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REVIEW ARTICLE

The Common Alzheimer's Disease Research Ontology (CADRO) for biomarker categorization

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Abstract

Biomarkers are vital to Alzheimer's disease (AD) drug development and clinical trials, and will have an increasing role in clinical care. In this narrative review, we demonstrate the use of the National Institutes on Aging/Alzheimer's Association (NIA/AA) Common Alzheimer's Disease Research Ontology (CADRO) system for the categorization of biomarkers based on the primary mechanism on which they report. We show that biomarkers are available (in various levels of validation) for all CADRO processes. Application of the CADRO system demonstrates gaps in the field where novel biomarkers are needed for specific aspects of the disease, and assays to detect and measure biological changes, in individuals with symptomatic or preclinical AD. We demonstrate the CADRO system as a means of categorizing established and candidate AD biomarkers, showing the feasibility and practicality of the system. CADRO can assist with biomarker selection for AD clinical trials and drug development, and may eventually be applied to implementing biomarkers in patient care.

KEYWORDS
Alzheimer's disease, biomarkers, clinical trial, Common Alzheimer's Disease Research Ontology, drug development

Highlights

- The Common Alzheimer's Disease Research Ontology (CADRO) system can be used to categorize biomarkers for drug development.
- We demonstrate the use of CADRO with Alzheimer's disease (AD) biomarkers.
- We identified AD biomarkers in each of the CADRO categories.
- CADRO can be incorporated into current AD drug development and clinical trial systems.

1 | INTRODUCTION

Alzheimer's disease (AD) dementia affects ≈57.4 million individuals globally, with numbers continuing to rise to an estimated 152.8 million by 2050.[1] AD pathologies begin in the brain up to two decades before the onset of clinical symptoms, supporting the plausibility of early detection and intervention in the disease.[2,3] There are currently three disease-modifying therapies (DMTs) approved by the U.S. Food and Drug Administration (FDA; aducanumab, lecanemab, and donanemab), all anti-amyloid monoclonal antibodies (mAbs) used for the treatment

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of early AD.[4] Biomarkers have become increasingly important to clinical trials and drug development and were critical to the approval of these new therapies. Biomarkers will also assist in the development of therapies that may be used clinically in combination with or instead of mAbs.[5]

The FDA requires that when biomarkers are used as drug development tools (DDTs) in a clinical trial, the biomarker has a well-defined context of use (COU). The COU is a concise description of the biomarker's specified use in drug development.[6,7] The role of the biomarker will be categorized using the FDA/National Institutes of Health (NIH) Biomarker Working Group Biomarkers, Endpoints, and other Tools (BEST) classification. This system categorizes biomarkers as indicators for risk/susceptibility, diagnosis, monitoring, pharmacodynamic/response, predictive, prognostic, or safety. To choose a biomarker for a COU in drug development, the biological process on which the drug reports must be known.

Canonical biomarkers of amyloid beta (Aβ) and tau protein have been used extensively to inform clinical trials. They are embedded in the amyloid/tau/neurodegeneration (A/T/N) framework for the diagnosis and staging of AD.[8,9] Seventy-five percent of drugs currently in the AD drug development pipeline do not target canonical amyloid and tau pathways, and biomarkers representing a larger array of mechanisms are needed.[10,11] The Common Alzheimer's Disease Research Ontology (CADRO) classification system, developed by the NIA and Alzheimer's Association (NIA/AA) collaboration of the International Alzheimer's and Related Dementia Research Portfolio (IADRP), was developed to organize and compare basic, translational, and clinical AD/ADRD (Alzheimer's disease and related dementias) research projects across multiple funding organizations using a common terminology (Figure 1).[12] Published in 2012, CADRO was designed to aid in the evaluation of public and private investments across the AD landscape, identifying redundancies and gaps; inform future decisions in investment; and identify potential collaborations around AD research.[12] The CADRO system offers a methodology to catalog the primary mechanisms involved in AD as a means of classifying targets for drug development.[5] Integration of CADRO with FDA BEST and COU practices allows researchers to choose biomarkers needed to advance drug development and clinical trials. Here we demonstrate the feasibility of implementing CADRO to classify candidate biomarkers and their potential COU.

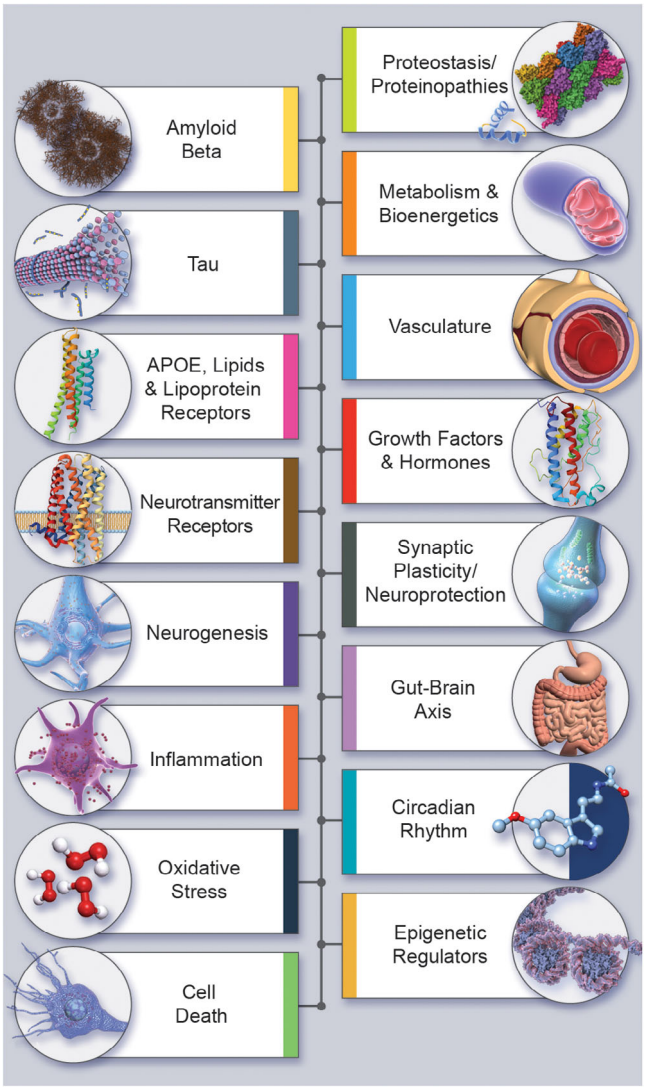

FIGURE 1 The Common Alzheimer's and Related Dementias Research Ontology (CADRO) categorization system (*© J Cummings; M de la Flor, PhD, illustrator*).

2 | METHODS

The aim of this narrative review is to demonstrate how established and candidate biomarkers for AD can be categorized using the CADRO system. The biomarkers and references chosen were identified through databases using search terms including "biomarkers for Alzheimer's disease," biomarkers for each CADRO category, and related words and phrases. Our goal is not to provide an exhaustive review of the biomarkers, but rather to demonstrate how existing biomarkers can be organized according to CADRO categories. The biomarkers were categorized manually using the CADRO classification as available on the IADRP website and defined in Figure 2.[13]

In this perspective, we focus on neuroimaging and biofluids. Digital biomarkers were not included in our searches. The markers described can be used for predicting, diagnosing, monitoring, prognosticating, and determining treatment eligibility; markers derived at postmortem examination are not included. There is extensive information regarding genetic risk factors for AD; these trait markers are described elsewhere.[14] There is an emerging area of environmental biomarkers in which robust biomarkers have not yet emerged; we excluded these from our review and anticipate that they will be added in the future. Several viral infections have been implicated as risks for developing AD; this body of information is evolving, and specific biomarkers associated with viral infections in AD have not been identified. These infections are not included in the review.

IADRP Definition for CADRO Category C: Translational Research and Clinical Interventions (for Early-stage Clinical Drug Development (Phase I and Phase II Clinical Trials))

"*This category aims to capture projects focused on the identification, validation, and development of potential targets (including small molecule, natural products, and biologics) for AD and Related Dementias (ADRDs) from early therapeutic discovery through late-stage preclinical development and all stages of clinical testing. Also, included are projects focused on repurposing pharmacological agents already in use for other conditions as well as non-pharmacological interventions*" [12].

Website: https://iadrp.nia.nih.gov/about/cadro

FIGURE 2 International Alzheimer's and Related Dementia Research Portfolio (IADRP) definition for Common Alzheimer's Disease Research Ontology (CADRO) Category C: Translational Research and Clinical Interventions (for Early-stage Clinical Drug Development (Phase I and Phase II Clinical Trials).

