

PERSPECTIVE

Celebrating neuropathology's contributions to Alzheimer's Disease Research Centers

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Abstract

Our understanding of Alzheimer's disease (AD) and related dementias (ADRD) has grown exponentially, thanks to significant investments by the National Institute on Aging (NIA). This article celebrates the 40th anniversary of the NIA's Alzheimer's Disease Research Centers, highlighting the pivotal role of neuropathology as the bedrock for neurodegeneration research. Neuropathology has championed the key principles of proteinopathy, selective vulnerability, and stereotypic spread. Furthermore, neuropathologic studies advanced our understanding of ADRD prevalence, heterogeneity,

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clinical-pathological correlations, and genetic underpinnings, spurring biomarker development for target engagement and disease monitoring. Disease-modifying therapies for AD were inspired and informed by neuropathology. The neuropathology community is poised to refine diagnostics, leveraging digital pathology and integrating genetics and pathomics to enhance subtyping for novel precision medicine approaches. Despite some common misconceptions and logistical challenges, neuropathology continues to be a critical component of the ADRD research infrastructure, serving as a key bridge between allied basic and clinical sciences.

KEYWORDS

Alzheimer disease, dementia, neurodegenerative diseases, neuropathology, pathomics

Highlights

- We celebrate 40 years of NIA-funded ADRCs and their contributions through neuropathology studies that have significantly advanced our understanding and treatment of ADRD.
- Neuropathology uncovers principles of neurodegenerative disease: proteinopathy, selective vulnerability, and stereotypic spread, informing diagnostics and therapies.
- Development of AD biomarkers with reference to neuropathology enhances accuracy in diagnosis and monitoring, paving the way for targeted disease-modifying therapies.
- Integration of digital pathology, genetics, and novel tools in neurodegeneration research promises advanced precision medicine approaches and refined diagnostics.
- Misconceptions and logistical challenges to neuropathological research are addressed to improve understanding and collaboration.

1 | INTRODUCTION

Since the histologic observations of Alois Alzheimer and Oskar Fischer defined the neuropathologic entity Alzheimer's disease (AD) over a hundred years ago, our knowledge of AD and neurodegeneration has grown exponentially.^{1,2} This growth occurred through sustained investment by the U.S. National Institute on Aging (NIA) to build a robust research infrastructure for AD and related dementias (ADRD). This investment has translated into measurable benefit to those affected by AD and serves as a clear demonstration that an unyielding commitment to biomedical research is foundational to the betterment of human health. This *Alzheimer's & Dementia* special issue highlights some of the NIA's substantial returns on its investments while celebrating the 40th anniversary of the NIA's Alzheimer's Disease Research Centers (ADRCs) program (including the prior Alzheimer's Disease Core Centers and ADRCs, before their merger), the 25th anniversary of the National Alzheimer's Coordinating Center (NACC), the 10th anniversary of NIA Genetics of AD Data Storage Site (NIAGADS), and the 35th anniversary of the National Centralized Repository for AD and Related Dementias (NCRAD). The neuropathology community is broad and includes not only medically trained and board-certified

physician-scientists but also trainees, research staff, neurologists, basic and translational scientists, and others. Collectively, we neuropathologists join in celebrating the NACC and other programs; herein, we highlight a few examples of past research contributions, challenges in conducting research with human brain tissue, and some aspirations we have for future collaborative endeavors.

2 | THE DAWN OF ADRC NEUROPATHOLOGY CORES

Beginning with the first descriptions of AD, senile dementia, Pick's disease, and Creutzfeldt-Jakob disease (CJD), neuropathologists used dyes that revealed only the morphology of the pathologic lesions present in the human brain. In the 1960s, electron microscopy revealed the fine morphology and filamentous appearance of senile plaques and neurofibrillary tangles (NFTs) in AD and senile dementia. By the early 1970s, neuropathologists, using the techniques available at that time, began to recognize that the morphology of the lesions seen in AD and senile dementia were indistinguishable. The new awareness that a relatively rare, presenile disease (i.e., AD) presented a pathology

indistinguishable from the more commonly seen senile dementia, led to the investigation into the epidemiology of these two disorders. In 1976, an analysis of the prevalence of AD and senile dementia uncovered the magnitude of the problem.³ The emerging evidence of novel neuropathologic and epidemiological data led to the name AD to encompass both the presenile and senile forms of dementia and represented the prelude to the Alzheimer movement.

