. The templates were the same as the ones used by SCAN PET Core at UC Berkeley. Detailed methods are described in **SCAN_UCBerkeley_Tau_MRIfree_Methods.pdf**. SUVRs for tau PET are provided for ROIs in the NPDKA atlas, normalized to an inferior cerebellum [1].

A summary of the processed data is presented in **Table 1**.

Table 1: Summary of processed mixed protocol (MP) data. Additional details in Flowchart below.

	Amyloid MP PET				Tau MP PET	
Release Date	**# Unique Subjects**	**# Scans**	**# Scans with CL (standardized acquisition window)**	**# Scans with Amyloid Status released**	**# Unique Subjects**	**# Scans**
07/15/2024	919	929	822	907	0	0
11/14/2024	1815	1943	1822	1943	470	525
10/02/2025	2074	2236	2013	2184	616	671

All amyloid scans were assigned amyloid status: positive, negative, or unknown. Unknown status was assigned for scans with interpolated intermediate CL levels (**Appendix 1**) and scans that failed quality control.

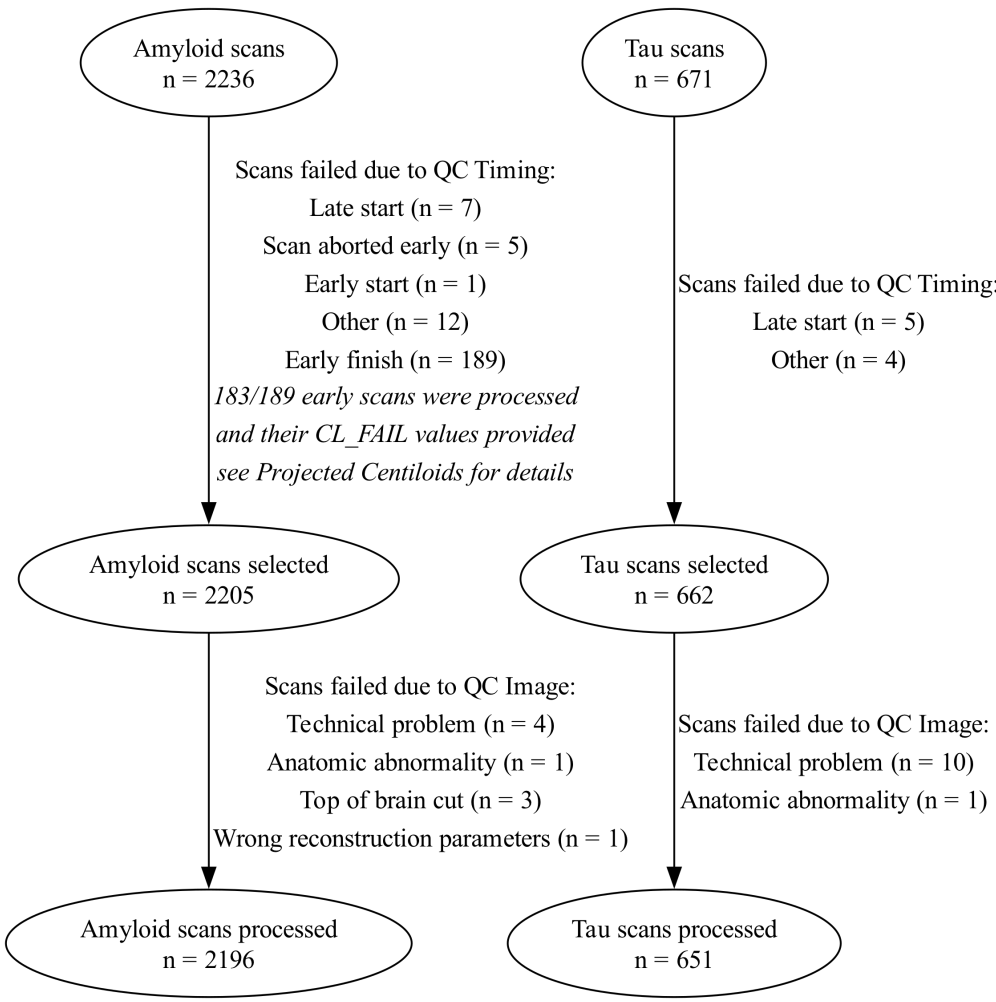
Tracer specific SUVR-to-centiloid equations for the MRI-free pipeline were derived using the level 2 GAAIN centiloid (CL) analysis method [3]. Conversion equations were derived by downloading paired PiB-FBB data from Rowe et al [4] and PiB-FBP data from Navitsky et al [5] and processing locally with the MRI-free pipeline. PIB scans from Klunk et al [3] were downloaded and processed to derive the equation for converting MRI-free PIB values to CLs. These equations differ slightly from UC Berkeley equations used in SCAN (Prospective) given that they were derived using data processed at Stanford and subtle differences related to software versions and default parameters likely exist between UC Berkeley and Stanford pipelines (**Table 2**). Previously established SUVR cutoff values from UC Berkeley were applied to classify participants as amyloid- and amyloid+ (**Table 2; UCBerkeley_SCAN_Amyloid_MRIfree_Methods.pdf**). Given slight differences in CL equations between Stanford and UC Berkeley, we converted the SUVR positivity threshold provided by the SCAN PET Core at UC Berkeley to create a SUVR positivity threshold that corresponded to values generated by Stanford processing. These conversion steps result in SUVR cutoffs that are nearly identical to the SUVR cutoffs used in SCAN (Prospective).

