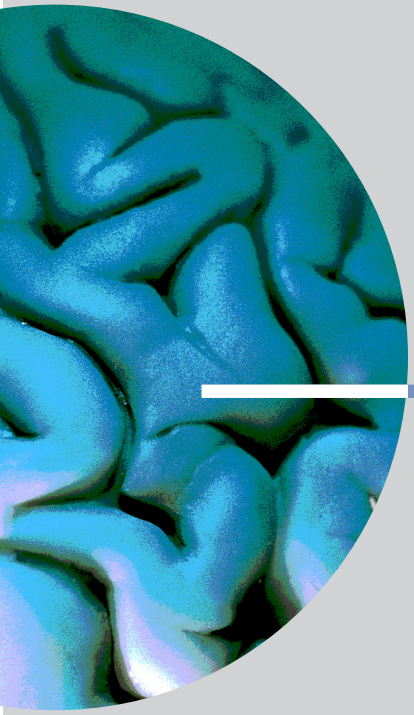

Coding Guidebook

FOR THE NACC NEUROPATHOLOGY FORM

Detailed, annotated explanations of the NACC Neuropathology Form on an item-level basis, with instructions, operational definitions, and references

Version 11, September 2020

Created and published by the Neuropathology Steering Committee of the ADC Program and the National Alzheimer's Coordinating Center (Walter A. Kukull, PhD, Director).

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Guide to abbreviations

AD	Alzheimer's disease
ADC	Alzheimer's Disease Center, any of ~30 Centers across the United States participating in the Alzheimer's Disease Centers Program conducted by NIA
ADNC	Alzheimer's disease neuropathologic change
ALS	Amyotrophic lateral sclerosis
ARTAG	Aging-related Tau gliopathology
CAA	Cerebral amyloid angiopathy
CBD	Corticobasal degeneration
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CSF	Cerebrospinal fluid
DN	Dystrophic neurite
FTLD	Frontotemporal lobar degeneration
FUS	Fused in sarcoma
GCI	Glial cytoplasmic inclusion
IHC	Immunohistochemistry
H&E	Hematoxylin and eosin
LB	Lewy body
MDS	Minimum Data Set, the original data set maintained by NACC from data submitted by the ADCs beginning in 1984
MND	Motor neuron disease
MSA	Multiple system atrophy
NACC	National Alzheimer's Coordinating Center, funded by NIA and charged with collecting data from the ADCs
NBIA	Neurodegeneration with brain iron accumulation
NCI	Neuronal cytoplasmic inclusion
NIA	National Institute on Aging, one of the U.S. National Institutes of Health
NII	Neuronal intra nuclear inclusion
NOS	Not otherwise specified
PiD	Pick's disease
PLS	Primary lateral sclerosis
PMI	Postmortem brain interval: time between death and brain removal
PSP	Progressive supra-nuclear palsy
SCA	Spinocerebellar ataxia
TDP-43	Tar-DNA-binding protein 43
UDS	Uniform Data Set, the longitudinal database maintained by NACC; the other components of the NACC database are the Minimum Data Set (MDS) and the Neuropathologic Data Set (NP)
VBI	Vascular brain injury
WM	White matter

Coding Guidebook

FOR THE NACC NEUROPATHOLOGY DATA FORM

1. MDS, UDS, or BDS patient ID	____ ____ ____ ____ ____ ____ ____ ____ ____ ____
2. Date form completed (MM/DD/YYYY)	____ ____ / ____ ____ / ____ ____ ____ ____
3. Neuropath ID	____ ____ ____ ____ ____ ____ ____ ____ ____ ____
4. Sex (CHECK ONE)	☐ 1 Male ☐ 2 Female
5. Age at death	____ ____ ____ years
6. Date of death (MM/DD/YYYY)	____ ____ / ____ ____ / ____ ____ ____ ____

Questions 1–6: Please provide identification and demographic information.

7. Postmortem interval (PMI): time between death and brain removal	____ ____ . ____ hours *(99.9 = unknown)*

Question 7: Please estimate PMI to the nearest hour if the exact number of minutes is unknown. If it is not possible to estimate PMI, please enter 99.9 (unknown).

8. Fixative	☐ 1 Formalin ☐ 2 Paraformaldehyde ☐ 7 Other (SPECIFY): _____
9. GROSS FINDINGS	
a. Whole brain weight (if half brain, multiply weight by two)	____ ____ ____ ____ grams *(9999 = unknown)*
b. Does the value in Question 9a represent fresh or fixed weight? (CHECK ONE)	☐ 1 Fresh ☐ 2 Fixed ☐ 8 Not applicable

This publication was funded by the National Institutes of Health through the National Institute on Aging (Cooperative Agreement U01 AG016976).

c. Severity of gross findings

(CHECK ONE BOX PER ROW)

	None	Mild	Moderate	Severe	Not assessed	Missing/ unknown
1. Cerebral cortex atrophy	☐ 0	☐ 1	☐ 2	☐ 3	☐ 8	☐ 9
2. Lobar atrophy (significant frontal and/or temporal atrophy)	☐ 0	☐ 1 Yes			☐ 8	☐ 9
3. Hippocampus atrophy	☐ 0	☐ 1	☐ 2	☐ 3	☐ 8	☐ 9
4. Substantia nigra hypopigmentation	☐ 0	☐ 1	☐ 2	☐ 3	☐ 8	☐ 9
5. L. ceruleus hypopigmentation	☐ 0	☐ 1	☐ 2	☐ 3	☐ 8	☐ 9
6. Atherosclerosis (of the circle of Willis)	☐ 0	☐ 1	☐ 2	☐ 3	☐ 8	☐ 9

10. METHODS USED FOR SCORING CASE

a. Tau antibody

(CHECK ONE)

- ☐ 1 Non-phospho specific
- ☐ 2 PHF1
- ☐ 3 CP13
- ☐ 4 AT8
- ☐ 7 Other (SPECIFY): _____
- ☐ 8 Not assessed

b. Amyloid beta antibody

(CHECK ONE)

- ☐ 1 4G8
- ☐ 2 10D5
- ☐ 7 Other (SPECIFY): _____
- ☐ 8 Not assessed

c. Alpha synuclein antibody

(CHECK ONE)

- ☐ 1 Non-phospho specific (e.g., LB509)
- ☐ 2 Phospho-specific (e.g., pSYN#64)
- ☐ 7 Other (SPECIFY): _____
- ☐ 8 Not assessed

d. TDP-43 antibody

(CHECK ONE)

- ☐ 1 Non-phospho specific
- ☐ 2 Phospho-specific
- ☐ 7 Other (SPECIFY): _____
- ☐ 8 Not assessed

e. Histochemical stains (CHECK ONE BOX PER ROW)

1.	Modified Bielschowsky	☐ 0 No	☐ 1 Yes
2.	Gallyas	☐ 0 No	☐ 1 Yes
3.	Other silver stain	☐ 0 No	☐ 1 Yes
4.	Thioflavin	☐ 0 No	☐ 1 Yes
5.	Other (SPECIFY): _____	☐ 0 No	☐ 1 Yes

Question 10 e5: If 1 = Yes is selected, specify the stain used.

11. ALZHEIMER'S DISEASE. Please score AD neuropathologic changes.

For minimum recommended brain regions to be sampled and evaluated, see Table 1 in Montine et al., 2012[1].

Questions 11a–11e2:

Enter **8=Not assessed** if the pathologic characteristic was not evaluated.
Enter **9=Missing/unknown** if the pathology was examined but the data cannot be found.

a. Thal phase for amyloid plaques by immunohistochemistry (IHC)

(A score — CHECK ONE**)**

Use only standard blocks (as described in Montine et al., Acta Neuropathol (2012) 123:1–11) to assign phase (i.e., midfrontal, superior/middle temporal, inferior parietal, hippocampus, entorhinal, basal ganglia, midbrain, cerebellum).

☐ 0 Phase 0 (A0)
☐ 1 Phase 1 (A1)
☐ 2 Phase 2 (A1)
☐ 3 Phase 3 (A2)
☐ 4 Phase 4 (A3)
☐ 5 Phase 5 (A3)
☐ 8 Not assessed
☐ 9 Missing/unknown

Excerpted from Montine et al.[1]:

Preferred method for β-amyloid (Aβ) plaques is immunohistochemistry for Aβ. Other acceptable methods are thioflavin S or sensitive silver histochemical stains.

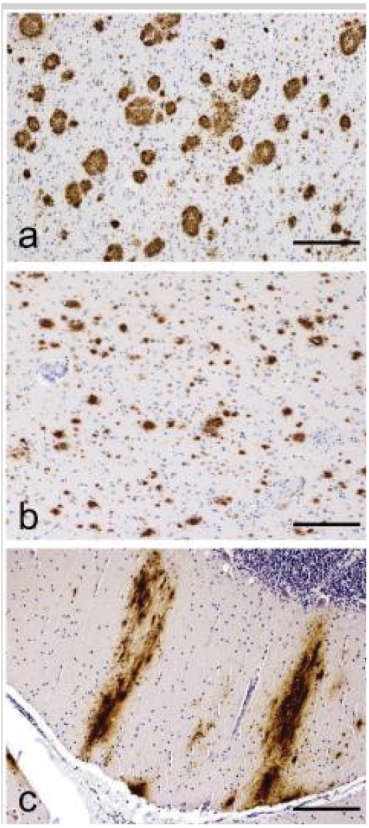
[1]Montine TJ, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. Acta Neuropathol. Jan 2012;123(1):1-11.

