PARKINSON'S PROGRESSION MARKERS INITIATIVE

Play a Part in Parkinson's Research

Aβ1-42, t-tau and p-tau181 measurements in PPMI CSF samples using the fully automated Roche Electrochemiluminescence Elecsys Immunoassay

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PPMI Project ID: 125

Summary: Over three thousand CSF samples, collected according to the Parkinson's Progression Markers Initiative (PPMI) Laboratory Manual LP procedure, were analysed for three biomarkers: Amyloid-beta(1-42) (Aβ42), total tau (t-tau) and tau phosphorylated at the threonine 181 position (p-tau181), using Elecsys electro-chemi-luminescence immunoassays on the cobas e 601 platform (Roche Diagnostics). Among the analysed samples were 2 pooled quality control CSF samples from PPMI (HC pool and PD pool), as well as a number of duplicate aliquots for the purpose of thoroughly evaluating the longitudinal as well as test-retest precision performance of the assay.

Method: CSF samples in this project were analysed using the Elecsys Abeta(1–42), t-tau and p-tau181 electrochemiluminescence (ECL) immunoassays on a fully automated cobas e 601 analyzer (Roche Diagnostics). These immunoassays are currently under development and are for investigational use only. The Aβ42 assay has a measurement range of 200 to 1700 pg/mL, the t-tau assay: 80 to 1300 pg/mL, and the p-tau181 assay: 8 to 120 pg/mL.

In the data report file, in 153 instances the values of Aβ42 have been extrapolated from the calibration curve above the 1700 pg/mL limit. See important disclaimer about use of these data:

> *The Elecsys β-Amyloid (1-42) CSF immunoassay in use is not a commercially available IVD assay. It is an assay that is currently under development and for investigational use only. The measuring range of the assay is 200 (lower technical limit) – 1700 pg/mL (upper technical limit). The performance of the assay beyond the upper technical limit has not been formally established. Therefore, use of values above the upper technical limit, which are provided based on an extrapolation of the calibration curve, is restricted to exploratory research purposes and is excluded for clinical decision making or for the derivation of medical decision points.*

More details about this method can be found in [1] and [2].

A total of 3541 CSF samples were processed in this project, including 3131 PPMI patient samples, 255 PPMI pools, and 128 internal pool controls. Among the 3131 patient samples, there were 2985 individual patient/visit samples, 61 samples retested for technical reasons and 85 planned retests. These 85 retests were planned for the purpose of evaluating the assay test-retest performance.

The PPMI pools: "HC Pool" and "PD Pool", were Healthy-Control-like and Parkinson's-Disease-like pools, respectively. The internal pool "56" was prepared from CSF samples of Alzheimer's Disease patients, leftover from other analyses.

The samples were processed at a rate of 80 per day, each day consisting of 2 batches of 40 samples each. The following reagent lots were used: Aβ42: P07 (2017-06-26 through 2017-09-21) & P09 (2017-09-22, 2 batches); t-tau: P02; and p-tau181: P02. All records with Aβ42 result obtained on 2017-09-22 were processed with the P09 reagent lot. Testing of the P07 vs P09 lots on another batch of CSF samples indicated no statistically significant difference (Figure 1).

The project was set-up in two phases. In the first phase a number of CSF pool samples (117 PPMI pools: 58 HC Pools and 59 PD Pools; and 42 internal Pools "56") were analysed in the course of two days to evaluate the within-day performance of the assay. In the second phase, the main study, patient samples were processed along with the remaining pools. The PPMI pools (HC Pool and PD Pool) were randomly scattered between patient samples, while the internal pool control (Pool "56") was always processed as the last sample of each batch. Results of these experiments are summarized in Tables 1 & 2, and in Figure 2.

Figure 3 summarizes the results of test-retest performance of the 85 planned retest samples.

	group	N	Mean	SD	CV	Median	LCI	UCI
Abeta	PPMI HC Pool	125	751.9	59.75	7.95	751.3	614.6	865.4
	PPMI PD Pool	126	546	51.49	9.43	544.8	439.9	643.8
	BRL Pool 56	126	463.7	18.66	4.02	460.6	427.2	507.0
Tau	PPMI HC Pool	127	143.9	5.051	3.51	143.5	135.1	155.8
	PPMI PD Pool	128	120.6	3.531	2.93	120.8	114	127.5
	BRL Pool 56	128	529	14.66	2.77	531.3	500.5	555.7
PTau	PPMI HC Pool	127	14.44	0.4949	3.43	14.39	13.77	15.97
	PPMI PD Pool	128	12.2	0.2813	2.31	12.16	11.71	12.73
	BRL Pool 56	128	41.82	0.7934	1.9	41.84	40.5	43.28

