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Brain collection, standardized neuropathologic assessment, and comorbidity in ADNI participants

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Abstract

Introduction—The Alzheimer's Disease Neuroimaging Initiative Neuropathology Core (ADNI-NPC) facilitates brain donation, ensures standardized neuropathologic assessments, and maintains a tissue resource for research.

Methods—The ADNI-NPC coordinates with performance sites to promote autopsy consent, facilitate tissue collection and autopsy administration, and arrange sample delivery to the NPC, for assessment using NIA-AA neuropathologic diagnostic criteria.

Results—The ADNI-NPC has obtained 45 participant specimens and neuropathologic assessments have been completed in 36 to date. Challenges in obtaining consent at some sites have limited the voluntary autopsy rate to 58%. Among assessed cases, clinical diagnostic accuracy for Alzheimer disease (AD) is 97%; however, 58% show neuropathologic comorbidities.

Discussion—Challenges facing autopsy consent and coordination are largely resource-related. The neuropathologic assessments indicate that ADNI's clinical diagnostic accuracy for AD is high; however, many AD cases have comorbidities that may impact the clinical presentation, course, and imaging and biomarker results. These neuropathologic data permit multimodal and genetic studies of these comorbidities to improve diagnosis and provide etiologic insights.

Keywords

Alzheimer's Disease Neuroimaging Initiative; autopsy consent; neuropathology; Lewy body; comorbidity; pathology heat map

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1. Background

The Alzheimer's Disease Neuroimaging Initiative (ADNI) began in October 2004 and was designed to find more sensitive and accurate methods to detect Alzheimer disease at earlier stages and mark its progress through biomarkers. The ADNI Neuropathology Core (ADNI-NPC) was established in 2007 to promote brain donation in ADNI participants, to facilitate the collection of brain tissues from those who come to autopsy, to perform a standardized neuropathologic assessment, and to maintain a brain bank of fixed and frozen tissues in order to facilitate research by ADNI investigators and those from other institutions. In collaboration with ADNI performance sites, the ADNI-NPC has established protocols for promoting brain donation, for coordinating arrangements for autopsy, and for the shipment of autopsy specimens to the ADNI-NPC in St. Louis, Missouri, USA. There are 59 participating ADNI sites in the US and Canada. The individuals enrolled in the third phase of ADNI (ADNI2) include older adults with normal cognition (controls) or with subjective memory concerns, mild cognitive impairment (MCI), or mild Alzheimer disease (AD dementia). Although most of the longitudinally studied participants who have come to autopsy have advanced dementia at the time of death, postmortem examination provides an opportunity to associate neuropathological changes retrospectively with antemortem clinical, neuropsychological, or biomarker data. In addition, the new focus in ADNI2 on presymptomatic stages of AD offers the opportunity to study brain changes early in disease pathogenesis in those who expire before developing advanced dementia.

The continued success of the ADNI-NPC is rooted in its utilization of the infrastructure of the Charles F. and Joanne Knight Washington University Alzheimer Disease Research Center, Washington University School of Medicine, St. Louis (WU ADRC; P50-AG05681, JC Morris, PI), funded continuously by the National Institute on Aging since 1985. The ADRC's Administrative and Neuropathology Cores provide the framework for the ADNI-NPC and both share a research coordinator.

2. Methods

2.1 Autopsy coordination

The protocols used by the ADNI-NPC for promoting autopsies at sites with and without neuropathology services, the administration of the autopsy, collection of tissues, transport of brain samples to the central laboratory, and neuropathologic assessment have been described previously [1]. Since the ADNI-NPC was established there have been variable levels of participation among individual ADNI sites in the coordination of the autopsy and collection of brain tissues. To further understand this variability in autopsy coordination among ADNI sites, we queried each site's principal investigator (PI) and site coordinator regarding their experience with obtaining autopsy consent, the coordination of the autopsy, and shipment of tissues to the NPC; we have also examined the electronic case report forms (eCRFs) to tabulate the reasons provided for declining an autopsy.