Thal stages refer to the anatomical location of Aβ-immunopositivity, which are then converted to A Scores. 6-point Thal staging scheme is as described[1,2], then converted to a 4-point scale[3]. Figures below show how a given distribution of Aβ plaques corresponds to Thal phase and A Score.

Alafuzoff et al., 2009[2]

Block	Region	Phase of Aβ aggregation				
		1	2	3	4	5
Frontal cortex	Grey/white matter	**One or more regions with Aβ**	One or more regions with Aβ	+	+	+
Temporal cortex	Grey/white matter			+	+	+
Parietal cortex	Grey/white matter			+	+	+
Occipital cortex	Grey/white matter			+	+	+
Hippocampus	Adjacent temporal cx grey/white matter			+	+	+
	Molecular layer of the dentate gyrus	–	**One or more regions with Aβ**	+/–	+	+
	CA4	–		+/–	+/–	+
	CA1	–		+	+	+
	Remnants of entorhinal area	–		+	+	+
Gyrus cinguli	Grey/white matter	–		+	+	+
Basal forebrain	Hypothalamus	–	–	**One or more regions with Aβ**	+	+
	Amygdaloid nuclei	–	–		+	+
	Nucleus basalis of Meynert	–	–		+	+
Striatum	Putamen	–	–		+	+
	Caudate nucleus	–	–		+	+
	Insular cortex grey/ white matter	–	+/–	+	+	+
Midbrain	Central grey	–	–	–	**One or more regions with Aβ**	One or more regions with Aβ
	Substantia nigra	–	–	–		
Cerebellum						**One or more regions with Aβ**

Montine et al.[3]



"ABC" Score for Alzheimer's disease neuropathologic change. Immunohistochemical detection of Aβ plaques in (a) neocortex with as an example of "A1", (b) neostriatum as an example of "A2", and (c) molecular layer of cerebellum as an example of "A3". Scale bars are 500 microns. Anti-Aβ was antibody 6F/3D (Novocastra, Newcastle, UK)

A=0: Thal phase 0.
A=1: Thal phase 1 or 2.
A=2: Thal phase 3.
A=3: Thal phases 4 or 5.

The focus of this staging scheme is on anatomical location, not lesion density, so for the sake of this evaluation, the staining should be considered present or absent. For example, even a small amount of Aβ-immunoreactive material in the cerebellum indicates Thal phase 5, A=3.

[1]Thal DR, Rüb U, Orantes M, Braak H. Phases of A beta-deposition in the human brain and its relevance for the development of AD. *Neurology*. Jun 2002;58(12):1791-1800.

[2]From Springer, *Acta Neuropathol.* Mar 2009;117(3):309-320, Assessment of beta-amyloid deposits in human brain: a study of the BrainNet Europe Consortium. Alafuzoff I, Thal DR, Arzberger T, et al., Copyright © 2009, reprinted with kind permission of Springer Science Business Media and author.

[3]From Springer, *Acta Neuropathol.* Jan 2012;123(1):1-11, National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach, Montine TJ, Phelps CH, Beach TG, et al. Copyright © 2012, reprinted with kind permission of Springer Science Business Media and author.

b. Braak stage for neurofibrillary degeneration

(B score — CHECK ONE)

Use standard blocks (as described in Montine et al., Acta Neuropathol (2012) 123:1–11) to assign phase (i.e., mid-frontal, superior/middle temporal, inferior parietal, occipital, hippocampus, entorhinal).

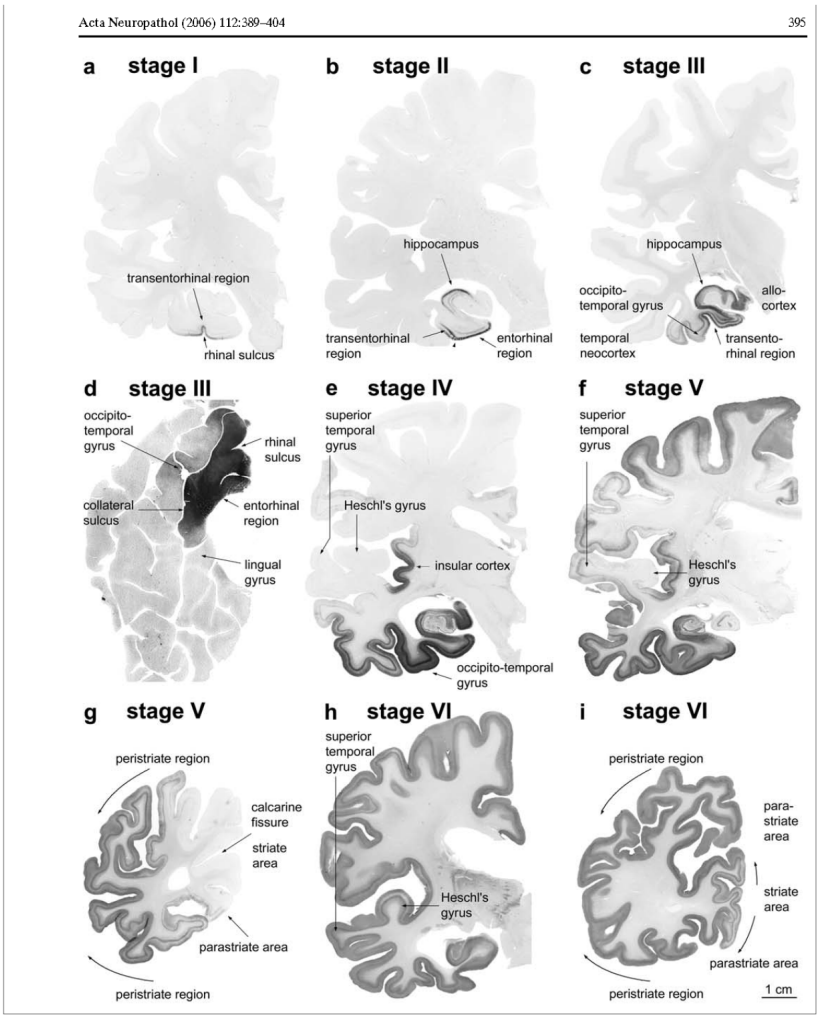
- ☐ 0 Stage 0: AD-type neurofibrillary degeneration not present (B0)
- ☐ 1 Stage I (B1)
- ☐ 2 Stage II (B1)
- ☐ 3 Stage III (B2)
- ☐ 4 Stage IV (B2)
- ☐ 5 Stage V (B3)
- ☐ 6 Stage VI (B3)
- ☐ 7 The presence of a tauopathy (other than aging/AD) precludes Braak staging
- ☐ 8 Not assessed
- ☐ 9 Missing/unknown

Indicate the stage according to the scheme proposed by Braak and Braak. While the original methods employed Gallyas stains, other stains for neurofibrillary pathology (e.g., tau immunostains, other silver stains or thioflavin-S) may be used. The focus is on the distribution of neurofibrillary tangles (NFTs). Especially if visualized with phospho-tau antibodies, the designation of Braak VI should be reserved for those cases with very dense and widely distributed NFTs in many neocortical regions (see figure at right).

If there is a tauopathy (other than aging/AD), Braak staging may not be appropriate. However, if there are distinguishable or concomitant aging or AD changes, the Braak score should still be indicated.

Please note that the order of the codes for Braak stage has changed since Version 9 of this form.

Braak & Braak neurofibrillary stage[1]



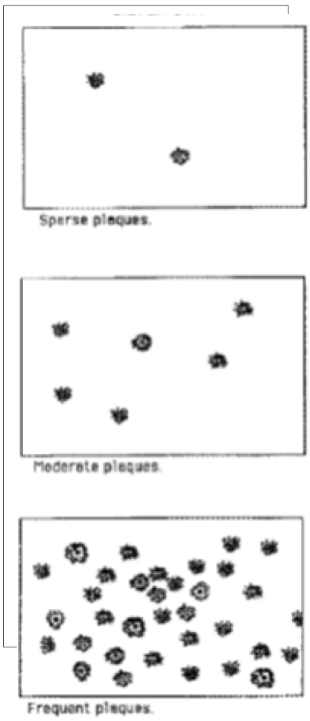
[1]From Springer, *Acta Neuropathol.* Oct 2006;112(4):389-404 Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry, Braak H n, Alafuzoff I, Arzberger T, et al., Copyright © 2006, reprinted with kind permission of Springer Science Business Media and author.

c. CERAD score for density of neocortical neuritic plaque (plaques with argyrophilic dystrophic neurites, with or without dense amyloid cores). Score without respect to age or diagnosis. **(C score — CHECK ONE)** *Use only standard blocks (as described in Montine et al., Acta Neuropathol (2012) 123:1–11) to assign phase (i.e., midfrontal, superior/middle temporal, inferior parietal).*	☐ 0 No neuritic plaques (C0) ☐ 1 Sparse neuritic plaques (C1) ☐ 2 Moderate neuritic plaques (C2) ☐ 3 Frequent neuritic plaques (C3) ☐ 8 Not assessed ☐ 9 Missing/unknown

