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REVIEW ARTICLE

Celebrating 40 years of the University of Kentucky Alzheimer's Disease Research Center

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Abstract

Four decades of the National Institute on Aging's sponsored research into Alzheimer's disease (AD) have resulted in symptomatic and mechanistic therapies, lifestyle interventions, increased understanding of genetic factors and protein misfolding, and descriptions of non-AD neuropathological entities that mimic AD clinical symptoms. This is an overview of contributions from one of the original ten Alzheimer Disease Research Centers (ADRCs), the University of Kentucky ADRC. We celebrate 40 years of helping the field to define early pathogenetic mechanisms underlying transitions from normal cognitive aging to impairment in our elderly community-based cohort, increased appreciation of the heterogeneity and multiple pathologies that characterize late-life dementia, strategies for therapeutic intervention, and novel statistical approaches. We also highlight our educational efforts to train the workforce of the future and our long-standing community outreach and partnerships.

KEYWORDS
aging-related tau astrogliopathy, biofluid, biomarkers, clinical trials, dementia genetic factors, limbic predominant age-related TDP-43 encephalopathy neuropathologic change, longitudinal cohort, multi-etiology dementia, multi-state cognition, neuroimaging, neuropathology, optimal brain aging, primary age-related tauopathy, reserve and resilience, transitions

Highlights

- The University of Kentucky Alzheimer's Disease Research Center (UK-ADRC) is an experienced and collaborative center celebrating its 40th year of National Institute on Aging funding in 2025.
- Our long-standing community-based cohort of motivated older adult volunteers and strong neuropathology program support the rationale for our overarching theme: "Transitions from Normal to Late-Life Multi-Etiology Dementia."
- The UK-ADRC's focus on normal aging and early cognitive transitions has been central to elucidating pathogenic mechanisms underlying transitions from nor-

mal cognitive aging to impairment and defining the heterogeneity and multiple pathologies that characterize late-life dementia.
- UK-ADRC infrastructure and resources support and create new opportunities for innovative and inclusive research, clinical programs across the cognitive continuum, educational and training opportunities, and community and national partnerships.

1 | INTRODUCTION

The University of Kentucky Alzheimer's Disease Research Center (UK-ADRC) is a mature, integrated ADRC that has facilitated pioneering research in Alzheimer's disease (AD) and related dementias (ADRD) since its funding by the National Institute on Aging (NIA) in 1985. As the UK-ADRC celebrates its 40th anniversary in 2025, we reflect on how the center has evolved over the years, summarize some of our most significant contributions to the field, and delineate how our strong collaborative infrastructure and resources will continue to support and create new opportunities for innovative and inclusive research, clinical programs across the cognitive continuum, educational and training opportunities, and community and national partnerships.

2 | HISTORY AND CHARACTERISTICS OF THE UK-ADRC

2.1 | UK-ADRC: the early years

The precursor to the UK-ADRC was an NIA-funded program project grant that was awarded in 1984, focusing on studies of trace elements in AD patients' brains.[1] In 1989, the project added a cohort of normal older adults that eventually became the foundation of the UK-ADRC longitudinal cohort. This program project also initially incorporated what later became the Neuropathology Core for the UK-ADRC.

Dr. William R. Markesbery led the UK-ADRC from its inception in 1985 until his death in 2010 and was ahead of his time in recognizing that to understand how disease changes the brain one must know what typical, healthy brain aging looks like in volunteers recruited from the community.[2,3] This led to the UK-ADRC's long-standing focus on recruiting cognitively intact older adults from community-based settings and then following them longitudinally with detailed annual medical, cognitive, and functional evaluations until death and brain autopsy. Another focus of the UK-ADRC pioneered by Markesbery et al. was to emphasize rapid brain autopsy for short (i.e., < 4 hours) *post mortem* interval (PMI) biospecimen collection and extensive neuropathological characterization. These signature resources enabled rigorous clinical–pathological association studies that have been central to our success in understanding the impact of neuropathological changes in transitions from normal aging to mild cognitive impairment (MCI), and early dementia.[3–6] Other major early scientific advances included increased understanding of the importance of oxidative stress and dysregulated brain inflammation in pathology progression,[7] and documentation of synapse loss in AD brains and its correlation with cognitive impairment severity.[8,9] Early work also supported advanced statistical models of transitions from normal aging to dementia,[10,11] along with efforts toward disease prevention.[12] For an overview of UK-ADRC contributions during the early years, readers are referred to a previous summary.[13] The current review will highlight some of the accomplishments of the UK-ADRC since 2010.

2.2 | UK-ADRC: thematic foci

In 2010, Dr. Linda Van Eldik became director of the UK-ADRC and Sanders-Brown Center on Aging. This provided an impetus to build on the historic strengths of the UK-ADRC while capitalizing on emerging opportunities to provide an infrastructure that supports translational research. To this end, in 2010 we developed a survey to gauge both internal use of UK-ADRC resources for research and to estimate research needs for future years. The survey was distributed throughout the University of Kentucky to faculty, staff, and trainees. Survey results for 2010, 2015, 2020, and 2024 are shown in Figure 1; the number of respondents ranged between 60 and 130 per year. Seventy percent to 90% of the respondents anticipated using ADRC resources to support their current and future research, documenting the critical importance of the UK-ADRC to research at the UK. As shown in Figure 1A, over the last decade, there has been an increase in the proportion of respondents who anticipated needing biostatistics/data management and brain tissue, and an increased need for *ante mortem* fluid biomarker specimens (blood, cerebrospinal fluid [CSF]) and neuroimaging data, primarily magnetic resonance imaging (MRI) data. There has also been an increase over the last few years in the desire for more training opportunities. In terms of participant recruitment (Figure 1B), the highest need (> 80%) continues to be cognitively normal individuals, but there was an increase in the projected need for persons with vascular and mixed dementia.

