

Alzheimer's Disease Neuroimaging Initiative - Neuropathology Core (ADNI-NPC)

Brain Donation and Neuropathology Manual

Protocols for ADNI/ADNI-GO/ADNI2/ADNI3

John C. Morris, MD
Core Leader

Nigel J. Cairns, PhD, FRCPath
Core Co-Leader

Erin Franklin, MS
Core Coordinator

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ADNI Neuropathology Core Contact Information:

John C. Morris, MD

Department of Neurology
Leader, Alzheimer's Disease Neuroimaging Initiative Neuropathology Core
Washington University School of Medicine
Campus Box 81114488 Forest Park Avenue, Suite 130
St. Louis, MO 63110
Tel. +1-314-286-2881
Fax. +1-314-286-2763
Email: morrisj@abraxas.wustl.edu

Nigel J. Cairns, PhD, FRCPath

Department Pathology & Immunology
Co-Leader, Alzheimer's Disease Neuroimaging Initiative Neuropathology Core
Washington University School of Medicine,
Campus Box 8118,
660 South Euclid Avenue,
St. Louis, MO 63110, USA
Tel. +1-314-362-2386
Fax. +1-314-362-4096
Email: cairns@wustl.edu

Erin Franklin, MS—contact person for the Core (all site issues/procedures/tissue shipment)

Department of Pathology and Immunology
Coordinator, Alzheimer's Disease Neuroimaging Initiative Neuropathology Core
Washington University School of Medicine
Campus Box 8118
660 South Euclid Ave.
St. Louis, MO 63110 USA
Tel. +1-314-362-8079
Fax. +1-314-362-4096
Email: efranklin@wustl.edu
After office hours pager: +1-314-841-4738

Introduction and ADNI-NPC Specific Aims

The aims of the ADNI-NPC are:

- (a) To provide and implement training materials and protocols to assist clinicians at ADNI sites in obtaining voluntary consent for brain autopsy in ADNI participants.
- (b) To maintain a central laboratory to provide uniform neuropathological assessments in all autopsied ADNI participants in accordance with standard criteria and to promote clinical-neuroimaging-neuropathological correlations.
- (c) To determine the relationship between the molecular neuropathology, structural, and functional changes, including Pittsburgh Compound-B (PiB), Florbetaben and Florbetapir, in early Alzheimer's disease.
- (d) To maintain a state-of-the-art resource for fixed and frozen brain tissue obtained from autopsied ADNI participants to support ADNI's biomarker studies (John Q. Trojanowski, Biomarker Core Leader) and to provide investigators with access to the tissue and data for research purposes.
- (e) To Interact with ADNI's Data Coordinating Center to ensure appropriate entry of the Core's data into LONI's (Laboratory of Neuroimaging) database, promote data sharing and collaborative research, and maintain the established integration of ADNI-NPC with all ADNI components to support its administration, operations, and progress toward goals.

To accomplish these aims, the ADNI-NPC capitalizes on the existing infrastructure of the Washington University Alzheimer Disease Research Center (WU ADRC; P50AG05681, JC Morris, PI), funded continuously by the National Institute on Aging since 1985. The ADRC's Administrative (Dr. Morris), Neuropathology (Dr. Cairns), and Data Management and Statistics (Dr. Grant) Cores provide the framework and support for the ADNI-NPC. Moreover, the Form developed by the National Alzheimer Coordinating Center (NACC; U01AG016976, W. Kukull, PI) for all Alzheimer Disease Centers (ADCs) to report neuropathological findings from autopsied cases will be the primary data collection instrument. In this way, the ADNI-NPC uses standard criteria for neuropathological diagnoses of dementing illness and existing protocols and procedures to achieve these diagnoses.

The ADNI-NPC does not interfere with or supercede neuropathological activities at any ADNI site. It uses brain tissue obtained at the sites to provide a uniform neuropathological assessment to support the clinical classifications and research aims of ADNI.

Guidelines for Obtaining Autopsy Consent

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 for demented participants).

