Biochemical Markers of Alzheimer Disease and Dementia

Policy Number: AHS – G2048 – Biochemical Markers of Alzheimer Disease and Dementia	Prior Policy Name and Number, as applicable: • AHS – G2048 – Biochemical Markers of Alzheimer's Disease
Effective Date: 10/01/2022	

I. Policy Description

Alzheimer disease (AD) is a neurodegenerative disease defined by a gradual decline in memory, cognitive functions, gross atrophy of the brain, and accumulation of extracellular amyloid plaques and intracellular neurofibrillary tangles (Karch, Cruchaga, & Goate, 2014).

II. Related Policies

Policy Number	Policy Title
AHS-M2038	Genetic Testing for Familial Alzheimer Disease

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Medical Policy Statements do not ensure an authorization or payment of services. Please refer to the plan contract (often referred to as the Evidence of Coverage) for the service(s) referenced in the Medical Policy Statement. If there is a conflict between the Medical Policy Statement and the plan contract (i.e., Evidence of Coverage), then the plan contract (i.e., Evidence of Coverage) will be the controlling document used to make the determination.

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. If there is a conflict between this Policy and any relevant, applicable government policy [e.g. National Coverage Determinations (NCDs) for Medicare] for a particular member, then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quicksearch.aspx?from2=search1.asp& or the manual website.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient's illness.

1. Measurement of cerebrospinal fluid biomarkers of Alzheimer disease, including but not limited to tau protein, amyloid beta peptides, α-synuclein, or neural thread proteins, **DOES NOT MEET COVERAGE CRITERIA**.

2. Measurement of plasma and/or serum biomarkers of Alzheimer disease, including but not limited to tau protein, amyloid beta peptides, neural thread proteins, ApoE, and ApoE4, **DOES NOT MEET COVERAGE CRITERIA.**

3. Measurement of urinary biomarkers of Alzheimer disease **DOES NOT MEET COVERAGE CRITERIA**, including but not limited to neural thread proteins, amyloid beta peptides, and urinary extracellular vesicle analysis.

4. The use of multianalyte assays and/or algorithmic analysis and/or any other tests not mentioned above for prognosis, diagnosis, and/or management of Alzheimer disease or dementia **DOES NOT MEET COVERAGE CRITERIA**.

IV. Scientific Background

Alzheimer disease (AD) is a devastating neurodegenerative disease with a strong genetic component and is the predominant form of dementia (50–75%) (M. Prince et al., 2013). In 2020, over 50 million people lived with dementia worldwide, and this number is estimated to increase to 152 million by 2050 (Martin Prince, 2016; WHO, 2020). The average lifetime risk of developing AD is 10–12%; this risk at least doubles with the presence of a first-degree relative with the disorder (Goldman et al., 2011). The genetic predisposition of AD, even for late-onset AD patients, is estimated to be 60–80% (Gatz et al., 2006). According to the Centers for Disease Control and Prevention (CDC), the total adjusted death rates in the U.S. varied according to ethnicity with white, non-Hispanics having a rate of 70.8 per 100,000 individuals as compared to 65.0 and 46.0 per 100,000 for non-Hispanic black and Hispanic individuals (Kramarow & Tejada-Vera, 2019).

Most patients develop clinical symptoms at or after the age of 65 (spontaneous or late-onset AD), however 2–10% of patients have an earlier onset of disease (early-onset AD) (Shea et al., 2016). AD is characterized by severe neuronal loss, aggregation of extracellular amyloid β plaques, and intraneuronal tau protein tangles, resulting in progressive deterioration of memory and cognitive functions and ultimately requiring full-time medical care (Frigerio & Strooper, 2016). There is an enormous burden on public health due to the high costs associated with care and treatment. Aside from drugs that temporarily relieve symptoms, no treatment exists for AD (Van Cauwenberghe, Van Broeckhoven, & Sleegers, 2016).