The UK-ADRC has strong cohesiveness and interactions among its cores with a reputation as a highly collaborative center that provides resources to numerous investigators across campus and outside the UK. Figure 2 provides a snapshot of how the UK-ADRC resources supported the scientific community from 2020 through February 2024. The needs of our researchers and our signature resources support the rationale for our continued focus on the overarching theme of the UK-ADRC: "Transitions from Normal to Late-Life Multi-Etiology Dementia." The UK-ADRC continues to leverage our strengths and

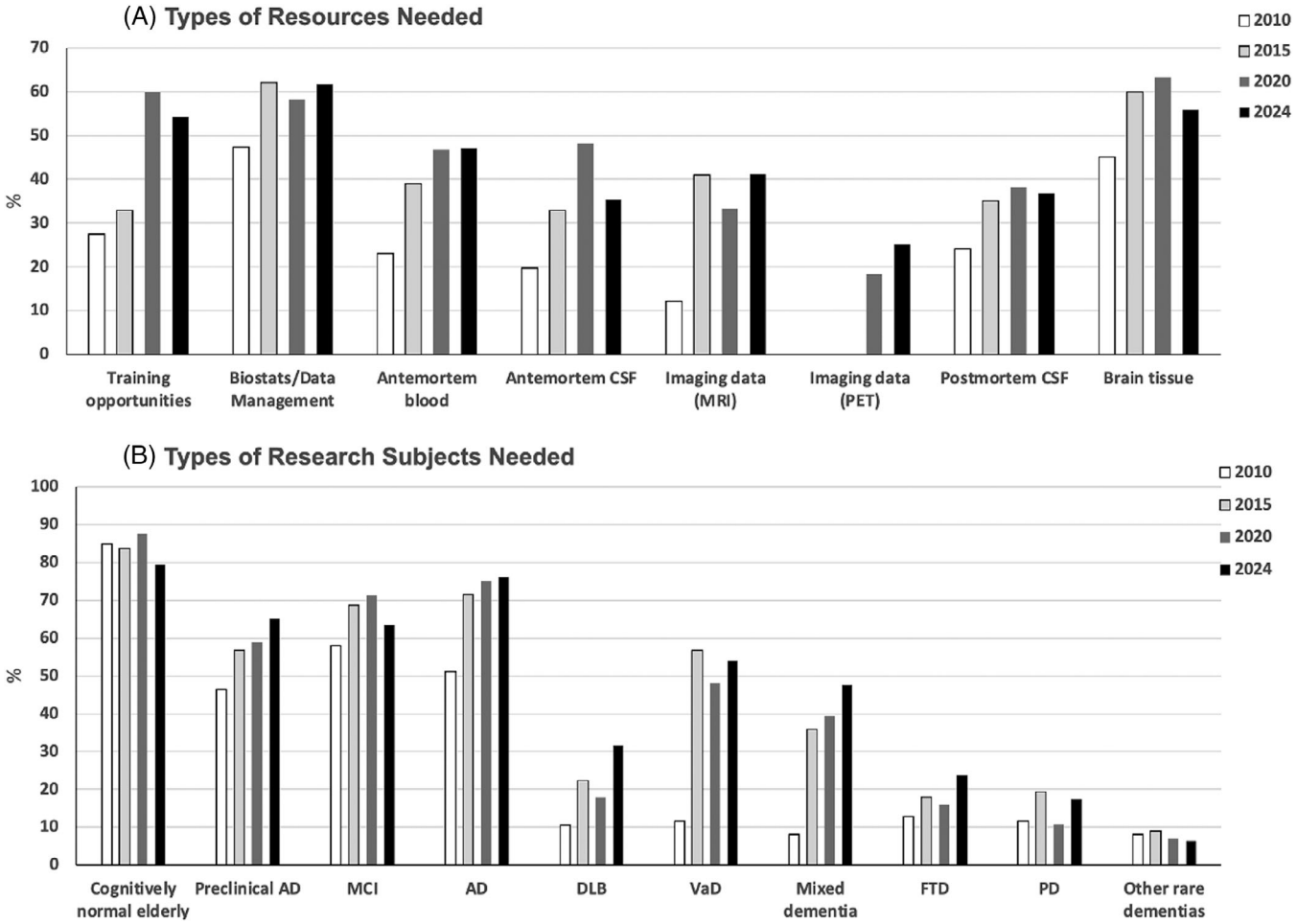


FIGURE 1 Survey results on UK-ADRC resources needed to support current and future research. Surveys were done in 2010, 2015, 2020, and 2024 to gauge the interest of University of Kentucky researchers (faculty, staff, trainees) to use UK-ADRC resources. A, Types of resources needed. B, Types of research subjects needed. AD, Alzheimer's disease; CSF, cerebrospinal fluid; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PD, Parkinson's disease; PET, positron emission tomography; UK, ADRC, University of Kentucky Alzheimer's Disease Research Center; VaD, vascular dementia.

resources to enhance our impact and "Center-ness" through our focus on this overarching theme.

Our well-characterized cohort and historically strong neuropathology program focused on normal aging, preclinical disease states, and early cognitive transitions have been central to our success in defining early pathogenic mechanisms underlying the transitions from normal cognitive aging to impairment in our elderly volunteers. In addition, these efforts have been a driving force in our recognition of the heterogeneity and multiple pathologies that characterize late-life dementia. This has led to the UK-ADRC's strong emphasis on mixed pathology, AD mimics, and co-morbidities that influence risk and outcomes in multi-etiology dementia.