Table 2: Centiloid (CL) Equations for MRI-Free Amyloid PET Scans.

	MRI-free CL ← MRI-free SUVR (Berkeley)	**SUVR Cutoff (Berkeley)**	**CL Cutoff (Berkeley)**
FBB	164.60 x (MRI-free FBB SUVR) - 171.97	**1.12**	**12**
FBP	192.40 x (MRI-free FBP SUVR) - 207.27	**1.17**	**18**
PiB	92.08 x (MRI-free PiB SUVR) – 95.83	**1.14**	**9**
NAV	88.86 x (MRI-free PiB SUVR) – 91.71	**1.14**	**10**

Quality Control and PET acquisition times

An overview of the MP PET data is shown in the **Flowchart** below.

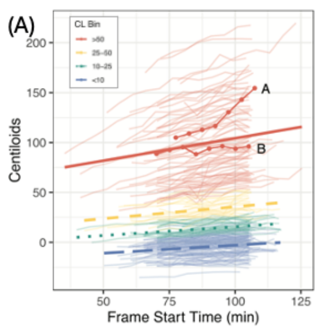


34 amyloid scans did not have sufficient information to allow any image analysis (7 started late, 5 were aborted early, 1 started early, 4 had technical problems, 1 had anatomic abnormality, 3 top of brain cut, 1 wrong reconstruction parameters, 12 other issues).

Of the remaining 2202 scans, 2019 scans had acquisition times within the recommended acquisition window for their amyloid PET ligand (defined as within 10 minutes before or after the recommended window) and 899 (45%) were determined amyloid+ using the SCAN SUVR cutoffs. There were 183 FBB scans that passed initial QC but had acquisition times varying by 10 minutes or more from the recommended acquisition time for FBB (90 – 110 min). Given that SUVR magnitude generally increases at later acquisition windows, continuous SUVR and corresponding CL values from earlier acquisition windows may be misleadingly low (**Figure 1A**). We therefore excluded SUVR and CL values for these 183 cases, but still released CLs for reference as a separate variable called "CL_FAIL"

(**Flowchart**). Using these CL values, we computed projected CL values and interpolated an AMYLOID_STATUS based on the likelihood that the shift in timing would assign them differently if data were collected during the recommended window. First, all FBB scans collected early that had a CL value of 12 or higher (82/183 FBB scans) were interpolated to be amyloid+ (given the cutoff value of 12 for FBB, and assuming that their magnitude would only increase if collected later). Of the remaining 101 scans below 12 CL, we computed projected CL values. Given that magnitude increases are slower for amyloid- scans compared to amyloid+ scans [6](**Figure 1B**), this projection was completed twice for each of the 101 scans, first assuming a slower rate of increase associated with amyloid- scans, then again assuming a higher rate of increase associated with amyloid+ scans (**Figure 1C**). Interpolated status was assigned negative if both projected values were below 12; was assigned positive if both projected values were above 12; and was assigned unknown if the two values were discordant. Projected values for the 101 cases and resulting interpolated AMYLOID_STATUS assignments are shown in **APPENDIX 1**.

(A)



(B)

Group	Estimated CL change per 20 minutes
<10 CL	2.95
10-25 CL	4.24
25-50 CL	5.79
>50 CL	13.07

(C)

FBB CL value at 50-70	Projected 90-110, assume A- (<10 CL)	Projected 90-110, assume A+ (25-50 CL)	Interpolated AMYLOID_STATUS
-10	-4.1	1.58	Negative
-5	0.9	6.58	Negative
0	5.9	11.58	Negative
5	10.9	16.58	UNKNOWN
10	15.9	21.58	Positive

Figure 1: (A) SUVRs and corresponding CLs increase at later acquisition windows. Spaghetti plots show 5-minute frame level data for a given participant/scan. (B) Model estimates of CL change per every 20-minute shift in post-injection time by amyloid group. (C) Example projected values based on assuming a A- (<10 CL) versus a A+ (25-50CL) scan, applied to all FBB scans that were collected more than 10 minutes before the recommended 90-110 window ***AND*** had CL values below the FBB cut-off of 12. We assumed the lowest (<10 CL) and second highest rates (25-50 CL) of increase by acquisition time to provide the most conservative range of projected values. We assume that these cases would not be in the >50CL group at 90-110 minutes post-injection. Based on projected CLs, scans were classified as amyloid negative, positive, or unknown.