2.2 Selection of neuroanatomical areas

Formalin-fixed hemi-brains or paraffin-embedded tissue blocks, typically from the left hemi-brain, are forwarded to the ADNI-NPC, allowing histological examination of the

following 16 areas: middle frontal gyrus, superior and middle temporal gyri, inferior parietal lobe (angular gyrus), occipital lobe (including the calcarine sulcus and peristriate cortex), anterior cingulate gyrus at the level of the genu of the corpus callosum, posterior cingulate gyrus and precuneus at the level of the splenium, amygdala and entorhinal cortex, hippocampus and parahippocampal gyrus at the level of the lateral geniculate nucleus, striatum (caudate nucleus and putamen) at the level of the anterior commissure, lentiform nucleus (globus pallidus and putamen), thalamus and subthalamic nucleus, midbrain, pons, medulla oblongata, cerebellum with dentate nucleus and, when available, spinal cord.

Where possible, to provide tissue for biochemical studies and to advance the aims of the Biomarkers Study, tissue is dissected, snap frozen, and sent to the ADNI-NPC. The following coronal hemi-brain slices (0.5 to 1cm thick) are prepared: frontal lobe to include striatum; frontal and temporal lobe at the level of the mammillary body; temporal and parietal lobes at the level of the lateral geniculate nucleus; occipital lobe (to include the calcarine sulcus), and cerebellum to include the dentate nucleus. ADNI sites are encouraged to undertake their own neuropathological assessment of the brain tissue that remains after the tissue blocks for ADNI have been sampled. For a site that does not perform its own assessment, the entire brain may be bisected, allowing the right hemisphere (unless there is visible pathology) to be snap frozen and the left hemi-brain to be fixed in formalin. Both the fixed and frozen hemi-brains are forwarded to the ADNI-NPC. The ADNI-NPC assists with costs of tissue procurement, when requested.

2.3 Histology

In all cases, the following stains are performed at the ADNI-NPC lab on 16 standard blocks, and/or as requested by the neuropathologist: hematoxylin and eosin, a modified Bielschowsky silver impregnation, and immunohistochemistry (IHC) using antibodies that bind the following antigens: phospho-tau (PHF1, a gift of P. Davies, North Shore-Long Island Jewish Health System), β-amyloid (10D5; Eli Lilly); phospho-α-synuclein (Cell Applications Inc.), and phospho-TDP-43 (Cosmo Bio USA). Additional histochemical stains and IHC are performed as required.

2.4 Neuropathologic assessment

The operational criteria for the classification of AD and other pathologies defined by the National Alzheimer Coordinating Center (NACC) are applied to all ADNI-NPC cases. The neuropathologic diagnosis is determined using consensus neuropathologic criteria for AD and for non-AD disorders where they exist. The NACC Neuropathology Form was updated in 2014 to Version 10 (https://www.alz.washington.edu/NONMEMBER/NP/npform10.pdf). This new data acquisition form reflects the new NACC guidelines for the standard neuropathologic assessment of AD at NIA-funded Alzheimer Disease Centers (ADCs) and incorporates the new neuropathologic diagnostic criteria for AD of the National Institute on Aging-Alzheimer's Association (NIA-AA) [2], which underscore the importance of Aβ plaques as a key morphological lesion that best discriminates AD pathology from non-AD [3]. The ADNI-NPC also applies three other sets of neuropathologic criteria: Khachaturian [4], CERAD [5], and NIA-Reagan [6] to each autopsied brain to allow coherence with legacy data as appropriate and to enable investigators who have yet to adopt the NIA-AA

criteria to benefit from the brain tissues collected by the ADNI-NPC [4–20]. This approach allows investigators maximal utility in applying the neuropathologic diagnoses most appropriate to their research aims. The new form also incorporates the explosion of new knowledge concerning the genetics and neuropathology of frontotemporal diseases The neuropathologic data from the NACC Neuropathology Data Form are entered at Washington University and transmitted to the Biostatistics and Informatics Cores at the ADNI Coordinating Center for upload to the Laboratory of Neuroimaging (LONI) database at http://adni.loni.usc.edu/ where it is freely available to authorized investigators. The final neuropathologic diagnosis and neuropathologic report generated by the ADNI-NPC are forwarded by the ADNI-NPC coordinator to the center that made available the tissue so that the site PI or other site clinician can discuss the findings with the participant's family.