2.3 | UK-ADRC: community-based cohort

The UK-ADRC's ability to facilitate impactful research is driven by our community-based cohort, which comprises a continuously recruited cohort of ≈ 500 cognitively normal participants and another ≈ 300 participants with varying degrees of cognitive impairment (MCI and dementia) primarily derived from cohort participants who transitioned, over time, from normal to impaired cognition.[14] As of October 2024, the UK-ADRC active cohort includes 741 participants (average age = 79). The cohort has 16.5 average years of education, is 31% male, 19% under-represented ethnic minority, and 27% have at least one apolipoprotein E (*APOE*) ε4 allele (Table 1). Since 2005, UK-ADRC's annual data collection has included the National Alzheimer's Coordinating Center Uniform Data Set (NACC UDS). The NACC UDS monthly report for October 2024 shows UK-ADRC has contributed 1954 total participants with at least one UDS assessment, with 8256 follow-up visits completed. These numbers are in addition to 3607 evaluations in the years prior to the establishment of the UDS in 2005.

The UK-ADRC research participants, reflecting high levels of motivation and engagement,[15] undergo deep phenotyping in addition to the UDS cognitive battery, including genetic profiles, *ante mortem* imaging and fluid biomarkers, and eventual brain autopsy as participants are followed to death with pre-arranged autopsy consent. Between January 2010 through October 2024, 91.6% (1492 of

TABLE 1 UK-ADRC community-based longitudinal cohort.

Last diagnosis	#	Age (years)	Education (years)	% Male	% Minority	% *APOE* ε4 (+)
Normal	485	78 ± 7.7	16.5 ± 2.4	27	15	22
MCI	127	80 ± 7.7	16.3 ± 3.2	46	29	31
Impaired	27	74 ± 7.8	16.0 ± 2.9	18	40	25
Demented	102	82 ± 8.1	16.9 ± 8.8	34	16	43
Total	741	79 ± 8.0	16.5 ± 4.0	31	19	27

Note: The UK-ADRC longitudinal cohort is recruited primarily from the community. As of October 2024, the active cohort includes 741 elderly participants (average age = 79). The cohort has 16.5 average years of education, are 31% male, 19% under-represented ethnic minority, and 27% having at least one *APOE* ε4 allele.
Abbreviations: *APOE*, apolipoprotein E; MCI, mild cognitive impairment; UK-ADRC, University of Kentucky Alzheimer's Disease Research Center.

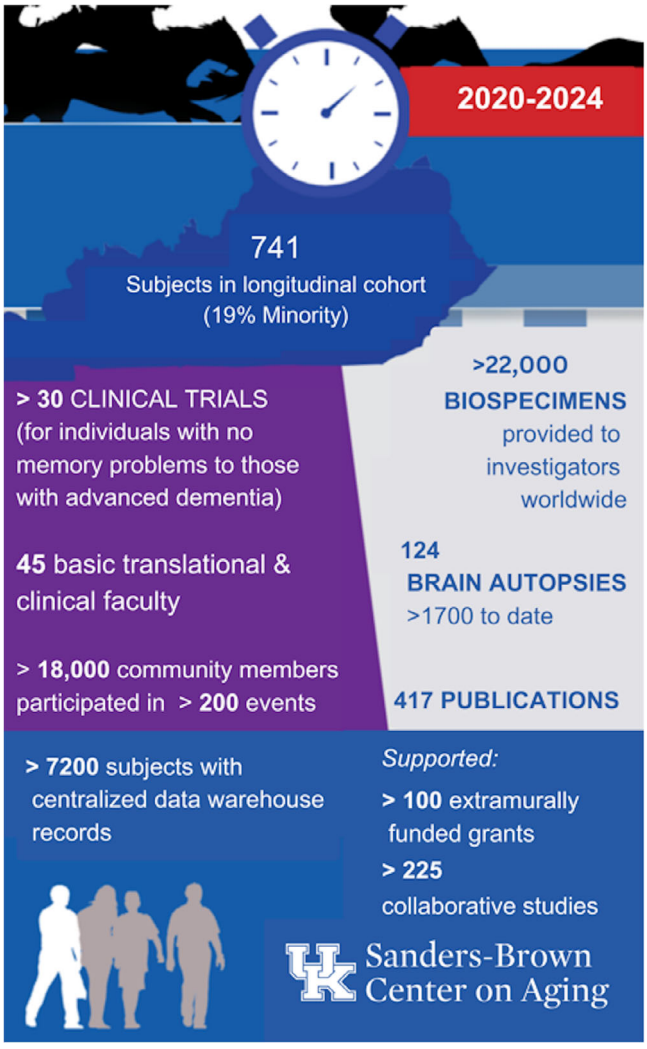


FIGURE 2 Infographic showing examples of how the University of Kentucky Alzheimer's Disease Research Center resources supported the scientific community from 2020 through February 2024.

1628) of participants consented to autopsy and 75.4% (402 of 533) of those who consented to autopsy and died were autopsied. With the maturity of the UK-ADRC cohort, an equilibrium has developed wherein the recruitment of cognitively intact participants is approximately offset by transitions, deaths, and attrition across all diagnostic groups (Figure 3). Therefore, we focus recruitment efforts on cognitively normal participants aged > 65 years to support the study of late-life pathologies such as AD neuropathologic change (ADNC), limbic predominant age-related TAR DNA-binding protein 43 (TDP-43) encephalopathy neuropathologic change (LATE-NC), Lewy body diseases (synucleinopathies), primary age-related tauopathy (PART), aging-related tau astrogliopathy (ARTAG), and vascular contributions to cognitive impairment and dementia (VCID), as well as multi-etiology dementia.[16–22] Figure 4 shows the growth in the number of cohort participants recruited as cognitively normal (Figure 4A) and the transitions to different cognitive states (Figure 4B).