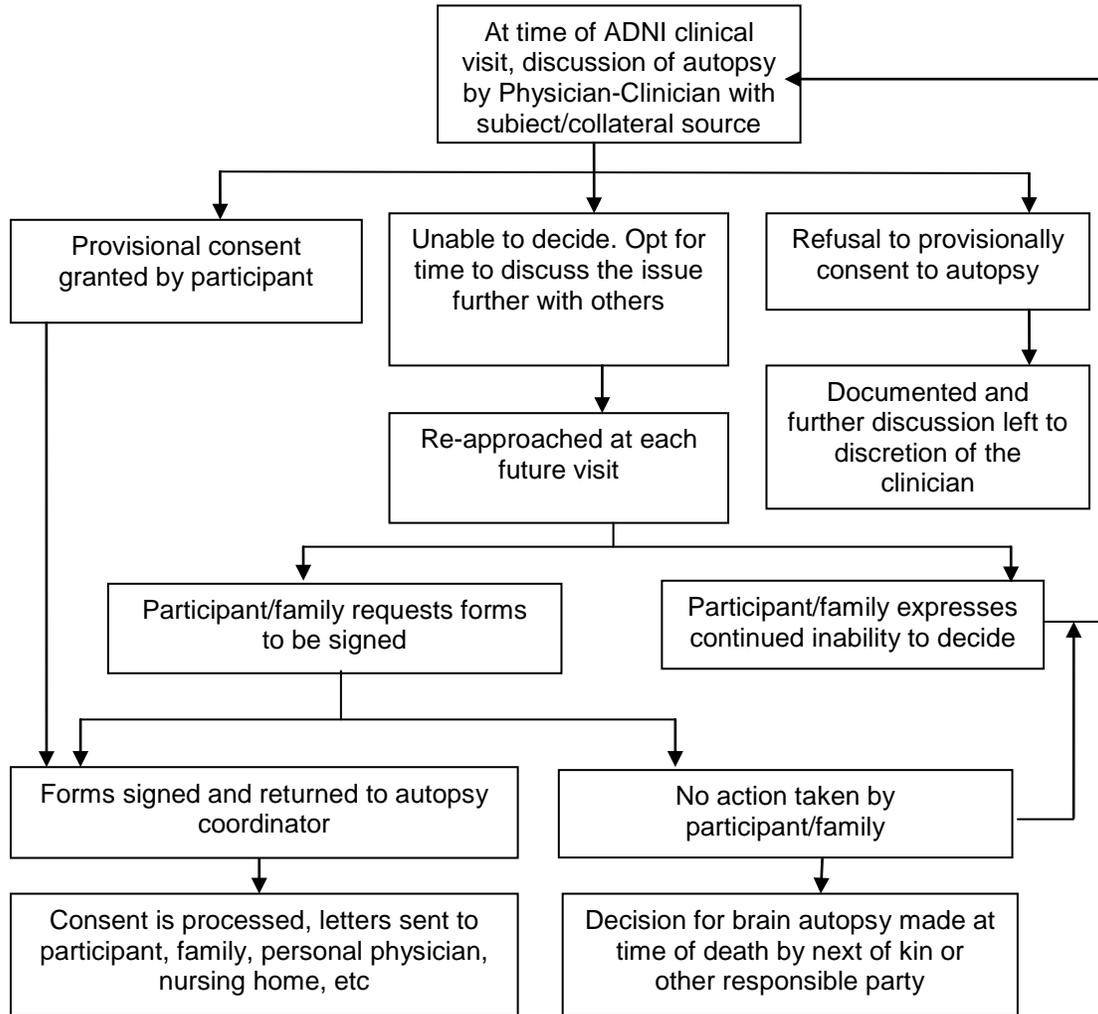
There are 3 objectives of the discussion:

- 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.
- 3) To answer questions, misconceptions, or concerns about autopsy.

The involvement of the physician in these discussions emphasizes the importance of autopsy.

- If the participant wishes to postpone their decision about autopsy, the discussions are 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 family members and/or other responsible party are aware of the participant's wishes.
- An individual may decide not to decide; they are encouraged to involve family members, clergy, physicians, or other appropriate persons in their decision-making. Participants are assured that a decision not to have autopsy in no way jeopardizes their research participation or any other participant rights.

When voluntary consent is granted, more detailed information is provided about procedures to follow at 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 next-of-kin, other responsible parties, and private physicians. In many states, final legal authorization by the next-of-kin must be obtained at the time of death. As ADNI is a multi-center study involving sites in the US and Canada, please be sure to follow state and local laws regarding autopsy consent procedures.



Autopsy Consent Protocol

Each ADNI site is encouraged to establish an autopsy coordinator (typically a research nurse or coordinator) who processes the autopsy consent, provides information as needed, and monitors the need to update any information (e.g., change in residence) at the ADNI participant's longitudinal assessments. The coordinator also will develop procedures for that site to facilitate autopsies outside of usual hours (e.g., evenings and weekends). The actual procedures are expected to vary in accordance with local needs and resources (one model used by many Alzheimer's Disease Centers is to provide 24-hour telephone access).

At the time of death, the autopsy coordinator (or a suitable representative) facilitates arrangements to ensure the completion of the autopsy. The coordinator

notifies the ADNI-NPC, who in turn verifies that the site neuropathologist or autopsy technician has the dissection protocol and necessary materials to send the required tissue to the ADNI-NPC.

The ADNI-NPC, in addition to instructing site personnel at each ADNI Steering Committee Meeting in these procedures, will be available at any time to answer questions. Contact information, including a 24-hour pager, for ADNI-NPC personnel is listed on page 3. ADNI sites that already have ADRC/ADC Neuropathology Services will continue to follow their own existing protocols. For ADNI sites that do not have established neuropathology services, reasonable costs related to brain donation such as transportation costs from point of death to the autopsy suite, costs of the autopsy procedure, and shipment of materials are covered by the ADNI-NPC so that the decedent's family and the individual ADNI site do not incur extra expense. The potential costs associated with ADNI autopsies ideally will be discussed with and approved by the ADNI-NPC **PRIOR** to the autopsy.