3 | CADRO system and biomarkers

Several established and candidate biomarkers for AD have been identified in each of the CADRO categories and presented in Table 1. Details regarding AD imaging biomarkers are provided in Table 2. A subset of biomarkers is discussed in the following sections to demonstrate the use of the CADRO system to assist with biomarker selection for AD clinical trials and drug development research, and in future implementation of biomarkers in clinical practice.

3.1 | Amyloid beta

AD is defined by the presence of Aβ pathology, and biomarkers for Aβ are central to the diagnosis of the disease. Advances in positron emission tomography (PET) neuroimaging now allow clinicians to determine the presence, abundance, and location of Aβ pathology in the brain. In clinical trials on mAbs, Aβ imaging is used as a diagnostic biomarker of disease presence and a pharmacodynamic marker of effectiveness of therapies. Pittsburgh compound B (PiB) was the first amyloid radiotracer developed for human use.[171,172] Currently, the fluorinated radiotracers florbetapir, flutemetamol, and florbetaben are approved ligands for amyloid PET, receiving FDA approval in 2012, 2013, and 2014, respectively.[173] The quantitative evaluation of Aβ via PET uses standardized uptake value ratios (SUVRs) or centiloids for measurement standardization. Visually read as Aβ-positive or Aβ-negative, SUVR or Centiloid threshold values can be used to qualify patients for clinical trials. In clinical trials using mAbs, when a threshold of 15–25 Centiloids is achieved, there is a corresponding slowing of cognitive and functional decline.[174] Trials that were unsuccessful in reaching that threshold did not show cognitive benefit.[174]

Fluid biomarkers for Aβ are commonly used as eligibility criteria or outcome measures in clinical trials. Levels of Aβ42 and the Aβ42/40 ratio in cerebrospinal fluid (CSF) and blood have demonstrated validity, accuracy, sensitivity, and specificity. Aβ40 and Aβ42 are amyloid isoforms. In patients with AD, Aβ40 is the primary isoform present in the brain; Aβ plaques have elevated levels of Aβ42.[175,176] A lower concentration of Aβ42, or ratio of Aβ42/40, in CSF and blood is associated with higher levels of Aβ plaques in the brain.[15,16]

Soluble forms of tau measured in CSF and blood relate more to the onset and progression of Aβ pathology than insoluble forms of tau observed via PET (described in 3.2). In the Revised Framework Criteria for the Diagnosis and Staging of AD, tau biomarkers are categorized as T1 and T2; T1 biomarkers consist of phosphorylated and secreted tau related to Aβ pathology, whereas T2 represents AD tau proteinopathy.[9] Herein we discuss the T1 biomarkers and their relationship with Aβ, including candidate markers phosphorylated tau-181 (p-tau181), p-tau217, and p-tau231.[34,177]

Investigations into T1 biomarkers are providing insight into the accuracy and timing of Aβ pathology. CSF p-tau217 has a higher correlation with Aβ-PET when compared to p-tau181, more accurately distinguishing AD dementia from non-AD dementia patients.[35] Furthermore, investigations into CSF p-tau231 revealed earlier sensitivity to detect Aβ in specific brain regions, compared to p-tau181 and p-tau217, prior to global Aβ-PET positivity.[178] Studies have shown that p-tau231 has the ability to discriminate stages of AD, with higher concentrations through the disease progression; however, p-tau217 demonstrates greater dynamic change, with greater increases in AD patients compared to p-tau231 and p-tau181.[178,179] Additional p-tau epitopes are being investigated in CSF, including p-tau202, 205, 299, 354, and 368, as independent measures, or in combination with total tau (t-tau) or Aβ as a ratio.[180,181]

The need for accessible, affordable, and less invasive biomarkers for patients and researchers has spurred investigations into blood-based biomarkers for soluble tau. As in CSF, p-tau181, p-tau217, and p-tau231 have been the most investigated tau targets in blood, demonstrating positive relationships with Aβ and tau pathologies. In preclinical AD patients, plasma p-tau217 and p-tau231 have a pos-

TABLE 1 Established and candidate biomarkers organized by CADRO classification (made with BioRender).

CADRO category	Biomarker	Abbr.	Marker type	References
Amyloid beta (Aβ)	Aβ42/40 ratio	Aβ42/40		[15, 16]
	Amyloid-related imaging abnormalities	ARIA		[4, 17]
	Beta-site amyloid precursor protein cleaving enzyme 1	BACE1		[18, 19]
	Stable isotope labeling kinetics	SILK		[20, 21]
	Standardized uptake value ratio/Centiloids	SUVR/CL		[17, 22]
	Soluble amyloid precursor protein	sAPP		[23, 24]
	Oligomeric Aβ	oAβ		[25]
Tau	Brain-derived tau			[26]
	Dual specificity tyrosine-phosphorylation-regulated kinase 1A	DYRK1A		[27]
	Microtubule binding region	MTBR		[28]
	N-terminal containing tau fragments	NTA-tau		[29]
	Phosphorylated tau-181	p-tau 181		[30, 31, 32]
	Phosphorylated tau-205	p-tau 205		[33]
	Phosphorylated tau-217	p-tau 217		[34, 35]
	Phosphorylated tau-231	p-tau 231		[34]
	Standardized uptake value ratio	SUVR		[36, 37, 38]
***APOE*, lipids, and lipoprotein receptors**	Apolipoprotein A1	ApoA1		[39, 40]
	Apolipoprotein C3	ApoC3		[41]
	Fatty acid-binding protein 3	FABP3		[42]
	Myelin			[43, 44]

(Continues)

TABLE 1 (Continued)

CADRO category	Biomarker	Abbr.	Marker type	References
Neurotransmitter receptors	Acetylcholinesterase	AChE		[45, 46, 47]
	Nicotinic acetylcholine receptors	nAChRs		[48, 49]
	Serotonin transporters	SERT		[50]
	Serotonin 1A receptors	5-HT1A		[51]
	Serotonin 2A receptors	5-HT2A		[52, 53]
	Sigma 1 receptor			[54]
	Vesicular acetylcholine transporters	VAChT		[55]
Neurogenesis	Brain volume			[11]
Inflammation	Alpha-1-antichymotrypsin	AACT		[56, 57]
	Alpha-1-antitrypsin	AAT		[57]
	Alpha-2 macroglobulin	α2M		[58]
	CC chemokine ligand 23	CCL23		[59]
	Ceramide (sphingolipid metabolism)			[60]
	Chitinase 3-like 1	YKL-40 /CHI3L1		[61, 62]
	C-reactive protein	CRP		[63]
	Cyclooxygenases	COX-1/2		[64]
	C4b-binding protein alpha chain	C4BPα		[56]
	Ferritin			[65]
	Fractalkine	CX3CL1		[66]
	Glial fibrillary acidic protein	GFAP		[67, 68]

(Continues)

TABLE 1 (Continued)

CADRO category	Biomarker	Abbr.	Marker type	References
	Intercellular adhesion molecule 1	ICAM-1		[69]
	Interleukin 1 beta	IL-1β		[70]
	Interleukin 6	IL-6		[57, 70, 71]
	Interleukin 8	IL-8		[72]
	Interleukin 10	IL-10		[73]
	Interleukin 12/interleukin 23 p40 subunit	IL-12/23p40		[73]
	Lipopolysaccharides	LPS		[64]
	Monocyte chemoattractant protein 1	MCP-1		[57, 74]
	Myostatin			[75]
	Oxidized low-density lipoprotein	oxLDL		[57]
	Regulated upon activation, normal T cell expressed and presumably secreted	RANTES		[76]
	SerpinA1			[77]
	Siglec-3	CD33		[78]
	Translocator protein	TSPO		[79]
	Triggering receptor expressed on myeloid cells 2	TREM2		[80, 81, 82]
	Tumor necrosis factor alpha	TNF-α		[83, 84]
	Tumor necrosis factor-related apoptosis-inducing ligand	TRAIL		[85]
Oxidative stress	Cooper			[72]
	Glucose-6-phosphate dehydrogenase	G6PD		[86]
	Isoaspartate	isoAsp		[87]
	Sirtuin	SIRT		[88]

(Continues)

TABLE 1 (Continued)