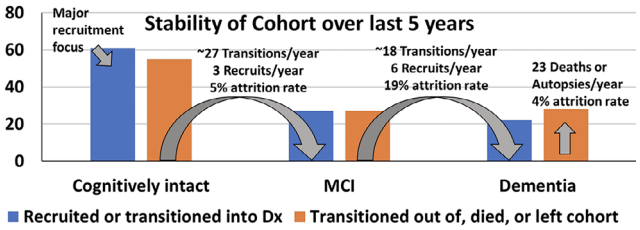
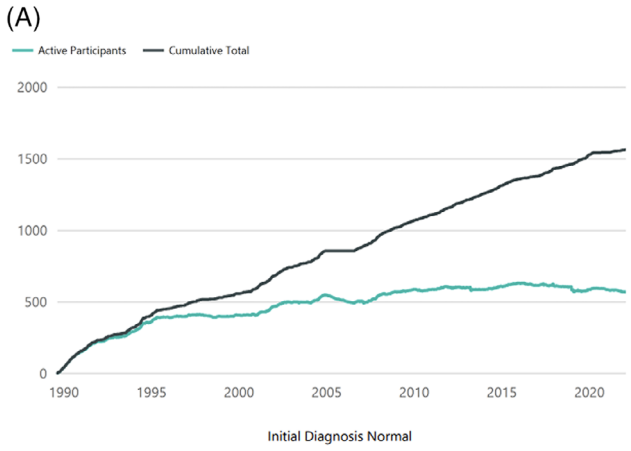


FIGURE 3 The University of Kentucky Alzheimer's Disease Research Center longitudinal cohort has developed an equilibrium wherein recruitment of cognitively intact participants is approximately offset by transitions, deaths, and attrition across all diagnostic groups. Therefore, the major recruitment focus for new cohort enrollees is on cognitively unimpaired participants. MCI, mild cognitive impairment.

UK-ADRC cohort participation is the result of years of community outreach focusing on healthy and disease-related brain aging. Information is disseminated through seminars provided to local and statewide organizations, an annual scientific and community multiple-day symposium that includes national speakers and topics based on community-suggested topics, community health fairs for older adults, regular print and electronic media presentations, quarterly care provider workshops, and a network of church leaders in the Black community. In addition, recruitment is often the result of word-of-mouth testimonials from research participants and their families as to the quality of service and care provided through the UK-ADRC Clinical Core. Retention efforts incorporate excellent clinical care and social work assistance, personalized communications that recognize important events in the lives of participants, town hall meetings, and newsletters describing



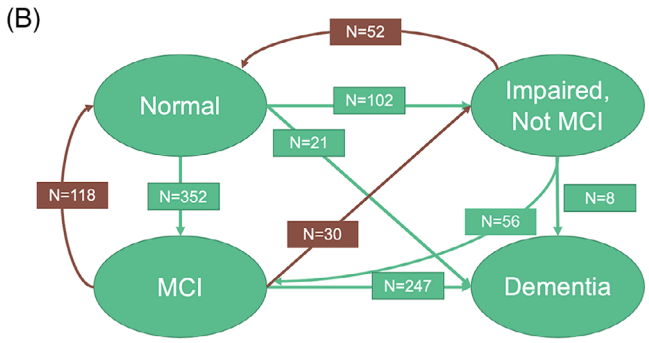


FIGURE 4 Growth of the University of Kentucky Alzheimer's Disease Research Center normal control cohort and transitions to different cognitive states. A, Active participants and cumulative total of participants enrolled in the longitudinal cohort without cognitive impairment. B, Numbers of cohort participants who transitioned to different cognitive states between 2005 and October 2024. MCI, mild cognitive impairment.

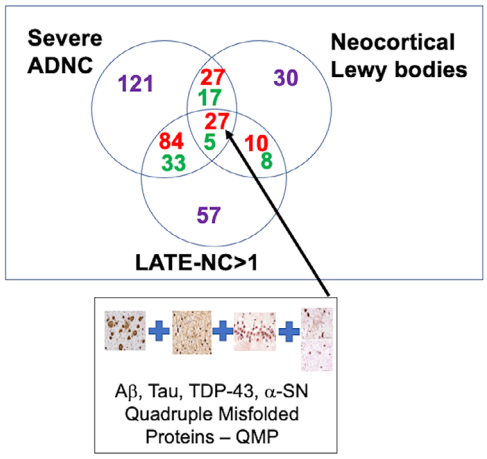


FIGURE 5 Depiction of UK-ADRC autopsy numbers by pathology. Key: Numbers in Purple represent "pure" pathology subtypes. Green reflects predicted numbers if co-pathologies occur at random. Red shows actual observed cases. α-syn, alpha-synuclein; Aβ, amyloid beta; ADNC, Alzheimer's disease neuropathologic change; LATE-NC, limbic predominant age-related TAR DNA-binding protein 43 encephalopathy neuropathologic change; QMP, quadruple misfolded proteins; TDP-43, TAR DNA-binding protein 43; UK, ADRC, University of Kentucky Alzheimer's Disease Research Center.

research advances associated with UK-ADRC involvement, as well as personalized feedback from research procedures, including *post mortem* reports for family members. Incorporated in these activities is information on the crucial importance of biomarkers, particularly brain donation, wherein the family is educated on the importance of autopsy, and participants share their desire to have their wishes granted upon their death.

