Form D1c: Biological and Clinical Staging

ADRC: _____ PTID: _____ Form date: __ __ / __ __ / __ __ __ __ Visit #: _____ Examiner's initials: _____

Language:
☐ 1 English
☐ 2 Spanish

Was this form completed?
☐ 1 Completed
☐ 0 Not completed *(reason)*: ___ ___

Key (not completed reason):
88 = Optional

Section 1 – Categorization of fluid analyte and imaging biomarkers

Biomarkers are categorized in this section based on four criteria:

1. Identify three broad mechanistic groupings
2. Subclassify based on the proteinopathy or pathophysiologic pathway that each biomarker measures (e.g., A,T,N, etc.)
3. Within the Core category, distinguish between Core 1 and Core 2 biomarkers
4. Imaging and fluid analyte biomarkers are listed separately within each category

Core Biomarkers

Core 1

A (Aβ proteinopathy) and **T_1** (phosphorylated and secreted AD tau)

CSF or plasma analytes

Plasma

1. Were plasma biomarkers used in the etiologic diagnosis? ☐ 0 No **(SKIP TO QUESTION 2)** ☐ 1 Yes

If yes, select all plasma biomarkers that were used:

1a. ☐ 1 p-tau 217

If checked:

1a1. p-tau 217 result ☐ 0 Normal ☐ 1 Abnormal

1a2. Where were the p-tau 217 values used in the diagnosis analyzed?
☐ 1 Analyzed by NCRAD
☐ 2 Analyzed in-house or elsewhere
☐ 9 Unknown

1a3. Was the plasma p-tau 217 sample used in the diagnosis from a date within +/- 12 months of the current UDS visit?
☐ 0 No
☐ 1 Yes
☐ 9 Unknown

1b. ☐ 1 %p-tau 217

If checked:

1b1. %p-tau 217 result ☐ 0 Normal ☐ 1 Abnormal

1b2. Was the plasma %p-tau 217 sample used in the diagnosis from a date within +/- 12 months of the current UDS visit?
☐ 0 No
☐ 1 Yes
☐ 9 Unknown

*%p-tau values not currently analyzed by NCRAD; only available in-house or elsewhere

1c. ☐ 1 Other plasma biomarker **(SPECIFY)**: _____

If checked:

1c2. Other plasma biomarker result ☐ 0 Normal ☐ 1 Abnormal

1c3. Where were the other plasma biomarker values used in the diagnosis analyzed?
☐ 1 Analyzed by NCRAD
☐ 2 Analyzed in-house or elsewhere
☐ 9 Unknown

1c4. Was the plasma sample used in the diagnosis from a date within +/- 12 months of the current UDS visit?
☐ 0 No
☐ 1 Yes
☐ 9 Unknown

CSF or plasma analytes *continued...*

CSF

2.	Were CSF biomarkers used in the etiologic diagnosis?	☐ 0 No **(SKIP TO QUESTION 3)**	☐ 1 Yes
	If yes, select all CSF biomarkers that were used:		
2a.	☐ 1 p-tau 181/ Aβ42		
	If checked:		
2a1.	p-tau 181/ Aβ42 result	☐ 0 Normal	☐ 1 Abnormal
2a2.	Where were the p-tau 181/ Aβ42 values used in the diagnosis analyzed?	☐ 1 Analyzed by NCRAD ☐ 2 Analyzed in-house or elsewhere ☐ 9 Unknown	
2a3.	Was the CSF p-tau 181/ Aβ42 sample used in the diagnosis from a date within +/- 12 months of the current UDS visit?	☐ 0 No ☐ 1 Yes ☐ 9 Unknown	
2b.	☐ 1 t-tau / Aβ42		
	If checked:		
2b1.	t-tau / Aβ42 result	☐ 0 Normal	☐ 1 Abnormal
2b2.	Was the CSF t-tau / Aβ42 sample used in the diagnosis from a date within +/- 12 months of the current UDS visit?	☐ 0 No ☐ 1 Yes ☐ 9 Unknown	
	*t-tau values not currently analyzed by NCRAD; only available in-house or elsewhere		
2c.	☐ 1 Aβ42 / 40		
	If checked:		
2c1.	Aβ42 / 40 result	☐ 0 Normal	☐ 1 Abnormal
2c2.	Where were the Aβ42 / 40 values used in the diagnosis analyzed?	☐ 1 Analyzed by NCRAD ☐ 2 Analyzed in-house or elsewhere ☐ 9 Unknown	
2c3.	Was the Aβ42 / 40 sample used in the diagnosis from a date within +/- 12 months of the current UDS visit?	☐ 0 No ☐ 1 Yes ☐ 9 Unknown	
2d.	☐ 1 Other CSF biomarker (**SPECIFY**): _____		
	If checked:		
2d2.	Other CSF biomarker result	☐ 0 Normal	☐ 1 Abnormal
2d3.	Where were the other CSF biomarker values used in the diagnosis analyzed?	☐ 1 Analyzed by NCRAD ☐ 2 Analyzed in-house or elsewhere ☐ 9 Unknown	
2d4.	Was the CSF sample used in the diagnosis from a date within +/- 12 months of the current UDS visit?	☐ 0 No ☐ 1 Yes ☐ 9 Unknown	