CADRO category	Biomarker	Abbr.	Marker type	References
	Unfolded p53			[89, 90]
	Uric acid			[91]
Cell death	Alzheimer-associated neuronal thread protein	AD7c-NTP		[92]
	Brain volume and cortical thickness			[82, 93]
	Formic acid			[94]
	Neurofilament light	NfL		[95, 96]
	Neuron-specific enolase	NSE		[97]
	Total tau	t-tau		[98, 99, 100]
	Visinin-like protein 1	VILIP-1		[101]
Proteostasis/proteinopathies	Alpha-synuclein	α-Syn		[102]
Metabolism and bioenergetics	Beta-alanine			[103]
	Clusterin			[104]
	D-serine level and D-/total serine ratio			[105]
	Fludeoxyglucose (glucose metabolism)	FDG-PET		[106, 107, 108]
	Glycogen synthase kinase-3 beta	GSK-3β		[109]
	Kynurenic acid			[110]
	Mitochondrial complex 1	MC1		[54, 111]
	P3-alcadein α	p3-Alcα		[112]
Vasculature	Albumin			[113]
	Arterial spin labelling	ASL		[114]
	Cerebrovascular carbon dioxide reactivity	CVR CO2		[115]
	Fibrinogen	FGN		[116, 117]

(Continues)

TABLE 1 (Continued)

CADRO category	Biomarker	Abbr.	Marker type	References
	Matrix metalloproteinase-9	MMP-9		[118, 119]
	Placental growth factor	PlGF		[120, 121]
	Platelet-derived growth factor receptor beta	PDGFRβ		[122]
	Vascular cell adhesion molecule 1	VCAM-1		[123]
	Water extraction with phase contrast arterial spin tagging	WEPCAST		[124]
Growth factors and hormones	Brain-derived neurotrophic factor	BDNF		[125, 126]
	Follicle-stimulating hormone	FSH		[127]
	Irisin			[125]
	Luteinizing hormone	LH		[127]
	Nerve growth factor	NGF		[128]
	Secretogranin-2			[129]
	Sex hormone-binding protein	SHBG		[130]
	Testosterone			[131]
	Thyroid hormone	TH		[132]
	Urinary free cortisol and creatinine ratio	UFC/Cr		[133]
	VGF nerve growth factor	VGF		[129]
Synaptic plasticity/neuroprotection	Electrical activity/brain signal alterations			[134]
	Blood oxygen level–dependent signal	BOLD		[135, 136]
	Event-related potential	ERP		[137, 138]
	Evoked potentials (somatosensory, brainstem auditory, visual, auditory event-related)			[139]
	Functional network connectivity			[140]
	Fluorodeoxyglucose PET	FDG		[141, 142, 143]

(Continues)

TABLE 1 (Continued)

CADRO category	Biomarker	Abbr.	Marker type	References
	Growth associated protein 43	GAP-43		[144, 145]
	Metabotropic glutamate receptor subtype 5	mGluR5		[146]
	Neural oscillations			[147]
	Neuregulin 1	NRG1		[148]
	Neurogranin	NRGN		[145, 149]
	Neuronal pentraxin receptor	NPTXR		[150]
	Synaptic vesicle glycoprotein 2A	SV2A		[151]
	Synaptosomal-associated protein 25	SNAP-25		[145, 152]
	Synaptotagmin-1	SYT1		[145]
Gut–brain axis	Branched-chain amino acids (valine, leucine, isoleucine)	BCAA		[153]
	Calprotectin			[154]
	Lithocholic acid (bile acids)	LCA		[155]
	Microbiome composition			[156, 157]
	Short chain fatty acids	SCFAs		[158, 159]
	Zonulin			[160]
Circadian rhythm	Orexin			[161]
	Sleep patterns			[162]
	Wake/sleep cortical activity			[163]
Multi-target	Allostatic load			[164]
	Phosphorylated tau-181/amyloid beta 42 ratio	p-tau181/Aβ42		[165]
	Phosphorylated tau-368/total tau ratio	p-tau368/t-tau		[166]
	Salivary proteomics			[167]
	Total tau/amyloid beta 42 ratio	t-tau/Aβ		[32]
Other	Sclerostin			[168]

Abbreviations: Abbr., abbreviation; *APOE*, apolipoprotein E; , imaging/device biomarker; , CSF biomarker; , blood-based biomarker; , other.

TABLE 2 Neuroimaging biomarkers by CADRO classification.

CADRO category	Outcome measure	Abbr.	Biomarker	Ligand	References
Amyloid beta	Amyloid-related imaging abnormalities	ARIA	MRI		[4, 17]
	Standardized uptake value ratio/Centiloids	SUVR/CL	PET	florbetaben; florbetapir; flutemetamol; Pittsburgh compound B	[17, 22]
Tau	Standardized uptake value ratio	SUVR	PET	18F-flortaucipir; [F18]-T808; 18F-MK6240;	[36, 37, 38]
***APOE*, lipids, and lipoprotein receptors**	Myelin		PET; MRI	^{18}F-florbetapir	[43, 44]
Neurotransmitter receptors	Acetylcholinesterase	AChE	PET	[^{11}C]MP4A	[46]
	Nicotinic acetylcholine receptor	nAChRs	PET	^{18}F-ASEM; ^{11}C-(R)-MeQAA	[48, 49]
	Serotonin transporters	SERT	PET	(11)C-DASB	[50]
	Serotonin 1A receptors	5-HT1A	PET	[^{11}C]WAY100635	[51]
	Serotonin 2A receptors	5-HT2A	PET	[^{18}F]altanserin	[52, 53]
	Sigma 1 receptor	σ1R	PET	[^{11}C]SA4503	[54]
	Vesicular acetylcholine transporters	VAChT	PET	^{18}F-FEOBV	[55]
Neurogenesis	Brain volume and cortical thickness		MRI		[11]
Inflammation	Ferritin		MRI		[65]
	Translocator protein	TSPO	PET	[18F]GE-180; [11C]PK11195	[79, 169]
Cell death	Brain volume and cortical thickness		MRI		[82, 93]
Metabolism and bioenergetics	Glucose metabolism		PET	[18F]FDG	[106, 107, 108]
	Mitochondrial complex 1	MC1	PET	[^{18}F]BCPP-EF	[54, 111]
Vasculature	Blood-brain barrier		MRI	Water extraction with phase contrast arterial spin tagging (WEPCAST)	[124]
	Cerebral blood flow		MRI	Arterial spin labelling (ASL)	[114]
	Cerebrovascular carbon dioxide reactivity	CVR CO_2	MRI		[114]
Synaptic plasticity/neuroprotection	Blood oxygen		fMRI	Blood oxygen level-dependent signal (BOLD)	[135, 136]
	Electrical activity/brain signal alterations; Event-related potential		EEG		[134]
	Event-related potential		EEG/ERP		[137, 138]
	Evoked potentials (somatosensory, brainstem auditory, visual, auditory event-related)		EEG/ERP		[139]
	Functional network connectivity		fMRI		[140]
	Metabotropic glutamate receptor subtype 5	mGluR5	PET	[^{18}F]FPEB	[146]
	Neural oscillations		MEG		[170]
	Neuronal activity through glucose metabolism		PET	[18F]FDG	[141, 142, 143]
	Neuronal oscillations		MEG		[147]
	Synaptic vesicle glycoprotein 2A	SV2A	PET	[^{11}C]UCB-J	[151]
Circadian rhythm	Sleep patterns		PSG		[162]
	Wake/sleep cortical activity		EEG		[163]

Abbreviations: Abbr., abbreviation; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; PET, positron emission tomography; PSG, polysomnography.

itive relationship with Centiloid levels of Aβ-PET.[34] Evaluations of plasma p-tau217 and p-tau231 show the strongest relationship with Aβ-PET when compared to p-tau181, Aβ42/40, glial fibrillary acidic protein (GFAP), and neurofilament light chain (NfL).[34] Plasma p-tau181 increases across the AD continuum, with the highest levels in mild cognitive impairment (MCI) and AD dementia patients with Aβ positivity; p-tau181 levels are associated with tau-PET (area under the curve [AUC] 83.08–93.11) and Aβ-PET (AUC 76.14–88.09).[177,182,183] Comparisons demonstrate that plasma p-tau217 measured by mass spectrometry detects Aβ status with the highest accuracy (AUC 0.947), compared to other p-tau markers, including p-tau181 and p-tau231 evaluated on different platforms.[184]