2.5 Methods Development

2.5a Unbiased assessment of beta-amyloid burden—To facilitate direct comparison between neuropathologic data and structural and functional imaging data, the ADNI-NPC has been employing computerized stereologic methods to assess beta-amyloid burden in defined areas for comparison with volumetric magnetic resonance imaging (MRI), functional positron emission tomography- fluorodeoxyglucose (PET-FDG), and beta-amyloid (PET-Pittsburgh compound B [PiB]) imaging data in a subset of participants.

2.5b Neuropathologic heat maps—To explore multimodal associations, the ADNI-NPC is generating spatial brain map representations (neuropathologic heat maps) of the different molecular pathologies (beta-amyloidosis, tauopathy, synucleinopathy and TAR DNA-binding protein 43 (TDP-43 proteinopathy) detected in the brains of ADNI participants by immunohistochemistry. Briefly, different molecular pathologies are assessed semiquantitatively using established protocols for estimating beta-amyloid plaques [5], neurofibrillary tangle burden [5], Lewy body density [15], and TDP-43 proteinopathy using a semiquantitative scale (none, mild, moderate, and severe) in twenty-one anatomical sites representing the neocortex, basal ganglia, brainstem and cerebellum. These data are then used to generate anatomic 'heat maps' using a modification of FreeSurfer software. These postmortem data may then be compared with structural, functional, and PET imaging data.

2.5c ADNI and DIAN neuropathologic comparisons—As the ADNI-NPC is also the Neuropathology Core for the Dominantly Inherited Alzheimer Network (DIAN), we are in a unique position to compare the neuropathologic data using standardized assessments of both early-onset autosomal dominant AD (ADAD) of the DIAN cohort with sporadic, late-onset AD (LOAD) participants in the ADNI cohort.

3. Results

3.1 Autopsy consent and coordination

The ADNI-NPC serves all 59 ADNI sites with support for obtaining brain donation and autopsy consent as well as coordination of autopsy services. However, for practical reasons, the NPC is reliant on each local site to contact its participants with an offer to accept brain donation and to help coordinate an autopsy where local help may be absent. In our protocol

operation study of site PIs and site coordinators, several reasons were given for not obtaining consent or brain collection. These reasons include: lack of funds, lack of site personnel to set up the protocol, difficulty in gaining local internal review board (IRB) approval to facilitate autopsy arrangements and handle deaths when they occur, and the lack of understanding regarding the importance of autopsy and brain donation to the ADNI project as a whole. Some sites were unable to solicit consent or coordinate an autopsy for unspecified reasons.

The majority of ADNI sites (43 of 59) are fully operational regarding their autopsy procedures (as defined by the site PI and coordinator), reliably approach participants regarding autopsy consent, and assist in providing their next-of-kin with a procedure to follow at the time of death. Many of these sites are affiliated with existing ADCs/ADRCs and therefore have strong foundations from which to build their autopsy programs (Table 1). These established sites may also contact the ADNI-NPC coordinator for assistance in finding autopsy services for individuals who expire outside of or are moving out of their immediate study site location. As there may be personnel changes over time, central monitoring of ADNI sites ensures that the ADNI autopsy protocols are being followed and maintained. Therefore, it is essential to maintain a dedicated coordinator to ensure these functions are performed over the period of the grant.