Table 1: Overall pool summary

	group	group	N	Mean	SD	CV	Median	LCI	UCI
Abeta	Pre-study	PPMI HC Pool	58	744.2	45.16	6.07	747.7	652.4	812.6
		PPMI PD Pool	59	565.7	46.35	8.19	561.6	493.2	649.7
		BRL Pool 56	42	463.9	11.07	2.39	464.1	449.7	482.7
	Study	PPMI HC Pool	67	758.5	69.63	9.18	754.2	605.8	878
		PPMI PD Pool	67	528.6	49.79	9.42	529	431.9	608.8
		BRL Pool 56	84	463.6	21.54	4.65	459.6	425.9	507.3
Tau	Pre-study	PPMI HC Pool	58	145.3	4.999	3.44	143.6	139.9	160
		PPMI PD Pool	59	121.7	2.788	2.29	121.1	118.3	129.6
		BRL Pool 56	42	534.2	7.849	1.47	533.6	521.5	548.1
	Study	PPMI HC Pool	69	142.7	4.821	3.38	143.2	133.8	151.4
		PPMI PD Pool	69	119.6	3.828	3.2	119	113.6	126.3
		BRL Pool 56	86	526.4	16.48	3.13	524	500.2	555.8
Ptau	Pre-study	PPMI HC Pool	58	14.67	0.5572	3.8	14.51	14.05	16.17
		PPMI PD Pool	59	12.34	0.2864	2.32	12.29	11.95	13.07
		BRL Pool 56	42	42.25	0.7668	1.82	42.16	41.37	43.48
	Study	PPMI HC Pool	69	14.25	0.3338	2.34	14.18	13.71	14.93
		PPMI PD Pool	69	12.09	0.2199	1.82	12.09	11.68	12.54
		BRL Pool 56	86	41.61	0.7234	1.74	41.61	40.4	43.21

Table 2: Pool summary by study phase.

References

1. Bittner T, Zetterberg H, Teunissen CE, et al. Technical performance of a novel, fully automated electrochemiluminescence immunoassay for the quantitation of β-amyloid (1-42) in human cerebrospinal fluid. Alzheimers Dement. 2016 May;12(5):517-26
2. Lifke V, Manuilova E, Knop C, et al. Elecsys®Total-Tau CSF and Elecsys®Phospho-Tau (181P) CSF: novel, fully automated immunoassays for rapid and accurate quantitation of CSF biomarkers for clinical use. Clinical trials of Alzheimer's disease; 2017.

About the Authors

This document was prepared by Michal J Figurski and Leslie M Shaw of University of Pennsylvania, Department of Pathology and Laboratory Medicine at the Perelman School of Medicine. We acknowledge and thank Leona Fields for performance of the CSF analyses using the Roche Elecsys immunoassays on the Cobas e 601 platform and reported in this document. For more information please contact Dr Leslie M Shaw at 215-662-6578 or by email at shawlmj@pennmedicine.upenn.edu.

