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Biomarker Core Aims and Progress for ADNI3

The Biomarker Core in ADNI3 is focusing on 4 areas of activity and studies including:
biofluid banking (CSF, plasma and serum) management and pre-analytical assessments;
standardization of CSF Aβ42, Aβ40, t-tau and p-tau181 measurement in ADNI patients using the highly validated Roche Elecsys cobas e 601 fully automated immunoassay platform and reference LC/MSMS methodology for CSF Aβ42, Aβ40 and Aβ38;
determination of cut-points for Aβ42, t-tau, p-tau181, and ratios using several approaches including ROC analyses using FBP amyloid PET imaging for disease detection and disease independent mixture modeling;
collaborative studies on new biomarker development/validation/testing in CSF or plasma by immunoassay or mrm LC/MSMS including NFL, total and phospho-α-synuclein, Vilip-1, sTREM2, progranulin, TDP-43, metabolomics/lipidomic biomarkers and proteomic quantitative assays.

Highlights of Biomarker Core activities include:

BIOFLUID BANKING | STANDARDIZATION | CUT POINTS

BIOFLUIDS
Continue to receive, aliquot, store and curate all biofluid samples (CSF, plasma, serum) collected from subjects enrolled in ADNI3, including all who "carry over" from ADNIGO/2 and all newly enrolled individuals, with 24/7 surveillance in the ADNI freezers that are housed in secure, dedicated space at UPENN. The updated (as of Feb 28, 2018) list of pristine aliquots of CSF, plasma and serum samples collected from ADNI subjects, "ALIQUOTS_LIST.csv" can be found on the ADNI LONI website under BIOSPECIMENS, but below in Table 1 is a brief summary of these samples.

▸ **Table 1.** Summary of ADNI CSF, plasma and serum samples received and aliquots prepared as of 3/2/2018.

Continue to monitor details involved in the preparation of Biofluid samples at study sites including time from obtaining each sample to the time of freezing on dry ice (a summary of this is provided in Figure 1 below). We continue to review details involved in the pre-analytical steps involved in biofluid samples. In the figure below a focus on sample preparation time shows that for CSF the mean, 95%CI and median values across 1,318 samples collected from ADNIGO/2 phase participants is: 44.8 min, (41.7-47.8 min) and 28 min respectively. For 3,908 plasma samples the respective values are: 71.7 min, (70.0-73.4 min) and 55 min. This information is available for each ADNI sample. The handling at each ADNI site of these biofluid samples is very important to assure the quality of each sample. Avoidance of hemolysis and time-efficient sample preparation are essential to the goal of sample quality. For plasma, the recommended time from collection to freezing is no longer than 120 min; for CSF the recommended time is 60 min or less in order to minimize risk for biomarker degradation due to metabolic processes.

▸ **Figure 1**. Sample collection to freezing time for ADNI GO/2 plasma and CSF primary samples

Regularly communicate with Clinical Core staff regarding biofluid collections and any issues concerning sample quality, labeling discrepancies, and provision of updated samples-received summaries.

Continue our collaborative studies on identifying and controlling pre-analytical factors that can contribute to variability in CSF or plasma biomarker measurements especially Aβ1-42 (Vanderstichele, etal, 2011; O'Bryant, etal, 2015; Hansson, etal, 2018). An example of this is a world-wide collaborative effort under the auspices of the Alz Association Global Biomarker Standardization Consortium(GBSC) whose members from industry and academic centers are defining a unified protocol for CSF sample collection for use in routine clinical practice and another for large multicenter studies such as ADNI. A new effort is the Biomarkers Consortium NSC - Plasma Aβ Working Group that is just being organized to pursue various aspects of plasma Aβ measurement. Although there have been mixed results for plasma Aβ42/Aβ40 for accurate detection of AD using a number of immunoassay approaches, it is fervently hoped that by identifying and controlling pre-analytcal factors, improved analytical techniques, and controlling for concomitant disease factors(Rissman, etal, 2012) that progress can be made on improving the diagnostic utility of these measurements (Ovod V, etal, 2017). We will provide updates of these developments at the annual ADNI Steering Committee meetings.