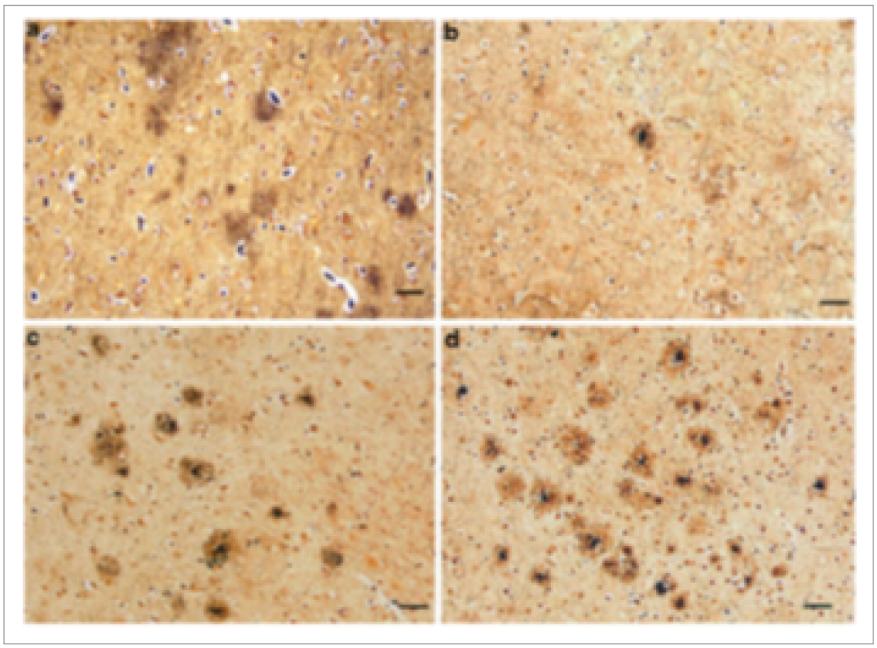
CERAD scores are derived from Mirra et al. (1993)[1]. However, starting in 2012, the score criteria have changed slightly (Montine et al., 2012)[2].

Neuritic plaques are considered to be plaques with argyrophilic, thioflavin-S-positive or tau-positive dystrophic neurites with or without dense amyloid cores. Answer 8=Not assessed if neuritic plaques have not been specifically analyzed. Score without respect to age or clinical diagnosis. (C score.)

Mirra et al., 1993[1]



Montine et al., 2012[2]



"ABC" score for Alzheimer's disease neuropathologic change. Bielschowsky stain of neocortex shows (a.) diffuse plaques but not neuritic plaques as an example of "C0," and increasing density of neuritic plaques as examples of (b.) "C1" (1–5 neuritic plaques per 1 mm^2), (c.) "C2" (≥6 but <20 neuritic plaques per 1 mm^2), and (d.) "C3" (≥20 neuritic plaques per 1 mm^2). Scale bars equal 100 μm.

Please note that the order of the codes for CERAD score for neuritic plaque density has changed since Version 9 of this form.

1Mirra SS, Hart MN, Terry RD. Making the diagnosis of Alzheimer's disease. A primer for practicing pathologists. Arch Pathol Lab Med. Feb 1993;117(2):132-144. Reproduced by permission of the author.

2From Springer, Acta Neuropathol. Jan 2012;123(1):1-11, National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach, Montine TJ, Phelps CH, Beach TG, et al. Copyright © 2012, reprinted with kind permission of Springer Science Business Media and author.

d. NIA-AA Alzheimer's disease neuropathologic change **(ADNC)**

(CHECK ONE)

- ☐ 0 Not AD
- ☐ 1 Low ADNC
- ☐ 2 Intermediate ADNC
- ☐ 3 High ADNC
- ☐ 8 Not assessed
- ☐ 9 Missing/unknown

AD neuropathologic change is evaluated with an "ABC" score (see table below)[1]: Aβ/amyloid plaques (A), NFT stage (B), and neuritic plaque score (C). The combination of A, B, and C scores is designated as "Not," "Low," "Intermediate," or "High" AD neuropathologic change. Intermediate or High AD neuropathologic change is considered sufficient explanation for dementia. The table below is directly derived from Montine et al. (2012)[1].

If the C score is 1, 2, or 3, then the A score must be A1, A2, or A3 (marked as at least "low" AD NP change).

Montine et al. (2012)[1]

AD Neuropathologic Change		B (Braak/Neurofibrillary Score; See 11b)		
A (Amyloid; see 11a)	C (CERAD; see 11c)	0 or 1	2	3
0	0	Not	Not	Not
1	0 or 1	Low	Low	Low
	2 or 3	Low	Intermediate	Intermediate
2	Any C	Low	Intermediate	Intermediate
3	0 or 1	Low	Intermediate	Intermediate
	2 or 3	Low	Intermediate	High

Question 11d: Enter **8=Not assessed** if there is missing data from A, B, or C. ADNC cannot be determined without all three scores (A, B, and C).

Enter **9=Missing/unknown** if the pathology was evaluated but the data cannot be found.

e. Other pathologic changes associated with AD

1. CERAD semi-quantitative score for diffuse plaques (plaques with non-compact amyloid and no apparent dystrophic neurites). Score from the neocortical field with the highest plaque density and without respect to age or diagnosis.

   (CHECK ONE)

- ☐ 0 No diffuse plaques
- ☐ 1 Sparse diffuse plaques
- ☐ 2 Moderate diffuse plaques
- ☐ 3 Frequent diffuse plaques
- ☐ 8 Not assessed
- ☐ 9 Missing/unknown

[1]From Springer, Acta Neuropathol. Jan 2012;123(1):1-11, National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach, Montine TJ, Phelps CH, Beach TG, et al. Copyright © 2012, reprinted with kind permission of Springer Science Business Media and author.

Question 11e1: Diffuse plaques are considered to be plaques with non-compact amyloid and no apparent dystrophic neurites.
Enter **8=Not assessed** if diffuse plaques have not been specifically analyzed.
Enter 9=Missing/unknown if diffuse plaques were evaluated but the data cannot be found.

Please note that the order of the codes for CERAD semi-quantitative score for diffuse plaques has changed since version 9 of this form.

2. Cerebral amyloid angiopathy
(CHECK ONE)

- ☐ 0 None
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 8 Not assessed
- ☐ 9 Missing/unknown

Provide semi-quantitative assessment of overall neocortical amyloid angiopathy.

Guidelines are adapted from prior studies[1,2] with the added aspect of referring to the global CAA according to the following scale that refers to the global CAA burden:

0 — None: Absent
1 — Mild: Scattered positivity in parenchymal and/or leptomeningeal vessels, possibly in only one brain area
2 — Moderate: Intense positivity in many parenchumal and/or leptomeningeal vessels
3 — Severe: Widespread (more than one brain area) intensive positivity in parenchymal and leptomeningeal vessels

Enter **8 = Not assessed** if cerebral amyloid angiopathy was not evaluated.
Enter **9 = Missing/unknown** if the pathology was examined by the data cannot be found.

12. CEREBROVASCULAR DISEASE (CVD). Report all CVD, macroscopic vascular brain injury (VBI), and microinfarcts or microhemorrhages.

SECTION 12: For minimum recommended brain regions to be sampled and evaluated, see Table 1 in Montine at al., 2012[3].

a. Old infarcts observed grossly, including lacunes?
(CHECK ONE)

- ☐ 0 No **(SKIP TO QUESTION 12b)**
- ☐ 1 Yes **(COMPLETE QUESTIONS 12a1–12a4)**
- ☐ 8 Not assessed **(SKIP TO QUESTION 12b)**
- ☐ 9 Missing/unknown **(SKIP TO QUESTION 12b)**

[1]Vonsattel JP, Myers RH, Hedley-Whyte ET, Ropper AH, Bird ED, Richardson EP. Cerebral amyloid angiopathy without and with cerebral hemorrhages: a comparative histological study. Ann Neurol. Nov 1991;30(5):637-649.

[2]Olichney JM, Hansen LA, Hofstetter CR, Lee JH, Katzman R, Thal LJ. Association between severe cerebral amyloid angiopathy and cerebrovascularlesions in Alzheimer disease is not a spurious one attributable to apolipoprotein E4. Arch Neurol. Jun 2000;57(6):869-874.

[3]Montine TJ, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment ofAlzheimer's disease: a practical approach. Acta Neuropathol. Jan 2012;123(1):1-11.

Questions 12a1–12a4: Enter **88** under the Number column if infarcts were not assessed for the region in question. Enter **99** if infarcts were assessed but the information cannot be found. NOTE: Number column cannot be left blank if Question 12a=Yes. Size of infarct columns should be left blank if not applicable.

For all subjects with 0=No on Question 12a, the Number column will we be set to 0 for 12a1-12a4. If the infarct number is zero for a particular region (e.g., cerebral cortex), no further information needs to be entered in that particular row. If the infarct number is ≥1, the Size of largest column must be completed. If the infarct number is ≥2, the first Size of next column must also be completed. If infarct number is ≥3, all columns in that row must be filled out.

If old infarcts were counted but the size was not assessed, enter **88.8** in the appropriate column. If an infarct was counted and size was assessed, but the information on infarct size cannot be found, enter **99.9** in the appropriate column(s).