Acknowledgement of Autopsy Authorization

Once the Participant has given consent (provisional or otherwise) the Acknowledgement of Autopsy Authorization letter and wallet cards (see appendix) should be sent to the following:

1. Participant and/or family and/or applicable other (e.g., Durable Power of Attorney)
2. Nursing home (include chart cover sheet)
3. Funeral home/transport service (as requested)
4. Private Physician (as requested)

Autopsy Costs to Family

The ADNI-Neuropathology Core (ADNI-NPC) will cover brain autopsy costs, with the following limitations:

1. ADNI sites **with** existing ADRC/ADC neuropathology arrangements in place for handling ADNI participant brain donations will continue to make their own arrangements for brain autopsies.
2. ADNI sites **without** an established autopsy system (making autopsy arrangements on a case by case basis): Any costs for transportation above \$200 will be incurred by the ADNI site or the deceased's estate. The additional costs are to be communicated to the participant's next-of-kin prior to transport.
 - i) Local transportation costs will be paid by ADNI-NPC if arrangements are approved by the ADNI-NPC (see the Out-of-Town Arrangements below). If not, ADNI-NPC will pay up to \$200. Brain removal performed out-of-state or out of local area: Brain removal costs will be paid by ADNI-NPC if

arrangements are approved by the ADNI-NPC in advance. Brain removal costs should be limited to \$500 whenever possible.

Death certificates and related paperwork and transport to funeral home or body donor programs post-autopsy are not covered by ADNI-NPC.

Exceptions: The ADNI-NPC Coordinator must approve any exceptions to the above costs via communication with the Leader or Co-Leader of the ADNI-NPC. However, if a death occurs after regular business hours or if the Leader or Co-Leader of the ADNI-NPC are unreachable, the Coordinator is empowered to allow charges of up to \$1000 (for transportation and brain removal) if the expenses seem justified. As a rule, this amount should be for the extreme exception. Please inform the transporter/ pathologist that ADNI-NPC is a research study with limited funds and suggest a cost reduction.

ADNI-NPC Neuropathology Protocols

Where possible, each center will undertake its own brain assessment and forward a standard set of fixed tissue blocks or sections and frozen tissue to ADNI-NPC (see below). For sites that do not routinely undertake neuropathologic studies, a separate brain removal protocol is listed in the Appendix.

Financial Assistance with Block Sampling, Preservation, and Shipping Costs

The ADNI-NPC will fund all costs in shipping frozen and fixed tissue samples to St. Louis. To assist participating centers and neuropathologists with the costs of obtaining frozen tissue blocks and/or formalin-fixed paraffin wax-embedded tissue the following costs will be reimbursed, if requested. Please address an invoice for these costs to the ADNI NPC Coordinator at Washington University School of Medicine. The ADNI NPC is unable to provide funds without an invoice.

1. Recovery of coronal frozen tissue slices and formalin-fixed paraffin wax-embedded tissue blocks (*see list of brain regions below) \$300.
2. Recovery of formalin-fixed paraffin wax-embedded tissue sections (*see list of brain regions below) \$100.

ADNI-NPC Block Sampling

Resources to defray the costs of sampling, tissue processing, administration, and transport will be made available to each center already undertaking neuropathology. These resources are to facilitate the provision of the standard set of blocks for ADNI-NPC. To minimize the burden on participating centers, formalin-fixed, paraffin wax-embedded tissue blocks from the following 16 areas from the left cerebrum will be forwarded to the ADNI-NPC. Whenever possible, blocks should be labeled with the

number below in parenthesis. If this is cannot be accommodated, a key to the block numbers should be included with block shipment.

1. Middle frontal gyrus (Block 1)
2. Superior and middle temporal gyri (Block 2)
3. Inferior parietal lobe (angular gyrus) (Block 3)
4. Occipital lobe to include the calcarine sulcus and peristriate cortex (Block 4)
5. Anterior cingulate gyrus at the level of the genu of the corpus callosum (Block 19)
6. Posterior cingulate gyrus and precuneus at the level of the splenium (Block 30)
7. Amygdala and entorhinal cortex (Block 23)
8. Hippocampus and parahippocampal gyrus at the level of the lateral geniculate nucleus (Block 5)
9. Striatum (caudate nucleus and putamen) at the level of the anterior commissure (Block 6)
10. Lentiform nuclei (globus pallidus and putamen) (Block 29)
11. Thalamus and subthalamic nucleus (Block 8)
12. Midbrain (Block 9)
13. Pons (Block 11)
14. Medulla oblongata (Block 12)
15. Cerebellum with dentate nucleus (Block 14)
16. Spinal cord (Block 13)

In the unusual situation where it is impractical to forward a tissue block (e.g., if the block is used for stereology), 10 paraffin wax sections (4-8 μm) from each block will be provided to ADNI-NPC for systematic neuropathology and diagnosis.