In 1984 and 1985, the first 10 ADRCs were established and included the neuropathology core as a mandatory component. As a result, neuropathologists became an essential element in diagnosis and research in AD and many different types of dementia that were still uncharted. The birth of the ADRCs coincided with the new way that neuropathologists looked at human neurodegenerative diseases. Neuropathology cores focused on the newly discovered proteins to determine the etiology and pathogenesis of AD, leading to a period of profound transformation in the neuropathologic methodologies used to study human neurodegenerative disease. This was most evident as chemical dyes were gradually being replaced by biological markers that could detect and recognize the protein component of the enigmatic senile plaques and NFTs.

Several landmark discoveries took place in the last quarter of the 20th century, including the discovery of microtubule-associated protein tau in 1975, the neuropathologic demonstration in 1985 that AD NFTs were immunolabeled by antibodies to tau, the cloning and sequencing, in 1988, of the cDNA encoding a core protein of the paired helical filaments (PHFs) of AD, and the biochemical purification of PHF tau that led to the demonstration that tau formed the PHF core in AD.^{4–7} In parallel, the biochemical characterization of the cerebral and vascular amyloid protein from the brains of individuals affected by AD and Down syndrome led to the identification of the amyloid beta ($A\beta$) peptide as published in 1984 and 1985.^{8,9} As the two key misfolded proteins involved in the biology of AD were discovered, in 1984, the purification and structural studies of a third protein, the prion protein, was identified from brains of animals affected by scrapie.¹⁰ These early discoveries seeded many more contributions from the neuropathology community.

3 | CONTRIBUTIONS OF NEUROPATHOLOGY

Building on these foundational discoveries, ADRC neuropathologists have made significant contributions to ADRC research. This is exemplified by the fact that at least six ADRC neuropathologists have been honored with the Potamkin Award, underscoring the significance and impact of their outstanding achievements in ADRC.

This prominence in the field can be attributed to the essential role of neuropathologic characterization in defining disease and assessing severity. More specifically, neurodegenerative diseases like AD are defined by three concepts derived from neuropathologic observations: (1) accumulation of abnormally folded proteins ("proteinopathy"), (2) selective vulnerability of specific cell populations, leading to neuronal loss, and (3) stereotypic spread involving connected neuroanatomical regions.¹¹ These frameworks have provided robust explanatory

power, with both diagnostic and therapeutic implications for the neurodegeneration field.

These three concepts are well illustrated in the case of AD neuropathologic change (ADNC). In the development of ADNC, the NFTs of ADNC can be detected first in neuromodulatory subcortical systems^{12–14} and in the pre-alpha layer (layer II) of the transentorhinal region before emerging in the hippocampus, other limbic structures, and later the neocortex.^{15–17} In contrast, $A\beta$ plaques first arise in select neocortical regions, for example, middle frontal gyrus, superior temporal gyrus, and inferior parietal lobule, and typically plaques sequentially involve the hippocampus, basal ganglia, brainstem, and cerebellum.¹⁸

These concepts are clinically relevant as well. For instance, tau accumulation correlates with degree of clinical symptoms and impairments on neuropsychological measures,^{19–22} and AD's definition formerly required the integration of clinical and pathological information.²³ Neuropathology studies helped to show that, although most individuals with ADNC present with an amnesic syndrome, AD can manifest as several distinctive clinical syndromes.^{24–26} Moreover, an amnesic dementia also can result from other non-AD neuropathologic entities.²⁷ These observations helped show that some failed clinical trials might have been hindered by the inclusion of a heterogeneous group of participants, some of whom may not have had ADNC. The community's response was a desire for greater biological homogeneity among participants in trials targeting disease modification, and as a result, AD was redefined from a clinicopathological construct into a purely biological one incorporating biomarker evidence for $A\beta$ plaques, NFTs, and neurodegeneration.²⁸ Though there are alternate views on disease definitions,²⁹ neuropathology has played a critical role in advancing our understanding of AD/ADNC prevalence and heterogeneity across diverse populations, as well as advancing the development of biomarkers and disease-modifying therapies.