Location of old infarcts	Number	Size of largest (greatest dimension in cm)	Size of next (greatest dimension in cm)	Size of next (greatest dimension in cm)	Size of next (greatest dimension in cm)
1. Cerebral cortex	__ __	__ __ . __	__ __ . __	__ __ . __	__ __ . __

Number: Indicate the total number of old gross infarcts seen within any region of cerebral cortex (including neocortical or limbic).

Size of largest: Indicate the greatest dimension of the largest of the cortical infarcts in centimeters.

Size of next largest: Indicate the greatest dimension of the largest of the cortical infarcts in centimeters.

Size of next largest Indicate the greatest dimension of the next largest cortical infarct.

2. Subcortical cerebral white matter and periventricular white matter	__ __	__ __ . __	__ __ . __	__ __ . __	__ __ . __

Number: Indicate the total number of old gross infarcts seen within hemispheric white matter.

Size of largest: Indicate the greatest dimension of the largest of the white matter infarcts in centimeters.

Size of next largest: Indicate the greatest dimension of the next largest white matter infarct in centimeters.

Size of next largest Indicate the greatest dimension of the next largest white matter infarct.

3. Deep cerebral gray matter or internal capsule	__ __	__ __ . __	__ __ . __	__ __ . __	__ __ . __

Number: Indicate the total number of old gross infarcts seen within deep cerebral gray matter or internal capsule.

Size of largest: Indicate the greatest dimension of the largest of the deep cerebral gray matter or internal capsule infarcts in centimeters.

Size of next largest: Indicate the greatest dimension of the next largest deep cerebral gray matter or internal capsule infarct in centimeters.

Size of next largest Indicate the greatest dimension of the next largest deep cerebral gray matter or internal capsule infarct.

4. Brainstem or cerebellum	__ __	__ __ . __	__ __ . __	__ __ . __	__ __ . __

Number:	Indicate the total number of old gross infarcts seen within brainstem or cerebellum.
Size of largest:	Indicate the greatest dimension of the largest of the brainstem or cerebellum infarcts in centimeters.
Size of next largest:	Indicate the greatest dimension of the next largest brainstem or cerebellum infarct in centimeters.
Size of next largest	Indicate the greatest dimension of the next largest brainstem or cerebellum infarct.

NOTE: For large cortical infarcts that include underlying white or gray matter, indicate as cortical infarct. For subcortical infarcts that include both white matter and gray matter, indicate whichever region is primarily affected.

b. Were single or multiple old hemorrhages observed grossly?

- ☐ 0 No **(SKIP TO QUESTION 12c)**
- ☐ 1 Yes **(COMPLETE QUESTIONS 12b1–12b3)**
- ☐ 8 Not assessed **(SKIP TO QUESTION 12c)**
- ☐ 9 Missing/unknown **(SKIP TO QUESTION 12c)**

IMPORTANT NOTES:

- Include only old gross nonpetechial hemorrhages. (Acute/subacute gross hemorrhages are assessed in Question 12g5.)
- Do not include microbleeds that are petechial or microscopic hemorrhages often seen on imaging (micr bleeds are assessed in Question 12d).

Question 12b:

Enter **1=Yes** if at least one old hemorrhage was observed grossly regardless of region and complete Questions 12b1–12b3.

Enter **0=No** if old hemorrhages were not observed grossly in the regions examined and skip to Question 12c. For all subjects with 0=No on Question 12b, Questions 12b1–12b3 will be set to 0.

Enter **8=Not assessed** if old gross hemorrhages were not assessed and skip to Question 12c.

Enter **9=Missing/unknown** if old gross hemorrhages were assessed but the data cannot be found and skip to Question 12c.

(CHECK ONE BOX PER ROW)	No	Yes	Not assessed	Missing/ unknown
1. Subdural or epidural hemorrhage	☐ 0	☐ 1	☐ 8	☐ 9
2. Primary parenchymal hemorrhage *Include those >5mm. If ≤5mm, include as microbleed; see Question 12d.*	☐ 0	☐ 1	☐ 8	☐ 9
3. Secondary parenchymal hemorrhage (e.g., tumor, vascular malformation)	☐ 0	☐ 1	☐ 8	☐ 9

Question 12b1 – 12b3:

Enter **8=Not assessed** if old hemorrhages were not observed grossly for the region in question.

Enter **9 = Missing/unknown** if old hemorrhages were observed grossly for the region in question but the data cannot be found.

c. Old microinfarcts (not observed grossly)?
(CHECK ONE)

☐ 0 No **(SKIP TO QUESTION 12d)**
☐ 1 Yes **(COMPLETE QUESTIONS 12c1–12c4)**
☐ 8 Not assessed **(SKIP TO QUESTION 12d)**
☐ 9 Missing/unknown **(SKIP TO QUESTION 12d)**

IMPORTANT NOTES:

- Include only old microfarcts, which include old infacts that are not seen grossly but are seen by microscopy
- Do not include acute/subacute microinfacts. (Acute/subacute microinfarcts are assessed in Question 12g4.)
- Indicate for each region if one old microinfarct, two old microinfarcts, or three or more old microinfarcts were observed.

Question 12c:

Enter **1=Yes** if at least one microinfarct was observed regardless of region and complete Questions 12c1–12c4.

Enter **0=No** if old microinfarcts were not observed in the regions examined, and skip to Question 12d. For all subjects with 0=No on Question 12c, Questions 12c1–12c4 will be set to 0.

Enter **8=Not** assessed if old microinfarcts were not assessed, and skip to Question 12d.

Enter **9=Missing/unknown** if old microinfarcts were assessed but the data cannot be found, and skip to Question 12d.

(OLD MICROINFARCTS — CHECK ONE BOX PER ROW)	0	1	2	3 or more	Not assessed	Missing/ unknown
1. Number in screening sections of cerebral cortex (gray matter of cerebral cortex)	☐ 0	☐ 1	☐ 2	☐ 3	☐ 8	☐ 9
2. Number in screening sections of subcortical white matter and periventricular white matter	☐ 0	☐ 1	☐ 2	☐ 3	☐ 8	☐ 9
3. Number in screening sections of subcortical gray matter	☐ 0	☐ 1	☐ 2	☐ 3	☐ 8	☐ 9
4. Number in brainstem and cerebellum	☐ 0	☐ 1	☐ 2	☐ 3	☐ 8	☐ 9

Questions 12c1 – 12c4:

Enter **8=Not assessed** if the number of microinfacts was not assessed for the region in question.

Enter **9 = Missing/unknown** if the number of microinfacts was assessed for the region in question but the data cannot be found.

d. Old cerebral microbleeds?

(CHECK ONE)

Include old hemorrhages that are ≤5mm.

☐ 0 No **(SKIP TO QUESTION 12e)**
☐ 1 Yes **(COMPLETE QUESTIONS 12d1–12d4)**
☐ 8 Not assessed **(SKIP TO QUESTION 12e)**
☐ 9 Missing/unknown **(SKIP TO QUESTION 12e)**

IMPORTANT NOTES:

- Include only old microbleeds — old petechial or microscopic hemorrhages seen by microscopy and that may not be seen grossly.
- Do not include acute or subacute microbleeds. (Acute/subacute microhemmorhages are assessed in Question 12g6.)
- Indicate for each region if one old microbleed, two old microbleeds, or three or more microbleeds were observed.

Question 12d:

Enter **1=Yes** if at least one old microbleed was observed regardless of region and complete Questions 12d1–12d4.

Enter **0=No** if microbleeds were not observed, and skip to Question 12e. For all subjects with **0=No** on Question 12d, Questions 12d1–12d4 will be set to 0.

Enter **8=Not assessed** if old microbleeds were not assessed, and skip to Question 12e.

Enter **9=Missing/unknown** if old microbleeds were assessed but the data cannot be found, and skip to Question 12e.

(OLD MICROBLEEDS — CHECK ONE BOX PER ROW)	0	1	2	3 or more	Not assessed	Missing/ unknown
1. Number in screening sections of cerebral cortex	☐ 0	☐ 1	☐ 2	☐ 3	☐ 8	☐ 9
2. Number in screening sections of subcortical white matter and periventricular white matter	☐ 0	☐ 1	☐ 2	☐ 3	☐ 8	☐ 9
3. Number in screening sections of subcortical gray matter	☐ 0	☐ 1	☐ 2	☐ 3	☐ 8	☐ 9
4. Number in brainstem and cerebellum	☐ 0	☐ 1	☐ 2	☐ 3	☐ 8	☐ 9

Question 12d1 – 12d4:

Enter **8=Not assessed** if microbleeds were not assessed for the region in question.

Enter **9 = Missing/unknown** if microbleeds were assessed for the region in question but the data cannot be found.

(CHECK ONE BOX PER ROW)	None	Mild	Moderate	Severe	Not assessed	Missing/ unknown
e. Arteriolosclerosis? (CHECK ONE) *(Assessed in subcortical white or gray matter)*	☐ 0	☐ 1	☐ 2	☐ 3	☐ 8	☐ 9

Judge arteriolosclerosis on a global scale of none, mild, moderate, or severe. Arteriolosclerosis is concentric hyaline thickening of the media of arterioles. Intimal fibrosis may also accompany this change. The term "lipohyalinosis" is sometimes used to refer to the same pathologic change. It is seen in aging and associated with vascular risk factors such as hypertension and diabetes. Do not include arterioles thickened secondary to CAA.