PrecivityAD2 is a test developed by C_2N Diagnostics (Missouri, USA) to measure plasma Aβ42/40 ratio and p-tau217 by mass spectrometry and calculates a score to aid in AD diagnosis and selection for clinical trials.[185] The PrecivityAD2 test results in a numerical value representing brain amyloidosis. Patients with scores from 0 to 35.5 are considered negative, and patients with scores 57.5 and higher are positive; there is an intermediate range for patients that have scores 35.6 to 57.4, in which the test cannot predict the outcome with high certainty and additional testing is suggested.[185]

Other candidate biomarkers subsumed in the amyloid CADRO category are those involved in the processing and production of Aβ. Beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) is an enzyme responsible for the cleavage of the amyloid precursor protein (APP), resulting in amyloidogenic Aβ peptides.[186] Elevated levels of BACE1 in CSF are observed in patients with MCI compared to controls, and correlate with Aβ40, t-tau, and p-tau181, representing a prognostic biomarker for AD.[19,187] In patients with MCI due to AD and AD dementia, there are increases in serum BACE1, with a proposed threshold concentration of 11.04 kU/L used to differentiate controls from individuals with AD pathology.[18,188]

Soluble amyloid precursor protein-beta (sAPPβ) is one of the byproducts of APP processing.[189] In patients with AD, there are increased levels of sAPPβ in CSF and plasma, and these correlate significantly with Clinical Dementia Rating (CDR) and Mini-Mental State Examination (MMSE) scores.[23,24] There are currently no candidate biomarkers for oligomeric Aβ or oligomeric tau species, representing a gap in the field.

3.2 | Tau

Neurofibrillary tangles (NFTs), attributed to aggregation of p-tau into paired helical filaments, are a core pathology of AD. As described above, the Revised Framework Criteria for the Diagnosis and Staging of AD divides tau biomarkers as T1 and T2. T1 biomarkers include forms of soluble tau, which have strong relationships with Aβ pathology (discussed in 3.1); however, it is important to note that they show a relationship with tau PET as well.[9] In patients with mild to moderate AD, plasma p-tau181 levels correlate positively with tau-PET in the inferior temporal and meta-temporal regions, and globally.[190] In patients with MCI or AD dementia positive for Aβ, there is strong association between plasma p-tau217 and tau-PET, especially in the temporoparietal and dorsolateral frontal cortices.[191,192]

T2 biomarkers are measures of AD tau proteinopathy, such as insoluble tau. The gold standard biomarker method for measurement of NFTs is tau-PET, allowing clinicians and researchers to observe the presence, abundance, and location of the pathology. Currently, the only FDA-approved tau tracer for PET is [18F]flortaucipir ([^{18} F]AV1451), approved in 2020.[180] Other tracers being used in clinical trials and research include derivative [F18]-T808 and 6-(fluoro-18F)-3-(1H-pyrrolo[2,3-c]pyridin-1-yl)isoquinolin-5-amine ([18F]-MK6240). Tau-PET with [^{18} F]AV1451 is able to successfully discriminate between patients that are Aβ positive and Aβ negative with an AUC of 0.92–0.94.[193]

Microtubule binding region (MTBR)-tau243 and N-terminal containing tau fragments (NTA-tau) demonstrate utility as biomarkers with higher specificity to tau pathology.[28,194] CSF MTBR-tau243 correlates with insoluble tau aggregates and shows the strongest association with tau-PET compared to p-tau181, p-tau217, and p-tau231.[28] Furthermore, MTBR-tau243 shows the lowest association with Aβ-PET.[28] NTA-tau levels in CSF and plasma increase significantly through AD progression, with a relationship to tau accumulation (tau-PET), brain atrophy, and cognitive decline.[29,192]

Additional biomarkers in the tau CADRO category include those associated with the formation, accumulation, and byproducts of tau pathology. For example, dual specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A) is involved in the phosphorylation of tau, and patients with AD dementia have significant reductions compared to cognitively normal controls (CNCs).[27] Furthermore, DYRK1A concentrations are correlated with CSF t-tau and p-tau181 levels, but show no association with CSF Aβ42 and Aβ-PET.[27] Additional biomarkers and novel assays are being investigated to accurately measure tau-related targets in AD patients as risk/susceptibility, diagnosis, monitoring, and pharmacodynamic/responsiveness biomarkers.

3.3 | *APOE*, lipids, and lipoprotein receptors

After age, the most influential risk factor for late-onset AD (LOAD) is the apolipoprotein E (*APOE*) ε4 allele(s).

Investigations into apolipoproteins (Apo) in biofluids comprise important biomarkers, including ApoA1 and ApoC3 protein. ApoA1 is the second most abundant Apo protein in the CSF and is essential to cholesterol homeostasis.[39] Significant increases in CSF ApoA1, and significant decreases in plasma levels, have been associated with progressive cognitive decline in *APOE* ε4 positive individuals.[39,195] In addition, decreases in plasma ApoA1 have been reported in patients with symptomatic AD compared to CNCs.[40] ApoC3 is detectable in urine, and research using enzyme-linked immunosorbent assay (ELISA) demonstrates mixed results in two cohorts of patients with AD dementia; whereas ApoC3 may be a potential urinary biomarker for AD, further research is necessary to validate the initial observations.[41] Additional Apo biomarkers being evaluated include ApoA2, ApoB, ApoH, and ApoJ.[195]

Dysregulation of lipids has been proposed as a key factor in AD pathogenesis. Fatty-acid binding protein 3 (FABP) is associated with lipid metabolism and is shown to be significantly increased in the CSF of patients with AD dementia, compared to MCI due to AD and CNCs.[42] FABP correlates negatively with MMSE scores and CSF Aβ42/40 ratios.[42] Myelin is composed primarily of lipids and is responsible for insulating neurons, fundamental to neuron signaling. White matter, a proxy to measure myelin, is significantly altered in patients with AD.[196–198] Although this is typically measured by magnetic resonance imaging (MRI), new developments in PET radiotracers aim to assess myelin and myelin-related proteins to provide a measure with greater sensitivity.[44] Biomarkers associated with *APOE*, lipids, and lipoprotein receptors can be used for the COU of risk, monitoring, or pharmacodynamic/response.

3.4 | Neurotransmitter receptors

Alterations of neurotransmitter systems in AD are well documented, including changes in serotonin and acetylcholine signaling pathways.[199] In patients with probable AD dementia, there is decreased binding of serotonin 1A receptor (5-HT1A) observed through PET with radioligand [carbonyl-^{11}C]Desmethyl-WAY-100635 ([^{11} C]WAY100635), compared to CNCs.[51] Decreases in serotonin 2A receptor (5-HT2A) binding is observed in patients with MCI using 3-[2-[4-(4-[18F]Fluorobenzoyl)-1-piperidyl]ethyl]-2-sulfanyl-3H-quinazolin-4-one ([^{18} F]altanserin) PET, compared to CNCs, demonstrating it as an early biomarker for AD.[52] Using the same radiotracer, an ≈30% decrease in 5-HT2A binding was reported in several brain regions, including the anterior cingulate, prefrontal cortex, and sensorimotor cortex of patients with symptomatic AD dementia compared to CNCs.[53] Serotonin transporters (SERTs) are decreased significantly in patients with AD dementia, compared to CNCs, evaluated by [11C]-3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)benzonitrile ([11C]DASB) PET.[50] AD patients with depressive symptoms have greater reductions in SERT binding compared to AD patients without depressive symptoms; there is a reduction of SERT in nondepressed AD dementia patients, suggesting that alterations in serotonergic signaling precede the onset of depressive symptoms and may provide an early biomarker for mood disorders in AD.[50]

Disruption of the cholinergic system is observed in AD with degeneration of cholinergic neurons and acetylcholine deficiency.[200] In patients with AD dementia, there is a reduction in α7 subtype of the nicotinic acetylcholine receptor (α7-nAChR) compared to CNCs using (R)-2-methylamino-benzoic acid 1-aza-bicyclo[2.2.2]oct-3-yl ester (^{11}C-(R)-MeQAA) PET.[49] A negative correlation between α7-nAChR binding and Aβ PET has been reported.[49] Patients with AD dementia have normal dopamine transporter scans (DaT scans); abnormal DaT scans are observed in dementia with Lewy bodies (DLB), with 78% sensitivity for probable DLB, and 90% specificity for excluding non-DLB dementia, representing a diagnosis biomarker for the differentiation of the diseases.[201]

Acetylcholinesterase (AChE) is an enzyme involved in the degradation of acetylcholine. In patients with early cognitive impairment, enzymatic activity of AchE is significantly higher in those who have increased levels of CSF t-tau, p-tau181, and inflammatory markers S100 calcium-binding protein B (S100B) and chitinase-3-like protein 1 (YKL-40).[47]

Overall, biomarkers of neurotransmitter receptor dysregulation have emerged utilizing primarily PET imaging. Studies are underway investigating not only potential biomarkers, but also the most sensitive and reliable PET radiotracers for the targets being evaluated.