The ADRCs have been critical to discovering and studying previously unrecognized neurodegenerative diseases and pathologies often coexisting with AD. Human *post mortem* studies led to the discovery of transactive response DNA binding protein 43 kDa (TDP-43) as the molecular signature of the most common frontotemporal lobar degeneration (FTLD) subtypes, amyotrophic lateral sclerosis (ALS), and limbic-predominant and age-related TDP-43 encephalopathy neuropathologic change (LATE-NC).^{30–35} The discovery of FTLD of fused in sarcoma protein (FUS) was made from human *post mortem* tissue, as were the discoveries of other proteinopathies of FTLD.³⁶ Neuropathologists have also defined and characterized other tau-related entities, including primary age-related tauopathy (PART),³⁷ which may be a part of the AD spectrum,³⁸ chronic traumatic encephalopathy,^{39,40} aging-related tau astroglialopathy (ARTAG),⁴¹ argyrophilic grain disease,^{42,43} MAPT-variant associated tauopathy, vacuolar tauopathy,⁴⁴ and tuberosclerosis complex-associated tauopathy,⁴⁵ among many others. Neuropathologists also expanded the spectrum of Lewy body disease (LBD) to include amygdala-predominant LBD. Significant contributions to our understanding of PrP proteinopathies were achieved through histologic, biochemical, and genetic analyses of human tissue that have contributed to the classification of diseases associated with PrP proteinopathy including Kuru, familial CJD, sporadic CJD, iatrogenic CJD,

Gerstmann-Sträussler-Scheinker disease, fatal familial insomnia, and variant CJD linked to bovine spongiform encephalopathy.^{46–53}

Coincident with these advances in our understanding of diverse proteinopathies are cryogenic electron microscopy studies. These studies have revolutionized our understanding of neurodegenerative diseases by enabling high-resolution visualization of protein aggregates extracted from human brain tissue, including A β , tau, and alpha-synuclein, and demonstrating heterogeneity of filament structures that correspond to the widening spectrum of neurodegenerative disease subtypes.^{54–65} Burgeoning efforts have even demonstrated that unfixed and vitrified human brain tissue can be studied via cryogenic electron tomography.^{66,67} These structural insights have deepened our understanding of disease mechanisms and are accelerating the development of targeted therapeutics.

Given the plethora of neuropathologically defined entities, ADRC neuropathologists have been at the forefront of many of the efforts in terms of coming to consensus as new pathologies have been identified. Of note, in the most recent consensus-based guidelines describing ADNC, PART, and LATE-NC, the NACC data were used to bolster clinical-pathological concepts for a data-driven approach.^{37,68,69} In collaboration with international partners, ADRC neuropathologists have developed the Rainwater progressive supranuclear palsy (PSP) diagnostic criteria, the revised LATE-NC staging scheme, and the revised LBD staging scheme.^{35,70,71} Together, neuropathology studies continue to provide a clearer picture of heterogeneity in persons with neurodegenerative diseases, and the ADRC neuropathology cores are a model for similar efforts around the world.

3.1 | Neuropathologic contributions to understanding ADRC prevalence and heterogeneity

Estimating the population prevalence of AD and other neurodegenerative diseases is challenging due to factors such as limitations in *ante mortem* diagnosis, low autopsy rates, and difficulties in accessing all populations. Population- and community-based autopsy studies, which have received critical support from NIA, provide a valuable means of addressing this question. From centers with large cohorts (e.g., Rush University Medical Center's ADRC and others), we have observed ADNC in approximately half of older adults (generally defined as over 65 years of age), but the frequency and severity vary widely depending on the study population.^{72–76} Growing evidence supports the need to study representative populations to ensure more generalizable findings and to address the unique needs and challenges of the communities each ADRC serves,⁷⁷ and collaborating with international partners may help achieve this goal. The neuropathology community is a critical partner for this work that has led to seminal findings. For example, neuropathologic examination of the Rush longitudinal cohort improved our understanding of dementia prevalence trends in the United States by revealing three trends: (1) vascular brain injury was reduced; (2) tau tangle burden may be increasing; and (3) cognitive decline for a given disease burden was mitigated by greater brain resilience.⁷⁸ Large community-based cohorts supported by the

NIA demonstrated that vascular brain injury and LATE-NC were frequent and important contributors to cognitive decline.^{73,76} In another important recent study from the Arizona ADRC, PSP was identified at 50-fold greater population incidence than predicted and often without *ante mortem* clinical suspicion (i.e., perhaps with neurological deficits but lacking PSP-specific clinical features), shining a light on the public health impact of PSP and a clinical need for more specific diagnostic tools.⁷⁹

Early degeneration of neuromodulatory subcortical systems in AD was observed through *post mortem* examinations made possible through the Brain Bank of the Brazilian Aging Brain Study.¹² This would shift the timeline for early detection of ADNC back many years and offers a possible explanation for prodromal neuropsychiatric symptoms – such as sleep dysfunction – that precede memory decline in a significant number of individuals.^{12,13} Of importance, locus coeruleus tau pathology has been shown to occur simultaneously or even before any ADNC-related tau is found in transentorhinal cortex.^{14,80–82} In normal aging series, it is now clear that tau pathology invariably occurs before A β plaques, raising the issue of whether these cases are PART or in fact the earliest stages of AD.^{37,38,83}