Frozen Tissue

To provide tissue for biochemical studies and to advance the aims of the Biomarkers Study, snap frozen tissue will be dissected, frozen, and sent to ADNI-NPC. The following coronal hemibrain slices (0.5 to 1cm thick), where possible, will be taken:

1. Frontal lobe to include striatum;
2. Frontal and temporal lobe at the level of the mamillary body;
3. Temporal and parietal lobes at the level of the lateral geniculate nucleus;
4. Occipital lobe to include the calcarine sulcus.
5. Cerebellar hemisphere to include the dentate nucleus

Histology

In all cases, the following stains will be performed at the ADNI-NPC lab on the blocks indicated above: hematoxylin and eosin. Routine immunohistochemistry will be performed using the following antibodies: phosphorylated tau (PHF1), beta--amyloid (10D5), phosphorylated-alpha-synuclein, and phosphorylated TDP-43 (pTDP-43).

Histology Review

The ADNI-NPC Co-Leader reviews the histological slides in a systematic manner. The data are entered into the National Alzheimer's Coordinating Center (NACC) Neuropathology Data Form and transmitted by Dr. Grant (Biostatistics Core) to LONI (Laboratory of Neuroimaging). The final neuropathologic diagnosis and neuropathologic report will be forwarded to the center that made available the tissue. The coordinator can then share the report with the participant's family if the family wishes to receive the report.

Neuropathologic Assessment and Diagnostic Criteria

The operational criteria for the classification of AD and other pathologies defined by NACC will be applied to all ADNI-NPC cases (and are currently applied to all WU ADRC cases). The neuropathologic diagnosis will be determined by Dr. Nigel Cairns and Dr. Richard Perrin (Division of Neuropathology, WUSTL) using consensus neuropathologic criteria for AD, and for non-AD disorders. Four sets of neuropathologic criteria for AD will be used: NIA-AA, CERAD, NIA-Reagan, and Khachaturian. ADNI-NPC cases thus will be diagnosed in accordance with each of these sets of criteria, as no consensus currently exists in favor of one set in relation to the others (particularly for the incipient stages of AD addressed by the ADNI study). This will allow investigators maximal utility in applying the neuropathological diagnoses most appropriate to their research aims.

Providing Participant Data to ADNI-NPC at Time of Death

At the time of death, the ADNI-NPC will ask for information regarding the participant's cause of death and the individual's cognitive status since the time of the last ADNI assessment. An ADNI site clinician will review possible changes that occurred with the participant from time of last assessment including a medical record review to capture the circumstances leading to death and interviews with next of kin to capture cognitive and health changes. The clinician will provide this review to the Neuropathology Core along with the brain tissue. Please see Appendix doc. "Preparing Brief Expiration Summary for Deceased ADNI Participants with Postmortem Examination" on page 18 for details. This information is required to safeguard ADNI NPC personnel from potentially infectious (prion) tissue and to update the research record with information relevant to the neuropathological examination. The ADNI3 site will be reimbursed \$50 for providing this information to the ADNI NPC at the time of death.

Accessing Autopsy Data and Tissue from the ADNI Neuropathology Core

Data Data generated by the ADNI-NPC will be transmitted securely to LONI for storage, management and distribution according to the ADNI procedures. These de-identified data will be available with the relevant clinical, biological and imaging data on LONI's public access web site.

Tissue Applications for Biospecimens, including brain tissue, will follow the format of NIH RO1 grants limited to 5 pages. Only manuscripts accepted for publication, published manuscripts, and submitted grants will be considered as appendix material. Applications will be sent to the Chairman of the Resource Allocation Review Committee (RARC; Thomas J. Montine, MD, PhD, Chairman, Department of Pathology, University of Washington, Seattle, WA). The criteria used by RARC will be: scientific merit, feasibility, appropriateness of principal investigator qualifications, burden on ADNI samples, and appropriateness to ADNI goals/themes. Case selection for approved tissue requests will be achieved through discussion with the requesting investigator, the ADNI-NPC staff, and the ADNI Coordinating Center. A Data Use Agreement and Material Transfer Agreement must be executed prior to the shipment of tissue. Upon shipment, a final list of samples shipped is shared with the ADNI Coordinating Center for purposes of reporting and tracking the transfer.

In return for the use of ADNI autopsy tissue, we ask the following of investigators: acknowledgment of the ADNI grant number in publications and presentations, productivity reports on publications or funding that were derived from the project, and no third-party sharing without notification. We do not charge for sharing materials/data unless the request requires effort beyond what can be subsumed under normal ADNI-NPC budgeted effort (as recommended by NIA). If the request justifies a charge, the cost is kept to a minimum and based on actual expenses (effort and materials).