Very few biomarkers of neurotransmitter receptors have been recognized in fluid samples, CSF and blood. With 29% of DMTs currently in the drug development pipeline targeting neurotransmitters, biomarkers to measure these processes are vital for the progression of AD treatment development. These markers could be used as risk/susceptibility, monitoring, and pharmacodynamic/response in terms of COU.

3.5 | Neurogenesis

Biomarkers of neurogenesis would be useful as new treatments for AD continue to develop; however, no robust biomarkers specific to neurogenesis have emerged.

3.6 | Inflammation

Neuroinflammation is observed in several neurodegenerative diseases (NDDs), including AD, Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS).[202,203] In AD, neuroinflammation exacerbates disease pathology, including Aβ and NFTs, making it a target for novel therapeutics.[11] Drugs aimed at inflammatory mechanisms comprise a substantial aspect of the current AD drug development pipeline.[10]

Microglia are the resident immune cells of the central nervous system (CNS). These cells maintain an inactive profile unless activated by neuronal damage or the presence of a threat, including Aβ and NFTs. Microglia activation can be measured via PET scan using mitochondrial 18kDa translocator protein (TSPO) as a biomarker. With TSPO radiotracers 11C-[1-(2-chlorophenyl)-N-methyl-N-(1-methyl-propyl)-3-isoquinolinecarboxamide ([11C]PK11195), AD patients have a significantly higher SUVR in the hippocampus, negatively correlated with CSF Aβ levels and predicting further cognitive decline.[79] Although TSPO is recognized as a marker of activated microglia, it can be found on other cells types, including astrocytes and endothelial cells. PET biomarkers more specific to inflammation are being sought.[204]

Investigations into relationships between microglia and AD identified loss-of-function variants in the triggering receptor expressed on myeloid cells 2 (*TREM2*) gene through genome-wide association studies (GWAS), indicating that patients with these variants are more susceptible to AD.[82,205] This led to research evaluating the TREM2 protein in biofluids—CSF and blood. TREM2 is involved in several microglia

processes including proliferation, migration, phagocytosis, lysosomal degradation, and metabolism, emphasizing the role of TREM2 alterations as biomarkers of microglia dysfunction.[206] In patients with AD dementia, significantly higher levels of CSF soluble TREM2 (sTREM2) are observed compared to CNCs.[81] In patients with autosomal dominant AD, there are elevated levels of sTREM2 in the CSF, associated with the decrease of CSF Aβ; relationships between CSF sTREM2 and t-tau, p-tauS199, and NfL have also been reported.[81,82,207] Some studies have investigated sTREM2 in blood with little consensus, meriting further investigation.[80,205,208,209]

Astrocytes are the most abundant glial cell in the CNS and are involved in neuroinflammation; they are responsible for different aspects of the immune response compared to microglia, making them another biomarker target for AD.[210] Glial fibrillary acidic protein (GFAP) plays a role in astrocytic mobility, proliferation, autophagy, and cellular communication, indicating astrocytic activation.[211] In cognitively unimpaired individuals positive for Aβ pathology, plasma GFAP is elevated compared to those negative for Aβ. A meta-analysis reveals elevated levels of plasma GFAP in individuals with MCI and AD dementia.[68] Research demonstrates GFAP as a biomarker for distinguishing AD from other diseases, particularly frontotemporal dementia (FTD) and progressive supranuclear palsy, with higher accuracy in plasma compared to CSF (plasma GFAP AUC = 0.703; CSF GFAP AUC = 0.584).[67]

Overall, chronic neuroinflammation has been demonstrated in AD patients and attributed to the imbalance of numerous pro- and anti-inflammatory cytokines, released by activated glia cells.[203] Cytokines, tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β) are a few of the exploratory inflammatory biomarkers being investigated in AD. These pro-inflammatory cytokines have been shown to be altered in CSF and serum samples from MCI and AD patients.[70,83,212,213] Inconsistent results demonstrate the need for further research into the role of cytokines as AD biomarkers.[214] Biomarkers of inflammation and the immune response are being investigated in fluid samples primarily as risk/susceptibility, monitoring, pharmacodynamic/response, and prognostic biomarkers for AD COU.

3.7 | Oxidative stress

Through the process of metabolism, free radicals are released, with the most important being reactive oxygen species (ROS) and reactive nitrogen species (RNS).[215] The imbalance of free radicals results in oxidative stress, with the brain being particularly prone to oxidative damage due to its high metabolic activity.[215] Oxidative stress is observed with aging and inflammatory processes in several NDDs, including AD.[216] Oxidative changes have been reported early in AD pathogenesis.[217]

Products of lipid peroxidation, including isoprostanes and neuroprostanes, are biomarkers of oxidative stress. In plasma, markers of lipid peroxidation are higher in CNCs and non-AD dementia patients, compared to AD dementia, and are associated with cognition and tau pathology.[218,219] Recent data support the use of isoprostanes and neuroprostanes in a biomarker panel to increase the accuracy for detecting AD, although inconsistencies between plasma and CSF levels merit further investigation.[220]

Endogenous proteins with antioxidant properties, including uric acid and sirtuins, are reduced in AD dementia patients and can be used as biomarkers of oxidative stress. Serum uric acid is significantly decreased in AD dementia patients compared to CNCs, with a downward trend in patients with MCI.[91] Serum from AD dementia patients also shows reductions in multiple sirtuins, including SIRT1, SIRT3, and SIRT6, compared to MCI and CNCs.[88] Mechanisms of sirtuins have been linked to AD pathology, although many of these studies are in postmortem tissues and non-clinical models.[221] The oxidative stress CADRO category consists primarily of blood-based biomarkers, which could be used as a risk/susceptibility, monitoring, pharmacodynamic/response, or prognostic marker of AD.

3.8 | Cell death

AD is characterized by neurodegeneration, as recognized in the A/T/N system.[9] MRI allows visualization of brain atrophy as a biomarker of cell density. Region-specific changes can assist with differentiation of AD from other NDDs, as well as classification of disease progression.[222] Atrophy in AD is manifested as decreased overall brain volume, including shrinkage in cortical volume, cortical thickness, hippocampal size, and ventricle expansion.[223] Brain volume reductions are ≈2.4% per year in AD dementia patients, with CNCs having an average of 0.4% loss.[224] MRI atrophy is a nonspecific marker that may detect cell loss, reduction in other space-occupying elements including Aβ, and fluid shifts. MRI can be used in the COU of monitoring and pharmacodynamic/response to assess the impact of therapy on volume.

Fluid biomarkers of cell death are also being investigated. Total tau (or t-tau) has been established as a marker of neurodegeneration and injury in several diseases including AD, traumatic brain injury (TBI), and stroke. In patients with AD dementia, elevated levels of plasma tau are detected compared to patients with MCI and CNCs, with and without Aβ pathology.[99] In patients with mild to moderate AD dementia, high levels of t-tau in CSF were associated with greater cognitive decline in individuals who were *APOE* ε4 carriers.[100] Furthermore, in patients who are cognitively normal with positivity for Aβ, there is a significantly higher level of plasma t-tau, compared to Aβ-negative CNCs.[98]

Neurofilament light chain (or NfL) is another biomarker that is increased in relation to neuronal damage and cell death and can be measured in CSF and blood.[95] In plasma, NfL is elevated in patients with MCI and AD dementia compared to those with subjective cognitive decline; this elevation is dependent on Aβ status and age.[95,225]

Although t-tau and NfL are indicative of cell death in NDDs, they are not specific biomarkers for AD, but rather markers of disease progression and neurodegeneration. Markers of cell death and their relationships to biomarkers in other CADRO categories may offer a more accurate and reliable combination diagnostic marker, such as t-tau/Aβ (Roche), which received FDA 510(k) clearance in

2023, facilitating diagnosis of symptomatic AD.[32] Biomarkers of cell death are important to AD research for COU of monitoring and pharmacodynamic/response.[32]

3.9 | Proteostasis/proteinopathies

Proteostasis is the process of regulating proper folding of proteins after synthesis. If misfolding occurs, it results in unfolding, refolding, and/or abnormal degradation and aggregation of the protein. NDDs, including AD, PD, and ALS, are characterized by dysfunction of proteostasis and the presence and accumulation of protein aggregates. In AD, misfolding of Aβ leads to self-assembly and aggregation into oligomers, fibrils, and plaques; p-tau aggregates to form NFTs. Within the CADRO classification system, biomarkers for these proteinopathies are organized into specific categories of their own: amyloid and tau. We do not include biomarkers of these processes in the proteostasis/proteinopathies category, as they are discussed above. Alpha-synuclein (α-syn) and TAR DNA-binding protein 43 kDa (TDP-43) are other protein aggregation disturbances commonly present in the AD brain that we discuss.