Neuropathology has also revealed the phenotypic heterogeneity attributable to ADNC. First, ADNC may be found in clinically asymptomatic persons, including some with a burden of disease where clinical symptoms would be expected.⁸⁴ Neuropathology is critical for identifying these cases and a key partner in studies on cognitive resilience. Moreover, *post mortem* studies have highlighted the heterogeneity of ADNC; corticolimbic heterogeneity of NFTs is associated with divergent clinical presentations, age of onset, and glial reactivity.^{26,85} ADNC commonly occurs alongside other neuropathologic entities, even in sporadic early-onset or autosomal-dominant cases.^{27,86–89} Coexisting neuropathologic entities include vascular brain injury, LBD, LATE-NC, and age-related tauopathies (e.g., argyrophilic grains, PART, and ARTAG), and many of these have correlated with greater cognitive decline. Vascular brain injury increases odds of dementia and amplifies the cognitive effects of AD,^{90–92} and arteriolosclerosis, even when present in other brain regions, increases the likelihood of hippocampal sclerosis.⁹³ Cerebral amyloid angiopathy (CAA), which is commonly seen with AD, contributes to cognitive decline as well.^{94,95} LATE-NC worsens cognitive decline in parallel with ADNC,^{75,96–98} as does the added presence of LBD.^{99–101} Of note, argyrophilic grain pathology may be associated with an attenuated clinical course in amnesic dementia.^{102,103} Neuropathology demonstrates that multiple-etiology dementia is the “rule,” even in early-onset or familial cases,^{87,104–110} and the latest clinical criteria for diagnosis and staging of AD now include inflammation, vascular disease, and α -synuclein (I, V, and S) along with the ATN framework.²⁸ Reflecting the advancement of the science, the NACC neuropathology forms include the variables for multiple etiologies, and proposals for including others, like LATE-NC or ARTAG, are periodically discussed.

Neuropathology also laid bare the tenuous relationships between clinical syndromes and specific neuropathologic entities. First, the concept of clinical-anatomic convergence captures how several neurodegenerative diseases can underlie the same clinical syndrome due to

involvement of similar brain regions.^{111,112} For example, corticobasal degeneration, ADNC, PSP, and FTLD-TDP Type A all may cause a corticobasal syndrome.¹¹³ Second, a single neurodegenerative disease can lead to distinct clinical syndromes, a concept sometimes referred to as phenotypic diversity.^{111,112} PSP can result in the classical Richardson's syndrome, the non-fluent/agrammatic variant of primary progressive aphasia, behavioral variant of frontotemporal dementia (FTD), corticobasal syndrome, or more pure motor syndromes.¹¹⁴ Similarly, regional variability in the distribution of neurofibrillary degeneration in ADNC is associated with a wide range of clinical phenotypes ranging from typical amnesic AD to the logopenic variant of primary progressive aphasia, posterior cortical atrophy, behavioral variant of AD, and others.^{26,115} These complex clinical-pathological relationships remain centrally important to current efforts to improve diagnosis, prognosis, and treatment.

3.2 | Biomarkers

Ante mortem diagnosis of AD has improved significantly through the widespread development of biomarkers. Given the approximate 70% accuracy of clinical diagnosis for predicting the presence of underlying ADNC,^{116,117} there is a good case for developing biomarkers with high accuracy for predicting neuropathologic diagnosis.¹¹⁸ Measurement of AD-related proteins in cerebrospinal fluid has been adopted worldwide and shows high accuracy in symptomatic patients when compared to *post mortem* gold-standard validation.¹¹⁹⁻¹²² Although sensitivity for detecting preclinical and early-stage ADNC still needs improvement, ongoing efforts by multiple research groups are actively addressing this challenge.^{119,122,123} Human tissue studies have also been instrumental in developing and validating other biomarkers, such as real-time quaking-induced conversion assays for the diagnosis of prion disease.¹²⁴⁻¹²⁶ Autopsy studies have also supported validation and careful interpretation of seeding amplification assays for α -synuclein as a detection method for LBD¹²⁷⁻¹³³ and evolving markers of cryptic exon expression for TDP-43 proteinopathy.¹³⁴ Validating biomarkers against neuropathology has been critical for understanding their predictive value and clinical relevance. Lastly, given logistical barriers and public perceptions regarding lumbar punctures, tremendous effort is being devoted to developing and deploying blood-based biomarkers for ADNC and other neuropathologic entities, and validating those biomarkers with an autopsy gold standard will ensure continued excellence in this space and promote trust across stakeholders.¹³⁵⁻¹³⁷