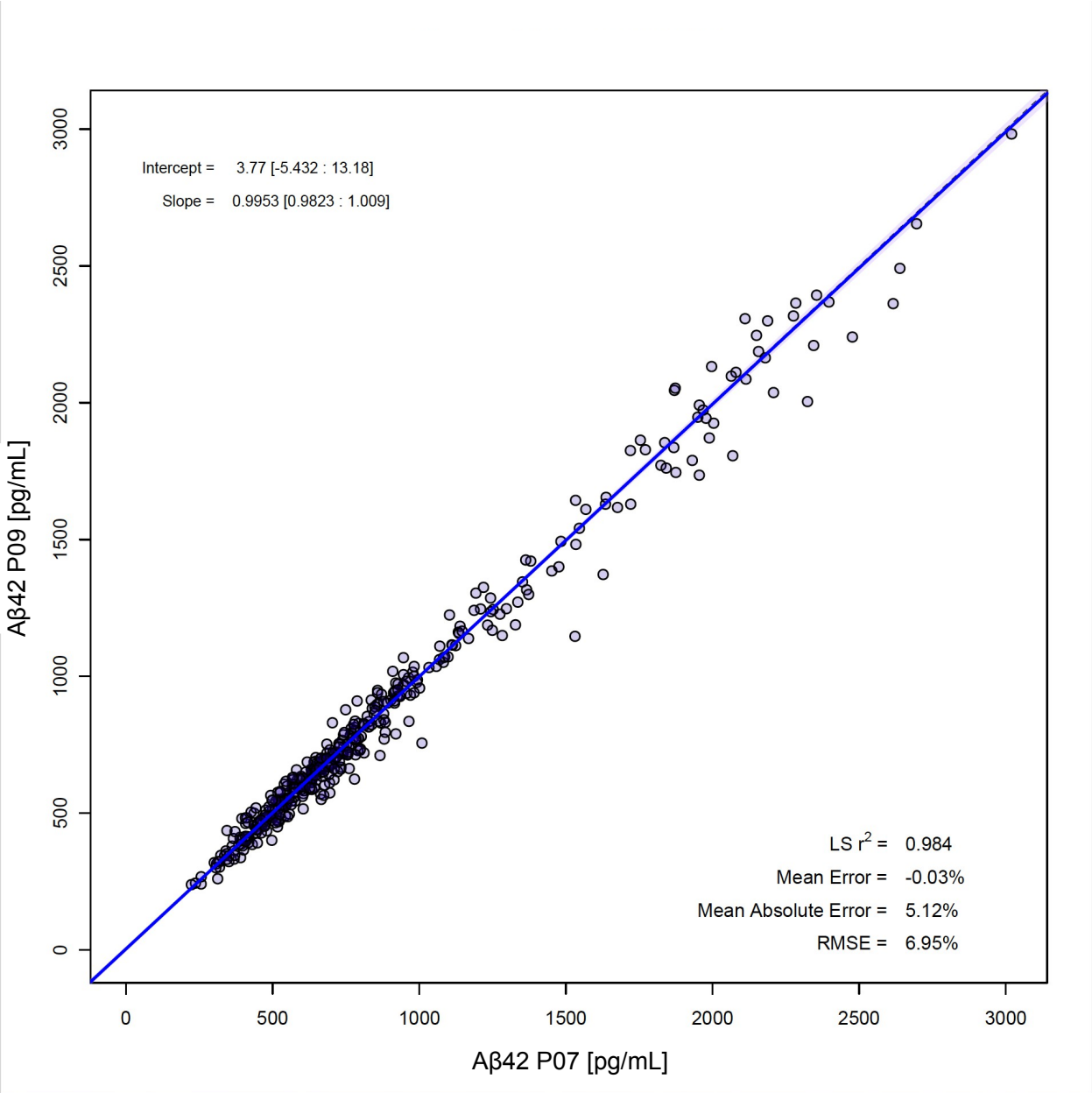

Figure 1: Correlation of Aβ42 *results between reagent lots P07 and P09*

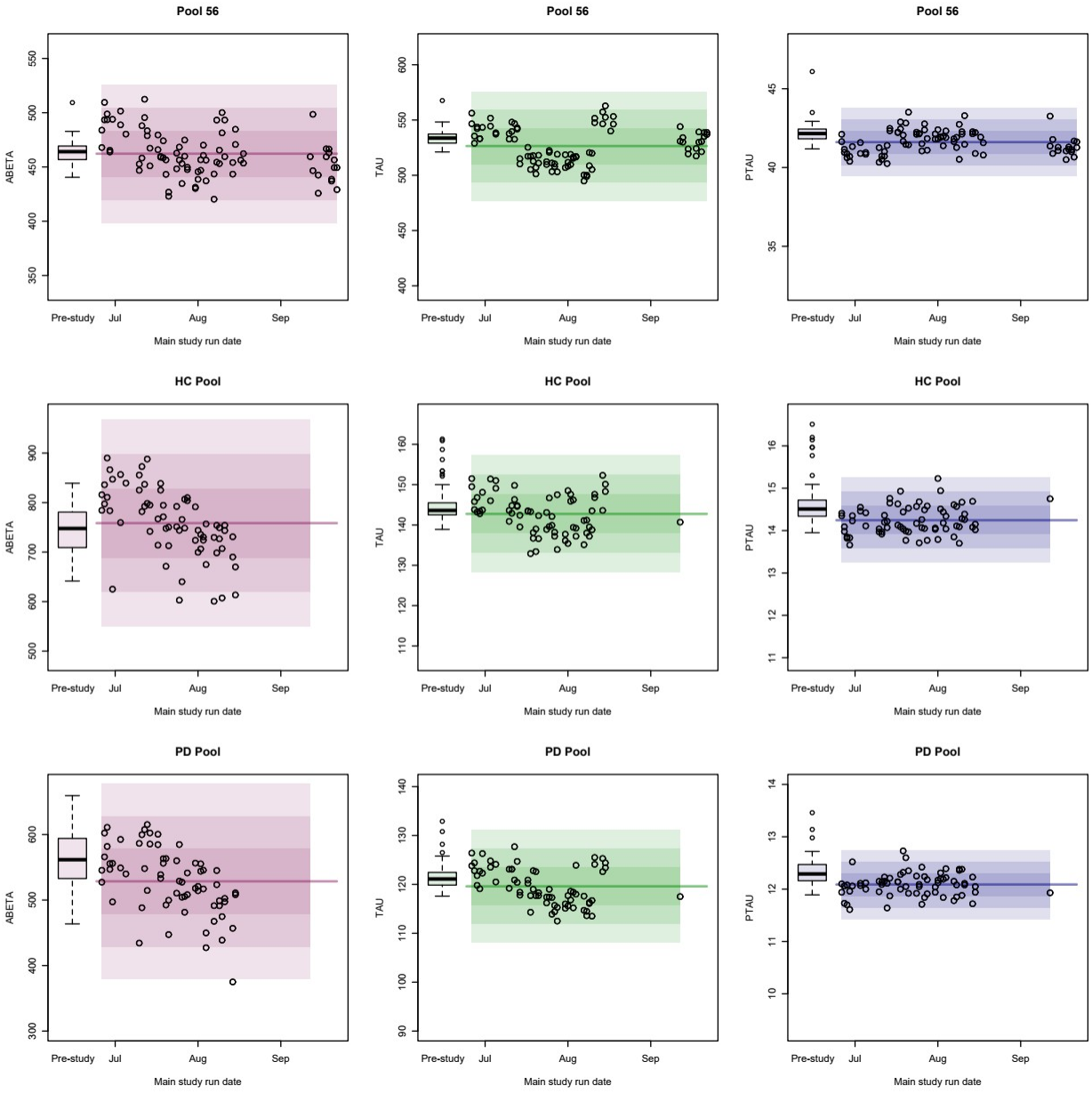