Question 12e:

Enter **8 = Not assessed** if the pathology was not assessed.
Enter **9 = Missing/unknown** if the pathology in question was assessed but the data cannot be found.

f.	White matter rarefaction? (CHECK ONE) *(H&E or myelin stain may be used)*	☐ 0	☐ 1	☐ 2	☐ 3	☐ 8	☐ 9

Judge white matter pallor in the centrum semiovale and subcortical white matter on a scale of none, mild, moderate, or severe. This category refers to both multifocal and diffuse white matter pathology.

Question 12f:

Enter **8 = Not assessed** if the pathology was not assessed.
Enter **9 = Missing/unknown** if the pathology in question was assessed but the data cannot be found.

g. Other pathologic changes related to ischemic or vascular disease not previously specified?

- ☐ 0 No **(SKIP TO QUESTION 13)**
- ☐ 1 Yes **(COMPLETE QUESTIONS 12g1–12g12)**
- ☐ 8 Not assessed **(SKIP TO QUESTION 13)**
- ☐ 9 Missing/unknown **(SKIP TO QUESTION 13)**

Question 12g:

Enter 0 = No if no other ischemic/vascular disease was noted, and skip to Question 13. For all subjects with 0 = No on Question 12g, Questions 12g1 – 12g12 will be set to 0.
Enter 1 = Yes if other ischemic or vascular disease was observed, and choose from the list in Questions 12g1 – 12g12.
Enter **8 = Not assessed** if other ischemic and vascular disease was not assessed.
Enter **9 = Missing/unknown** if other ischemic and vascular disease was assessed but the data cannot be found.

Questions 12g1 – 12g11:

Enter **8 = Not assessed** if the pathology was not assessed.
Enter **9 = Missing/unknown** if the pathology was assessed but the data cannot be found.

(CHECK ONE BOX PER ROW)	No	Yes	Not assessed	Missing/ unknown
1. Laminar necrosis	☐ 0	☐ 1	☐ 8	☐ 9

Question 12g1: Laminar necrosis is the linear severe degeneration of the cortical mantle, often but not always due to ischemia (especially layers 3 and 5). The degeneration is typically of such severity that the cortex appears to have a line of necrosis.

2.	Acute neuronal necrosis	☐ 0	☐ 1	☐ 8	☐ 9

Question 12g2: Red neurons in one or more selectively vulnerable regions (such as CA1 sector of the hippocampus, purkinje cell layer or cortical mantle, suggesting global hypoxic injury).

3.	Acute/subacute gross infarcts	☐ 0	☐ 1	☐ 8	☐ 9
4.	Acute/subacute microinfarcts	☐ 0	☐ 1	☐ 8	☐ 9
5.	Acute/subacute gross hemorrhage	☐ 0	☐ 1	☐ 8	☐ 9
6.	Acute/subacute microhemorrhage	☐ 0	☐ 1	☐ 8	☐ 9
7.	Vascular malformation of any type	☐ 0	☐ 1	☐ 8	☐ 9
8.	Aneurysm of any type	☐ 0	☐ 1	☐ 8	☐ 9
9.	Vasculitis of any type	☐ 0	☐ 1	☐ 8	☐ 9
10.	CADASIL	☐ 0	☐ 1	☐ 8	☐ 9
11.	Mineralization of blood vessels	☐ 0	☐ 1	☐ 8	☐ 9

Question 12g11: Brain mineralization of blood vessels includes Fahr's disease, Fahr's syndrome, and idiopathic basal ganglia calcification.

12.	Other (SPECIFY): _____	☐ 0	☐ 1

Question 12g12:

Enter **0=No** if no other ischemic/vascular disease was observed beyond what was indicated in Questions 12g1–12g11.

Enter **1=Yes** if another ischemic/vascular disease was observed beyond those assessed in Questions 12g1–12g11; if Yes is selected, a value must be written in the Specify field.

13. LEWY BODY PATHOLOGY (as determined by alpha-synuclein IHC). This score is independent of the clinical presentation.

For minimum recommended brain regions to be sampled and evaluated, see Table 1 in Montine et al., 2012[1].

[1]Montine TJ, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. *Acta Neuropathol.* Jan 2012;123(1):1-11.

Is there evidence of Lewy body pathology?

(CHECK ONE)

- ☐ 0 No
- ☐ 1 Brainstem predominant
- ☐ 2 Limbic (transitional)
- ☐ 3 Neocortical (diffuse)
- ☐ 4 Amygdala predominant
- ☐ 5 Olfactory bulb
- ☐ 8 Not assessed
- ☐ 9 Missing/unknown

Following the suggestions of Montine et al. (2012)[1]:

Recommended brain regions for tiered evaluation: screen for LBs with immunohistochemistry or hematoxylin and eosin (H&E) in brainstem and with immunohistochemistry in amygdala. If positive, then expand immunohistochemistry for LBs in brainstem, limbic, and neocortical regions.

Immunohistochemistry for alpha-synuclein is strongly preferred. LBs may be detected in neurons of medulla, pons, and midbrain with H&E–stained sections; however, greater sensitivity can be achieved with immunohistochemistry. Abnormal neuropil and neuronal cytoplasmic α-synuclein immunoreactivity are usually present with LBs but will not be apparent by H&E, and in some instances, these changes occur in the absence of LBs.

CLASSIFICATION

Classification of LB pathology is modified from McKeith et al. (2005)[2]:

0 = No LB pathology:	No LBs or related changes in α-synuclein immunohistochemistry
1 = Brainstem predominant:	LBs in medulla, pons, or midbrain
2 = Limbic (transitional):	LBs in cingulate or entorhinal cortices, usually with brainstem involvement
3 = Neocortal (diffuse):	LBs in frontal, temporal, or parietal cortices, usually with involvement of brainstem and limbic sites, which may include amygdala
4 = Amygdala predominant:	LBs in amygdala with paucity of LBs in the above regions

Question 13:

Enter **8 = Not assessed** if Lewy body pathology was not assessed.

Enter **9 = Missing/unknown** if Lewy body pathology was assessed, but the data cannot be found.

14. NEURON LOSS IN THE SUBSTANTIA NIGRA (CHECK ONE)

- ☐ 0 None
- ☐ 1 Mild
- ☐ 2 Moderate
- ☐ 3 Severe
- ☐ 8 Not assessed
- ☐ 9 Missing/unknown

[1]Montine TJ, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. *Acta Neuropathol.* Jan 2012;123(1):1-11.

[2]McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology.* Dec 2005;65(12):1863-1872.

15. HIPPOCAMPAL SCLEROSIS (CA1 and/or subiculum) (CHECK ONE)

- ☐ 0 None
- ☐ 1 Unilateral
- ☐ 2 Bilateral
- ☐ 3 Present but laterality not assessed
- ☐ 8 Not assessed
- ☐ 9 Missing/unknown

For minimum recommended brain regions to be sampled and evaluated, see Table 1 in Montine et al., 2012[1]. Include cases with severe neuronal loss and gliosis in CA1 and/or subiculum.

Questions 14 and 15:

Enter **8 = Not assessed** if the pathology in question was not assessed.

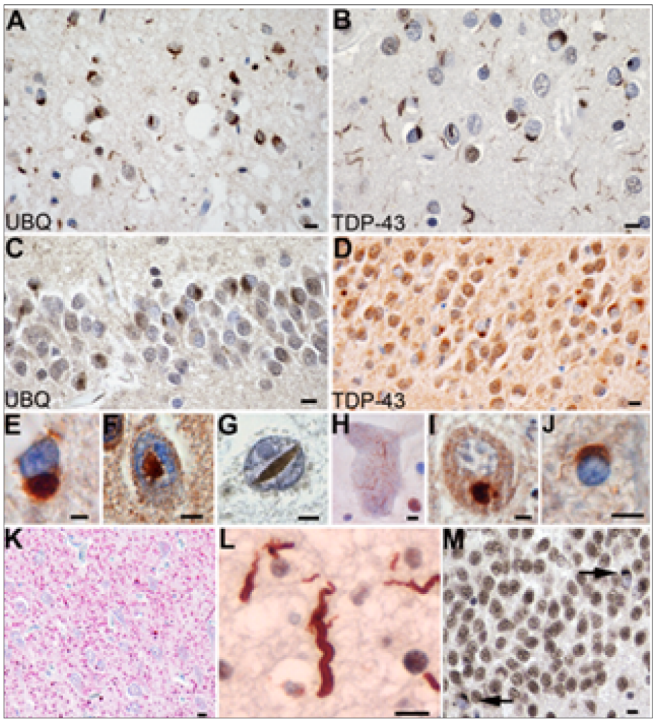
Enter **9 = Missing/unknown** if the pathology was assessed but the data cannot be found.

[1]Montine TJ, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. *Acta Neuropathol.* Jan 2012;123(1):1-11.

16. DISTRIBUTION OF TDP-43 IMMUNOREACTIVE INCLUSIONS

Include any TDP-43-immunoreactive inclusion: neuronal cytoplasmic inclusion (NCI), neuronal intra nuclear inclusion (NII), dystrophic neurite (DN), and glial cytoplasmic inclusion (GCI). The GCI of FTLD-TDP are distinct from the GCI of MSA, which are alpha-synuclein positive but TDP-43 negative. Neuronal cytoplasmic inclusions may take variable forms: globose and skein-like; the latter is most frequently found in FTLD-MND and ALS/MND. Different patterns of TDP-43-immunoreactive inclusions may be associated with different genotypes (*GRN, VCP, TARDBP, C9orf72*) and sporadic cases with variable clinical phenotypes, but subtyping is not recommended for routine neuropathologic assessment.