In parallel with fluid biomarkers, neuroimaging is playing a growing role in diagnosis and disease monitoring. Atrophy patterns on structural magnetic resonance imaging can suggest certain neurodegenerative diseases and more often can rule out others.^{138,139} Of importance, radioligands for molecular neuroimaging have become powerful tools for ADNC detection, prognosis/staging, and exploring disease heterogeneity.^{22,140-147} Several approved positron emission tomography (PET) tracers exist for detecting $A\beta$ and tau proteinopathies as part of an AD/ADNC picture. The rapid approval for the first amy-

loid tracer was the result of a neuropathologist's insights: patients on hospice were scanned and their brains examined after their death soon after, avoiding the delay of enrolling participants with AD and longer life expectancies.¹⁴⁸ Test characteristics of amyloid and tau tracers still are being determined, particularly in earlier stages of the disease. While enthusiasm for PET is well justified, neuropathologic validation remains essential, especially for advancing efforts to detect neurodegeneration at even earlier stages. For instance, neuropathologic validation studies indicate flortaucipir, a first-generation tau PET tracer, lacks sensitivity for detecting ADNC-related tau pathology until the later Braak NFT stages,^{147,149,150} and similar conclusions were drawn for amyloid PET. These findings raise broader concerns about relying solely on neuroimaging patterns to assess the extent of ADNC. Just as chest radiographic findings lag behind clinical course in pneumonia, PET imaging can underestimate the actual burden of ADNC. Therefore, caution is warranted when applying neuropathologic staging terminology to PET findings, as the latter may underrepresent the true extent of disease. Lastly, there is a critical role for neuropathology in the development of novel PET radiotracers for non-ADNC diseases.

3.3 | Human neuropathology contributions to disease-modifying therapies and precision medicine

The treatment era for targeting proteinopathy in AD/ADNC has arrived and will likely come soon for other neurodegenerative diseases as well. Amyloid-targeting drugs were advanced in close partnership with the neuropathology community. Beyond identifying biomarkers and helping adjust the amyloid cascade hypothesis, different forms of amyloid-beta aggregates were identified, including truncated forms, oligomers, and protofibrils, and they became targets for therapeutic development and U.S. Food and Drug Administration-approved treatments.¹⁵¹⁻¹⁵⁷ Additional possible targets for disease modification have emerged from neuropathologic studies, including tau and the immune system.¹⁵⁸

Precision medicine approaches rely on using an individual patient's characteristics to inform the therapeutic plan. Current efforts for amyloid-targeting drugs focus on prediction and risk mitigation strategies for amyloid-related imaging abnormalities (ARIA) that are associated with CAA, a neuropathologic entity frequently co-occurring with ADNC. Clinical and neuroimaging criteria for CAA have improved over time, though their sensitivity still offers room for improvement when compared to the gold standard of neuropathologic diagnosis.¹⁵⁹ A key neuropathologic insight underlying precision medicine efforts is that most affected individuals have more than one disease (e.g., combinations of ADNC, LBD, CAA, vascular brain injury). This likely influences prognosis and may temper expectations for individual therapeutic benefit from some interventions. Anti- $A\beta$ antibody therapy increases risk for hemorrhage, especially from thrombolytics,^{160,161} and may increase risk for other unwanted outcomes.^{162,163}

Related to clinical course heterogeneity, multiple-etiology dementia is the rule, and a perspective informed by neuropathologic studies can empower the clinician. In the disease-modifying treatment era for AD,

neuropathology is beginning to explore the influence of therapies on the histologic hallmarks of AD, like remnant plaques and their effects on microglia.^{164–166} These and future studies will likely yield deeper insight into their drugs' actual mechanisms of action, which may have been hypothesized in non-clinical models, and downstream effects on the natural history of AD/ADNC.

3.4 | Neuropathology and genetics synergy

Neuropathologic studies leveraging genetics have revealed important pathophysiological mechanisms and new therapeutic targets across the neurodegenerative disease space. A seminal study of late-onset AD families established the connection to APOE ϵ 4 and plaque deposition, giving rise to numerous studies on risk for ADNC, cognitive decline, and side effects from anti-amyloid therapies,^{167–170} and the use of NACC neuropathology data has called into question the relationship between APOE ϵ 4 and LBD.¹⁷¹ Studies of people with Down syndrome, a genetically driven form of AD, have shown that the shifting of biomarker curves in this disease resembles sporadic AD and thus represents a trial-ready cohort.¹⁷² Down syndrome genetics underscore the strong effect of APP gene dosage on risk for AD and the deleterious effects from other chromosome 21 genes on metabolism, resulting in chronic inflammation, blood–brain barrier disruption, and oxidative stress.¹⁷³ In contrast, a case report of Down syndrome and substantial ADNC without cognitive decline is an example of how neuropathology may generate fresh perspectives on resilience factors that may be leveraged into therapeutic interventions.¹⁷⁴ In a seminal set of studies, a genetic clue from ANXA11 variant carriers with FTD/ALS led to the discovery that FTLT-TDP Type C inclusions contain annexin A11 due to its formation as an aberrant heterodimer with TDP-43,^{65,175,176} opening a new line of inquiry into protein co-misfolding and pathogenetic mechanisms of selective vulnerability.