The ADNI-NPC coordinator can facilitate discussions between the site coordinator, site PI, and others at the ADNI site by providing them with topics for consideration and advising the site staff (usually the study coordinator) regarding what has worked at other sites. The ADNI-NPC coordinator will contact area neuropathologists or other individuals qualified to remove a brain at autopsy (e.g., staff at a local Medical Examiner's office, a medical school, or independent autopsy technician). The ADNI-NPC will assist in identifying a suitable person who is a good fit for the site and is willing to follow the ADNI-NPC protocol for removal and dissection within the budget allocated to the ADNI-NPC for this purpose. The pathologist/technician may also be recommended by the site PI. The ADNI-NPC coordinator will work with the site to outline a consent form for submission to the site's local IRB, and provide consultation on any contingencies or questions from the IRB that may arise during the process. The ADNI-NPC remains dedicated to ensuring the proficiency of sites in obtaining autopsy consent and collecting brain tissue from consented participants.

Three ADNI sites (3 of 59) have declined participation at this time. The ADNI-NPC coordinator periodically checks in with these sites to see if they are ready to adopt an autopsy protocol for their ADNI participants. Some report insufficient resources to set up a program or that their local fee for brain extraction exceeds the amount reimbursable by the ADNI-NPC. The ADNI-NPC coordinator may also elicit assistance from the ADNI leadership to approach these sites when necessary. The neuropathology portion of the study was written into the grant as a sub-study midway through the grant cycle of ADNI and later integrated into the parent project as a Core with its own aims. A few sites maintain that they are not required to participate in the neuropathology portion of the study since it was originally optional. The ADNI-NPC works to dispel the misconception that sites can choose whether or not to approach participants about brain donation. These sites may be persuaded

to approach participants, obtain consent for autopsy, and rely upon the ADNI-NPC to make arrangements, on a case-by-case basis.

An ADNI clinician will lead a discussion about autopsy with all ADNI participants (demented and cognitively normal) at their initial assessment (study partners and families are welcomed in the discussion and required when the participant is cognitively impaired). There are three objectives of the discussion: 1) to convey information about the value of brain autopsy in confirming the clinical diagnosis and advancing knowledge regarding dementing illnesses; 2) to initiate consideration of the individual's wishes concerning an autopsy; and 3) to answer questions, misconceptions, or concerns about the autopsy. The involvement of the physician in these discussions emphasizes the importance of an autopsy. If the participant wishes to postpone their decision about the autopsy, the discussion is repeated at each of the participant's annual visits until a decision is made (consent or refusal). If provisional consent is provided, the ADNI site team works to ensure the participant's wishes regarding brain donation are carried out and that the family/or participant's Durable Power of Attorney (DPOA) are aware of the participant's wishes. The participant is encouraged to involve family members, clergy, physicians, or other appropriate persons in their decision-making. Participants are assured that a decision not to have an autopsy in no way will jeopardizes their research participation or any other participant rights.

When voluntary consent is granted, more detailed information is provided about procedures to follow at the time of death, including telephone numbers to call and other guidelines (sample forms available in manual appendix and on line). Participants are strongly encouraged to share this information with their next-of-kin, legally authorized representatives (e.g. DPOA), and private physicians. In many states, final legal authorization by the DPOA or next-of-kin must be obtained at the time of death. Sites need to be cognizant of state and local laws regarding autopsy procedures.

Ultimately, the autopsy rate for ADNI relies upon the combined efforts of the individual ADNI sites, the ADNI-NPC and, most importantly, on the ADNI participants and their families. Even with consented cases, missed opportunities for specimen collection may result from non-communication or delayed communication of a participant's death to ADNI-NPC or local ADNI site personnel, or when an autopsy is performed as part of another study. As shown in Table 2, the cumulative autopsy rate since the inception of the ADNI-NPC is 58% (45 deaths/78 autopsies). This rate spans the funding periods of ADNI, ADNI-GO, and ADNI2.

