# Biological and Clinical Staging

In-person ☐ Remote ☐

ADRC name: _____ Participant ID: _____ Form date: ___ ___ / ___ ___ / ___ ___ ___ ___

Visit #: _____ Examiner's initials: _____ Language: English ☐ Spanish ☐

***INSTRUCTIONS:*** This form is based on the Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup (2024). This form is to be completed by the clinician for all participants, including cognitively unimpaired.

## 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

| Biomarker Category | CSF or plasma analytes | Imaging |
|---|---|---|
| **Core Biomarkers** | | |
| **Core 1** | | |
| **A** (Aβ proteinopathy)<br><br>and<br><br>**$T_1$** (phosphorylated and secreted AD tau) | | **Amyloid PET** |
| | 1. Were plasma biomarkers used in the etiologic diagnosis?<br><br>☐ 0 No **(SKIP TO QUESTION 2)**<br>☐ 1 Yes<br><br>*If yes, select all plasma biomarkers that were used:* | 3. Was Amyloid PET used in the etiologic diagnosis?<br><br>☐ 0 No **(SKIP TO QUESTION 4)**<br>☐ 1 Yes |
| | 1a. ☐ 1 p-tau 217<br>*If checked:* | 3a. Amyloid PET result:<br><br>☐ 0 Not elevated<br>☐ 1 Elevated |
| | 1a1. p-tau 217 result<br><br>☐ 0 Normal<br>☐ 1 Abnormal | 3b. How were amyloid PET results obtained *(select all that apply)*?<br><br>☐ 1 Visual read<br>☐ 1 Quantitative |
| | 1a2. Where were the p-tau 217 values used in the diagnosis analyzed?<br><br>☐ 1 Analyzed by NCRAD<br>☐ 2 Analyzed in-house or elsewhere | 3c. Where were amyloid PET results obtained?<br><br>☐ 1 Central (CLARiTI, ADNI, LEADS)<br>☐ 2 Local or other interpretation (e.g., SCAN, other clinical trials) |
| | 1b. ☐ 1 %p-tau 217<br>*If checked:* | |
| | 1b1. %p-tau 217 result<br><br>☐ 0 Normal<br>☐ 1 Abnormal | |
| | *%p-tau values not currently analyzed by NCRAD; only available in-house or elsewhere | |

## Section 1 – Categorization of fluid analyte and imaging biomarkers *continued...*

**A** (Aβ proteinopathy)

and

**$T_1$** (phosphorylated and secreted AD tau)

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

1c2. Other plasma biomarker result:

☐ 0 Normal
☐ 1 Abnormal

1c3. Where were the other plasma biomarker values used in the diagnosis analyzed?

☐ 0 Analyzed by NCRAD
☐ 1 Analyzed in-house or elsewhere

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

☐ 0 Normal
☐ 1 Abnormal

2a2. Where were the p-tau 181/ Aβ42 values used in the diagnosis analyzed?

☐ 0 Analyzed by NCRAD
☐ 1 Analyzed in-house elsewhere

2b. ☐ 1 t-tau / Aβ42
*If checked:*

2b1. t-tau / Aβ42

☐ 0 Normal
☐ 1 Abnormal

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

2c. ☐ 1 Aβ42/40
*If checked:*

2c1. Aβ42/40

☐ 0 Normal
☐ 1 Abnormal

2c2. Where were the Aβ42/40 values used in the diagnosis analyzed?

☐ 0 Analyzed by NCRAD
☐ 1 Analyzed in-house or elsewhere

## Section 1 – Categorization of fluid analyte and imaging biomarkers *continued...*

**A** (Aβ proteinopathy)

and

**$T_1$** (phosphorylated and secreted AD tau)

2d. ☐ 1 Other CSF biomarker **(SPECIFY):** _____

2d2. Other CSF biomarker result:

☐ 0 Normal
☐ 1 Abnormal

2d3. Where were the other CSF biomarker values used in the diagnosis analyzed?

☐ 0 Analyzed by NCRAD
☐ 1 Analyzed in-house or elsewhere

### 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, LEADS)
☐ 2 Local or other interpretation (e.g., SCAN, other clinical trials)

**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, LEADS)
☐ 2 Local or other interpretation (e.g., SCAN, other clinical trials)

## Section 1 – Categorization of fluid analyte and imaging biomarkers *continued...*

### 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 (*select all that apply*):

☐ 1 Infarction on MRI
*(select all that apply below)*
☐ 1 Lacunar
☐ 1 Cortical
☐ 1 Microbleeds
☐ 1 WMH
☐ 1 Superficial siderosis

**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?

_____

** 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*

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 moderate to high neocortical uptake | |
| | $A+T_{2-}$ | $A+T_{2MTL+}$ | $A+T_{2MOD+2HIGH+}$ | |
| **Core 1 fluid** | CSF Aβ42/40, p-tau181/Aβ42, t-tau/Aβ42, and accurate Core 1 plasma assays can establish that an individual is in biological stage A or higher, but cannot discriminate between PET stages A–D at present. | | | |
| 9. Select the biological stage of the participant: | ☐ 1 (A) | ☐ 2 (B) | ☐ 3 (C-D) | ☐ 9 Unable to determine stage (e.g., missing biomarkers) |

## 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 corroborated 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<br>☐ 1 Stage 1<br>☐ 2 Stage 2<br>☐ 3 Stage 3<br>☐ 4 Stage 4<br>☐ 5 Stage 5<br>☐ 6 Stage 6<br>☐ 9 Unable to determine stage (e.g., missing biomarkers) |