Genetic studies can lead the pathology, and the pathology can likewise lead the genetics. Tau's role in AD and FTLT was known first from neuropathology, followed by the discovery of MAPT mutations as genetic causes of FTLT.^{4,177–180} Neuropathology was necessary to accurately diagnose familial AD before the mutations in amyloid precursor protein (APP) and presenilin 1 and 2 (PSEN1/2) could be identified.^{181–184} Leading the genetics further in a PSEN1 mutation carrier, resilience to development of NFTs and cognitive decline despite A β plaque deposition led to the discovery of the APOE3 Christchurch (R136S) variant.¹⁸⁵ In addition, observation of a temporal-predominant, neuro-astroglial tauopathy in FTLT cases due to C9ORF72 repeat expansion led to the identification of the tauopathy's association with TMEM106B.¹⁸⁶ Lastly, genome-wide association studies employing autopsy-confirmed cases and controls, or neuropathologically derived traits, have enabled the identification of novel, disease-relevant, common genetic variants that may otherwise have been overlooked in studies relying solely on neurologically diagnosed, *ante mortem* cases.^{187–192} Ultimately, integrating genetics with neuropathology within ADRCs and at meetings allows for cross pollination and advancement of the science.

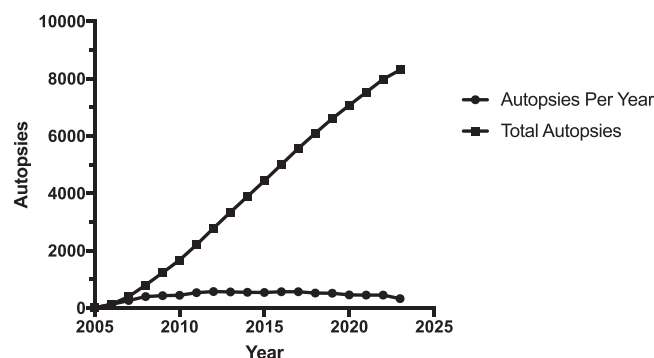


FIGURE 1 NACC neuropathology data since inception. The number of participants in the NACC dataset with neuropathology forms was queried as of June 2025 data freeze and plotted since NACC's inception (analysis using R and graphed with Prism) through only 2023, due to the delay from the time required to process tissue, analyze results, and submit data to the NACC. The number of autopsies performed at ADRCs has remained relatively constant over two decades, maintaining linear growth of the total number of cases over time. NACC, National Alzheimer's Coordinating Center.

3.5 | Harmonization of neuropathology across ADRCs via NACC Neuropathology Guidelines

Given the heterogeneity of neurodegenerative diseases, harmonized data collection and analysis across multiple cohorts are key for making new discoveries. The ADRCs and NACC have been instrumental in promoting common forms and data elements, widely accepted diagnostic frameworks, and data sharing, including the integration of neuropathologic datasets with clinical, imaging, and other biomarker data (Figure 1).¹⁹³ Early on, the introduction of standard templates for semi-quantitative scoring of neuritic plaque and NFT density was shown to have greater interlaboratory agreement than actual counts.¹⁹⁴ Immunohistochemistry using improved antibodies has mostly replaced the more technically challenging (and less specific) silver staining methods, enabling greater consistency and broader implementation across laboratories.¹⁹⁵ Earlier versions of the NACC neuropathology forms allowed for the use of multiple diagnostic criteria for ADNC that introduced considerable interobserver variability.¹⁹⁶ Uniform use and interlaboratory validation of the NIA-Alzheimer's Association 2012 neuropathologic diagnostic criteria for ADNC^{197,198} across ADRCs harmonized our efforts and elevated the field by improving the quality of the gold-standard diagnosis. There have been efforts to understand current practices and benchmarking to aid in the harmonization across ADRC neuropathology cores.^{199,200}