Imaging

Amyloid PET

3.	Was Amyloid PET used in the etiologic diagnosis?	☐ 0 No **(SKIP TO QUESTION 4)**	☐ 1 Yes
3a.	Amyloid PET result:	☐ 0 Not elevated	☐ 1 Elevated
3b.	How were amyloid PET results obtained *(select all that apply)*?	☐ 1 Visual read	☐ 1 Quantitative
3c.	Where were amyloid PET results obtained?	☐ 1 Central (CLARiTI, ADNI, LEADS, SCAN) ☐ 2 Local or other interpretation (e.g., other clinical trials) ☐ 9 Unknown	
3d.	Was the amyloid PET scan used in the diagnosis from a date within +/- 12 months of the current UDS visit?	☐ 0 No ☐ 1 Yes ☐ 9 Unknown	

Core 2

T_2 (AD tau proteinopathy)

4.	Was tau PET used in the etiologic diagnosis?	☐ 0 No **(SKIP TO QUESTION 5)** ☐ 1 Yes

MTL

4a.	Tau PET MTL result:	☐ 0 Not elevated ☐ 1 Elevated
4b.	How were tau PET MTL results obtained (*select all that apply*)?	☐ 1 Visual read ☐ 1 Quantitative
4c.	Where were tau PET MTL results obtained?	☐ 1 Central (CLARiTI, ADNI, LEADS, SCAN) ☐ 2 Local or other interpretation (e.g., other clinical trials) ☐ 9 Unknown

Neocortical

4d.	Tau PET Neocortical result:	☐ 0 Not elevated ☐ 1 Elevated
4e.	How were tau PET neocortical results obtained (*select all that apply*)?	☐ 1 Visual read ☐ 1 Quantitative
4f.	Where were tau PET neocortical results obtained?	☐ 1 Central (CLARiTI, ADNI, LEADS, SCAN) ☐ 2 Local or other interpretation (e.g., other clinical trials) ☐ 9 Unknown
4g.	Was the tau PET scan used in the diagnosis from a date within +/- 12 months of the current UDS visit?	☐ 0 No ☐ 1 Yes ☐ 9 Unknown

Biomarkers of non-AD co-pathology

V (vascular brain injury)

Infarction on MRI or WMH consistent with ischemia

5.	Was infarction on MRI or WMH consistent with ischemia or blood products consistent with CAA used in the etiologic diagnosis?	☐ 0 No **(SKIP TO QUESTION 6)** ☐ 1 Yes
5a.	Imaging result:	☐ 1 Infarction on MRI *(select all that apply below)* ☐ 1 Lacunar ☐ 1 Cortical ☐ 1 Microbleeds ☐ 1 WMH ☐ 1 Superficial siderosis ☐ 1 Other (**SPECIFY**): _____
5b.	Was the imaging scan used in the diagnosis from a date within +/- 12 months of the current UDS visit?	☐ 0 No ☐ 1 Yes ☐ 9 Unknown

S (α-synuclein)