Accumulation of α-syn to form Lewy bodies is a predominant feature in PD and DLB; α-syn is also present in AD.[102] Recently, α-syn has been measured using α-synuclein seed amplification assays (αSyn-SAA). The αSyn-SAA method relies on in vitro replication of protein from a template, or seed, acquired through a patient fluid sample. The cyclical process makes protein copies resulting in higher levels for detection and determination of α-syn presence.[226,227] Novel technology is emerging for digital quantification of αSyn-SAA.[228] Through meta-analysis, α-syn was determined to be highest in patients with MCI, especially in those who progress rapidly to AD dementia[102]; α-syn correlates with Aβ levels in asymptomatic individuals, demonstrating it to be an early detection marker for AD.[102] α-Syn is detectable in the skin biopsies of patients with PD, DLB, multiple system atrophy (MSA), and pure autonomic failure (PAF); α-syn from skin biopsies of AD patients have not yet been reported.[229]

TDP-43 is involved in RNA processing and gene expression regulation; however, mislocalization of TDP-43 results in multiple post-translational modifications and ultimately insoluble aggregation of TDP-43.[230] TDP-43 aggregation is a key pathology of ALS and FTD and has been observed in postmortem tissues from AD patients as well.[231]

Quantification of plasma extracellular vesicle TDP-43 is significantly increased in patients with ALS and behavioral variant FTD (bvFTD), correlating with disease severity. Complete plasma TDP-43 levels do not differ between diagnostic groups, demonstrating the importance of evaluating extracellular vesicles.[232] Recent studies have proposed a novel method: measuring TDP-43-dependent cryptic exon hepatoma-derived growth factor-like protein 2 (HDGFL2) in the CSF of patients with ALS.[233] This method was verified as detecting TDP-43 loss of cryptic splicing and demonstrated significant increases in HDGFL2 in the CSF of patients with familial ALS-FTD and sporadic ALS compared to CNCs.[233] Furthermore, HDGFL2 was present in patients with presymptomatic ALS-FTD who were positive for the *C9orf72* gene mutation associated with the disease.[233] If substantiated in further studies, this novel method could be employed in AD research, advancing the understanding of TDP-43 in AD. Biomarkers of proteostasis/proteinopathies are used as risk/susceptibility, monitoring, or pharmacodynamic/response COU markers.

3.10 | Metabolism and bioenergetics

Metabolic dysfunction is well documented in NDDs, such AD, PD, ALS, and HD. Using fluorodeoxyglucose (FDG)–PET, progression from MCI to dementia can be determined with reductions in the medial temporal lobe metabolism (94.7% sensitivity; 80.5% specificity).[108] These alterations can be detected up to 8 years prior to progression to dementia.[108] In patients with lower levels of FDG-PET activity, there is a faster rate of cognitive decline and greater shrinkage of the middle temporal lobe, compared to individuals with higher FDG-PET activity.[107] FDG-PET provides a COU biomarker for risk/susceptibility, monitoring, and pharmacodynamic/response.

Mitochondria are responsible for cellular bioenergetics, calcium signaling, and apoptosis.[234] In AD, mitochondrial dysfunction, including imbalance of fission and fusion, reduction of adenosine triphosphate (ATP) generation, defects in mitophagy, increased ROS, and mitochondrial fragmentation, have all been reported and proposed as contributors to AD pathogenesis.[235] As mitochondria use the electron transport chain to produce ATP, mitochondrial complex 1 (MC-1) is the rate-limiting enzyme for this process and a step involved in ROS production.[111] Using PET tracer 2-tert-butyl-4-chloro-5-{6-[2-(2[18F]fluoroethoxy)-ethoxy]-pyridin-3-ylmethoxy}-2H-pyridazin-3-one ([^{18}F]BCPP-EF), which binds specifically to MC-1, there is a significant decrease in SUVR in the medial temporal region in patients with AD dementia; mitochondrial PET has a significant negative correlation with tau-PET.[111] Additional biomarkers of mitochondrial dysfunction overlap with markers of increased ROS (as described in Section 3.8). Biomarkers measuring metabolism and bioenergetics are important as COU for risk/susceptibility, monitoring, and pharmacodynamic/response.

3.11 | Vasculature

Cardiovascular disease (CVD) can lead to vascular dementia (VaD) and vascular cognitive impairment (VCI), attributed to interrupted blood flow to the brain leading to cognitive deficits. CVD is associated with AD, although the relationship is complex, with many overlapping risk factors. Individuals at high risk for developing VaD and AD are patients with metabolic disorders, including type 2 diabetes (DM2), and an *APOE* ε4 allele.[236]

Arterial spin labeling (ASL) MRI can be used to measure cerebral blood flow. In patients with AD dementia, there is a decrease in cerebral blood flow in several brain regions, including the entorhinal, hippocampus, inferior temporal, and posterior cingulate.[114] Independent of diagnosis, patients who are Aβ positive have lower cerebral

blood flow than patients who are Aβ negative.[114] Single-photon emission computed tomography (SPECT) and oxygen-15-labeled water (^{15}O-H_2O)PET are alternative measures of cerebral blood flow.[237,238]

The blood–brain barrier (BBB) is protective barrier between the brain and the vascular system. Although biomarkers are being sought to characterize the integrity of the BBB, there is no consensus on whether the BBB is compromised in AD. Patients with MCI have demonstrated BBB permeability through water extraction with phase contrast arterial spin tagging (WEPCAST) MRI, suggesting a deterioration of the BBB in these patients compared to CNCs.[124] In relation to AD pathology, the BBB shows higher water permeability in patients with lower CSF Aβ42/40 ratio.[124] However, BBB permeability to albumin is not associated with AD pathology, but rather hypercholesterolemia, demonstrating a potential biomarker for differentiation of AD and VaD.[124]

Biomarkers of vascular health and BBB integrity are being investigated in biofluids, including fibrinogen, platelet-derived growth factor receptor-β (PDGFRβ), vascular cell adhesion molecule 1 (VCAM-1), placental growth factor (PlGF), and matrix metalloproteinase-9 (MMP-9). Fibrinogen is responsible for coagulation, inflammation, and repair of vascular damage.[117] In the CNS, the presence of fibrinogen is a marker of BBB dysfunction and mediates microglia processes.[117] In patients with AD dementia, plasma fibrinogen correlates positively with plasma Aβ40 and Aβ42, and negatively with CSF Aβ42; fibrinogen correlates positively with CSF t-tau and p-tau181.[116] In CNCs, there are no reported associations between fibrinogen and Aβ and tau pathology.[116]

PDGFRβ is a protein involved in the development and maintenance of the BBB.[239] In patients with amnestic MCI who are positive for all A/T/N biomarkers (CSF Aβ42, unspecified p-tau epitope, and t-tau), CSF PDGFRβ is significantly increased compared to amnestic MCI patients with a negative A/T/N profile.[122]

VCAM-1 is found on endothelial and immune cells responsible for interactions between the two cell types.[240] In patients with AD, significant increases were observed in CSF VCAM-1, associated with Clinical Dementia Rating–Sum of Boxes (CDR-SB) scores, modified by *APOE* ε4 status; this was not observed in MCI.[241] Furthermore, plasma VCAM-1 levels are significantly increased in patients with AD dementia, correlating with cognitive decline and brain atrophy.[123]

Placental growth factor (or PlGF) is part of the vascular endothelial growth factor family involved in angiogenesis.[120] Patients with AD dementia have elevated levels of PlGF in CSF and blood compared to patients who are cognitively impaired with no dementia and CNCs.[120,121] PlGF levels are associated with higher white matter hyperintensity burden and cerebral microbleeds in patients with AD.[120] Non-clinical data show PlGF messenger RNA (mRNA) levels increase with the presence of Aβ.[242] These findings indicate that PlGF could be used as a biomarker for concomitant cerebrovascular diseases in AD.