3 | SCIENTIFIC ADVANCES SUPPORTED BY THE UK-ADRC

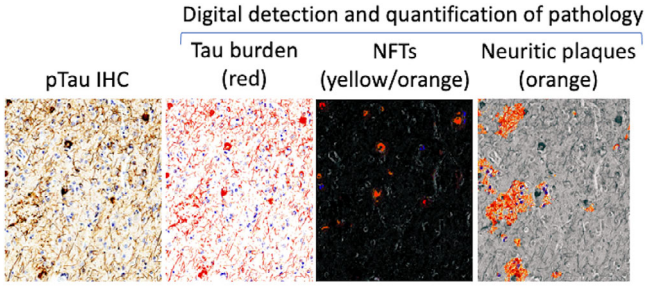
It is not possible to discuss all of the scientific advances enabled by UK-ADRC resources, but a few notable examples are discussed below.

3.1 | Quantitative/digital pathology and multi-etiology dementia

The UK-ADRC has a long-established strength in the research area of neurodegenerative disease neuropathology, stemming from the groundbreaking work of Dr. William Markesbery et al. that began in the 1970s. The UK-ADRC community-based cohort study design, in which many research volunteers were evaluated longitudinally with yearly clinic visits for up to 30 years prior to brain autopsy, has yielded a rich cross-section of neuropathologic outcomes. One contribution to the field by UK-ADRC was to help describe the complex but coherent basic relationships between classical ADNC hallmarks, that is, amyloid plaques and neurofibrillary tangles (NFTs), and cognitive impairment, based partially on observations from the UK-ADRC cohort.[23] The UK-ADRC also played a role in the NIA and Alzheimer's Association–sponsored consensus-based neuropathologic system for assessing the presence and severity of ADNC.[17]

A historic strength of the UK-ADRC is brain region–specific quantitative neuropathologic readouts. These were manually counted for more than two decades, until 2012 when digital scanning and machine learning provided a more rigorous assessment (and quantitation) of pathology.[24] At present, each UK-ADRC autopsy case is scanned into a virtual biobank and each autopsy report contains digitally determined quantification of pathology (see examples in Figures 5 and 6). Currently, a funded U24 grant is focusing on moving this field forward across different research centers; this grant is entitled "Federated digital pathology platform for AD/ADRD research and diagnostics" (NS133945).

Against this backdrop, it became quite clear that neuropathologic phenomena in addition to ADNC existed and are impactful in the sense of clinical–pathological correlation. For example, UK-ADRC researchers and others noticed that the brains of ≈ 20% of people, even nonagenarians and beyond, don't harbor amyloid beta (Aβ) plaques. However, every late-life brain eventually accumulates at least a modicum of NFTs in advanced age and, in cases with relatively dense NFTs,



Sample of pathologic readouts included in each autopsy report

Limbic	Aβ Amyloid Burden	Aβ Amyloid Plaque Density	NFT density	Neuritic plaque burden	Tau burden
Ento Cortex	n/a	n/a	94.7	99.3	95.9
CA1	30.5	35.4	147.2	183.4	145.4
Subiculum	17.3	25.2	72.6	128.6	133.3
Amygdala	n/a	n/a	105.5	106.8	94.7
Neocortex					
Frontal Area 9	103.8	119.0	57.1	80.3	184.8
Sup/med temp	121.0	102.6	78.3	234.4	212.3
Inf Parietal	80.9	98.3	16.3	71.3	97.2
Occipital	58.8	51.6	29.7	95.0	152.0
	Positive pixels/mm²/10⁴	Amyloid Plaques/mm²	NFTs/mm²	Positive pixels/mm²/10⁴	3+ pixels/mm²/10⁴

FIGURE 6 Example of digital detection and quantification of pathology in an autopsy report from a UK-ADRC longitudinal cohort participant. Aβ, amyloid beta; IHC, immunohistochemistry; NFT, neurofibrillary tangle; pTau, phosphorylated tau; UK, ADRC, University of Kentucky Alzheimer's Disease Research Center.

shows correlated cognitive loss.[25] Drawing from these observations, PART refers to an aging-associated pathologically defined entity with NFTs but without amyloid plaques.[18]

UK-ADRC work has also shown that in advanced age "mixed" brain pathologies are the rule and not the exception and contribute substantially to dementia. In fact, UK researchers reported[16] that the presence of four misfolded proteins (Aβ, tau, alpha-synuclein, and TDP-43) in the same brain is a relatively common feature in aging, seen in 20% of dementia diagnoses in our longitudinal cohort. This phenotype was termed quadruple misfolded proteins (QMP) and was shown to be associated with a swifter rate of late-life cognitive decline and more severe final dementia status compared to individuals with fewer brain pathologies.[16,26]

3.2 | LATE-NC: from genome-wide association study to clinical trial

A unique example of a UK-ADRC collaborative effort that spans the basic/translational/clinical research spectrum is the study of LATE-NC, which became a named entity in 2019.[20] LATE-NC is strongly associated with hippocampal sclerosis of aging (HS-A), which is in turn characterized by cell loss and gliosis in the hippocampal formation.[27] UK-ADRC investigators showed that HS-A is associated with cognitive impairment[28] and were awarded a Special Analysis Grant from the Alzheimer's Disease Genetics Consortium (ADGC) in late 2011 to uncover the genetic contributions to HS-A. This led to the first-ever genome-wide association study (GWAS) of HS-A, which found HS-A–associated variants in the *ABCC9* gene.[29] The GWAS results were later replicated.[30,31] Downstream analyses using the well-characterized UK-ADRC brain bank discovered relevant brain-expressed transcripts and mechanistic insights.[29] The *ABCC9* gene encodes the SUR2 protein, part of the "metabolic sensor" K_{ATP} channel. Importantly, SUR2 is pharmacologically targetable by the agonist nicorandil, a vasorelaxant drug used for congestive heart failure (although widely used internationally, nicorandil is not US Food and Drug Administration approved). These findings provided the mechanistic rationale for the first clinical trial for LATE/HS-A (NCT04120766), funded by the NIA (R01 AG061111), designed to test the safety of nicorandil in participants aged ≥ 75. Whereas LATE-NC and HS-A are definitively diagnosed only via brain autopsy, trial recruitment was focused on enriching for persons at risk for LATE/HS-A. The clinical trial stratification was thus biomarker based and enrolled individuals with a LATE-NC/HS-A "ATN" profile (neurodegeneration without amyloidosis) rather than an ADNC-associated profile (neurodegeneration with amyloidosis) with evidence for an amnestic clinical phenotype and at least moderate hippocampal atrophy on MRI. The inclusion/exclusion criteria developed for this clinical trial were developed at UK 7 years prior to the recent consensus criteria for LATE that was developed in 2024, yet the two criteria are virtually superimposable.[32]