The two equations used to project CLs for scans acquired outside the standard timing windows are shown here:

1. *<u>Projected 90-110 CL, assuming A- scan:</u>*

$$CL_{90\text{-}110}=CL_{ACTUAL}+([(Recommended\_Midpoint-Actual\_Midpoint)/20]*Negative\_Rate)$$

2. *<u>Projected 90-110, assuming A+ scan:</u>*

$$CL_{90\text{-}110}=CL_{ACTUAL}+([(Recommended\_Midpoint-Actual\_Midpoint)/20]*Positive\_Rate)$$

<u>Model Variables</u>

Recommended_Midpoint=Midpoint of recommended acquisition window. For FBB, this is set to 100 minutes since the recommended window is 90-110 minutes post-injection.

Actual_Midpoint=Midpoint of actual acquisition. For an FBB scan that was acquired from 50-70 minutes, this would be set to 60.

Negative_Rate=Estimated rate of CL increase per 20 minutes for the A- group (from Table 2 in Johns et al [5]). This is set to 2.95 CL/20 minutes for A-, which corresponds to the estimated rate for CL values below 10.

Positive_Rate= Estimated rate of CL increase per 20 minutes for the A+ group (from Table 2 in Johns et al [5]). This is set to 5.79 CL/20 minutes for A+, which corresponds to the estimated rate for CL values between 25-50 CL.

APPENDIX 1

		ACQUISITION			CENTILOIDS			
	NACCID	START	END	MIDPOINT	ACTUAL	PROJECTION NEGATIVE	PROJECTION POSITIVE	AMYLOID STATUS
1	NACC394918	72	92	82	-27	-24.35	-21.79	0
2	NACC531033	54	74	64	-23	-17.69	-12.58	0
3	NACC447617	65	85	75	-21	-17.31	-13.76	0
4	NACC929628	63	83	73	-18	-14.02	-10.18	0
5	NACC313118	62	82	72	-17	-12.87	-8.89	0
6	NACC432970	77	97	87	-17	-15.08	-13.24	0
7	NACC603054	70	90	80	-17	-14.05	-11.21	0
8	NACC150921	78	98	88	-16	-14.23	-12.53	0
9	NACC177791	75	95	85	-15	-12.79	-10.66	0
10	NACC128735	59	79	69	-14	-9.43	-5.03	0
11	NACC289341	60	80	70	-14	-9.58	-5.31	0
12	NACC488584	70	90	80	-14	-11.05	-8.21	0
13	NACC144627	61	81	71	-13	-8.72	-4.60	0
14	NACC394918	56	76	66	-13	-7.98	-3.16	0
15	NACC978120	60	80	70	-13	-8.58	-4.31	0
16	NACC857431	73	93	83	-13	-10.49	-8.08	0
17	NACC723838	70	90	80	-13	-10.05	-7.21	0
18	NACC891547	58	78	68	-12	-7.28	-2.74	0
19	NACC289341	73	93	83	-12	-9.49	-7.08	0
20	NACC875947	70	90	80	-12	-9.05	-6.21	0
21	NACC457613	62	82	72	-11	-6.87	-2.89	0
22	NACC936961	68	88	78	-11	-7.75	-4.63	0
23	NACC977463	59	79	69	-11	-6.43	-2.03	0
24	NACC693083	70	90	80	-11	-8.05	-5.21	0
25	NACC607552	60	80	70	-10	-5.57	-1.31	0
26	NACC045774	70	90	80	-10	-7.05	-4.21	0
27	NACC127021	56	76	66	-9	-3.98	0.84	0
28	NACC096483	79	99	89	-9	-7.38	-5.82	0
29	NACC361364	71	91	81	-9	-6.20	-3.50	0
30	NACC679484	65	85	75	-8	-4.31	-0.76	0
31	NACC846146	66	86	76	-8	-4.46	-1.05	0
32	NACC962474	70	90	80	-8	-5.05	-2.21	0
33	NACC761064	77	97	87	-8	-6.08	-4.24	0
34	NACC323023	71	91	81	-8	-5.20	-2.50	0
35	NACC689189	56	76	66	-7	-1.98	2.84	0

