

# **Longitudinal A4 & Gene Expression Project**

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# 1 Project Overview

The data used for this project includes **all** A4 and LEARN participants (including screen fails) with Autosomal and X-linked RNAseq data available ( $N = 1,737$ ). The longitudinal data includes all available follow up, including the open label period.

Project Aims:

1. Test the association of gene expression with longitudinal PACC, longitudinal amyloid, longitudinal tau, longitudinal ptau, and baseline ptau.
2. See if these associations are modified by sex, APOEε4 status, sex x APOEε4 status, amyloid burden, amyloid burden x sex.

Sensitivity Analyses:

1. Run significant sex moderated models in just females and just males.
2. Run analyses in just LEARN vs A4 Placebo and LEARN vs A4 Treated.

## 2 Demographics

### 2.1 PACC Sample

#### 2.1.1 All Participants

Characteristic	N	Overall, N = 1,737 <sup>1</sup>	A4, N = 459 <sup>1</sup>	LEARN, N = 3
Baseline Age	1,737	71.31 (4.70) [64.63, 85.89]	71.97 (4.81) [65.00, 85.51]	70.36 (4.31) [65.00, 84.46]
Sex	1,737			
Female		1,083 (62.35%)	291 (63.40%)	189 (60.77%)
Male		654 (37.65%)	168 (36.60%)	122 (39.23%)
Years of Education	1,737	16.55 (2.75) [7.00, 32.00]	16.56 (2.72) [7.00, 30.00]	16.57 (2.46) [9.00, 27.00]
APOEε4 Status	1,715			
ε4-		1,116 (65.07%)	193 (42.05%)	232 (75.08%)
ε4+		599 (34.93%)	266 (57.95%)	77 (24.92%)
PACC Score	1,737	-0.81 (2.33) [-12.08, 5.58]	-1.15 (2.43) [-11.15, 5.17]	-0.71 (2.24) [-6.79, 4.38]
Baseline Amyloid Status	1,737			
Ab-		1,278 (73.58%)	0 (0.00%)	311 (100.00%)
Ab+		459 (26.42%)	459 (100.00%)	0 (0.00%)
Baseline Global Amyloid Burden	1,737	1.09 (0.19) [0.79, 2.00]	1.33 (0.16) [1.01, 2.00]	0.99 (0.07) [0.79, 1.15]
Treatment Group	1,737			
A4 Placebo		236 (13.59%)	236 (51.42%)	0 (0.00%)
A4 Treated		223 (12.84%)	223 (48.58%)	0 (0.00%)

Characteristic	N	Overall, N = 1,737 <sup>1</sup>	A4, N = 459 <sup>1</sup>	LEARN, N = 311 <sup>1</sup>
LEARN/SF		1,278 (73.58%)	0 (0.00%)	311 (100.00%)

<sup>1</sup>Mean (SD)  
[Range]; n (%)

## 2.1.2 Longitudinal Participants

Demographics for participants with at least two PACC visits

Characteristic	N	Overall, N = 771 <sup>1</sup>	A4, N = 459 <sup>1</sup>	LEARN, N = 311 <sup>1</sup>
Baseline Age	771	71.33 (4.68) [65.00, 85.51]	71.97 (4.81) [65.00, 85.51]	70.36 (4.31) [65.00, 84.46]
Sex	771			
Female		481 (62.39%)	291 (63.40%)	189 (60.77%)
Male		290 (37.61%)	168 (36.60%)	122 (39.23%)
Years of Education	771	16.57 (2.61) [7.00, 30.00]	16.56 (2.72) [7.00, 30.00]	16.57 (2.46) [9.00, 27.00]
APOEε4 Status	769			
e4-		425 (55.27%)	193 (42.05%)	232 (75.08%)
e4+		344 (44.73%)	266 (57.95%)	77 (24.92%)
PACC Score	771	-0.97 (2.36) [-11.15, 5.17]	-1.15 (2.43) [-11.15, 5.17]	-0.71 (2.24) [-6.79, 4.38]
Baseline Amyloid Status	771			
Ab-		312 (40.47%)	0 (0.00%)	311 (100.00%)
Ab+		459 (59.53%)	459 (100.00%)	0 (0.00%)
Baseline Global Amyloid Burden	771	1.19 (0.21) [0.79, 2.00]	1.33 (0.16) [1.01, 2.00]	0.99 (0.07) [0.79, 1.15]
Treatment Group	771			
A4 Placebo		236 (30.61%)	236 (51.42%)	0 (0.00%)
A4 Treated		223 (28.92%)	223 (48.58%)	0 (0.00%)
LEARN/SF		312 (40.47%)	0 (0.00%)	311 (100.00%)