4 | FUTURE DIRECTIONS FOR NEUROPATHOLOGY RESEARCH IN NEURODEGENERATION

The neuropathology community and its ongoing research efforts hold great promise for the ADRC field, particularly by enhancing the ability

to subtype and explain disease heterogeneity. New neuropathologic diagnostic and staging criteria will continue to refine our descriptions and categorization of cases. In two recent examples, the diagnostic criteria for PSP were updated, and the staging criteria for LBD were revised with noted improvements in interrater reliability.^{70,71} Future subtyping through histologic methods may leverage advances in digital pathology,⁸⁵ which already are improving the surgical pathology space.²⁰¹ Significant activity in this area is ongoing and includes quantification of ADNC-related features and non-canonical hallmarks like dystrophic neurites, estimation of brain age, and prediction of cognitive impairment using gray and white matter features from whole-slide images.^{202–212} In addition, the integration of advanced techniques, such as three-dimensional scanning combined with standard gross photographs of brain slices, enables accurate volumetric analysis and facilitates meaningful correlations between microscopic pathology and gross anatomical changes.²¹³ Tissue clearing and machine learning-enabled spatial analyses may deepen a “pathomics” approach to computerized quantitative analyses for neuropathologic characterization, aiding in scalable quantitative workflows that will facilitate a much more nuanced phenotyping of cases as well as augment the ability of experts.^{214–220}

Another means of subtyping is to look upstream. The histologic hallmarks of ADNC, and of other neurodegenerative diseases, likely represent a pathogenetic confluence,²²¹ i.e., heterogeneous, upstream mechanisms across cases result in similar or overlapping neuropathologic changes. Genetics provides a powerful lens for subtyping in neuropathology. In the common scenario of late-onset, amnesic dementia, there are now known to be dozens of risk alleles in the human genome, each of which may provide a separate opportunity for insights into diagnosis, prognosis, or potential therapy,^{222–224} and the neuropathologic implications of these alleles have only begun to be assessed.²²⁵ Alleles unrelated to ADNC, including *GRN* and *TMEM106B*, also offer opportunities to subtype cases by their contributions to the overall neuropathologic picture.²²⁶

A pathomics approach leveraging advanced, spatially resolved techniques to extract quantitative features from whole-slide images, combined synergistically with multi-omics techniques, may allow for transcriptome, epigenome, proteome, and metabolome profiling of single cells to understand heterogeneous populations across cases. For instance, single-cell polygenic risk scores for AD implicated multiple glial cell types with changes starting before clinical diagnosis,²²⁷ and integrated RNA sequencing, proteomic, and metabolomic data have illustrated tau-related immune responses.^{228–230} Recent advances in transcriptomics have opened new avenues for integrating neuropathologic insights with molecular profiling. By applying neuropathologic staging and isolating nuclei from defined brain regions, researchers now can identify cell type-specific transcriptional signatures associated with ADNC.^{231,232} The development of spatial transcriptomics further enhances this integration by enabling the mapping of gene expression directly onto neuropathologic substrates, and a detailed cartography of gene expression changes in AD and Down syndrome illustrates the power of this approach.²³³ Spatially resolved transcriptomics has also been used to characterize cellular and regional

responses to A β immunotherapy, offering insights into treatment mechanisms and efficacy.¹⁶⁵ Together, these technologies bridge histopathology and molecular biology, providing a powerful framework for understanding disease mechanisms and refining therapeutic strategies.

5 | CHALLENGES FOR NEUROPATHOLOGIC RESEARCH

The neuropathology community has enjoyed many successes and fruitful collaborations in the neurodegenerative disease field, yet there remain misconceptions and logistic hurdles to conducting research using *post mortem* human tissue.

First, some may suggest that neuropathologic studies are limited by examining cases that are “end-stage.” While a person may be clinically late-stage just before death, the tissue can demonstrate a wider timeline. A practicing neuropathologist will readily observe that brain tissue samples capture neurons and glia at all stages of progression, even within the same neuroanatomical region and in patients who died of end-stage dementia. By leveraging single-cell technologies or detailed histologic analyses, a scientist can study a “sick” neuron in an early stage of its illness without the decedent coming to autopsy at an early stage of clinical severity. For example, sorting of human brain tissue for affected versus unaffected neurons allows for the separation of neurons at different stages of disease, providing important insights into mechanisms of pathogenesis.^{234–238} Furthermore, community-based cohorts receive brain donations from individuals at all levels of disease progression, enabling natural history modeling.