3.3 | Genetics research related to brain pathologies

Since the discovery of *APOE* ε4 and its strong association with AD,[33] the search for genetic contributions to ADRD beyond the presenilins and amyloid precursor protein mutations has constituted an important area of research. UK-ADRC contributions of samples to the National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD) provide a crucial component of this avenue of research. For example, as of January 2025, UK has sent 1481 samples to NCRAD for DNA analysis and GWAS. Most of these DNA samples were from participants that were cognitively normal or MCI prior to death, with gold-standard autopsy confirmation as to their neuropathologies.

LATE-NC and other neuropathologically defined endophenotypes continue to be a focal point of genetics research at UK-ADRC. As examples, our recent studies analyzing genes implicated in risk for LATE-NC and HS-A found evidence that specific risk alleles can differentially affect LATE-NC and HS-A,[34] that the frequencies of the LATE risk-associated alleles are significantly different between persons of primarily African (versus European) ancestry,[31] and that examination of 11 separate neuropathology endophenotypes confirmed previous findings from clinically defined ADRD and also found novel ADRD-associated genetic variants.[35] We recently published a comprehensive review of LATE-NC and other co-pathologies seen in the aging brain and the risk genes associated with LATE-NC,[36] which provided new insights into pathogenetic mechanisms and their inter-relationships that contribute to clinical manifestations.

3.4 | Clinical research

We have a major focus on translation of our basic science discoveries into human studies as rapidly as possible. We support extensive pharmacologic and non-pharmacologic clinical trials ranging from investigator-initiated to ADRC network (e.g., Alzheimer's Disease Cooperative Study [ADCS], Alzheimer's Clinical Trials Consortium [ACTC], Alzheimer's Disease Neuroimaging Initiative [ADNI], Alzheimer's Therapeutic Research Institute [ATRI], Alzheimer Prevention Trials, Standardized Centralized Alzheimer's and Related Dementias Neuroimaging Initiative [SCAN], ADRC Consortium for Clarity in ADRD Research Through Imaging [CLARiTI], NACC, and NCRAD), to industry, and to community-based participatory studies. For example, of the 999 participants at UK enrolled in clinical or biomarker trials that were active for the year between March 2023 to February 2024, 424 are also ADRC participants (42%). Our clinical studies recruit individuals at different stages along the cognitive continuum, providing extensive opportunities to engage research participants who range from cognitively unimpaired to those with severe dementia. Participant engagement, neuroimaging, and biofluids from 512 ADRC volunteers further supported 11 research grants in February 2024. Because of our track record of performing numerous AD clinical trials over the last decade, ranging from observational to prevention to intervention studies, investigators from the UK-ADRC participated in the development of consensus guidance for both protocol development and conduct of high-quality AD clinical trials[37] as well as for decentralized clinical trials.[38] These guidance documents represent international efforts focused on advancing clinical research ethically and rigorously as we move closer toward pragmatic and decentralized clinical trials. We also have published articles about the new Aβ immunotherapy drugs,[39,40] with the goals of providing perspectives needed to propel clinical interventional research forward. We closely track participant enrollment across studies, thus allowing us to include or exclude participants from particular analyses if necessary. We are currently collecting samples from, and other data related to, ADRC participants on anti-Aβ therapy treatments, and will be able to both study treatment effects and control for them in our subsequent analyses.

3.5 | ADRD risk factor research

The UK-ADRC has supported research that has contributed significantly to understanding the roles and impacts of risk factors on the onset and progression of disease. A few examples include: the study of aging and dementia in an adult Down syndrome cohort;[41] mechanisms and contributions of VCID to disease progression and diagnosis, including participation in Mark-VCID and Diverse-VCID consortia;[42–44] the influence of self-reported memory complaints;[45] diabetes and risk of cardiovascular pathology;[46] and the impact of lifestyle interventions such as exercise, diet, music, and sensory modalities.[47,48]

Several collaborative studies of neuroinflammatory pathways and metabolic dysfunction as ADRD risk factors are supported by UK-ADRC resources. Some examples include: a program project grant (P01 AG078116) addressing the (patho)physiological roles of reactive astrocytes in ADRD;[49–52] astrocyte inflammatory signaling and exosomes;[53] a first-in-patient clinical trial in intracerebral hemorrhage (NCT05020535) of a novel anti-neuroinflammatory small molecule drug candidate;[54] blood–brain barrier leakage mechanisms;[55] neuroinflammation, metabolic changes, and *APOE* genotype;[56–58] and exploration of genetic risk factors associated with inflammatory signaling, such as *TREM2*, *CD33*, and *INPP5D*.[59–62]

3.6 | Neuroimaging and fluid biomarkers

The UK-ADRC supports a growing number of research studies on ADRD biomarkers, especially neuroimaging and fluid biomarkers. Efforts around MRI biomarkers include an emphasis on multiple pathologies that contribute to cognitive decline in aging. This includes multiple neuroimaging measures of cerebral small vessel disease, including the impact of cerebrovascular reactivity, enlarged perivascular spaces, white matter hyperintensities (WMHs), and MRI diffusion metrics on cognitive function.[63–65] Recently, we have shown that increased brain iron negatively impacts cognitive functions and is associated with lower functional connectivity and structural connectivity of white matter tracts.[66,67]

A goal of our Biomarker Core (BMC) is to validate our non-invasive MRI/biofluid metrics against CSF markers and/or neuropathology. In an early study, we linked an MRI measure of water exchange across the blood–brain barrier (BBB k_w) with CSF levels of Aβ42, suggesting that this non-invasive MRI metric could be indexing Aβ clearance functions.[68] Another early study showed an association between blood-based biomarkers of Aβ42/Aβ40 and phosphorylated tau181 with neuropathology.[69] Other research explores novel fluid biomarker development, including post-translational modifications (citrullination and arginine moieties), exosome microRNAs, and various -omics profiles.