Many genetic studies have recently identified that late-onset Alzheimer disease is associated with the apolipoprotein E (*APOE*), apolipoprotein J (*APOJ*), and sortilin-related receptor (*SORL*) genes mainly expressed by various types of glial cells such as microglia, oligodendrocytes, and astrocytes; this has helped AD-related research stray from neurons and toward glial cells and neuroinflammation (Arranz & De Strooper, 2019).

Because the pathological processes of AD and other degenerative dementias are likely well underway before clinical symptoms manifest, biomarkers may have potential utility in the early diagnosis of dementia (McDade & Peterson, 2020). Mild cognitive impairment (MCI) is an intermediate state between normal cognition and dementia, recognizable as an early manifestation of dementia. MCI due to AD is the most common type of MCI (Bennett et al., 2002).

Studies have examined the use of cerebrospinal fluid (CSF) markers for predicting conversion from MCI to dementia. The most replicated CSF biomarkers include tau protein or phosphorylated tau

protein and amyloid beta 42 (Aß42) peptide, which may be represented by a low ratio of Aß42 to Aß40 levels, or a low ratio of Aß42 to tau levels. However, these tests vary in sensitivity (36 to 100 percent) and specificity (29 to 91 percent), and in types of assay used. Recent research notes that the Aß42/40 ratio should be used over the measurement of Aß42 alone, as this ratio gives a more accurate diagnosis when analyzing CSF AD biomarkers (Hansson, Lehmann, Otto, Zetterberg, & Lewczuk, 2019). Currently, these markers are of marginal clinical utility and do not have an established role in the evaluation of patients in the clinical setting (McDade & Peterson, 2020; Wolk & Dickerson, 2020).

Other biomarkers in CSF such as cargo proteins (e.g. chromogranin-B, α-synuclein), carnosinase I, chromogranin A, and NrCAM (neuronal cell adhesion molecule) have been proposed to provide clinical value for assessment of AD. Levels of each of the above CSF proteins are found to be statistically different among clinically defined patient groups with different degrees of cognitive impairment. However, the absence of a clinical treatment makes this relatively invasive test of questionable clinical utility (Schaffer et al., 2015; Wolk & Dickerson, 2020).

Plasma levels of the E4 variant of apolipoprotein E (ApoE4) may be a less invasive option for diagnosing patients. *ApoE* facilitates the delivery of cholesterol and promotes neuronal functionality and decreased apoE4 levels associated with neuronal degradation are suggestive of AD (Farrer et al., 1997). However, results are inconsistent across various studies. The correlation between altered levels of *ApoE* and ApoE4 with AD pathology is still not definitive, and standardization of methods is needed (Schaffer et al., 2015).

Several studies have been conducted comparing the telomere length of peripheral blood leukocytes with those in the cerebellum (Patel, Shah, Coleman, & Sabbagh, 2011). The shortening of telomere length is indicative of chronic stress on the human body, common in AD patients. However, cerebellar telomere length is not considered a diagnostic tool to evaluate the risk of inherited AD (Patel et al., 2011). Moreover, many other diseases also contain pathologies that induce stress on the body, so results may be confounded with other underlying health problems (Schaffer et al., 2015).

High concentrations of neuronal thread protein (NTP), specifically AD-associated NTP (AD7c-NTP), in urine is found to be representative of AD pathology (Patel et al., 2011). NTP is a brain protein that interacts with antibodies produced against pancreatic thread protein (PTP), a protein that contains structural components highly similar to the fibrils found in neuronal plaques in AD patients (Blennow, Zetterberg, & Fagan, 2012; Patel et al., 2011). Moreover, AD7c-NTP is reflective of neuronal cell dysfunction. Unfortunately, NTP is more useful in determining the progression of the disease in patients who already have AD and not for early diagnosis (Lonneborg, 2008; Schaffer et al., 2015).

Recent studies have also identified a potential relationship between nanoscale extracellular vesicles (exosomes) and AD. Researchers note that exosomes may be an important factor in the progression of AD pathogenesis, but first need to identify the underlying AD-related mechanisms (Jiang et al., 2019).