Cairns et al. (2007)[1]



The figure at left shows the spectrum of TDP-43 pathology in FTLD-TDP. Adjacent sections of superficial frontal neocortex showing NCIs, DNs, and isolated NIIs, stained for both ubiquitin (A) and TDP-43 (B). NCIs in the dentate granule cells stained for ubiquitin (C) and TDP-43 (D). Neuronal and glial inclusions include NCIs (E), round and lentiform NIIs (F and G); skein-like (H) and compact round (I) NCIs in lower motor neurons; and a glial cytoplasmic inclusion (J). Low-power micrograph showing numerous DNs in the hippocampus CA1 subfield (K). High-power micrograph showing a tortuous DN in a case of FTLD-U, subtype 1 (L). NCIs in the dentate fascia of a case of hippocampal sclerosis (M). A and C: Ubiquitin immunohistochemistry. B, D, E–M: TDP-43 immunohistochemistry. Bars: 10µm (A–D and K–M); 5µm (E–J).[1]

NOTE: FTLD-TDP is addressed in Question 17c. ALS is addressed in Question 17d.

Questions 16a – 16e:

Enter **8 = Not assessed** if TDP-43 immunoreactive inclusions were not assessed for the region in question.

Enter **9 = Missing/unknown** if TDP-43 inclusions were assessed for that region but the data cannot be found.

Region (CHECK ONE BOX PER ROW)	No	Yes	Not assessed	Missing/unknown
a. Spinal cord	☐ 0	☐ 1	☐ 8	☐ 9
b. Amygdala	☐ 0	☐ 1	☐ 8	☐ 9
c. Hippocampus	☐ 0	☐ 1	☐ 8	☐ 9
d. Entorhinal/inferior temporal cortex	☐ 0	☐ 1	☐ 8	☐ 9
e. Neocortex	☐ 0	☐ 1	☐ 8	☐ 9

[1]From Am J Pathol. Jul 2007:171(1), Cairns NJ, Neumann M, Bigio EH, et al. TDP-43 in familial and sporadic frontotemporal lobar degeneration withubiquitin inclusions, pages 227-240, Copyright © 2007, reprinted with permission of Elsevier and author.

17. FRONTOTEMPORAL LOBAR DEGENERATION AND OTHER TAUOPATHIES

Evaluation should follow published guidelines. For details of specific diagnoses and a classification diagram of FTLD subtypes, see the Coding Guidebook for the NACC Neuropathology Data Form.

For minimum recommended brain regions to be sampled and evaluated, see Table 1 in Montine et al., 2012[1].

a. FTLD with tau pathology (FTLD-tau) or other tauopathy

(CHECK ONE)

- ☐ 0 No **(SKIP TO QUESTION 17c)**
- ☐ 1 Yes **(COMPLETE QUESTIONS 17b1 – 17b10)**
- ☐ 8 Not assessed **(SKIP TO QUESTION 17c)**
- ☐ 9 Missing/unknown **(SKIP TO QUESTION 17c)**

Question 17a:

Enter **0=No** if no FTLD tau pathology/other tauopathy was observed regardless of brain region, and skip to Question 17c. For all subjects with 0=No on Question 17a, Questions 17b1–17b10 will be set to 0.

Enter **1=Yes** if any FTLD tau pathology/other tauopathy was identified, and complete Questions 17b1-17b10.

Enter **8=Not assessed** if FTLD tau pathology/other tauopathy was not evaluated, and skip to Question 17c.

Enter **9=Missing/unknown** if FTLD tau pathology/other tauopathy was assessed but the data cannot be found, and skip to Question 17c.

b. FTLD-tau subtype[2–8]

(CHECK ONE BOX PER ROW)

	No	Yes	Not assessed	Missing/unknown
1. FTLD-tau (PiD)	☐ 0	☐ 1	☐ 8	☐ 9
2. Other 3R tauopathy (Includes *MAPT* mutation tauopathy)	☐ 0	☐ 1	☐ 8	☐ 9
3. FTLD-tau (CBD)	☐ 0	☐ 1	☐ 8	☐ 9
4. FTLD-tau (PSP)	☐ 0	☐ 1	☐ 8	☐ 9
5. Argyrophilic grains	☐ 0	☐ 1	☐ 8	☐ 9

[1]Montine TJ, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. *Acta Neuropathol.* Jan 2012;123(1):1-11.

[2]Cairns NJ, Neumann M, Bigio EH, et al. TDP-43 in familial and sporadic frontotemporal lobar degeneration with ubiquitin inclusions. Am J Pathol. Jul 2007;171(1):227-240.

[3]Dickson DW. Pick's disease: a modern approach. Brain Pathol. Apr 1998;8(2):339-354.

[4]Dickson DW, Bergeron C, Chin SS, et al. Office of Rare Diseases neuropathologic criteria for corticobasal degeneration. J Neuropathol Exp Neurol. Nov 2002;61(11):935-946.

[5]Dickson DW. Neuropathologic differentiation of progressive supranuclear palsy and corticobasal degeneration. J Neurol. Sep 1999;246 Suppl 2:II6-15.

[6]Bigio EH, Lipton AM, Yen SH, et al. Frontal lobe dementia with novel tauopathy: sporadic multiple system tauopathy with dementia. J Neuropathol Exp Neurol. Apr 2001;60(4):328-341.

[7]Kovacs GG, Majtenyi K, Spina S, et al. White matter tauopathy with globular glial inclusions: a distinct sporadic frontotemporal lobar degeneration. J Neuropathol Exp Neurol. Oct 2008;67(10):963-975.

[8]McKee AC, Stein TD, Nowinski CJ, et al. The spectrum of disease in chronic traumatic encephalopathy. Brain. Jan 2013;136(Pt 1):43-64.

6. Other 4R tauopathy (Includes sporadic multiple systems tauopathy, globular glial tauopathy, *MAPT* mutation tauopathy)	☐ 0	☐ 1	☐ 8	☐ 9
7. Chronic traumatic encephalopathy	☐ 0	☐ 1	☐ 8	☐ 9
8. Amyotrophic lateral sclerosis (ALS)/ Parkinsonism-dementia complex of Guam	☐ 0	☐ 1	☐ 8	☐ 9
9. Tangle dominant disease	☐ 0	☐ 1	☐ 8	☐ 9
10. Other 3R + 4R tauopathy (Includes unclassifiable, focal, glial only, *MAPT* mutation tauopathy, NOS)	☐ 0	☐ 1	☐ 8	☐ 9

Questions 17b1 – 17b10:
Enter **8 = Not assessed** if the particular FTLD-tau subtype was not assessed for the region in question.
Enter **9 = Missing/unknown** if the particular FTLD-tau subtype was assessed for that region but the data cannot be found.

c. FTLD with TDP-43 pathology (FTLD-TDP)[1]? (CHECK ONE)	☐ 0 No ☐ 1 Yes ☐ 8 Not assessed ☐ 9 Missing/unknown

Question 17c:
Enter **8 = Not assessed** if FTLD-TDP was not assessed.
Enter **9 = Missing/unknown** if FTLD-TDP was assessed but the data cannot be found.

[1]Cairns NJ, Neumann M, Bigio EH, et al. TDP-43 in familial and sporadic frontotemporal lobar degeneration with ubiquitin inclusions.Am J Pathol. Jul 2007;171(1):227-240.

d. ALS/motor neuron disease (MND) present? (CHECK ONE)	☐ 0 No ☐ 1 Yes, with TDP-43 inclusions in motor neurons ☐ 2 Yes, with FUS inclusions in motor neurons ☐ 3 Yes, with SOD1 inclusions in motor neurons ☐ 4 Yes, with other inclusions ☐ 5 Yes, with no specific inclusions ☐ 8 Not assessed ☐ 9 Missing/unknown

Question 17d:
Enter **8 = Not assessed** if ALS/MND was not assessed.
Enter **9 = Missing/unknown** if ALS/MND was assessed but the data cannot be found.

e. Other FTLD? (CHECK ONE)	☐ 0 No **(SKIP TO QUESTION 18a)** ☐ 1 Yes **(COMPLETE QUESTIONS 17f1 – 17f5)** ☐ 8 Not assessed **(SKIP TO QUESTION 18a)** ☐ 9 Missing/unknown **(SKIP TO QUESTION 18a)**

Question 17e:
Enter **0 = No** if no FTLD subtypes in addition to those already specified in 17b – d were observed, and skip to Question 18a. For all subjects with 0 = No on Question 17e, Questions 17f1 – 17f5 will be set to 0.
Enter **1 = Yes** if any other FTLD subtype was identified, and complete Questions 17f1 – 17f5.
Enter **8 = Not assessed** if FTLD subtypes in addition to those already specified in 17b – d were not evaluated, and skip to Question 18a.
Enter **9 = Missing/unknown** if other FTLD subtypes were assessed but the data cannot be found, and skip to Question 18.

f. Other FTLD subtype

(CHECK ONE BOX PER ROW)

	No	Yes	Not assessed	Missing/ unknown
FTLD-FUS[1,2]				
1. Atypical FTLD-U (aFTLD-U)	☐ 0	☐ 1	☐ 8	☐ 9
2. NIFID (neuronal intermediate filament inclusions disease)	☐ 0	☐ 1	☐ 8	☐ 9
3. BIBD (basophilic inclusion body disease)	☐ 0	☐ 1	☐ 8	☐ 9
FTLD other				

[1]Mackenzie IR, Munoz DG, Kusaka H, et al. Distinct pathological subtypes of FTLD-FUS. Acta Neuropathol. Feb 2011;121(2):207-218.

