ADNI -NPC

Leader: John C. Morris, MD
Co-Leader: Richard Perrin, MD, PhD

"ADNI Autopsies"

2019 Fall ADC Meeting – NP Core Leaders Session
Friday, October 11, 2019
Saint Louis, Missouri

Disclosures

SUPPORT (Neuropathology Core Laboratory)

NIH/NIA

Knight Alzheimer Disease Research Center
P50-AG05681; PI: J. Morris

Healthy Aging & Senile Dementia
P01-AG03991; PI: J. Morris

Dominantly Inherited Alzheimer Network
U01-AG032438; PI: R. Bateman

Alzheimer Disease Neuroimaging Initiative
U01-AG02490409; PI: M. Weiner
U19AG024904; PI: Morris)

Department of Defense

The Brain Aging in Vietnam War Veterans
DoD-W81XWH1310259; PI M. Weiner

Other NIH Support (Perrin)
R01AG054567-01A1 (Benzinger/Wang)
R01AG052550-01A1 (Benzinger/Ances)
RF1AG053550 (Xiong)
R01NS097799 (Kotzbauer)
R01NS092865 (Xu)
R01AG054513-01A1, Yablonskiy (PI)
RF1NS103276-01A1 (Zipfel)

Speakers Bureau
None

Foundations
American Parkinson Disease Association (Perlmutter)

Clinical Trials
None

Consultant
None

Royalties
None

I own no stock or equity in any pharmaceutical company

ADNI Autopsies

The Goal

- Increase the number

Challenges and Obstacles

- Historical
- Cultural
- Infrastructure/Budgetary

Proposed Solution(s)

- Prioritization (Shift of Culture/Perspective on importance of Autopsy/Neuropathology)
- Encourage Consent for Autopsy
- Increase Participant Monitoring after Study Withdrawal (Coordination / Communication)
- Infrastructure – Support of ADNI Site Coordinators and Full-time ADNI-NPC Coordinator
- Incentivization – Adequate remuneration / reward / acknowledgement and appreciation

Timeline and Evolution of ADNI and the ADNI-NPC – Two works in progress

2004 2009

	ADNI-1
Primary goal	Develop biomarkers as outcome measures for clinical trials
Cohort	200 elderly controls 400 MCI 200 AD

Modeled after ACDS clinical trial.
5-year consent.
No autopsy plan.
59 sites; many w/o autopsy capability

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2004 2007 2009 2011

	ADNI-1	ADNI-GO
Primary goal	Develop biomarkers as outcome measures for clinical trials	Examine biomarkers in earlier stages of disease
Cohort	200 elderly controls 400 MCI 200 AD	Existing ADNI-1 + 200 early MCI

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Timeline and Evolution of ADNI and the ADNI-NPC – Two works in progress

2004 2007 2009 2011 2014 2016

	ADNI-1	ADNI-GO	ADNI-2
Primary goal	Develop biomarkers as outcome measures for clinical trials	Examine biomarkers in earlier stages of disease	Develop biomarkers as predictors of cognitive decline, and as outcome measures
Cohort	200 elderly controls 400 MCI 200 AD	Existing ADNI-1 + 200 early MCI	ADNI-1 & ADNI-GO + 150 elder controls 100 early MCI 150 late MCI 150 AD

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NP phone checks extended until death, even for ADNI-3 ineligibles

But: no funding for phone checks; only 17 sites have IRB, participate

Timeline and Evolution of ADNI and the ADNI-NPC – Two works in progress

2004 2007 2009 2011 2014 2016 2019 2021

	ADNI-1	ADNI-GO	ADNI-2	ADNI-3
Primary goal	Develop biomarkers as outcome measures for clinical trials	Examine biomarkers in earlier stages of disease	Develop biomarkers as predictors of cognitive decline, and as outcome measures	Study use of tau PET & functional imaging techniques in clinical trials
Cohort	200 elderly controls 400 MCI 200 AD	Existing ADNI-1 + 200 early MCI	ADNI-1 & ADNI-GO + 150 elder controls 100 early MCI 150 late MCI 150 AD	ADNI-1, ADNI-GO, ADNI-2 + 133 elder controls 151 MCI 87 AD