Frequently Asked Questions

1. Who may give consent?

Priority order of Next-of-Kin: participant for him/herself, in writing prior to death (some states do not acknowledge this consent prior to death), patient's guardian at the time of death, agent designated by the patient in a Durable Power of Attorney that specifically refuses to consent for autopsy/postmortem examination (please note that a Power of Attorney expires when an individual dies), spouse, adult son or daughter (if there is a spouse incapable of giving consent or if separated and living apart from the decedent or if living outside of the U.S.), either parent (if adult son or daughter is not available and if there is a spouse incapable of giving consent or if separated and living apart from the decedent or if living outside of the U.S.), any adult grandchild of the participant (if either parent is not available, if an adult son or daughter not available and if there is a spouse incapable of giving consent or if separated and living apart from the

decedent or if living outside of the U.S.), any person who assumes custody of and responsibility for the burial of the body.

2. Who will cover the transportation and brain removal costs?

For ADNI sites that do not have established neuropathology services, transportation costs from point of death to the autopsy suite, costs of the autopsy procedure, and shipment of materials are covered by the ADNI-NPC so that the decedent's family and the individual ADNI site do not incur extra expense. If the ADNI site or other tissue procurement mechanism do not have funds to pay for the transportation of the body from the place of autopsy to the funeral home the family of the decedent may be asked to cover this cost.

3. Who will cover the extra expenses incurred in my lab from the additional work required to fulfill the ADNI-NPC protocols?

Resources to defray the costs of sampling, tissue processing, administration, and transport will be made available to each center already undertaking neuropathology. These resources are to facilitate the provision of the standard set of blocks for ADNI-NPC. (See page

4. What if a participant expires in the middle of the night? When should the autopsy be performed?

While it is important that the brain be removed as soon as possible after death, for participants that expire outside of normal business hours the brain removal can be performed the following morning. For sites that currently undertake neuropathology, please follow the established after hours procedures.

5. Whom should I contact if I need assistance at night or on the weekend?

The ADNI-NPC Coordinator is available by pager at **+1-314-841-4738** should you need emergency assistance.

Arranging Autopsy Service for Sites without Neuropathology Resources

These procedures should be used to identify a person and location where a brain removal can be performed at an ADNI site that does not currently undertake neuropathology. These arrangements should be made in advance with the assistance of the ADNI-NPC Coordinator.

1. Contact the participant, informant or collateral source to clarify the autopsy procedure. Obtain information about the closest hospital and the funeral home that will be used at the time of death.
2. Contact the closest hospital and request to speak to the Department of Pathology (Autopsy Service). Inquire with the Pathology Department staff, the availability of a pathologist or deputy to perform brain removal. If they do not have a pathologist/mortuary assistant who is available to assist, inquire as to whom they use when autopsies are needed.
 - If there is a local ADC/ADRC, contact the autopsy coordinator to make arrangements for autopsy.
 - If you are unable to find someone, contact the local funeral home for any suggestions they may have.
 - Look up neurologists in the area in the membership directories of the American Academy of Neurology www.aan.com/ or the American Association of Neuropathologists www.neuropath.org/ and ask them for suggestions.
 - Contact the local Alzheimer's Association for any recommendations they may have regarding local autopsy services.
 - Consider other hospitals, medical schools, and the local coroner or medical examiner.
3. Once a named pathologist is identified, contact the participant's funeral home and make preliminary arrangements for transportation to the autopsy location at time of death. Obtain a preliminary cost for these services. Discuss any atypical cost with the ADNI-NPC Coordinator.
4. Fax, mail, and/or email a copy of the Autopsy Brain Protocol to the out-of-town pathologist. Answer any questions they may have or refer them to Dr. Cairns at ADNI-NPC.
5. Inquire as to the cost for the pathologist's services. Remind them we are a research study and have limited funds.

Please contact the ADNI-NPC Coordinator should you need assistance in arranging for autopsy/brain removal for ADNI participants.

Autopsy Procedures

To be carried out by the site ADNI coordinator at the time of death.

1. Notify the ADNI-NPC Core of the death of the ADNI participant. If the participant passes away overnight and assistance with handling the death is not required, this can be done via e-mail or by phone the following business day.
2. Contact family or informant/collateral source to clarify autopsy procedure. Obtain information about the funeral home they plan to use.
3. Contact the pathologist or technician who has agreed to perform the brain removal. These arrangements should be made in advance with the assistance of the ADNI-NPC Coordinator. If arrangements have not been made in advance or you are unaware of the arrangements, contact the ADNI-NPC Coordinator.
4. Ensure that the pathologist or person performing the brain removal has a copy of the ADNI-NPC Brain Removal Protocol. This should also be supplied in advance; however, copies are available in the document repository at the ADNI website or download. If there are any questions, the person recovering the brain should contact Erin Franklin at 1-314-362-8079 or by pager at 1-314-841-4738 **before** he or she begins the procedure.
5. Schedule the brain removal in accordance with the pathologist's schedule. While it is important that the brain removal take place as soon as possible after death, participants that die outside of normal business hours (i.e. overnight) can have the brain removed the following morning.
6. Once the pathologist and brain removal location have been identified, contact the participant's funeral home and make arrangements for transportation to and from the autopsy location. Obtain a preliminary cost for these procedures. Discuss any atypical costs with the ADNI-NPC Coordinator.
7. After brain removal, the pathologist should ship the fixed (two weeks following the removal) and frozen brain tissue to the ADNI-NPC following the Brain Removal Protocol (see below).
8. The ADNI-NPC Coordinator will follow up with the pathologist to ensure that the tissue is shipped and received at the ADNI-NPC lab. The ADNI-NPC will provide approved shipping containers to the pathologist for the shipment of tissue.
9. The ADNI-NPC will send letters of thanks to the participant's family and the pathologist after the brain removal is completed.
10. The neuropathological examination of the brain is completed and usually takes 6-12 months after the brain tissue is received at the ADNI-NPC to generate a final neuropathologic report. It is left to the ADNI Clinician's discretion to obtain the neuropathology autopsy reports and share the findings with the participant's family or other responsible party.