None of these tests or biomarkers are valid as a stand-alone diagnostic test. The lack of standardized techniques makes diagnostic accuracy across all scenarios difficult to achieve. Current AD diagnostic standards using evaluation of clinical presentation have maintained a high level of accuracy, combined with the lack of a clinical treatment make all early AD diagnostic tests and biomarkers of limited clinical utility (François, Bull, Fenech, & Leifert, 2019; Schaffer et al., 2015). However, research criteria have incorporated both molecular and topographic biomarker data into the research definitions of both symptomatic and pre-symptomatic forms of AD, anticipating that once biomarkers

become more standardized they will be incorporated into clinical diagnostic algorithms for AD (Morris et al., 2014; Wolk & Dickerson, 2020).

Proprietary tests exist for assessment of AD biomarkers. C2N Diagnostics received a "Breakthrough Device Designation" from the FDA in January 2019 for their test measuring the ratio of Aß42 to Aß40 (C2N, 2019a). C2N also offers tests evaluating ApoE levels and other biomarkers, as well as a "Multi-Analyte Dementia Panel" (C2N, 2019b). Other media, such as saliva, have been proposed to provide diagnostic information for AD. A total of 6230 metabolites from saliva were tested, and 3 were found to differentiate between MCI, AD, and cognitively normal patients (Huan et al., 2018).

Clinical Validity and Utility

Dage et al. (2016) studied the correlation of tau protein levels (in plasma) with neuronal damage. A total of 378 cognitively normal (CN) patients were examined, along with 161 patients with mild cognitive impairment (MCI). Baseline plasma tau protein levels were measured. The authors found that plasma tau levels were higher in MCI patients compared to CN patients (4.34 pg/mL for MCI compared to 41.4 pg/ML for CN, p = .078). The authors also performed a regression accounting for age, gender, education, and ApoE, which suggested that higher plasma tau levels were associated with worse memory loss and abnormal cortical thickness (Dage et al., 2016).

Lewczuk et al. (2017) compared the ratio of Aβ42/40 to just Aβ42 as measurements of clinical AD. A total of 200 patients (150 PET-negative, 50 PET-positive for amyloid) were examined and compared to the positron emission tomography (PET) results. The authors found that the ratio of Aβ42/40 agreed more strongly with the PET results (89.4% concordance compared to 74.9% concordance for Aβ42 only). A larger area under the curve was found for the Aβ42/40 measurement compared to just Aβ42 (0.936 compared to 0.814). The authors concluded that "the CSF Aβ42/40 ratio is superior to Aβ42 alone as a marker of amyloid-positivity by PET" (Lewczuk et al., 2017).

Talwar et al. (2016) performed a meta-analysis on CSF ApoE levels in AD patients. Twenty-four studies, including 1064 AD cases and 1338 healthy controls, were reviewed. The authors found that although the total sample did not indicate a significant association between AD and ApoE levels, a subgroup analysis controlling for sample size (n > 43) indicated significantly lower ApoE levels in AD patients compared to controls. The authors considered CSF ApoE levels to have "potential" as an indicator of AD association (Talwar et al., 2016).

H. Wang et al. (2018) evaluated the clinical value of α-synuclein in MCI and AD. The investigators added α-synuclein and phosphorylated α-synuclein to a biomarker panel containing Aβ42, tau, and phosphorylated tau and evaluated the new panel's performance. A total of 729 CSF samples were taken. The phosphorylated version of α-synuclein was found to weakly associate with diagnosis at baseline, but total α-synuclein was not. CSF α-synuclein was found to predict the Alzheimer's Disease Assessment Scale-Cognitive, memory, executive function, and progression from MCI to AD. Longitudinal biomarker changes were not found to differ between groups. Overall, α-synuclein was found to potentially better predict AD changes better than the classic biomarkers (H. Wang et al., 2018).

Zhang et al. (2014) performed a meta-analysis focusing on urinary Alzheimer-associated neuronal thread protein (AD7c-NTP)'s diagnostic ability for AD. Nine studies were reviewed for probable and possible AD, and the authors evaluated AD7c-NTP's sensitivity at 0.87, specificity at 0.89, positive likelihood ratio at 8.13, and negative likelihood ratio at 0.15 (Zhang et al., 2014).