Figure 2: Longitudinal pool performance for Abeta, Tau and PTau.

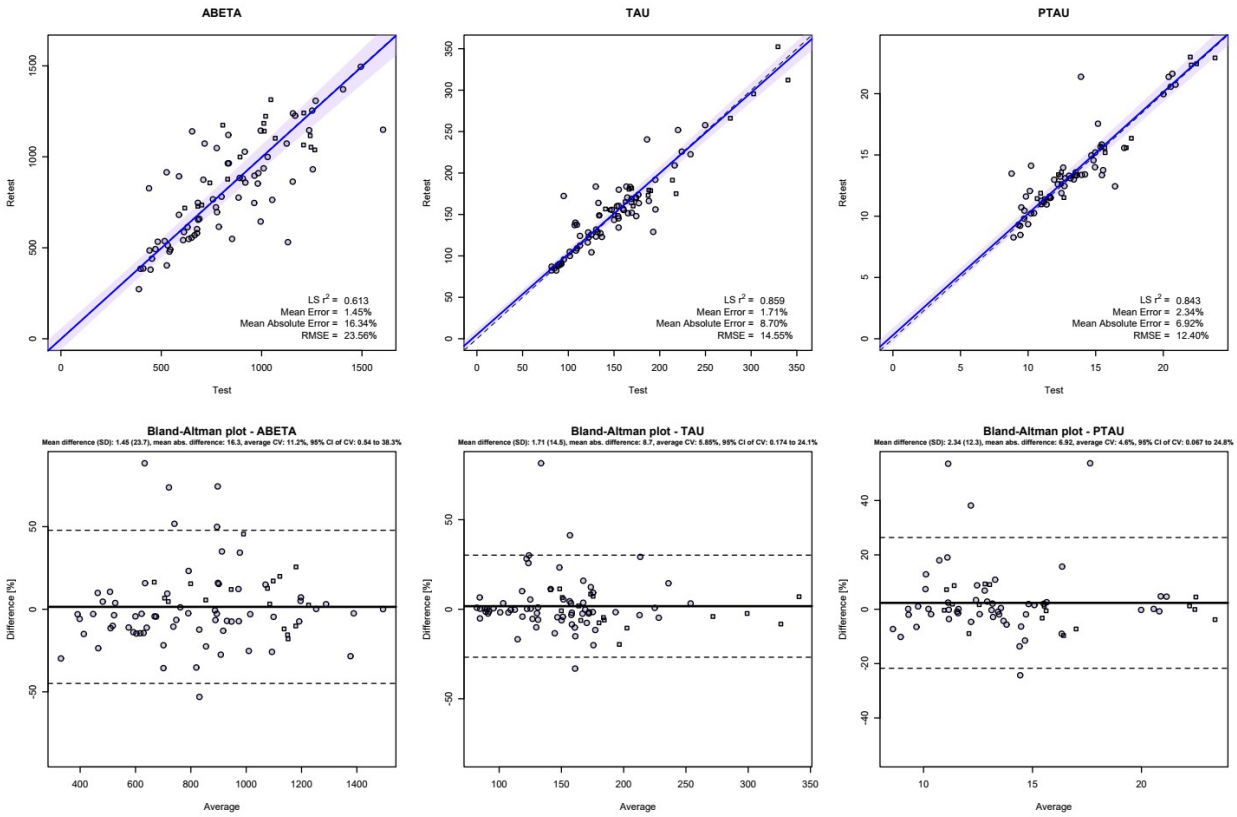

Figure 3: Summary of test-retest results for Abeta, Tau and PTau assays