ADNI Neuropathology Core Brain Removal and Shipping Protocol

Thank you for helping with the donation of this brain. Your contribution will help us to find the causes and more effective treatment of neurodegenerative diseases.

1. Weigh the brain fresh with the dura removed. Record the weight and the time interval between death and removal of the brain and fixing/freezing of brain specimens.
2. Separate the two cerebral hemispheres and brainstem by a midline/sagittal cut. Separate the right brainstem and right cerebellum from the right cerebral hemisphere by a cut across the midbrain (third cranial nerve to superior colliculus). Place the **RIGHT** half brain (medial surface face down) on aluminum foil on a pre-cooled metal plate/tray (e.g. brass, aluminum), on dry ice, if available. If no dry ice is available, freeze hemisphere by placing on foil on a tray or plate in freezer (at below -20°C, -70°C is better). The right half brainstem and cerebellum should be frozen with the medial (cut) surface flat to the plate. Once frozen, remove aluminum foil and place: (1) the right half brain and (2) the right brainstem and cerebellum in labeled zip-lock plastic bags. Ship frozen tissue in container with dry ice.
3. Place the **LEFT** half-brain, brainstem and -cerebellum in 10% neutral buffered formalin **at room temperature** for at least two weeks prior to shipping to St. Louis. For shipping, wrap brain in tissues/cloth soaked in formalin to provide physical support in transit (**DO NOT SHIP FORMALIN FIXED TISSUE IN DRY ICE**). Place in sealed plastic bag. Place in rigid watertight container and in a rigid outer container for transport. Use separate containers for frozen and fixed material. **IT IS CRITICAL THAT YOU DO NOT TRANSPORT FROZEN AND FIXED BRAIN IN THE SAME CONTAINER. THIS WILL PRODUCE ARTIFACTS ON THE SLIDES USED FOR DIAGNOSTIC PURPOSES.** The ADNI-NPC will send to you two shipping boxes that are approved for this type of shipment, if you have not discussed this shipment with the ADNI-NPC or requested boxes, please contact Erin Franklin (information below).

If you have any queries regarding this protocol please contact:

Nigel J. Cairns, PhD, FRCPath
Co-Director, ADNI Neuropathology Core,
Department of Pathology & Immunology,
Washington University School of Medicine,
Campus Box 8118,
660 South Euclid Avenue,
St. Louis, Missouri 63110, USA
Tel. +1-314-362-2386 Fax. +1-314-362-4096
Email: cairns@wustl.edu

Erin Franklin, MS
ADNI Neuropathology Core Coordinator
Department of Pathology and Immunology
Washington University School of Medicine
Campus Box 8118
660 South Euclid Ave.
St. Louis, MO 63110 USA
Tel. +1-314-362-8079 Fax. +1-314-362-4096
Email: efranklin@wustl.edu
After office hours/emergency pager:
+1-314-841-4738

ADNI-NPC Neuropathology Protocols

Recovering Brain Tissue from ADNI Participants Centers that DO NOT Perform Neuropathology

For those centers that DO NOT currently undertake neuropathology, and do not plan to do so during the period of this project, ADNI-NPC will assist in arrangements in consultation with a local center to recover the brain and to ship tissue to ADNI-NPC where a systematic neuropathological evaluation will be performed which will include the following:

Tissue Processing

Routine sampling for histology includes taking blocks from the **LEFT** brain hemisphere which are fixed in neutral buffered (10%) formalin (NBF), or similar. All remaining tissue is preserved until the neuropathological assessment is complete and a report has been issued. The ADNI Neuropathology Core currently samples multiple sites for neuropathologic diagnosis and research needs: olfactory bulbs, middle frontal gyrus, orbitofrontal cortex, olfactory cortex, anterior cingulate gyrus, caudate nucleus and putamen at the level of the nucleus accumbens, anterior commissure and nucleus basalis of Meynert, lentiform nucleus (globus pallidus, putamen), superior and middle temporal gyri, inferior temporal gyrus, amygdala, hippocampus pes to include entorhinal cortex, hippocampus at level of lateral geniculate nucleus, hypothalamus, thalamus and subthalamic nucleus, precentral gyrus, postcentral gyrus, inferior parietal lobe (angular gyrus), posterior cingulate gyrus and precuneus, occipital lobe (calcarine sulcus), posterior inferior frontal gyrus (Broca's area), posterior superior temporal gyrus (Wernicke's area), midbrain, pons, medulla oblongata, cerebellum with dentate nucleus, vermis, and spinal cord from all dementia cases and cervical, thoracic, lumbar and sacral spinal cord from all FTLD and movement disorder cases, when possible. Any additional pathology or abnormality is also sampled. The **RIGHT** hemibrain is stored at -80°C for biochemistry.