Modeled after ACDS clinical trial.
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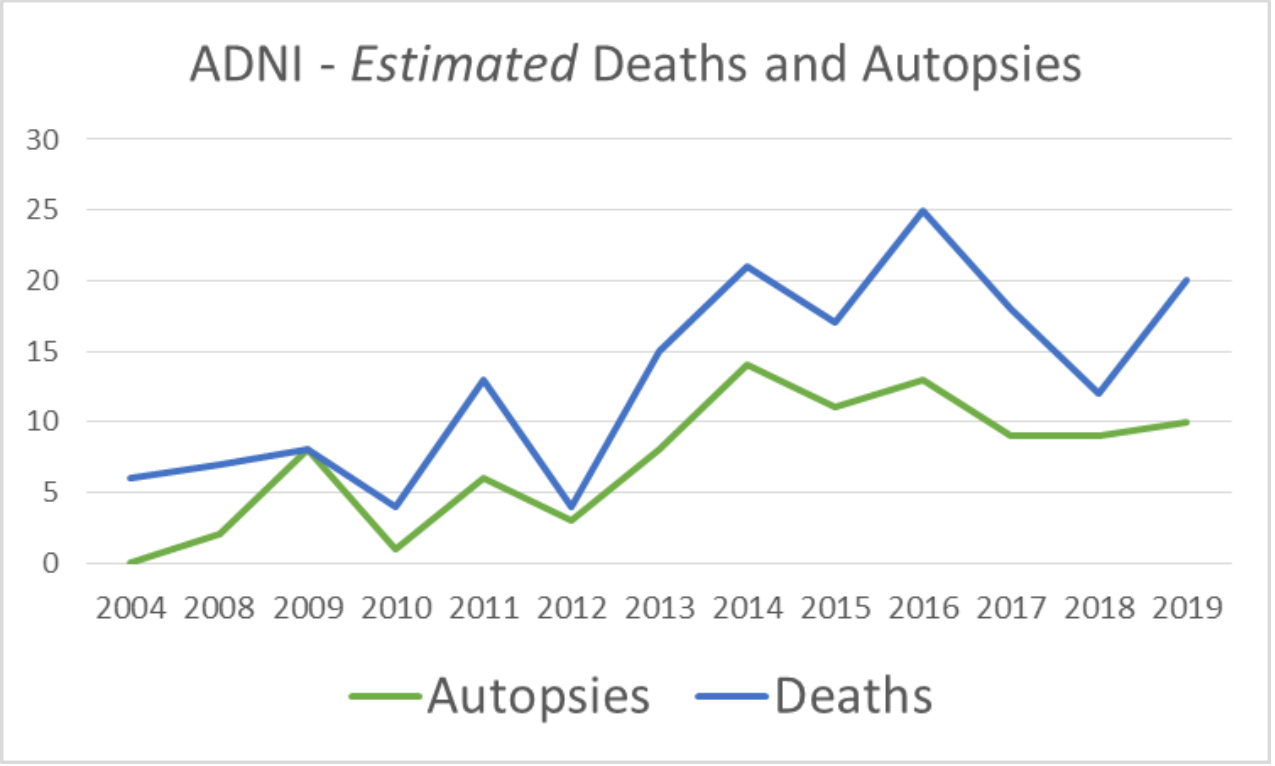
How has the autopsy rate changed over time?



(Under)Estimated Deaths are increasing

Autopsy rate – fairly stable, but low (<55%)

ADNI has already missed > 75 datapoints!

Why so few autopsies?

Why so many autopsies?

The dedication of a small number of sites!

(Many of which are established ADCs)

ADNI Site		Autopsies
33	University of Kansas, KS	12
11	Washington University School of Medicine, MO	8
32	Emory University, GA	7
23	University of Kentucky, KY	6
27	University of Rochester Medical College, NY	6
127	University of Wisconsin, WI	5
116	University of California, Davis, CA	4
14	Rush University Medical Center, IL	4
31	University of Texas Southwestern Medical Center, TX	3
24	University of Pittsburgh, PA	3
123	Dent Neurologic Institute, NY	3
114	Case Western Reserve University, OH	3
29	University of California, Irvine, CA	3
3	University of Southern California, CA	3
99	Banner Sun Health Research Institute, AZ	2
5	University of California, San Diego, CA	2
141	Rhode Island Hospital, RI	2
98	Stanford University School of Medicine, CA	2
73	University of California, San Francisco, CA	2
41	Yale University School of Medicine, CT	2
2	Oregon Health Sciences University, OR	2
126	SJHC London Ontario Canada	2
941	Butler Hospital, RI	1
131	Albany Medical College, NY	1
129	Banner Alzheimer's Institute, AZ	1
37	Indiana University, IN	1
16	Wien Center for Clinical Research, FL	1
6	University of Michigan, MI	1
82	Georgetown University, DC	1

Why are there so few ADNI autopsies?

Insufficient efforts to obtain consent

Insufficient tracking of Participants after study withdrawal

What are the obstacles?

Autopsy/neuropathology has historically been undervalued in ADNI as an optional sub-study;
At some sites → Autopsy Consents and IRB approvals are not sought; No phone monitoring

No financial support for individual ADNI site coordinators to track participants until death
Many sites still lack IRB approval to do so!

Insufficient support for a Full-time ADNI-NPC Coordinator to guide/assist/monitor sites

Skeptics: Why do we need autopsies?