In response to the increased need of UK investigators for neuroimaging results (Figure 1), the BMC has developed a pipeline for generation and dissemination of user-friendly MRI summary measure results. These results are shared with our Data Management and Statistics Core, where they become available to other investigators. This allows other investigators, both at UK and at other institutions, to integrate neuroimaging results into their analyses. Current summary measures include volumetrics, cerebral perfusion, and brain iron concentrations in a common set of gray matter regions of interest (ROIs). We also generate and disseminate summary results of WMH volumes in deep and periventricular regions and diffusion MRI metrics in ROIs representing a broad range of tracts of relevance to ADRD.

At present, MRI summary measures are available from 241 deeply phenotyped participants enrolled in the UK-ADRC longitudinal cohort. The participants have been scanned as part of our annual MRI battery, SCAN or VCID (for whom additional MRI measures of cerebrovascular reactivity and enlarged perivascular space counts are available). The majority of participants have been scanned at multiple timepoints (ranging from 1–4 annual scans), resulting in a total of 446 datasets of

available summary measures. At the time of their baseline scan, participants with MRI summary measures (63% female) had an average age of 74.5 years old (standard deviation [SD] = 7.5) and an average education level of 16.8 years (SD = 5.9). A more select set of summary measures have also been computed for 199 UK-ADRC participants involved in clinical trials (such as our previous gemfibrozil trial and our current SMART-HS trial), which may be made available to investigators in consultation with the UK-ADRC Clinical Core.

4 | EDUCATION, OUTREACH, AND COMMUNITY PARTNERSHIPS

4.1 | Education and training programs

The UK-ADRC supports numerous educational programs and training opportunities. A few examples are listed below. The TRIAD (Translational Research in Alzheimer's and Related Dementias) T32 grant AG078110 continues to provide predoctoral and postdoctoral trainees with cross-disciplinary training from bench to bedside to produce a new translational workforce that is critically needed to advance effective discoveries and treatments for AD/ADRD. This T32 provides a pathway to our Research Education Component Scholar program that supports early career faculty. With support from the UK Department of Neurology, a geriatric neurology fellowship has been launched in the past 2 years. Here, trainees engage in clinical and research activities involving patient consultation and care for persons with cerebrovascular disease, movement disorders, and dementia.

In conjunction with the Office of the Inspector General of Kentucky as well as Kentucky Tele-care and CECentral, we have developed an enduring tele-network and web-based video training series[70] for Certified Nursing Facility Staff to meet a critical need for health professional training focused on care for residents with dementia. The series is broadcast throughout certified nursing facilities nationally at the request of the Centers for Medicare and Medicaid Services. With philanthropic support, we have recently developed a web-based "Brain Boost" and "BrainHealth 101" activities programming series[71] designed for those with cognitive impairment and their caregivers. Release through the National Institutes of Health Alzheimer's Disease Outreach, Recruitment, and Engagement website[72] is increasing the reach of this programming.

4.2 | Outreach and community partnerships

The UK-ADRC has had a long-standing partnership with the Kentucky Black and African American community, the largest under-represented minority (URM) group in Kentucky. Currently, UK-ADRC has 741 active cohort members, and 19% of the cohort comprises Black and African American volunteers (Table 1). This proportion remains well above the demographics for the local catchment area for adults > 65 years, where Black and African Americans comprise ≈ 6% of the population. These outreach efforts focus not only on education and research recruitment strategies but also on the needs of the community we serve. We have developed relevant products such as a recipe calendar, flyers, brochures, health pocket guides, toolkits, and the popular "Book of Alzheimer's for African American Churches." These materials have been used extensively by many organizations to build community relationships and encourage research participation. Other examples of URM-related initiatives/partnerships include: (1) establishment of Louisville clinics within our partner churches to engage participants within their local community; (2) a multi-center proposal with the Maya Angelou Center for Health Equity at Wake Forest University geared toward ADRD outreach and collaborations with researchers at historically Black colleges and universities; (3) continued partnership with The Balm in Gilead (a faith-based organization working to reduce health disparities for African Americans) through our "Memory Sunday" and "Healthy Churches of Kentucky" programs; (4) Emory University and the Alter Program's faith-based program that aims to give churches and faith leaders of predominately African American churches the resources and tools they need to ensure members affected by dementia are welcomed, supported, and accepted; (5) a collaboration with the Massachusetts ADRC to further develop our Memory Sunday approach for their URM recruitment efforts; (6) collaborations with "Dementia Friendly Lexington", our local government-sponsored training and information network; and (7) the "No One Left Behind" project (ACTC funded) collaborating with the ADRC supported Vascular Cognitive Impairment studies outreach to local URM organizations.

Many of these community outreach programs and educational materials were made possible because of generous support from the Commonwealth of Kentucky, the UK Vice President for Research, UK Healthcare and the College of Medicine, and philanthropic gifts. These other funding sources have enabled us to leverage ADRC funding to create programming and establish enduring partnerships and programs with the community.