αSyn-SAA*

6.	Was αSyn-SAA used in the etiologic diagnosis:	☐ 0 No **(SKIP TO QUESTION 7)** ☐ 1 Yes
6a.	αSyn-SAA result:	☐ 0 Normal ☐ 1 Abnormal
6b.	αSyn-SAA assay:	☐ 1 CSF ☐ 2 Other (**SPECIFY**): _____
6c.	Where were αSyn-SAA values obtained?	_____
6d.	Was the αSyn-SAA sample used in the diagnosis from a date within +/- 12 months of the current UDS visit?	☐ 0 No ☐ 1 Yes ☐ 9 Unknown

** If a fluid analyte is presently informative only when measured in CSF this is denoted by (*), if informative with plasma or CSF then no specific notation added*

Biomarkers of non-AD co-pathology *continued...*

7. Did the participant meet the AA biological biomarker criteria for Alzheimer's based on a positive Core 1 biomarker?	☐ 0 No **(END FORM HERE)** ☐ 1 Yes
8. Which Core 1 biomarker was used to make this determination *(select all that apply)?*	**Imaging:** ☐ 1 Amyloid PET **Plasma:** ☐ 1 p-tau217 ☐ 1 %p-tau217 **CSF:** ☐ 1 p-tau181/Aβ42 ☐ 1 t-tau/Aβ42 ☐ 1 Aβ42/40 **Other (SPECIFY):** _____

Section 2 – Biological staging for individuals on the Alzheimer's disease continuum

Use the information above to select the biological stage of the participant:

	Initial-stage biomarkers	Early-stage biomarkers	Intermediate- to advanced-stage biomarkers	
PET	Amyloid PET	Tau PET medial temporal region	Tau PET neocortical uptake	
	$A+T_{2-}$	$A+T_{2MTL+}$	$A+T_{2MOD+2HIGH+}$	
9. Select the biological stage of the participant:	☐ 1 (A)	☐ 2 (B)	☐ 3 (C-D)	☐ 9 Unable to determine stage (e.g., missing necessary biomarkers like tau PET)

Section 3 – Clinical staging for individuals on the Alzheimer's disease continuum

Stage 0 Asymptomatic, deterministic gene

- No evidence of clinical change. Biomarkers in normal range.

  ** Participants with Down Syndrome may not be fully independent even in stage 0 because of underlying intellectual disability. In these participants, decline in functional independence from baseline may be a more appropriate indicator of stage.*

Stage 1 Asymptomatic, biomarker evidence only

- Performance within expected range on objective cognitive tests.
- No evidence of recent cognitive decline or new symptoms.

Stage 2 Transitional decline: Mild detectable change, but minimal impact on daily function

- Normal performance within expected range on objective cognitive tests.
- Decline from previous level of cognitive or neurobehavioral function that represents a change from individual baseline within the past 1 to 3 years, and has been persistent for at least 6 months.
- May be documented by evidence of subtle decline on longitudinal cognitive testing, which may involve memory or other cognitive domains but performance still within normal range.
- May be documented through subjective report of cognitive decline (SCD).
- May be documented with recent-onset change in mood, anxiety, motivation not explained by life events.
- Remains fully independent with no or minimal functional impact on activities of daily living (ADLs).

Stage 3 Cognitive impairment with early functional impact

- Performance in the impaired/abnormal range on objectives cognitive tests.
- Evidence of decline from baseline, documented by the individual's report or by an observer's (e.g., study partner) report or by change on longitudinal cognitive testing or neurobehavioral assessments.
- Performs daily life activities independently but cognitive difficulty may result in detectable functional impact on complex ADLs (i.e., may take more time or be less efficient but still can complete — either self-reported or corraborated by an observer).

Stage 4 Dementia with mild functional impairment

- Progressive cognitive and mild functional impairment on instrumental ADLs, with independence in basic ADLs.

Stage 5 Dementia with moderate functional impairment

- Progressive cognitive and moderate functional impairment on basic ADLs requiring assistance.

Stage 6 Dementia with severe functional impairment

- Progressive cognitive and functional impairment, and complete dependence for basic ADLs.

10.	Clinical AD stage	☐ 0 Stage 0 ☐ 1 Stage 1 ☐ 2 Stage 2 ☐ 3 Stage 3 ☐ 4 Stage 4 ☐ 5 Stage 5 ☐ 6 Stage 6 ☐ 9 Unable to determine stage