To examine which sites are asking participants about brain donation and what responses they are receiving, the ADNI-NPC reviewed the "NPSTATUS" forms responses from each site. The NPSTATUS form, one of the eCRFs from the Alzheimer's Disease Cooperative Study's (ADCS) electronic data capture system, encapsulates useful information regarding where a participant falls in the spectrum of autopsy consent. It is a required form for ADNI participants who are undecided or have consented to brain donation and is collected at every clinic visit; it is considered supplemental to phone interviews. The ADNI Site coordinator enters data into the form to indicate if the participant remains undecided or has made a

decision regarding brain donation. Within the ADN1 2 NPSTATUS forms (see below), responses include: 1) remains undecided (326 of 1165 responses: 28.0%); 2) refused autopsy (214 of 1165 responses: 18.4%); 3) signed provisional consent (404 of 1165 responses: 34.7%); 4) in the process of reviewing consent (59 of 1165 responses: 5.1%), and 5) indicated that consent may be completed by the decedent's family at the time of death (148 of 1165: 12.8%). The remaining forms (14 of 1165: 1.0%) were 'not done,' 'unknown,' or coded 'other.'

For those 214 participants coded as 'refused' in the NPSTATUS eCRF, the reason for refusal is requested in a free text format (Table 3). The most common reasons for refusal are based on unspecified personal or religious views that may be immutable. However, a significant proportion of refusals are attributed to the non-participation of the ADNI site, the perceived absence of local neuropathology services/resources in the area of residence, or the decision to donate brain or body elsewhere. As discussed above, these latter obstacles can often be overcome within the existing workflow of the ADNI-NPC (e.g. by locating regionally available neuropathology services or obtaining samples of tissue already procured by other studies) with guidance from the ADNI-NPC coordinator.

3.2 Neuropathologic findings in ADNI participants

Forty-five ADNI participants with a mean age at death of 81.7 y have come to autopsy. For the 36 ADNI autopsy cases for whom neuropathologic examination has been completed (mean postmortem interval of 12. 5h [range: 2–76 h]), all had symptomatic AD (MCI/AD dementia) at death. The accuracy of the primary clinical diagnosis of symptomatic AD at ADNI sites is very high (Table 4); in the vast majority of AD dementia cases, the severity of AD neuropathologic change is sufficient to account for dementia. Only one participant (Clinical Dementia Rating [CDR] of 3 at death) was found to have only a non-AD pathology, argyrophilic grain disease (AGD), at autopsy. However, comorbidities (Lewy body disease, TDP-43 proteinopathy, hippocampal sclerosis, AGD, vascular disease and infarcts) are common among cases with neuropathologic AD.

3.3 Clinical information and genetics

The ADNI-NPC requests clinical information from a site regarding the participant (e.g., dementia severity, atypical features, rapidity of progression, relevant known comorbidities, and cause of death) which may inform the neuropathologic assessment. This requirement for information also includes cases of former ADNI participants who have withdrawn or been withdrawn from active participation but remained willing and consented brain donors. Although many sites do not routinely formulate a retrospective "expiration" CDR, we ask them to estimate this for clinical/neuropathologic comparison. Of the 36 ADNI cases neuropathologically assessed, 29 expiration CDRs were provided by site staff or clinicians; these include: CDR 0, n = 0; CDR 0.5, n = 5; CDR 1, n =2; CDR 2, n = 6; CDR 3, n = 16. To complement this retrospective clinical assessment, ADNI participants who come to autopsy also receive apolipoprotein E (*APOE)* genotyping by the Alzheimer's Disease Neuroimaging Initiative Genetics Core; to date, 65% of cases have been determined to be heterozygous or homozygous for the *APOE*-ε4 allele.

3.4 Spatial organization of molecular pathologies (pathologic heat maps)

In an effort to contextualize AD pathology with frequent comorbidities, the ADNI-NPC is also participating in a project to facilitate comparisons of their spatiotemporal distributions. Various staging schemes have been developed to reflect the spread of neuropathologic lesions from a site of highest vulnerability in the earliest stage of disease to more widespread cerebral involvement in later stages of disease. For example, the Thal anatomical staging of beta-amyloid deposits [21], the anatomical Braak neurofibrillary stages [22], and the CERAD criteria [5] based on neuritic plaque density (but not distribution) are incorporated into the new NIA-AA assessment of AD neuropathologic change [3]. Likewise, other instruments, including those of McKeith [14] and Braak [12], allow for the staging of Lewy body pathology. However, these schemes do not lend themselves readily to comparisons of the spatial organizations of different molecular pathologies in a systematic manner. To correct for this deficiency, we and others are recording semiquantitative measurements of beta-amyloidosis, tauopathy, TDP-43 proteinopathy, and alpha-synucleinopathy to map the density of lesions in sixteen standard brain areas. This spatial organization of pathology data will facilitate clinicopathological correlations and multimodal studies including structural and functional imaging. For a preliminary description of the generation of pathologic heat maps see Toledo *et al*. [23].