Characteristic	N	Overall, N = 771 <sup>1</sup>	A4, N = 459 <sup>1</sup>	LEARN, N = 311 <sup>1</sup>
PACC Timepoints	771	12.07 (4.12) [2.00, 18.00]	12.31 (4.08) [2.00, 18.00]	11.75 (4.13) [2.00, 18.00]
PACC Years of Follow Up	745	5.27 (2.05) [0.12, 7.60]	5.25 (1.96) [0.18, 7.46]	5.31 (2.16) [0.12, 7.60]

<sup>1</sup>Mean (SD)  
[Range]; n (%)

## 2.2 Amyloid Sample

### 2.2.1 All Participants

Characteristic	N	Overall, N = 1,737 <sup>1</sup>	A4, N = 459 <sup>1</sup>	LEARN, N = 311 <sup>1</sup>
Baseline Age	1,737	71.31 (4.70) [64.63, 85.89]	71.97 (4.81) [65.00, 85.51]	70.36 (4.31) [65.00, 84.46]
Sex	1,737			
Female		1,083 (62.35%)	291 (63.40%)	189 (60.77%)
Male		654 (37.65%)	168 (36.60%)	122 (39.23%)
Years of Education	1,737	16.55 (2.75) [7.00, 32.00]	16.56 (2.72) [7.00, 30.00]	16.57 (2.46) [9.00, 27.00]
APOEε4 Status	1,715			
e4-		1,116 (65.07%)	193 (42.05%)	232 (75.08%)
e4+		599 (34.93%)	266 (57.95%)	77 (24.92%)
PACC Score	1,737	-0.81 (2.33) [-12.08, 5.58]	-1.15 (2.43) [-11.15, 5.17]	-0.71 (2.24) [-6.79, 4.38]
Baseline Amyloid Status	1,737			
Ab-		1,278 (73.58%)	0 (0.00%)	311 (100.00%)
Ab+		459 (26.42%)	459 (100.00%)	0 (0.00%)
Baseline Global Amyloid Burden	1,737	1.09 (0.19) [0.79, 2.00]	1.33 (0.16) [1.01, 2.00]	0.99 (0.07) [0.79, 1.15]
Treatment Group	1,737			

Characteristic	N	Overall, N = 1,737 <sup>1</sup>	A4, N = 459 <sup>1</sup>	LEARN, N = 3
A4 Placebo		236 (13.59%)	236 (51.42%)	0 (0.00%)
A4 Treated		223 (12.84%)	223 (48.58%)	0 (0.00%)
LEARN/SF		1,278 (73.58%)	0 (0.00%)	311 (100.00%)
<sup>1</sup> Mean (SD) [Range]; n (%)				

## 2.2.2 Longitudinal Participants

Demographics for participants with at least two amyloid scans

Characteristic	N	Overall, N = 536 <sup>1</sup>	A4, N = 367 <sup>1</sup>	LEARN, N = 169 <sup>1</sup>
Baseline Age	536	71.17 (4.59) [65.00, 85.26]	71.77 (4.68) [65.00, 85.26]	69.88 (4.13) [65.00, 81.73]
Sex	536			
Female		346 (64.55%)	237 (64.58%)	109 (64.50%)
Male		190 (35.45%)	130 (35.42%)	60 (35.50%)
Years of Education	536	16.55 (2.52) [7.00, 27.00]	16.50 (2.63) [7.00, 27.00]	16.65 (2.26) [12.00, 21.00]
APOEε4 Status	535			
e4-		283 (52.90%)	148 (40.33%)	135 (80.36%)
e4+		252 (47.10%)	219 (59.67%)	33 (19.64%)
PACC Score	536	-0.84 (2.40) [-11.15, 5.17]	-1.05 (2.44) [-11.15, 5.17]	-0.38 (2.26) [-6.73, 4.38]
Baseline Amyloid Status	536			
Ab-		169 (31.53%)	0 (0.00%)	169 (100.00%)
Ab+		367 (68.47%)	367 (100.00%)	0 (0.00%)
Baseline Global Amyloid Burden	536	1.23 (0.21) [0.83, 2.00]	1.33 (0.16) [1.01, 2.00]	0.99 (0.07) [0.83, 1.15]
Treatment Group	536			
A4 Placebo		189 (35.26%)	189 (51.50%)	0 (0.00%)