[2]Mackenzie IR, Neumann M, Bigio EH, et al. Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration:an update. Acta Neuropathol. Jan 2010;119(1):1-4.

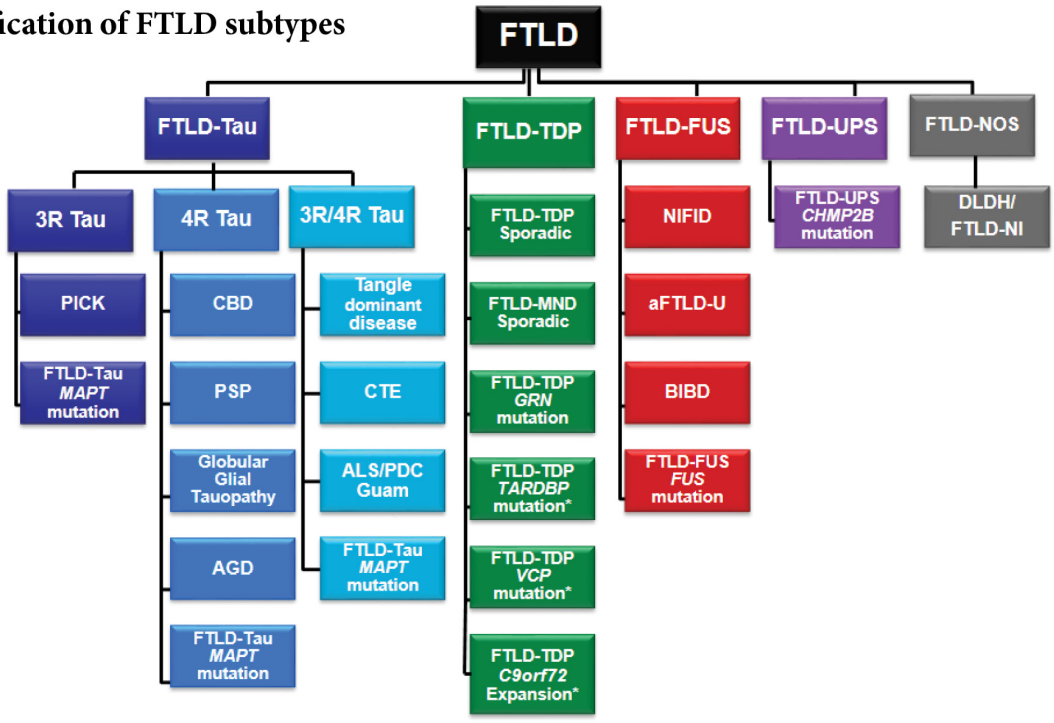
4.	FTLD-UPS (ubiquitin-proteasome system [ubiquitin or p62 positive, tau/TDP-43/FUS negative inclusions])	☐ 0	☐ 1	☐ 8	☐ 9
5.	FTLD-NOS (includes dementia lacking distinctive histology (DLDH) and FTLD with no inclusions (FTLD-NI) detected by tau, TDP-43, or ubiquitin/p62 IHC)	☐ 0	☐ 1	☐ 8	☐ 9

Atypical FTLD-U, NIFID, and BIBD contain inclusion bodies that are immunoreactive for FUS protein and collectively are called FTLD-FUS. Additional proteins may also be present in the inclusion bodies.

Questions 17f1–17f5:

Enter **8=Not assessed** if the particular FTLD subtype was not assessed.
Enter **9=Missing/unknown i**f the particular FTLD subtype was assessed but the data cannot be found.

Classification of FTLD subtypes



This figure describes a classification of frontotemporal lobar degeneration (FTLD) entities and other tauopathies. Three distinct neuropathologic categories may be identified based on the molecular pathology of the misfolded protein within the inclusion: FTLD-Tau, FTLD-TDP, and FTLD-FUS. The molecular pathology of a rare fourth category, FTLD with epitopes of the ubiquitin-proteasome system (FTLD-UPS), remains indeterminate. A now rare fifth category, FTLD-NOS, contains dementia lacking distinctive histology (DLDH) and FTLD with no inclusions (FTLD-NI) detected by tau, TDP-43, FUS, or ubiquitin/p62 IHC. FTLD-Tau may be categorized by IHC morphologically and/or according to the predominant tau isoform within the inclusion (3 or 4 microtubule-binding domains/repeats - 3R, 4R, or 3R/4R tau). FTLD-Tau (3R) includes Pick's disease (PICK) and FTLD with microtubule-associated protein tau (MAPT) mutation with inclusions of 3R tau protein. FTLD-Tau (4R) encompasses: corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), globular glial tauopathy (GGT), argyrophilic grain disease (AGD), and FTLD with MAPT mutation with inclusions of 4R tau protein. FTLD-Tau (3R/4R) and other tauopathies include: tangle dominant disease, chronic traumatic encephalopathy (CTE), amyotrophic lateral sclerosis/parkinsonism-dementia complex (ALS/PDC) of Guam, and FTLD with MAPT mutation with inclusions of both 3R and 4R tau protein. FTLD-TDP is neuropathologically and genetically heterogeneous; it encompasses sporadic FTLD-TDP with and without motor neuron disease (MND), FTLD with progranulin (GRN) mutation; FTLD with TAR DNA-binding protein 43 (TARDBP) mutation; FTLD with valosin-containing protein (VCP) mutation, and FTLD with C9orf72 intronic hexanucleotide repeat expansion. FTLD with fused in sarcoma (FUS) inclusions include: neuronal intermediate filament inclusion disease (NIFID), atypical FTLD with ubiquitin inclusions (aFTLD-U), basophilic inclusion body disease (BIBD), and rare cases of FTLD with FUS mutation. FTLD with inclusions containing epitopes of the proteasome-ubiquitin system include FTLD with charged multivesicular body protein 2B (CHMP2B) mutation. Within each molecular pathology there may be unclassified entities.

NOTES

* MND may be present in cases with TARDBP, VCP, and C9orf72 mutations.

FTLD and MND may be present with SOD1 mutation.

TDP-43 may be a comorbidity in CTE and other molecular pathologies.

FTLD-TDP may be subdivided into subtypes based on the morphology and distribution of inclusions but this is only recommended in a research setting.

Gene status, if known, may be entered in Question 19q.

18. AGING-RELATED TAU ASTROGLIOPATHY (ARTAG) Evaluation should follow published guidelines. See the Coding Guidebook for the NACC Neuropathology Data Form.	
a. Is ARTAG pathology present?	☐ 0 No **(SKIP TO QUESTION 19)** ☐ 1 Yes **(CONTINUE)** ☐ 8 Not assessed **(SKIP TO QUESTION 19)** ☐ 9 Missing/unknown **(SKIP TO QUESTION 19)**

Question 18a: Based on review of all available slides (not restricted to amygdala, frontal neocortex, basal ganglia or medulla oblongata).

Enter **8=Not assessed** if ARTAG pathology was not evaluated.

Enter **9=Missing/unknown** if the pathology was examined but the data cannot be found.

b. Overall severity of ARTAG pathology	☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe ☐ 8 Not assessed ☐ 9 Missing/unknown

Question 18b: Provide semi-quantitative assessment of overall ARTAG pathology as stained for p-Tau via immunohistochemistry. Since some may preferentially sample amygdala and frontal cortex, the pathology in these two regions should be the foci of this semiquantitative measure.

1 — Mild: Minimal or sporadically distributed ARTAG p-Tau proteinopathy
2 — Moderate: An intermediate level of ARTAG p-Tau proteinopathy
3 — Severe: Numerous and widespread p-Tau proteinopathy

Enter **8=Not assessed** if ARTAG pathology severity was not evaluated or if the regions were not available for evaluation.

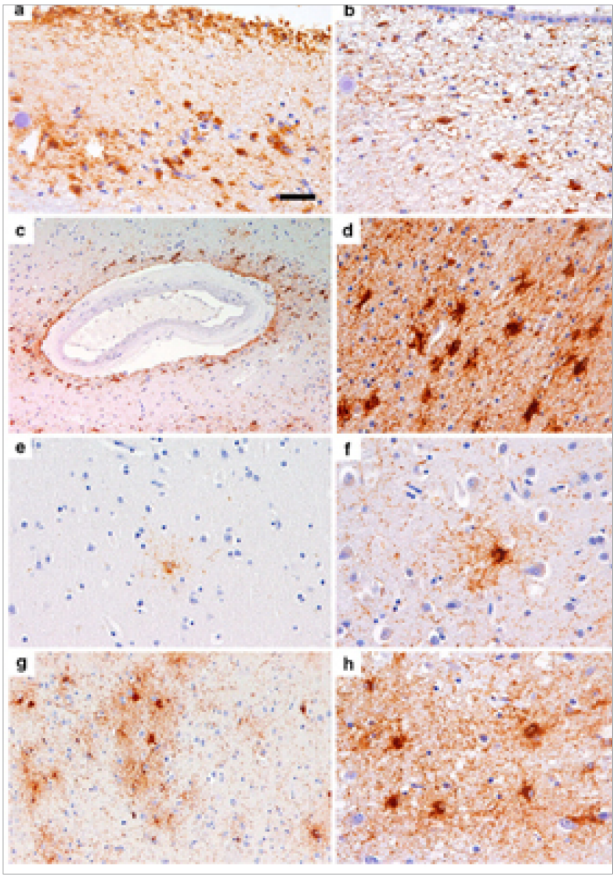
Enter **9=Missing/unknown** if the pathology was examined but the data cannot be found.