36	NACC718501	55	75	65	-7	-1.84	3.13	0
37	NACC863637	64	84	74	-7	-3.16	0.53	0
38	NACC306451	70	90	80	-7	-4.05	-1.21	0
39	NACC390162	77	97	87	-7	-5.08	-3.24	0
40	NACC000941	61	81	71	-6	-1.72	2.40	0
41	NACC987344	70	90	80	-6	-3.05	-0.21	0
42	NACC276128	75	95	85	-6	-3.79	-1.66	0
43	NACC140729	70	90	80	-6	-3.05	-0.21	0
44	NACC571778	70	90	80	-6	-3.05	-0.21	0
45	NACC232368	60	80	70	-5	-0.57	3.69	0
46	NACC358491	73	93	83	-5	-2.49	-0.08	0
47	NACC065547	71	91	81	-5	-2.20	0.50	0
48	NACC000941	74	94	84	-5	-2.64	-0.37	0
49	NACC931655	70	90	80	-5	-2.05	0.79	0
50	NACC853737	70	90	80	-5	-2.05	0.79	0
51	NACC679484	70	90	80	-5	-2.05	0.79	0
52	NACC683886	70	90	80	-5	-2.05	0.79	0
53	NACC757736	64	84	74	-4	-0.16	3.53	0
54	NACC821074	59	79	69	-4	0.57	4.97	0
55	NACC910486	61	81	71	-4	0.28	4.40	0
56	NACC967821	70	90	80	-4	-1.05	1.79	0
57	NACC031324	74	94	84	-4	-1.64	0.63	0
58	NACC771864	70	90	80	-4	-1.05	1.79	0
59	NACC086906	65	85	75	-3	0.69	4.24	0
60	NACC089260	59	79	69	-3	1.57	5.97	0
61	NACC808828	70	90	80	-3	-0.05	2.79	0
62	NACC132756	77	97	87	-3	-1.08	0.76	0
63	NACC205519	64	84	74	-2	1.84	5.53	0
64	NACC278952	67	87	77	-2	1.39	4.66	0
65	NACC327646	59	79	69	-2	2.57	6.97	0
66	NACC706890	64	84	74	-2	1.84	5.53	0
67	NACC092983	71	91	81	-2	0.80	3.50	0
68	NACC325360	72	92	82	-1	1.66	4.21	0
69	NACC241865	52	72	62	0	5.61	11.00	0
70	NACC347412	79	99	89	1	2.62	4.18	0
71	NACC314217	58	78	68	2	6.72	11.26	0
72	NACC119048	70	90	80	2	4.95	7.79	0
73	NACC508533	73	93	83	3	5.51	7.92	0
74	NACC809915	69	89	79	3	6.10	9.08	0

75	NACC514207	70	90	80	3	5.95	8.79	0
76	NACC553138	62	82	72	4	8.13	12.11	9
77	NACC631666	60	80	70	4	8.43	12.69	9
78	NACC995355	70	90	80	4	6.95	9.79	0
79	NACC137580	61	81	71	5	9.28	13.40	9
80	NACC350619	57	77	67	5	9.87	14.55	9
81	NACC954058	58	78	68	5	9.72	14.26	9
82	NACC965628	70	90	80	5	7.95	10.79	0
83	NACC437231	78	98	88	5	6.77	8.47	0
84	NACC407403	56	76	66	6	11.02	15.84	9
85	NACC439652	62	82	72	6	10.13	14.11	9
86	NACC960442	70	90	80	7	9.95	12.79	9
87	NACC971527	75	95	85	7	9.21	11.34	0
88	NACC919034	70	90	80	7	9.95	12.79	9
89	NACC383094	70	90	80	7	9.95	12.79	9
90	NACC765463	73	93	83	7	9.51	11.92	0
91	NACC002601	79	99	89	7	8.62	10.18	0
92	NACC633775	73	93	83	8	10.51	12.92	9
93	NACC278345	70	90	80	8	10.95	13.79	9
94	NACC268074	70	90	80	8	10.95	13.79	9
95	NACC306916	77	97	87	8	9.92	11.76	0
96	NACC589877	77	97	87	8	9.92	11.76	0
97	NACC602829	62	82	72	10	14.13	18.11	1
98	NACC033228	74	94	84	10	12.36	14.63	1
99	NACC189894	70	90	80	11	13.95	16.79	1
100	NACC278345	61	81	71	11	15.28	19.40	1
101	NACC731890	64	84	74	11	14.84	18.53	1

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