Histology

In all cases, the following stains will be performed at the ADNI-NPC lab on the blocks indicated above: hematoxylin and eosin. Routine immunohistochemistry will be performed using the following antibodies: phosphorylated tau (PHF1), beta-amyloid (10D5), phosphorylated-alpha-synuclein, and phosphorylated TDP-43 (pTDP-43).

Histology Review

Dr. Cairns reviews the histological slides in a systematic manner. The data are entered into the NACC Neuropathology Data Form and transmitted by Dr. Grant (Biostatistics Core) to LONI (Laboratory of Neuroimaging). The final neuropathologic diagnosis and neuropathologic report will be forwarded to the center that made available the tissue. The coordinator can then share the report with the participant's family if the family wishes to receive the report.

Neuropathologic Assessment and Diagnostic Criteria

The operational criteria for the classification of AD and other pathologies defined by NACC will be applied to all ADNI-NPC cases (and are currently applied to all WU ADRC cases). The neuropathologic diagnosis will be determined by Dr. Cairns and Dr. Robert Schmidt (Division of Neuropathology, WUSTL) using consensus neuropathologic criteria for AD, and for non-AD disorders. Four sets of neuropathologic criteria for AD will be used: NIA-AA, CERAD, NIA-Reagan, and Khachaturian. ADNI-NPC cases thus will be diagnosed in accordance with each of these sets of criteria, as no consensus currently exists in favor of one set in relation to the others (particularly for the incipient stages of AD addressed by the ADNI study). This will allow investigators maximal utility in applying the neuropathological diagnoses most appropriate to their research aims.

Appendix

Preparing Brief Expiration Summary for Deceased ADNI Participants with Postmortem Examination

Purpose:

1. Capture any information about changes in health or cognition since the final in-person ADNI assessment.
2. Identify any safety concerns for personnel involved in conducting the post mortem examination, with specific notes about rapidly progressive dementia * and/or prion disease and other potentially transmissible diseases.

Information to be recorded:

1. ADNI ID#, date of birth, date of expiration, age of onset of symptomatic Alzheimer disease (if applicable).
2. Place of death and cause(s) of death (even if presumptive), dates of first and last ADNI in-person assessment, with clinical diagnosis and CDR score at each of those assessments.
3. State other relevant information (e.g., history of Alzheimer dementia in a first degree relative).
4. In the interval from last ADNI in-person assessment to death, describe cause of cognitive impairment/dementia (if present) using information gleaned from medical records/nursing home records and from a postmortem interview with the decedent's family and/or caregiver. Estimate an "expiration CDR" just prior to the terminal illness. Provide the expiration diagnosis (include relevant comorbidities) and predict the neuropathological diagnosis.

***Rapidly progressive dementia can be operationalized as a dementia course of 5 years' duration or less from symptomatic onset (encompassing MCI due to Alzheimer disease) to death, OR by a change in more than two global Clinical Dementia Rating stages in two years or less (e.g., from CDR 0.5 to CDR3 in two years). In all cases, fulfilling these criteria for rapidly progressive dementia and/or a clinical diagnosis of Creutzfeldt-Jakob disease or other prion disorder, appropriate precautions should be taken by the local autopsy service with tissue being sent to the National Prion Disease Pathology Surveillance Center (NPDPS; <http://case.edu/med/pathology/centers/npdpssc/>) and cleared prior to tissue being sent to the ADNI NPC. The ADNI NPC coordinator can facilitate this process. The ADNI NPC will pay for shipment of tissue to the NPDPS.**

Sample Forms and Letters

****Please check with your site's IRB to determine if the following letters require IRB approval **prior** to sending them.****

****PLEASE UPDATE THESE ITEMS WITH YOUR SITE-SPECIFIC INFORMATION AND PUT ON SITE LETTERHEAD BEFORE SENDING TO PARTICIPANT OR OUT UPON HIS/HER BEHALF****

Acknowledgement of Autopsy Authorization Letter-Participant Copy

Date:

Name and Address

Re: Research participant's name

Dear:

Thank you for your continued support of the Alzheimer's Disease Neuroimaging Initiative3 (ADNI3). We very much appreciate your cooperation regarding our brain donation program because it is an extremely important component of our research.

Please share your wishes about brain donation and the details with your family and/or persons who will be taking care of those arrangements. Enclosed are several copies of this letter as well as wallet-sized cards with instructions about how to contact us at the time of death for your/their convenience.