Matrix metalloproteinase-9 (or MMP-9) is a proteolytic enzyme, capable of Aβ degradation.[243] Patients with AD dementia who are positive for Aβ have elevated levels of CSF MMP-9 compared to Aβ-positive MCI patients.[118] High MMP-9 level is associated with greater decline in hippocampal volume and cognitive function.[244] Elevated levels of MMP-9 may affect AD pathology as well as cognition differently in men and women.[118] The dual roles of MMP-9 in degradation and promotion of Aβ, and the differences between sexes, require further research.

Overall, the CADRO category of vasculature biomarkers includes assessments of vascular inflammation, BBB dysfunction, and vascular health associated with AD. Quantification of these markers could provide risk/susceptibility, monitoring, and pharmacodynamic/response biomarkers in terms of COU.

3.12 | Growth factors and hormones

Sex influences AD prevalence, with two-thirds of patients being women.[245] Although several factors may be involved, menopause is a risk factor for dementia, with the onset of AD brain changes coinciding with the time of menopausal transition.[246] Alterations in sex hormones during menopause exacerbate AD pathologies. Postmenopausal women have higher Aβ deposition, tau burden, neuroinflammatory responses, and reduced cerebral glucose metabolism compared to premenopausal women.[247,248,249] There are significant reductions in estrogen and progesterone during the menopausal transition, and depletions of these hormones are biomarkers of risk/susceptibility for AD.[250,251] Elevated levels of gonadotropins, including follicle stimulating hormone (FSH) and luteinizing hormone (LH), have been reported in patients with dementia; however, the findings are mixed, potentially due to variables in the studies, including the type of dementia evaluated, sex of the patients, hormonal replacement therapy (HRT) status, and time since menopause.[127,252,253]

Through aging, men experience a gradual loss of testosterone, impacting the risk for AD. A meta-analysis found that in elderly men, lower levels of testosterone are associated with worse cognitive function.[254] Decreased levels of testosterone correlate with increases in CSF p-tau181 in men who are *APOE* ε4 carriers.[131] Like HRT in women, inconsistencies in studies involving testosterone therapy in men may be attributed to differences in drug formulation, administration, and study design.

Growth factors, such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), represent biomarkers of AD. BDNF promotes cell growth and is essential to learning and memory. Serum BDNF in patients with MCI due to AD is significantly lower than in CNCs, correlating with CSF Aβ42 levels and medial temporal lobe atrophy.[126] CSF BDNF has associations with CSF Aβ42 and MMSE scores in patients with AD dementia compared to CNCs.[125] NGF supports neuronal growth, development, and differentiation in the brain and is increased in blood samples from patients with AD dementia.[255,256] Patients with Down syndrome, a population in which individuals develop AD with age, demonstrate alterations in the NGF pathway through CSF and plasma biomarkers, supporting the link between NGF and AD.[128] Hormone and growth factor biomarkers are important for the COU of risk/susceptibility, monitoring, and pharmacodynamic/response.

3.13 | Synaptic plasticity/neuroprotection

Synaptic loss and dysfunction of synaptic plasticity are more closely associated with cognitive decline than other pathological changes in patients with AD dementia.[257] Several neuroimaging techniques, including fluorodeoxyglucose–positron emission tomography (FDG-PET), electroencephalography (EEG), functional MRI (fMRI), and synaptic vesicle glycoprotein 2A (SV2A) PET, are used to measure synaptic plasticity. Synaptic function can be evaluated through EEG, detecting electrophysiological changes in the brain primarily including slowing of EEG signal and coherence of signals among brain regions.[134,137] The use of EEG to monitor event-related potentials (ERPs) as a response to specific events or stimuli is another candidate biomarker for AD, predicting cognitive decline.[138,258] Gradual changes in delta activity from MCI to AD dementia on EEG may represent a biomarker of disease progression.[163] EEG and polysomnography (discussed further in 3.15) can serve the COU of monitoring or pharmacodynamic/response characterization in drug development.

Evaluation of synaptic function using fMRI to measure blood oxygen level–dependent (BOLD) signal demonstrates neuronal activity through alterations in blood flow and oxygenation in the brain. Greater variability in BOLD is observed in patients with AD dementia, compared to CNCs.[135,136] Resting-state fMRI (rs-fMRI) detects changes in neuronal networks, including the salience network and default mode network (DMN), and in patients with MCI and AD, substantial alterations in these networks have been observed in relation to CNCs.[259,260] In undiagnosed patients who later developed dementia, changes in the DMN can be identified at an individual level, providing a risk biomarker for AD.[259]

Radiotracers for PET allow detection of specific proteins related to synaptic function and density. FDG is an analog of glucose, used to demonstrate glucose metabolism levels in the brain. With glucose necessary for neuronal activity, FDG-PET uptake reflects synaptic function. Patients with MCI or AD dementia have significantly lower FDG-PET SUVRs than CNCs, with hypometabolism severity being associated with Braak staging of NFTs.[141,143] FDG-PET SUVR is significantly correlated with CSF t-tau, p-tau181, and Aβ42.[142] However, FDG-PET cannot distinguish AD from other NDDs; combinations of FDG-PET with other biomarkers are being investigated to increase the reliably of both markers for the diagnosis COU.

Synaptic vesicle glycoprotein 2A (or SV2A) is located in the synapse, observed by radiotracer (R)-1-((3-([11C]methyl)pyridin-4-yl)methyl)-4-(3,4,5-trifluorophenyl)pyrrolidin-2-one ([^{11}C]UCB-J) as a marker of synaptic density. Research shows reductions of SV2A in patients with AD dementia compared to CNCs using this radiotracer.[151] Additional radiotracers for SV2A are being explored, including derivatives [^{11}C]UCB-A and [^{18}F]UCB-H.[257]

CSF markers of synaptic damage and loss are promising fluid biomarkers. Synaptosomal-associated protein 25 (SNAP-25) aa40 species, neurogranin (NRGN), growth associated protein 43 (GAP-43), and synaptotagmin-1 (SYT1) all show a positive correlation with Aβ levels, determined by CSF Aβ42/40 and Aβ-PET imaging. These biomarkers are associated with CSF p-tau181 and NfL in CNCs.[144] Patients with MCI-AD and AD dementia have higher levels of GAP-43, NRGN, SNAP-25 aa40, and SYT1, compared to CNCs and patients with non-AD MCI or non-AD dementias.[145] Blood-based biomarkers for synaptic plasticity/neuroprotection are being investigated, although no robust markers have emerged. Overall, biomarkers of synaptic plasticity/neuroprotection have a COU for risk/susceptibility, monitoring, or pharmacodynamic/response.

3.14 | Gut-brain axis

Gut microbiota includes bacteria, fungi, viruses, and helminths in the gastrointestinal tract.[261] Bi-directional communication between the gut and the brain is termed the gut–brain axis (GBA). Gut microbes have been shown to synthesize several neurotransmitters, including γ-aminobutyric acid (GABA), serotonin, dopamine, and acetylcholine.[262] Dysbiosis is observed in NDDs including AD and PD.[262] The composition of the microbiome may influence AD pathogenesis. In patients who are Aβ positive, there are higher levels of fecal *Escherichia/Shigella* (pro-inflammatory) and lower levels of *E. rectale* (anti-inflammatory).[156] Gut microbiota–related inflammatory processes could provide a link between the gut and brain health. In patients with uncharacterized dementia, significant increases in the inflammatory marker soluble cluster of differentiation-14 levels (sCD14) and the gut permeability marker, serum diamine oxidase (DAO), were observed in serum and fecal samples, respectively, compared to CNCs.[157] Gut health influences AD pathogenesis, with Aβ detected in the gut.[263] Through intra-intestinal injection of fluorescence-labeled Aβ in transgenic mice, Aβ42 from the gut was observed being transported to the brain, suggesting that peripheral Aβ may be contributing to the aggregation of Aβ in the brain.[263]

Metabolites of gut microbiota, specifically fecal volatile organic compounds, are potential biomarkers for severity of AD, with early stages having high levels of fecal short-chain fatty acids (SCFAs) and bacteria *Faecalibacterium* and *Lachnoclostridium;* advanced stages of AD show greater levels of fecal hexanoic acid, *Ruminococcus*, and *Blautia*.[159] In patients with cognitive complaints, plasma levels of the SCFAs acetate and valerate positively correlate with Aβ-PET.[158] Biomarkers of gut health are important to be used as COU markers of risk/susceptibility, monitoring, or pharmacodynamic/response.