Characteristic	N	Overall, N = 536 <sup>1</sup>	A4, N = 367 <sup>1</sup>	LEARN, N = 169 <sup>1</sup>
A4 Treated		178 (33.21%)	178 (48.50%)	0 (0.00%)
LEARN/SF		169 (31.53%)	0 (0.00%)	169 (100.00%)
PACC Timepoints	536	13.94 (2.68) [3.00, 18.00]	13.66 (2.93) [3.00, 18.00]	14.56 (1.90) [9.00, 18.00]
PACC Years of Follow Up	518	6.13 (1.30) [0.42, 7.60]	5.89 (1.40) [0.42, 7.46]	6.70 (0.78) [4.36, 7.60]

<sup>1</sup>Mean (SD)  
[Range]; n (%)

## 2.3 TAU Sample

### 2.3.1 All Participants

Characteristic	N	Overall, N = 244 <sup>1</sup>	A4, N = 196 <sup>1</sup>	LEARN, N = 46 <sup>1</sup>
Baseline Age	244	71.65 (4.74) [65.00, 85.51]	72.11 (4.64) [65.00, 85.51]	69.47 (4.53) [65.08, 84.46]
Sex	244			
Female		153 (62.70%)	127 (64.80%)	26 (56.52%)
Male		91 (37.30%)	69 (35.20%)	20 (43.48%)
Years of Education	244	16.34 (2.74) [9.00, 30.00]	16.26 (2.82) [9.00, 30.00]	16.74 (2.39) [12.00, 20.00]
APOEε4 Status	244			
e4-		120 (49.18%)	87 (44.39%)	33 (71.74%)
e4+		124 (50.82%)	109 (55.61%)	13 (28.26%)
PACC Score	244	-1.06 (2.59) [-11.15, 5.17]	-1.26 (2.51) [-11.15, 5.17]	0.02 (2.47) [-6.33, 4.38]
Baseline Amyloid Status	244			
Ab-		48 (19.67%)	0 (0.00%)	46 (100.00%)
Ab+		196 (80.33%)	196 (100.00%)	0 (0.00%)



Characteristic	N	Overall, N = 244 <sup>1</sup>	A4, N = 196 <sup>1</sup>	LEARN, N = 46 <sup>1</sup>
Baseline Global Amyloid Burden	244	1.28 (0.20) [0.86, 1.85]	1.34 (0.16) [1.05, 1.85]	1.00 (0.06) [0.86, 1.11]
Treatment Group	244			
A4 Placebo		100 (40.98%)	100 (51.02%)	0 (0.00%)
A4 Treated		96 (39.34%)	96 (48.98%)	0 (0.00%)
LEARN/SF		48 (19.67%)	0 (0.00%)	46 (100.00%)
<sup>1</sup> Mean (SD) [Range]; n (%)				

### 2.3.2 Longitudinal Participants

Demographics for participants with at least two tau scans

Characteristic	N	Overall, N = 217 <sup>1</sup>	A4, N = 174 <sup>1</sup>	LEARN, N = 43 <sup>1</sup>
Baseline Age	217	71.59 (4.68) [65.00, 85.51]	72.10 (4.57) [65.00, 85.51]	69.54 (4.63) [65.08, 84.46]
Sex	217			
Female		137 (63.13%)	112 (64.37%)	25 (58.14%)
Male		80 (36.87%)	62 (35.63%)	18 (41.86%)
Years of Education	217	16.35 (2.73) [11.00, 30.00]	16.26 (2.80) [11.00, 30.00]	16.70 (2.43) [12.00, 20.00]
APOEε4 Status	217			
e4-		109 (50.23%)	78 (44.83%)	31 (72.09%)
e4+		108 (49.77%)	96 (55.17%)	12 (27.91%)
PACC Score	217	-1.05 (2.57) [-11.15, 5.17]	-1.30 (2.55) [-11.15, 5.17]	-0.04 (2.45) [-6.33, 4.38]
Baseline Amyloid Status	217			
Ab-		43 (19.82%)	0 (0.00%)	43 (100.00%)
Ab+		174 (80.18%)	174 (100.00%)	0 (0.00%)

Characteristic	N	Overall, N = 217 <sup>1</sup>	A4, N = 174 <sup>1</sup>	LEARN, N = 43 <sup>1</sup>
Baseline Global Amyloid Burden	217	1.27 (0.20) [0.86, 1.85]	1.34 (0.16) [1.07, 1.85]	1.00 (0.06) [0.86, 1.11]
Treatment Group	217			
A4 Placebo		87 (40.09%)	87 (50.00%)	0 (0.00%)
A4 Treated		87 (40.09%)	87 (50.00%)	0 (0.00%)
LEARN/SF		43 (19.82%)	0 (0.00%)	43 (100.00%)
PACC Timepoints	217	13.65 (2.63) [6.00, 18.00]	13.79 (2.55) [6.00, 18.00]	13.07 (2.87) [6.00, 17.00]
PACC Years of Follow Up	208	5.97 (1.26) [1.88, 7.56]	5.96 (1.19) [1.88, 7.46]	6.05 (1.56) [2.06, 7.56]