At the time of death our office should be called at **XXX-XXX-XXXX**. If the office is closed, a recorded message instructs the caller to ***(Please fill in your site-specific after hours autopsy procedures here)***.

The Alzheimer's Disease Neuroimaging Initiative2 (ADNI2) Coordinator will arrange for the autopsy and transportation of your body to ***(insert autopsy location)*** where the autopsy takes place. A complete report of the brain autopsy findings will be sent to your Power of Attorney, next of kin, or person you have designated.

Thank you again for participating in our project. If you have additional questions, please feel free to contact the autopsy coordinator at the ADNI3 office. Please notify us of any changes in your address, telephone number or other contact information.

Sincerely,

(Include signature for Site ADNI3 Director and/or Autopsy Coordinator with contact information)

Acknowledgement of Autopsy Authorization- Nursing Home Copy

Date:

Attn: Administration
(address)

RE: Participant Name

Dear Administrator:

One of your residents, **Subject Name**, is a participant in the research study program of the Alzheimer's Disease Neuroimaging Initiative3 (ADNI3) at ***(insert site location)***. He/She has given consent for a brain autopsy at the time of death.

We greatly appreciate your assistance in the collection of this valuable human tissue to be utilized in advancing our knowledge about Alzheimer's disease. We have enclosed instructions for this. Please place these instructions in the resident's chart. We are also enclosing a sticker to be placed on the face sheet in order to alert the staff to the family's wishes.

At the time of death, we ask that you fax a copy of the following medical record to our office at ***(insert site fax number)***: most recent physician progress note, last two weeks of nursing notes, and the current medication record.

Thank you for your cooperation and interest. Should you have any questions concerning this protocol, please do not hesitate to contact us at ***(insert ADNI3 site coordinator contact number)***.

Sincerely,

(Insert ADNI3 coordinator signature)

(Place Participant's Name Here)

PROTOCOL FOR PREPARATION FOR BRAIN DONATION

At the time of death, the following steps should be taken after notifying the family members and personal physician of the deceased patient:

1. Contact the Alzheimer's Disease Neuroimaging Initiative 3 (ADNI3) Coordinator's office during working hours (**XXX-XXX-XXXX**). If after 5:00 PM or on weekends, (***insert site specific after hours autopsy protocol here***)
2. The Alzheimer's Disease Neuroimaging Initiative 3 (ADNI3) Coordinator will arrange for transportation of the body to (***insert autopsy location***) where autopsy will be performed.
3. **IMPORTANT:** If at all possible, the body should reach the morgue within six hours of death, sooner if possible.

Acknowledgement of Autopsy Authorization Letter- Funeral Home Copy

Date

Funeral home

(Address)

Ladies and Gentlemen:

(insert participant's name), a resident at ***(insert location)***, is a participant in the Alzheimer's Disease Neuroimaging Initiative3 (ADNI3) at ***(insert site name/location)***. Consent for a brain autopsy at the time of his/her death has been granted by ***(insert person granting consent)***. Plans have been made to have the autopsy performed by ***(insert pathologist)*** at ***(insert location)***

(Insert participant's name) family has made the decision to use your funeral home when his/her mother's death occurs. Should you have any questions, do not hesitate to contact me at the ADNI3 Coordinator's office at ***(XXX-XXX-XXXX)***.

Thank you for your time and consideration of this matter.

Sincerely,

(Insert ADNI3 Coordinator's signature)

***Acknowledgment of Autopsy Authorization Letter - Personal Physician
Copy***

Date:

Physician Address

RE: Participant Name

Dear Dr.:

We have been informed by ***(insert participant's name)*** that he/she is under your medical care. ***(Insert participant's name)*** is a participant in Alzheimer's Disease Neuroimaging Initiative3 (ADNI3) and consent for a brain autopsy at the time of his/her death has been granted by ***(insert person granting consent)***. Plans have been made to have the autopsy performed by ***(insert pathologist)*** at ***(insert location)***.

We realize that your awareness of this information will aid in the success of this endeavor. Should you have any questions, please do not hesitate to call. Our number is ***(XXX-XXX-XXXX)***.

Sincerely,

(Insert ADNI3 Coordinator signature)



Wallet-sized cards, front and back, given to participant when consent signed:

<p>The undersigned has registered intent for BRAIN DONATION upon death, for purpose of research, with the Alzheimer's Disease Neuroimaging Initiative3 (ADNI3), <i>(Insert ADNI3 site location)</i></p> <p>Name _____ Date _____</p> <p>Signature _____</p>	<p>AT TIME OF DEATH: Contact the Alzheimer's Disease Neuroimaging Initiative3</p> <p>(XXX-XXX-XXXX): Monday-Friday, 8 a.m - 5 p.m. (XXX-XXX-XXXX): Weekends or evenings</p> <p>As soon as practicable after death, the body of the deceased should be moved to a place of cold storage.</p>
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