3.15 | Circadian rhythm

Sleep disturbances affect 25%–66% of patients with AD, including alterations in sleep duration, fragmentation of sleep, breathing disorders during sleep, changes in sleeping brain wave activities, and reduction in rapid eye movement (REM).[264] Sleep disorders have a bidirectional relationship with Aβ and tau pathology, and biomarkers of circadian rhythms may indicate risk and progression of AD.[265,266] Polysomnography provides a biomarker that can be used to evaluate sleep through several physiologic measures. Patients with mild to moderate AD dementia, who spend more time in light sleep stages eval-

uated via polysomnography, have a significant decrease in cognition after 12 months.[162] EEG studies report alterations in sleep brain wave patterns, including increased sleep latency, and reduced slow-wave sleep in patients with MCI and AD dementia.[163]

Orexin (also known as hypocretin) is a neuropeptide involved in the regulation of sleep and wakefulness. Increases in CSF orexin have been reported in patients with MCI due to AD and patients with moderate to severe AD dementia, compared to CNCs.[161,267] In CSF, there is a positive correlation between orexin and t-tau, as well as orexin and p-tau181, in patients with moderate to severe AD dementia compared to CNCs.[161] Nonclinical research through BV2 cell cultures demonstrates that orexin inhibits the phagocytosis and degradation of Aβ by microglia cells, supporting this relationship between the orexin and AD pathologies.[268] Further research into the relationship between orexin and AD is needed and may provide risk/susceptibility, monitoring, or pharmacodynamic/response biomarkers for the disease.

3.16 | Multi-target, unknown target, and other

We defined multi-target biomarkers as single biomarkers that assess more than one mechanism. This includes ratios and panels in which the result is a numerical value from multiple different measures. Multi-targeted biomarkers for AD have emerged frequently as ratios, with one of the most widely used being CSF and plasma Aβ42/40, associated with amyloid PET.[269,270] This ratio has been used in AD clinical trials, including in trials investigating DMTs.[17] Combinations of markers measuring different mechanisms are being evaluated, especially between the A/T/N categories. An example is plasma p-tau181/Aβ42, which can accurately distinguish AD patients (Aβ positive) from patients with VaD (Aβ negative), and is correlated with hippocampal atrophy.[165] This biomarker was categorized as a multi-target marker.

As the investigation for novel biomarkers continues, and new technologies are emerging, proteomic panels evaluating large numbers of proteins are being used to identify proteins of interest and develop AD profile scores.[271,272,273] Through proteome studies, potential AD biomarkers may emerge that are not yet associated with a specific mechanism; these markers would also be included in this CADRO category.

4 | DISCUSSION

We identify current and candidate biomarkers for AD and demonstrate the feasibility and practicality of classifying them using the CADRO system. Categorization of biomarkers by their biological processes provides a tool for drug development. Researchers can select an appropriate biomarker based on the target of the mechanism of the intervention, routes of detection (neuroimaging, CSF, blood), and COU for their trial or research program. Here we show that all categories of CADRO addressing disease processes have at least preliminary biomarkers measurable by imaging or biofluid analyses.

We focus specifically on AD biomarkers; some of the markers have been described in other NDDs, including dopaminergic markers, α-syn, and NfL.[274,275] A few of the biomarkers are associated with multiple categories, and when determining the most appropriate CADRO category, we classified them based on the primary mechanism as it was related to AD. Decisions were also informed by considering the mechanism being measured. For example, the revised NIA/AA Research Framework for Alzheimer's Diagnosis classifies biomarkers by the pathologic process endpoint and includes t-tau as a marker of neurodegeneration.[8] We applied this framework to the CADRO system and included t-tau as a biomarker of cell death in the CADRO system.[8,276] As our knowledge and understanding of AD biomarkers evolve, the CADRO system can be adapted to changes.

The biomarkers presented are in different states of validation.[277] Biomarkers including amyloid-PET, FDG-PET, and CSF Aβ42/40 are well-established and commonly used in the diagnosis of AD. Candidates in advanced stages of validation include GFAP, some p-tau epitopes, and markers of cell death, such as NfL. Many biomarkers are not as well characterized, or the relationship to the associated biology is less well established. Incorporation of the Strategic Biomarker Roadmap (SBR) into the CADRO system could further denote the biomarker validation status as fully achieved, partly achieved, or supported by preliminary evidence.[277]

There is a critical need for blood-based biomarkers to offer a more cost-effective, non-invasive, and accessible test for AD. Although blood-based markers are less proximate to the brain, a simple, low risk, low-cost blood draw can be performed in rural and low-resource areas; samples can be easily stored, collected longitudinally, and rendered clinically useful.

Minority populations are at greater risk for developing AD. Hispanic/Latinos are at a 1.5 times greater risk for AD, whereas African Americans are twice as likely than non-Hispanic White individuals to manifest dementia.[278,279] Several studies have demonstrated that AD neurobiology differs among ethnoracial groups, with differences in neuroimaging, CSF, and blood-based biomarkers for the disease.[280–284] Racial disparities in clinical trials and research of AD biomarkers prevents deeper understanding of how ethnicity and race influence AD and affects the development of new tests and treatments for AD in underrepresented populations. The CADRO system can be used to categorize biomarker findings by ethnoracial group, providing insights and helping to decrease racial disparities in AD.

Expansion of the A/T/N system in the revised NIA/AA Research Framework for Alzheimer's Diagnosis introduced inflammation as a biomarker of non-specific processes involved in AD pathophysiology, and vascular and α-syn as biomarkers of non-AD co-pathology frequently found in patients with AD.[9] As presented as ATX(N), amyloid-beta (A), tau (T), and neurodegeneration (N), where X represents novel canidate biomarkers, additional biomarkers can be added to the framework to better characterize patients and provide therapies specific to a patient profile, paving the way for precision medicine.[285] The CADRO system offers the structure for these biomarker categories to be integrated into the framework, providing a patient profile in which several

aspects of the disease can be captured for diagnosis and therapeutic intervention.

Organization of AD biomarkers into the CADRO classification system can reveal gaps in the field related to the types of markers available for each of the biological processes. For example, new approaches to measuring α-syn and TDP-43 are currently in the preliminary stages of development, validation, and interpretation. Understanding of these co-pathologies is a key next step for the field.

Limitations to the use of the CADRO system to classify biomarkers include the focus of CADRO disproportionately on AD. The CADRO system could be adapted to encompass biomarkers for other NDDs, thereby strengthening this approach. There is overlap of some categories, making application ambiguous. For example, the CADRO category on metabolism and bioenergetics could include some of the biomarkers for oxidative stress. Similarly, whether a biomarker is optimally seen as a marker of cell death or of neuroprotection can be difficult to discern, as these categories involve similar processes. Additional complexity is added when specific biomarkers touch on more than one CADRO category, presenting a challenge when evaluating specific target engagement.

5 | CONCLUSION

We identified current and candidate biomarkers for AD and demonstrated the CADRO system to be a practical approach to the organization of biomarkers as they relate to AD. We demonstrate that CADRO is a comprehensive catalogue of AD-related processes and that biomarkers exist or are in progress for all aspects of CADRO. Analysis of the biomarkers relevant to the CADRO system reveals gaps in biomarker research allowing growth in the field toward more accurate, reliable, and accessible biomarkers for AD. This system is adaptive to changes as we expand our knowledge in this complex disease. CADRO can be incorporated into several systems in use, including the COU, FDA BEST classification, and A/T/N. The CADRO system will assist researchers in choosing the most appropriate biomarkers and advance drug development for AD.

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CONFLICT OF INTEREST STATEMENT

J.L.C. has provided consultation to Acadia, Acumen, ALZpath, Annovis, Aprinoia, Artery, Biogen, Biohaven, BioXcel, Bristol-Myers Squib, Eisai, Fosun, GAP Foundation, Green Valley, Janssen, Karuna, Kinoxis, Lighthouse, Lilly, Lundbeck, LSP/eqt, Merck, MoCA Cognition, New Amsterdam, Novo Nordisk, Optoceutics, Otsuka, Oxford Brain Diagnostics, Praxis, Prothena, ReMYND, Roche, Scottish Brain Sciences, Signant Health, Simcere, sinaptica, TrueBinding, and Vaxxinity pharmaceutical, assessment, and investment companies. J.L.C. owns the copyright of the Neuropsychiatric Inventory and has stocks/options in Artery, Vaxxinity, Behrens, Alzheon, MedAvante-Prophase, and Acumen. A.O. and J.K. have no disclosures.Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

Consent was not necessary for this 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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