3.5 Multimodal studies

A preliminary study of the first twenty two ADNI cases to come to autopsy has been performed [23]. This analysis included neuropathologic heat maps, structural MRI volumetric data, functional (PET-FDG) activity, clinical information, and antemortem CSF data. This study demonstrated that most cases with Lewy bodies could be detected antemortem by PET-FDG and CSF α-synuclein data. No association was found with the *APOE* ε4 genetic risk factor.

4. Discussion

The ADNI-NPC has been successful in obtaining brain samples from 45 ADNI participants. Data generated from the associated neuropathologic assessments have already facilitated multimodal studies that are providing new insights into the nature and detection of AD's common neurodegenerative comorbidities. Strategies for increasing brain donation and tissue collection will be the focus of additional effort in the proposed ADNI3. Also, as part of ADNI3, we propose to expand the power of our preliminary multimodal studies by including larger collection of neuropathological assessments (>50). This approach will also facilitate planned neuropathologic-genetic studies that seek to explain the coexistence of additional brain lesions in some ADNI participants.

4.1 Challenges

Seventy-eight deaths have occurred and the ADNI-NPC has been successful in facilitating the collection of 45 autopsy brain specimens to date. As ADNI2 draws to a close, the number of participants approaching the predicted age at death is increasing and resources may not be available to capture this wave at the time of expiration. Currently, no resources are in place to support the tracking of ADNI participants who develop severe dementia and

these participants are at risk of expiration without autopsy procedures being in place. Loss of participants diminishes the power of neuropathologic-genetic associations and restricts any antecedent biomarker studies to clinical diagnoses, which are often insensitive to comorbidities that may be clinically relevant. Coexisting neurological diseases that are clinically silent may introduce variance into imaging and other experimental data and only become apparent through neuropathologic examination.

4.2 Proposed Aims for ADNI3

Anticipating ADNI3, the ADNI-NPC proposes the following aims: 1) to encourage and facilitate brain autopsy for all ADNI participants; 2) to provide uniform neuropathologic assessments on all autopsied ADNI participants; 3) to determine the relationship between the molecular neuropathology, structural, and functional changes in early AD; 4) to determine the contribution of comorbidities (Lewy bodies, TDP-43 proteinopathy, vascular disease, hippocampal sclerosis, and AGD) to variance in clinical and CSF biomarker and neuroimaging data; and 5) to maintain a repository of frozen and fixed brain tissue from ADNI participants.

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Research in Context

1. Systematic Review

The authors reviewed the Alzheimer's Disease Cooperative Study electronic data capture system to determine the autopsy rates for ADNI participants at 59 participating sites. Reasons for not seeking consent or coordinating an autopsy were recorded. The neuropathologic findings of participants who came to autopsy are reviewed.

2. Interpretation

Our findings lead to an increased understanding of factors that influence the autopsy rate for ADNI participants. Our data indicate that further education and resources are required to enhance the overall autopsy rate and coordination of the autopsy. The neuropathology of ADNI participants indicates the presence of comorbidity. The presence of coexisting diseases affects the interpretation of data.

3. Future Directions

In ADNI 3 we propose to enhance education and the resources available for brain autopsy coordination. We propose to include the available genetic information to help explain the presence of comorbidity in multimodal studies.

Table 1

Brain donation/autopsy consent status of ADNI 2 performance sites according to their ADC/ADRC affiliation and donation of tissue to the ADNI-NPC.