S. Wang, Kojima, Mobley, and West (2019) explored the potential of urinary extracellular vesicle (EV) biomarkers in neurological disorders, including AD, Parkinson Disease (PD), and Huntington Disease (HD). A discovery cohort of 50 individuals was used to create the initial set of EV proteins and a set of 108 individuals was used to further develop the list of biomarkers. The authors identified "hundreds" of commonly expressed EV proteins with stable expression. SNAP23 and calbindin were most elevated in PD cases, with an 86% prediction of diagnostic success in the discovery cohort and 76% prediction of diagnostic success in the replication cohort. Moreover, "Broad Gene set analysis (GSEA) further reveals a prominent link to Alzheimer's disease with 10.4% of the genes known to be down-regulated in the brains from patients with Alzheimer's disease identified in urinary EVs" (S. Wang et al., 2019).

Liu et al. (2018) examined the urinary metabolic profile of β-amyloid 25-35 (Aβ 25-35)-injected rats. This was intended to establish AD in the rats, allowing the impairment of spatial learning and memory to be tested in the rats after 8 weeks. The authors identified the characteristic AD symptoms after 8 weeks (cognitive dysfunction, hippocampus damage, Aβ formation and tau phosphorylation) as well as 45 altered metabolites involving 8 metabolic pathways. The investigators concluded that "pathogenesis of AD was mainly due to gut microbiome dysbiosis, inhibition of energy metabolism, oxidative stress injury and loss of neuronal protective substances" (Liu et al., 2018).

Fossati et al. (2019) studied the correlation of plasma tau with cerebrospinal fluid (CSF) tau and phosphorylated tau (P-tau). A total of 97 subjects were included (68 healthy controls and 29 AD patients). Plasma tau was found to be higher in AD patients compared to healthy controls (area under curve: 0.79). However, CSF tau and plasma tau were "poorly" correlated. The addition of plasma tau to the receiver operating curve of CSF tau increased the area under curve to 0.82 from 0.80 and increased the curve of P-tau to 0.88 from 0.87. The authors concluded that "adding plasma tau to CSF tau or P-tau improves diagnostic accuracy, suggesting that plasma tau may represent a useful biomarker for AD" (Fossati et al., 2019).

Tatebe et al. (2017) developed an immunoassay to quantify plasma p-tau181. Three cohorts were used to validate the assay. In the first cohort (20 AD patients, 15 controls), the tau levels were found to be higher in the AD patients (0.171 ± 0.166 pg/ml in AD versus 0.0405 ± 0.0756 pg/ml in controls). In the second cohort (20 Down Syndrome patients, 22 controls), the tau levels were higher in the Down Syndrome patients (0.767 ± 1.26 pg/ml in DS versus 0.0415 ± 0.0710 pg/ml in controls). Finally, in the third cohort (8 AD patients, 3 other neurological diseases), the tau levels were found to correlate well with the CSF tau levels (r^2 = 0.4525). Overall, the authors suggested that "that the plasma p-tau181 is a promising blood biomarker for brain AD pathology" (Tatebe et al., 2017).

Shen et al. (2019) completed a meta-analysis review of 170 studies to research the role of inflammatory markers in AD and MCI. Increased periphery levels, compared to controls, were found with many types of biomarkers including high-sensitivity C reactive protein, $p<0.05$; interleukin-6, $p<0.005$; soluble tumour necrosis factor receptor 1, $p<0.005$; soluble tumour necrosis factor receptor 2, $p<0.005$; alpha1-antichymotrypsin, $p<0.005$; IL-1β, $p<0.05$; soluble CD40 ligand, $p<0.05$; CSF levels of IL-10, $p<0.05$; monocyte chemoattractant protein-1, $p<0.005$; transforming growth factor-beta 1, $p<0.05$; soluble triggering receptor expressed on myeloid cells2, $p<0.001$; YKL-40, $p<0.001$; α1-ACT, $p<0.001$; nerve growth factor, $p<0.005$; and visinin-like protein-1, $p<0.005$ (Shen et al., 2019). The authors conclude that all of the significant relationships found in this large meta-analysis help to support "the notion that AD and MCI are accompanied by inflammatory responses in both the periphery and CSF" (Shen et al., 2019).