Neuropathologists: Because clinical diagnosis is not perfect and human tissue is essential for research

Clinical Characteristics of Autopsy Cases assessed by the ADNI NPC (N = 67)

Age: Mean = 82.6 y (range = 59-97 y)

Sex: 75% male

Clinical Diagnosis at Expiration	Number of cases
Normal	3
MCI	2
Alzheimer Disease Dementia ONLY (ADD; includes DAT)	55
ADD + Other	6 (total)
+ Dementia with Lewy bodies (DLB)	2
+ Parkinson disease (PD)	3
+ Vascular	1
Progressive Supranuclear Palsy (PSP)	1

27 additional cases are pending shipment and/or review.

Clinical Diagnostic Accuracy for AD: Good, but not Perfect

(Clinical Accuracy for AD Neuropathologic Change in ADNI)

Clinicopathologic Correlations		AD Neuropathologic Change		
		High/Int	Low	Not
Clinical Dx	ADD only (n=55)	47	7	1
	ADD + other (n=6)	2	4	0
	Not ADD (n=6)	0	4	2

Clinical Dx Accuracy for AD:

ADD only: 47/55 = **85%**
ADD + other: 2/6 = **33%**
Not ADD: 6/6 = **100%**

Clinical Dx details:

'ADD + other' includes: Parkinson Dz = 3; Dementia with Lewy bodies = 2; Vascular = 1

'Not ADD' includes: MCI = 2; Progressive Supranuclear Palsy = 1; Normal (CDR0) = 3

AD Neuropathologic Change is seldom "pure"

(Frequencies of Neuropathologic Findings in ADNI)

Neuropathologic Finding(s)	% of assessed cases
ADNC only (High/Intermediate)	**25** (17/67)
ADNC + other (High/Intermediate)	**69** (46/67)
+ LBD (DLB / ALB / Olf LB)	**46** (31/67)
+ Vascular (infarctions)	**4.5** (3/67)
+ HS	**7.5** (5/67)
+ AGD	**18** (12/67)
+ TDP-43	**31** (21/67)
+ FTLD-TDP	**1.5** (1/67)
+ ARTAG (since criteria 1st applied)	**60** (12/20)
Low ADNC **+ HS + AGD (3) + TDP-43**	**1.5** (1/67)
Not ADNC (**PART** [+ **AGD** and/or **ARTAG**])	**4.5** (3/67)

Major Implications for ADNI:

Neuropathologic assessment is essential for optimal evaluation of novel biomarkers
→ Biomarker analyses must factor in clinical misdiagnosis and non-AD pathology
→ Without autopsy confirmation, associated biomarker datapoints are questionable

Proposed Solutions to Increase Autopsy Rate:

ADNI Leadership & Site PIs must emphasize the importance of autopsy at all sites

Full-time ADNI-NPC Central Coordinator to interface with and support ADNI sites

Financially support ADNI Site Coordinators to track Participants until death

Reimburse/incentivize/reward Sites (PIs, Neuropathologists, Coordinators) for:
tracking Participants,
discussing autopsy consent
recording deaths,
pursuing autopsy,
securing brain specimens
→ benefits may be financial, professional, and/or academic

Action Plan:

<u>Administrative Supplement Applications to NIA</u>:
(**Application #1** – Just awarded!) To support a **full-time ADNI-NPC Coordinator**
(**Application #2** – In preparation) To support **efforts of all 59 ADNI-sites** to:

- pursue autopsy consent,
- assist family members with autopsy plans,
- monitor Participants until death,
- arrange autopsy (in advance, and at time of death)
- adequately reimburse and reward Sites and NPs for brain autopsy

Suggestions how best to Prepare, Incentivize, and Reward ADNI sites are welcome

We also invite ADNI tissue requests to support AD and Related Dementia research

Thank you for your attention!

ADNI Participants

ADNI Leadership
Michael Weiner, MD, PI

ADNI Site PIs, Coordinators, and associated personnel

ADNI Site Neuropathologists and associated personnel

ADNI Neuropathology Core
John C. Morris, MD, NPC Leader
Erin Franklin, MS
Aime Burns, MS
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Joel Brown, BS

ATRI
Yuliana Cabrera, ATRI-Clin Ops
Brittany Sloan, ATRI-Regulatory

2019 FALL ADC MEETING
October 11–12 • Hyatt Regency at the Arch • St. Louis, MO

National Institute on Aging

ADNI

NACC
National Alzheimer's Coordinating Center

Knight ADRC
Alzheimer's Disease Research Center
WASHINGTON UNIVERSITY ST. LOUIS

Keck School of Medicine of USC

Alzheimer's Therapeutic Research Institute

Washington University in St. Louis
SCHOOL OF MEDICINE