ARTAG requires the presence of thorn-shaped astrocytes (TSA) and/or solitary or clustered astrocytes with plump cytoplasmic tau immunoreactivity that extend into the astroglial processes as fine granular immunopositivity (GFA) distinguishable from astrocytic plaque (AP), tufted astrocyte (TA), ramified astrocyte (RA), or globular astroglial inclusions (GAI). [1]

Types are distinguished according to the location (i.e., subpial, subependymal, gray matter, white matter, perivascular) and major anatomical distribution (i.e., medial temporal lobe, lobar, subcortical, brainstem). The recommended regions to sample are (a) the amygdala for the medial temporal lobe, (b) the frontal neocortex for the lobar region, (c) the basal ganglia of the subcortex region, and (d) the medulla oblongata of the brainstem. ARTAG may appear in focal clusters or in a widespread distribution.

Kovacs et al. (2016)[1]

Diagnostic screening				
STEP 1		**STEP 2**		**STEP 3**
Type	→	**Major anatomical involvement**	→	**Severity**
Subpial	→	MTL	→	occasional or numerous (focal/widespread)
		Lobar	→	
		Subcortical	→	
		Brainstem	→	
Subependymal	→	MTL	→	
		Lobar	→	
		Subcortical	→	
		Brainstem	→	
Gray matter	→	MTL	→	
		Lobar*	→	
		Subcortical	→	
		Brainstem	→	
White matter	→	MTL	→	
		Lobar*	→	
		Subcortical	→	
		Brainstem	→	
Perivascular	→	MTL	→	
		Lobar	→	
		Subcortical	→	
		Brainstem	→	



The figure on the right includes representative photomicrographs of ARTAG types. Plump cytoplasmic tau immunoreactivity of astrocytes and tau-positive lining in subpial (a) and subependymal (b) location. Perivascular type: tau-immunoreactive astrocytic processes arranged around vessels (c). White matter (WM)-type: astrocytes in the subcortical white matter with plump cytoplasmic immunoreactivity (d). Gray matter (GM)-type: single-appearing (e, f) or clusters (g, h) of astrocytes with fine granular tau immunoreactivity in the processes without (e) or with (f) plump perinuclear cytoplasmic tau immunoreactivity.

[1]Kovacs GG et al. Acta Neuropathologica. 2016 Jan;131(1):87-10. Used by permission.

c. Is ARTAG pathology present in the **AMYGDALA?**

- ☐ 0 No **(SKIP TO QUESTION 18e)**
- ☐ 1 Yes **(CONTINUE)**
- ☐ 8 Not assessed **(SKIP TO QUESTION 18e)**
- ☐ 9 Missing/unknown **(SKIP TO QUESTION 18e)**

d. Localization of ARTAG pathology in the amygdala

(CHECK ONE BOX PER ROW)	None	Focal	Widespread	Not assessed	Missing/ unknown
Subpial	0 ☐	1 ☐	2 ☐	8 ☐	9 ☐
Subependymal	0 ☐	1 ☐	2 ☐	8 ☐	9 ☐
Gray matter	0 ☐	1 ☐	2 ☐	8 ☐	9 ☐
White matter	0 ☐	1 ☐	2 ☐	8 ☐	9 ☐
Perivascular	0 ☐	1 ☐	2 ☐	8 ☐	9 ☐

e. Is ARTAG pathology present in the **FRONTAL NEOCORTEX?**

- ☐ 0 No **(SKIP TO QUESTION 19)**
- ☐ 1 Yes **(CONTINUE)**
- ☐ 8 Not assessed **(SKIP TO QUESTION 19)**
- ☐ 9 Missing/unknown **(SKIP TO QUESTION 19)**

f. Localization of ARTAG pathology in the frontal neocortex

(CHECK ONE BOX PER ROW)	None	Focal	Widespread	Not assessed	Missing/ unknown
Subpial	0 ☐	1 ☐	2 ☐	8 ☐	9 ☐
Gray matter	0 ☐	1 ☐	2 ☐	8 ☐	9 ☐
White matter	0 ☐	1 ☐	2 ☐	8 ☐	9 ☐
Perivascular	0 ☐	1 ☐	2 ☐	8 ☐	9 ☐

19. OTHER PATHOLOGIC DIAGNOSES

(CHECK ONE BOX PER ROW)	No	Yes	Not assessed	Missing/ unknown
a. Pigment-spheroid degeneration/NBIA	☐ 0	☐ 1	☐ 8	☐ 9
b. Multiple system atrophy	☐ 0	☐ 1	☐ 8	☐ 9
c. Prion disease	☐ 0	☐ 1	☐ 8	☐ 9
d. Trinucleotide disease (Huntington disease, SCA, other)	☐ 0	☐ 1	☐ 8	☐ 9

e.	Malformation of cortical development	☐ 0	☐ 1	☐ 8	☐ 9
f.	Metabolic/storage disorder of any type	☐ 0	☐ 1	☐ 8	☐ 9
g.	WM disease, leukodystrophy	☐ 0	☐ 1	☐ 8	☐ 9
h.	WM disease, multiple sclerosis or other demyelinating disease	☐ 0	☐ 1	☐ 8	☐ 9
i.	Contusion/traumatic brain injury of any type, acute	☐ 0	☐ 1	☐ 8	☐ 9
j.	Contusion/traumatic brain injury of any type, chronic	☐ 0	☐ 1	☐ 8	☐ 9
k.	Neoplasm, primary	☐ 0	☐ 1	☐ 8	☐ 9
l.	Neoplasm, metastatic	☐ 0	☐ 1	☐ 8	☐ 9
m.	Infectious process of any type (encephalitis, abscess, etc.)	☐ 0	☐ 1	☐ 8	☐ 9
n.	Herniation, any site	☐ 0	☐ 1	☐ 8	☐ 9
o.	Trisomy 21/Down syndrome	☐ 0	☐ 1	☐ 8	☐ 9
p.	AD-related genes (dominantly inherited); do not include APOE or other polymorphisms or genetic risk factors.	☐ 0	☐ 1	☐ 8	☐ 9
q.	FTLD-related genes (dominantly inherited); do not include polymorphisms or genetic risk factors.	☐ 0	☐ 1	☐ 8	☐ 9
r.	Other (SPECIFY): _____	☐ 0	☐ 1		
s.	Other (SPECIFY): _____	☐ 0	☐ 1		
t.	Other (SPECIFY): _____	☐ 0	☐ 1		

Questions 19a–19q:

Enter **8=Not assessed** if the particular pathologic diagnosis or mutation was not assessed.

Enter **9=Missing/unknown** if the particular pathologic diagnosis or mutation was assessed but the data cannot be found.

Enter any other pathologic diagnoses not collected elsewhere on the NP form by selecting **1=Yes** for Question 19r (and Questions 19s and 19t, if applicable). If **1=Yes** is selected, specify the diagnosis. If no other pathologic diagnoses were noted, select **0=No** for Questions 19r–19t.

20. BANKED BIOSPECIMENS. Use this section to record information related to the storage and accessibility of brain, blood, plasma, serum, DNA, and CSF.

Indicate which of the following specimens are available in the Neuropathology Core at your Center, understanding that some of these biospecimens also may be banked in other Cores.

(CHECK ONE BOX PER ROW)	No	Yes	Missing/ unknown
a. Banked frozen brain or half brain	☐ 0	☐ 1	☐ 9
b. Banked frozen wedge of cerebellum or other sample for future DNA prep	☐ 0	☐ 1	☐ 9
c. Formalin- or paraformaldehyde-fixed brain	☐ 0	☐ 1	☐ 9
d. Paraffin-embedded blocks of brain regions	☐ 0	☐ 1	☐ 9
e. Banked postmortem CSF	☐ 0	☐ 1	☐ 9
f. Banked postmortem blood or serum	☐ 0	☐ 1	☐ 9
g. Banked DNA	☐ 0	☐ 1	☐ 9

Questions 20a – 20g:
Enter **1=Yes** if this subject's specimens are banked at your Center's Neuropathology Core.
Enter **0=No** if they are banked at another location in your Center, or if they are not banked at your Center.
Enter **9=Missing/unknown i**f you are not sure whether they are banked in your Neuropathology Core.

h. Full autopsy performed?	☐ 0	☐ 1	☐ 9

Question 20h: If unsure whether a full autopsy was performed, select **9=Missing/unknown**.

If full autopsy, major findings:

1. _____
2. _____
3. _____
4. _____

Questions 20h1 – 20h4: If a full autopsy was indicated in Question 20h, please provide a short description of the major findings.