RARC-approved studies using ADNI Biofluids

Prepare and ship biofluid samples(CSF, plasma or serum) to all investigators whose biomarker study proposals have been approved by the RARC (Resource Allocation Review Committee, appointed by the NIA) and following final review by NIA (see Table 2 for an up to date brief summary of these studies and status of results upload). Once completed the data from these studies, performed blinded, are uploaded on the LONI/ADNI website together with a Methods document that describes the methodology involved and quality control performance. Biomarker Core faculty, Drs Trojanowski and Shaw are happy to provide input on any study although this is not required but often we are asked. The procedure for making an application to the Resource Allocation Review Board(RARC) for ADNI biofluid aliquot samples can be found on the ADNI web site.

A study that builds upon the 2013-2014 proteomic study that used LC/MSMS mrm mass spectrometry methodology will be conducted in 2018 to determine accurate concentration values for 5 candidate biomarkers that showed promise in the earlier semi-quantitative-based study(see Table 2 for a brief synopsis of all of these studies). An important characteristic of this study is its emphasis on measurements in longitudinal CSF samples across time from entry into the ADNI study (BASELINE) to at least 4 years later in order to assess these biomarker trajectories. Such data can be informative to clinical trials that are seeking to use biomarkers as indices of drug engagement and drug effect.

We continue to collaborate with biomarker scientists at UPenn and elsewhere (Irwin et al, 2017, 2018; Hu, 2010, 2015; Toledo et al, 2013, 2018; Mattsson, etal, 2013, 2016; Zetterberg and Blennow, 2016). New CSF biomarker-neuropathology correlations done with UPenn collaborators resulted in studies involving CSF tau and histochemical tau in FTLD and CSF tau and Aβ42 and synucleinopathy in autopsied Lewy Body disorders (Irwin etal, 2017, 2018). Such studies take advantage of the large set of CSF collected at UPenn from individuals prior to death and for whom an autopsy diagnosis provides accurate detection of not only AD neuropathology but concomitant pathologies such as Lewy Bodies, TDP-43 deposits, hippocampal sclerosis. A list of the publications describing the results of these studies thus far is included in References. Figure 2 illustrates the timing for onset and progression of AD, trajectories for amyloid and plaque biomarkers and some highlight characteristics of the mixed pathologies such as synucleinopathy and TDP-43 deposits that likely impact the timeline for clinical decline in individual patients.

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Table 1. Summary of ADNI CSF, plasma and serum samples received and aliquots prepared as of 3/2/2018.

	CSF	Ser + Pla	Total
ADNI 1 Primary Biofluids Collected	1118	9756	10874
ADNI 1 Aliquots in Bank	24934	132581	157515
ADNI GO/2 Primary Biofluids Collected	1318	7816	9134
ADNI GO/ 2 Aliquots in Bank	35315	114919	150234
ADNI 3 Primary Biofluids Collected - Rollover Participants	100	574	674
ADNI 3 Primary Biofluids Collected - New Enrollees	67	162	229

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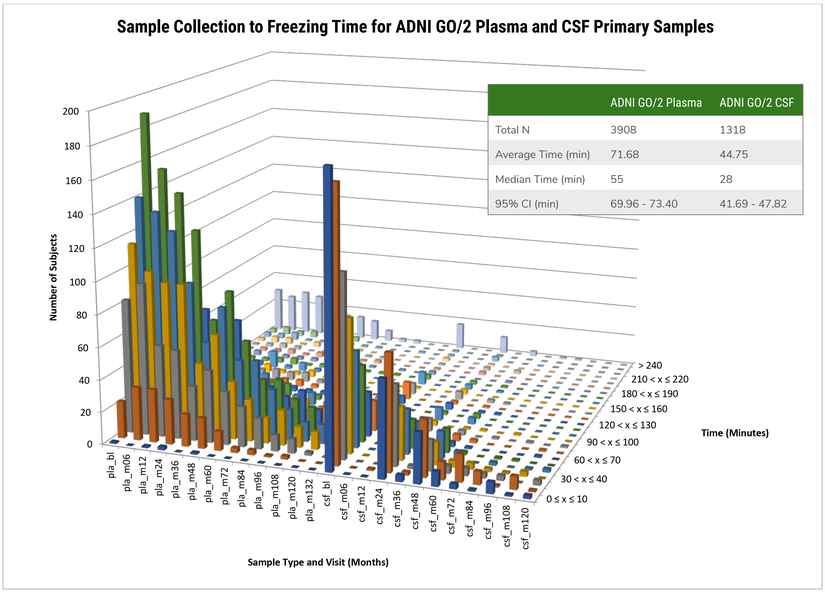
Figure 1. Sample collection to freezing time for ADNI GO/2 plasma and CSF primary samples