5 | HIGHLY COLLABORATIVE, TEAM SCIENCE

A defining characteristic of the UK-ADRC and the broader Sanders-Brown Center on Aging is our extremely integrated and interactive nature. Collaborations and team science are valued. Our faculty network is extensive and involves collaborations across the university, nation, and the world. For example, Figure 7A shows a bibliometric network diagram documenting the large number of shared publications among 43 Center researchers. Of 816 publications from 2019 through September 2024, 98% involved institutional, national, or international collaborations (Figure 7B), with only 14 publications (1.7%) with no collaborators.

In addition to collaborative publications and grants, as mentioned earlier, UK-ADRC researchers participate in and support NIA/National Institute of Neurological Disorders and Stroke large initiatives such as ACTC, ADCS, ATRI, ADNI, ADGC, NCRAD, SCAN, CLARiTI, Alzheimer Biomarker Consortium–Down Syndrome, MarkVCID, and Diverse-VCID. Center personnel serve in leadership roles in the national ADRC

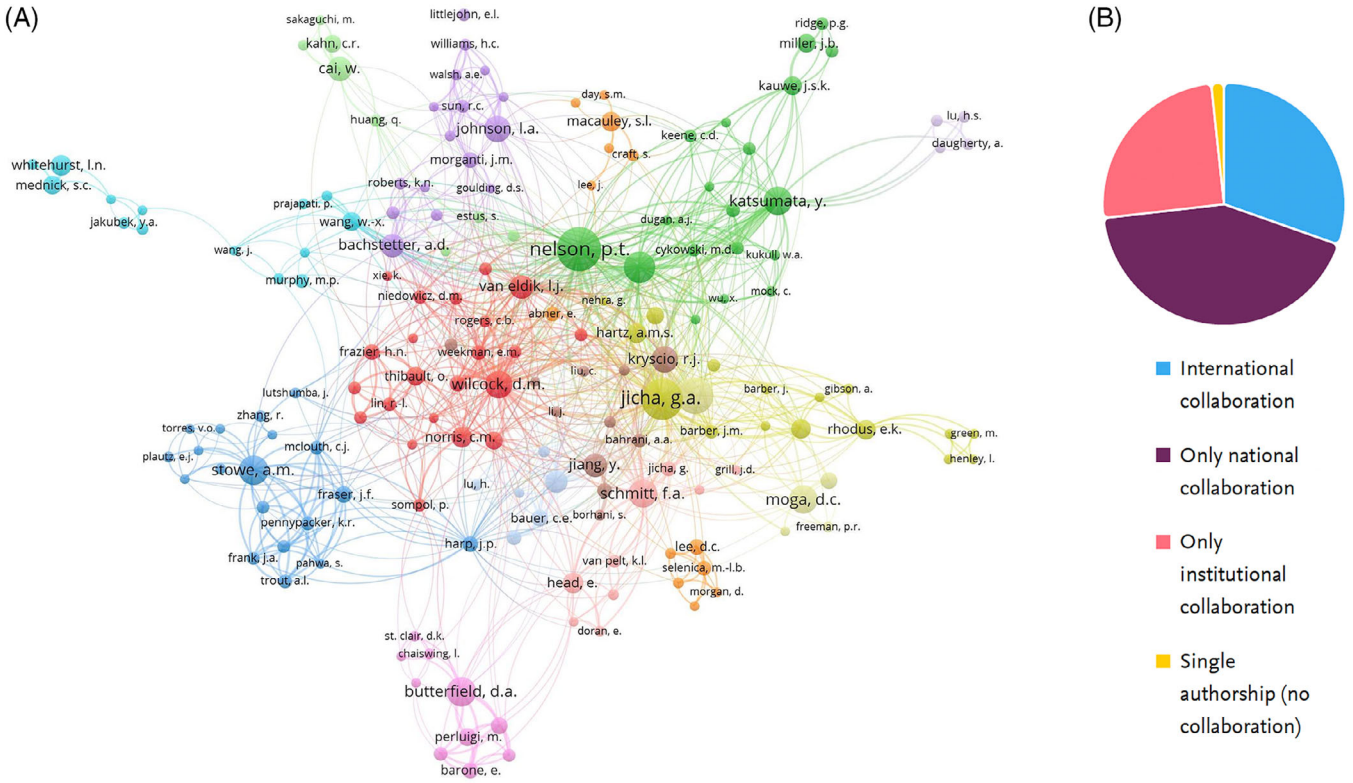


FIGURE 7 Bibliometric network diagram (A) and pie chart (B) depicting the extensive interactions and collaborative publications among 43 researchers within the UK-ADRC and the Sanders-Brown Center on Aging. Of 816 publications from 2019 through September 2024, 30.4%, 42.8%, and 25.1% involved international, national, or institutional collaborations, respectively. Only 14 publications (1.7%) had a single authorship (no collaboration). UK, ADRC, University of Kentucky Alzheimer's Disease Research Center.

network, including ADRC External Advisory Committees, national task forces, and other national steering committees and working groups.

6 | CONCLUSIONS

This paper provides a perspective on an established, long-standing ADRC where contributions from motivated older adult volunteers have resulted in advancing the understanding of brain aging from successful cerebral aging to newly -identified neuropathological entities. These contributions to science have revealed novel avenues for basic translational research and potential targets for future clinical interventions, especially in the area of multi-etiology dementia. More work and discoveries will certainly emerge from the UK-ADRC and other ADRCs as the field continues to tackle the complexities of risk factors, genetics, underlying mechanisms, and biological signals leading to ADRD. These efforts will continue to move the field forward in the development of therapies that maximize positive outcomes for the aging brain.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All human subjects provided informed consent.

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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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