Autopsy participation status of 59 ADNI sites	Number of sites	Number of sites that are affiliated with an ADC/ ADRC	Number of sites that have donated brain tissue to the ADNI-NPC
Sites that are fully operational to obtain brain donation/autopsy consent	43	26 (out of 41)	18 (11 are affiliated with an ADC/ ADRC, 8 are not)
Sites that have refused or opted out of participation in obtaining brain donation/autopsy consent	3	0	0
Sites in the process of becoming operational for brain donation/autopsy consent	12	3 (out of 12)	2 (1 affiliated with an ADC, 1 is not)
Total	**58***	**29**	**20**

*One approved ADNI 2 did not enroll any ADNI2 participants but is still counted in the overall figure of 59 ADNI sites. Therefore, this table only includes the autopsy status of 58 sites.

Table 2

Autopsy rate as determined by reported deaths, serious adverse events listing death, and withdrawn status for ADNI participants that were still enrolled in ADNI at the time of death.

ADNI/ADNI-GO/ADNI 2	ADNI-NPC	Deaths	Autopsies	Annual Autopsy Rate (%)
Funding Period				
9-1-05 to 8-31-07	NO	6	0	0
9-1-07 to 8-31-08	YES	7	2	28
9-1-08 to 8-31-09	YES	8	8	100
9-1-09 to 8-31-10	YES	4	1	25
9-1-10 to 8-31-11	YES	13	6	46
9-1-11 to 8-31-12	YES	4	3	75
9-1-12 to 8-31-13	YES	15	8	53
9-1-13 to 8-31-14	YES	20	13	65
9-1-14 to 1-25-15	YES	7	4	57
Total (2005–2015)	-	84	45	54
Total since NPC established	-	78	45	58*

* The cumulative autopsy rate (since NPC inception) decreases to 56% with the addition of two participants who died without autopsy after they had been discontinued or withdrawn from ADNI prior to death.

Table 3

Responses from ADNI2 *NPSTATUS* form (condensed for coding purposes) regarding non- participation in brain donation for ADNI.

Reasons for refusal to participate in brain donation and autopsy	Responses out of 214 total (%)
Not interested, personal choice, not comfortable, no reason, unspecified	87 (40.7)
Site not participating, no neuropathologist	49 (22.9)
Donating brain or whole body elsewhere	19 (8.9)
Family does not want autopsy, participant does not want to burden family after death	18 (8.4)
Religious or other beliefs	16 (7.5)
Wants body buried/cremated intact, does not want body altered after death	6 (2.8)
Moving, live out of study area	12 (5.6)
Undecided	4 (1.9)
No response entered, miscellaneous	3 (1.4)

Table 4

Neuropathologic diagnosis of ADNI participants who came to autopsy as compared to clinical diagnosis.

Clinical diagnosis at expiration	ADNI: Neuropathologic Diagnosis [N (%)]												TOTAL (%) ^
	AD	AD +DLB	AD +TDP	AD +DLB+TDP	AD+DLB +TDP+AGD	AD +ALB+TDP	AD+AGD	AD+ALB	AD +HS+AGD	AD +TDP +Infarcts	AGD	Pending	
DAT	14	10*	1	1			1	2	2†	1	1**	2	35 (78)
DAT+DLB				1	1	1							3 (7)
Pending												7	7 (16)
TOTAL (%) ^	14 (31)	10 (22)	1 (2)	2 (4)	1 (2)	1 (2)	1 (2)	2 (4)	2 (4)	1 (2)	1 (2)	9 (20)	45 (100)

AD, Alzheimer disease (NIA-AA score: A1, B0, C0 or greater); ALB, AD with amygdala Lewy bodies; DLB, dementia with Lewy bodies; AGD, argyrophilic grain disease; TDP, AD with TDP-43 proteinopathy in medial temporal lobe; HS, hippocampal sclerosis.

Note:

*One case had additional AGD;

†One case had additional TDP-43 proteinopathy;

**One case had additional tangles in the medial temporal lobe;

^Figures are rounded and may not equal 100%. Small vessel disease (arteriolosclerosis and cerebral amyloid angiopathy) was a feature of all cases.