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Highlights of Biomarker Core activities include:

BIOFLUID BANKING | STANDARDIZATION | CUT POINTS

STANDARDIZATION
Implementation of a fully validated reference LC/MSMS method for CSF Aβ42 and further validated for CSF Aβ40 and Aβ38. (see Korecka etal, 2014, Panee etal, 2016; Kuhlman, etal 2016) for measurements in all ADNIGO/2 BASELINE and LONGITUDINAL CSF samples. The Methods document and dataset for these analyses will be uploaded to LONI ADNI website, March, 2018. The methods document includes frequency plots for each analyte and for the Aβ42/Aβ40 ratio and mixture modeling to determine cut-points using disease-independent statistical methodology.
Analyses of CSF for Aβ, t-tau and p-tau181 moved from the Research-Use-Only Fujirebio AlzBio3 xMAP bead-based immunoassay to the fully automated Roche Elecsys platform following extensive validation studies, and for Aβ42, comparisons with validated reference method LC/MSMS using the primary reference standard preparation of Aβ42, provided by the Institute for Reference Materials and Measurements (IRMM) following finalization of replicate amino acid analyses(Kuhlman etal, 2017, Certification Report).

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DETERMINATION OF CUT-POINTS FOR Aβ42, t-tau, p-tau181, AND RATIOS USING SEVERAL APPROACHES
Completion and upload to LONI the Methods Report, "ADNI3: Batch analyses of Aβ42, t-tau and p-tau181 in ADNI1, GO, 2 CSF samples using the fully automated Roche Elecsys and cobas e immunoassay analyzer system". This dataset, uploaded April, 2017, includes a total of 2,401 never-before-thawed aliquots of ADNI1, GO and 2 CSF samples that had been collected between 9/7/2005 and 7/25/2016. See PPT set #101 for a description of major parts of the method validation for Aβ42, and some cut-point estimations and see PPT set # 102 for further analyses, determinations of cut-points and relationships of "abnormal" and "normal" biomarker results to cognitive decline and progression from MCI to AD dementia done so far and working toward:

- definition of cut-points for Aβ1-42, t-tau, p-tau181 and the ratios, Aβ1-42/t-tau and Aβ1-42/p-tau181 using Mixture Modeling and ROC analyses;
- an understanding of the predictive performance for cognitive decline and progression of MCI participants to a clinical diagnosis of AD dementia using these cut-points;
- assessments of the comparisons between Aβ-|tau-, Aβ-|tau+, Aβ|tau-, and Aβ+|tau+ for predictive performance of each pair [Aβ- is below CSF cut-point value; Aβ+ is at or above CSF cut-point value; tau-, tau+ is below or (at or above, respectively) the cut-point value for CSF tau; analogous pairs for Aβ and p-tau181] for cognitive, memory and functional decline and progression from MCI to a clinical diagnosis of AD.
- assessments of concordance between CSF Aβ1-42, t-tau, p-tau181, the ratios, Aβ1-42/t-tau and Aβ1-42/p-tau181 and Florbetapir PET imaging-based plaque burden assessments.
- Inclusion of validated CSF Aβ40 to Aβ1-42, t-tau and p-tau181 in ADNI3 will permit evaluation for the Aβ1-42/Aβ40 ratio for possible improvement over Aβ1-42 alone for clinical utility.

A manuscript describing the concordance performance of ADNIGO/2 Roche Elecsys CSF Aβ42, t-tau and p-tau181 biomarker data and that from the Swedish BioFINDER study with either Florbetapir PET or Flutemetamol amyloid PET imaging, respectively, in the respective study cohorts, has been accepted for publication (Hansson etal, 2018b).

Provided support for development of new immunoassays for CSF Aβ42, t-tau, p-tau181 by providing residual CSF aliquot samples to 3 vendor laboratories (see Table 2 for more information).

▸ **Figure 2.** Timing for the onset and progression of AD

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Figure 2. Timing for the onset and progression of AD

The figure below illustrates the timing for the onset and progression of AD in the upper right panel with examples of mixed pathologies found in AD brains in the upper left panel while the lower panel summarizes the timing of pathology deposition and neuron death as well as current considerations for the treatment of AD. This figure is from a recently published update of earlier ADNI reviews from Kang etal, 2015, that provides our current understanding of the hypothetical timeline for the onset and progression of Alzheimer's Disease neurodegeneration and cognitive impairments progressing from normal to mild cognitive impairment and then to Alzheimer's disease dementia.