Autopsy-based studies may also be viewed by some as cross-sectional and therefore unable to derive inferences regarding how disease progresses over time. This misconception ignores the foundational studies on neuropathologic staging^{15,16,18,69,239} that, by aligning data from many cases across a range of clinical disease severity, created models of disease progression; this approach continues to inform our mechanistic understanding of neurodegenerative disease progression, even in this era of longitudinal biomarker measurements. Given the limitations of current *in vivo* and *in vitro* models, neuropathologic “pseudotime” (i.e., modeling disease progression across cross-sectional data) may be the closest we get to the true molecular chronology of human disease.^{232,240–243} Rather than focusing on the limitations of *post mortem* tissue, the field can embrace the opportunities for longitudinal inference, an approach modeled in other branches of molecular neuroscience such as developmental neurobiology, that can be derived using modern molecular methods.^{232,240,244} Further, Bayesian, inferential, and causal mediation statistical methods allow for testing hypotheses in *post mortem* human tissue. Leaning into these newly emerging analytical methods can further advance neuropathologic research within our increasingly interdisciplinary field, given that research using *post mortem* human tissue inherently possesses disease relevance, bypassing the need for additional validation steps required by studies using other model systems.

There are formidable logistical challenges to conducting research with *post mortem* human tissue. The ADRCs include funding for neuropathology cores to acquire and diagnose *post mortem* human tissue, but the mandate to share tissue often goes largely unfunded. This leads to different cost recovery models and may deter early pilot studies for which limited funds exist. In addition, researchers new to human tissue research often benefit from a dialogue with a partnering neuropathologist to ensure the experiment's design answers the scientific question within the constraints of the available specimens. After an experiment is completed, a neuropathologist's perspective can also aid in interpretation. This is critical for understanding a particular tissue collection and for placing the findings in the context of the literature and the other brain banks. Each collection reflects the target population for enrollment that in turn reflects an intersection of the research priorities of the center and its historical outreach to local communities. More recent efforts by ADRCs to broaden recruitment to communities underrepresented in research may be reflected in future autopsy demographics, though that challenge remains. While harmonization efforts have brought many practices into alignment, residual differences in process also influence a brain bank's dataset. One key example is the challenge in capturing vascular brain injury consistently across centers, and addressing this is an opportunity for the field. Interpreting findings in light of these selection and process/local biases requires a nuanced institutional knowledge that often only resides with the neuropathology core director. However, the grant money flowing into neuropathology cores often prioritizes collection over distribution and collaboration, thereby limiting impact. Support for infrastructure to augment tissue sharing efforts, including inventory and laboratory process management (e.g., sample barcoding), whole-slide digitization (including considerable data storage needs), neuropathology data management within labs, and query tools within and across ADRCs could accelerate human tissue-based research projects by researchers within and outside the neuropathology community; the Path-NeuroDegeneration Consortium is one effort focusing on some of these components.²⁴⁵ Coordinated efforts across ADRCs could also leverage their collective inventories to ensure tissue requests are fulfilled using samples representing the broad diversity of the U.S. population and lead to more generalizable results, as has been done in some studies.^{246,247}

The challenges just outlined beget others. There are too few neuropathologists working in neurodegeneration at present, even when accounting for academic/experimental neuropathologists who were trained clinically as neurologists or those who came by way of post-doctoral research. The shortage of neuropathology professionals spans all stages of training and includes technical staff with hard-won expertise in tissue acquisition and processing. Further, the training pipeline is small and leaky, despite efforts like the NIA R13-funded Neurodegenerative Disease Scholars Program held in conjunction with the American Association of Neuropathologists (AANP) annual meeting. The AANP scholars include individuals from a wide range of academic backgrounds, and the field benefits when interdisciplinary practitioners – engineers, bioinformaticians, computational scientists, and others – engage in neuropathologic research. The neuropathology community

is welcoming and collaborative yet small and fragile for the important work to be done.

6 | PARTNERS FOR THE ROAD AHEAD

Since the inception of the NIA's ADRC program 40 years ago, the ADRD field has been transformed into an impactful research enterprise for promoting the health and well-being of older Americans and for the world, and during this time, the neuropathology community has been a critical, collaborative force. The selected examples provided above illustrate the power of partnership with neuropathology and the tremendous insights gained from studying human tissue. Although there are challenges to neuropathologic research, neuropathologists remain partners committed to the neuroscience community for the road ahead. We invite the larger neurodegenerative disease community to continue to learn about conducting human tissue research. We also seek partnerships in finding creative solutions to current limitations from funding streams in order to parlay our strengths to help the broader scientific community and expand upon the shrinking pipeline of trainees. We will strive to inspire and train the next generation of neuropathologists in neurodegeneration, so our community may continue to lead in ADRD research.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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