<sup>1</sup>Mean (SD)  
[Range]; n (%)

## 2.4 pTAU Sample

### 2.4.1 All Participants

Characteristic	N	Overall, N = 724 <sup>1</sup>	A4, N = 445 <sup>1</sup>	LEARN, N = 279 <sup>1</sup>
Baseline Age	724	71.29 (4.70) [65.00, 85.51]	71.98 (4.83) [65.00, 85.51]	70.19 (4.27) [65.00, 84.46]
Sex	724			
Female		457 (63.12%)	284 (63.82%)	173 (62.01%)
Male		267 (36.88%)	161 (36.18%)	106 (37.99%)
Years of Education	724	16.53 (2.60) [7.00, 30.00]	16.53 (2.71) [7.00, 30.00]	16.53 (2.42) [9.00, 26.00]
APOEε4 Status	723			
ε4-		398 (55.05%)	187 (42.02%)	211 (75.90%)
ε4+		325 (44.95%)	258 (57.98%)	67 (24.10%)
PACC Score	724	-0.92 (2.38) [-11.15, 5.17]	-1.14 (2.45) [-11.15, 5.17]	-0.57 (2.23) [-6.73, 4.38]

Characteristic	N	Overall, N = 724 <sup>1</sup>	A4, N = 445 <sup>1</sup>	LEARN, N = 279 <sup>1</sup>
Baseline Amyloid Status	724			
Ab-		279 (38.54%)	0 (0.00%)	279 (100.00%)
Ab+		445 (61.46%)	445 (100.00%)	0 (0.00%)
Baseline Global Amyloid Burden	724	1.20 (0.21) [0.83, 2.00]	1.33 (0.16) [1.01, 2.00]	1.00 (0.07) [0.83, 1.15]
Treatment Group	724			
A4 Placebo		228 (31.49%)	228 (51.24%)	0 (0.00%)
A4 Treated		217 (29.97%)	217 (48.76%)	0 (0.00%)
LEARN/SF		279 (38.54%)	0 (0.00%)	279 (100.00%)
<sup>1</sup> Mean (SD) [Range]; n (%)				

## 2.4.2 Longitudinal Participants

Demographics for participants with at least two ptau visits

Characteristic	N	Overall, N = 598 <sup>1</sup>	A4, N = 426 <sup>1</sup>	LEARN, N = 172 <sup>1</sup>
Baseline Age	598	71.41 (4.72) [65.00, 85.51]	72.03 (4.85) [65.00, 85.51]	69.90 (4.01) [65.00, 82.00]
Sex	598			
Female		382 (63.88%)	272 (63.85%)	110 (63.95%)
Male		216 (36.12%)	154 (36.15%)	62 (36.05%)
Years of Education	598	16.58 (2.60) [7.00, 30.00]	16.52 (2.74) [7.00, 30.00]	16.72 (2.24) [12.00, 21.00]
APOEε4 Status	598			
e4-		321 (53.68%)	183 (42.96%)	138 (80.23%)
e4+		277 (46.32%)	243 (57.04%)	34 (19.77%)
PACC Score	598	-0.87 (2.42) [-11.15, 5.17]	-1.11 (2.45) [-11.15, 5.17]	-0.29 (2.25) [-6.73, 4.38]
Baseline Amyloid Status	598			

Characteristic	N	Overall, N = 598 <sup>1</sup>	A4, N = 426 <sup>1</sup>	LEARN, N = 172 <sup>1</sup>
Ab-		172 (28.76%)	0 (0.00%)	172 (100.00%)
Ab+		426 (71.24%)	426 (100.00%)	0 (0.00%)
Baseline Global Amyloid Burden	598	1.23 (0.21) [0.83, 2.00]	1.33 (0.16) [1.01, 2.00]	0.99 (0.07) [0.83, 1.15]
Treatment Group	598			
A4 Placebo		220 (36.79%)	220 (51.64%)	0 (0.00%)
A4 Treated		206 (34.45%)	206 (48.36%)	0 (0.00%)
LEARN/SF		172 (28.76%)	0 (0.00%)	172 (100.00%)
PACC Timepoints	598	13.06 (3.54) [2.00, 18.00]	12.58 (3.85) [2.00, 18.00]	14.26 (2.17) [7.00, 18.00]
PACC Years of Follow Up	580	5.69 (1.74) [0.18, 7.60]	5.35 (1.86) [0.18, 7.46]	6.57 (0.95) [3.08, 7.60]
<sup>1</sup> Mean (SD) [Range]; n (%)				