Palmqvist et al. (2019) analyzed two different, cross-sectional, multicenter studies (n=1079). The CSF Aβ42/Aβ40 ratio was used to identify AD via Elecsys immunoassays from Roche Diagnostics; further, plasma neurofilament light chain (NFL), heavy chain (NFH), and *APOE* genotype were also analyzed in the first cohort of patients (n=842). "In cohort 1, plasma Aβ42 and Aβ40 predicted Aβ status with an area under the receiver operating characteristic curve (AUC) of 0.80 (95% CI, 0.77-0.83). When adding *APOE*, the AUC increased significantly to 0.85 (95% CI, 0.82-0.88)" (Palmqvist et al., 2019). Cohort 2 had similar results with a slightly higher AUC (0.86; 95% CI, 0.81-0.91). The authors conclude by stating that "Plasma Aβ42 and Aβ40 measured using Elecsys immunoassays predict Aβ status in all stages of AD with similar accuracy in a validation cohort. Their accuracy can be further increased by analyzing *APOE* genotype" (Palmqvist et al., 2019).

Kim et al. (2020) studied the diagnostic utility of multiplexed sensing to detect multiple AD biomarkers (t-tau, p-tau181, Aβ42, and Aβ40) in human plasma using densely aligned carbon nanotubes (CNT). The CNT sensor assay exhibited superior sensitivity and precision, enabling the platform to accurately quantify AD biomarkers despite the hundreds of other agents in the blood plasma. The densely aligned CNT sensor array was 10–10^3 times more sensitive than the commercially available sandwich-type or enzyme-linked immunosorbent assay. The authors conclude that "by measuring the levels of t-tau/Aβ42, p-tau181/Aβ42, and Aβ42/Aβ40 in clinical blood samples, the sensor array successfully discriminates the clinically diagnosed AD patients from healthy controls with an average sensitivity of 90.0%, a selectivity of 90.0%, and an average accuracy of 88.6%" (Kim et al., 2020).

Simrén et al. (2021) studied the diagnostic and prognostic potential of plasma biomarkers in Alzheimer's disease. Various biomarkers, including phosphorylated-tau181 (P-tau181), neurofilament light, amyloid-β (Aβ42/40), total-tau and glial fibrillary acidic protein, were analyzed in 99 cognitively unimpaired (CU) patients, 107 mild cognitive impairment (MCI) patients, and 103 Alzheimer's disease (AD) patients. According to the results, P-tau181 significantly outperformed all biomarkers in differentiating AD dementia from CU. Higher P-tau181 value was associated with increased cognitive decline and gray matter loss in temporal regions. The authors conclude that "these findings highlight the potential value of plasma P-tau181 as a non-invasive and cost-effective diagnostic and prognostic biomarker in AD" (Simrén et al., 2021).

V. Guidelines and Recommendations

National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) (McKhann et al., 2011)

In 1984, the NINCDS and ADRDA developed clinical criteria for the diagnosis of AD. While evidence to date has used NINCDS/ADRDA's AD classification, in 2011, the National Institute on Aging and the Alzheimer's Association workgroup revised diagnostic criteria for diagnosis of dementia due to Alzheimer's disease (McKhann et al., 2011).

The biomarkers reviewed in this policy are included in a category among revisions to AD diagnostic criteria- "probable AD dementia with evidence of the AD pathophysiological process". However, the diagnostic criteria workgroup publication noted "we do not advocate the use of AD biomarker tests for routine diagnostic purposes at the present time. There are several reasons for this limitation: 1) the core clinical criteria provide very good diagnostic accuracy and utility in most patients; 2) more research needs to be done to ensure that criteria that include the use of biomarkers have been appropriately designed, 3) there is limited standardization of biomarkers from one locale to another, and 4) access to biomarkers is limited to varying degrees in community settings. Presently, the use of

biomarkers to enhance certainty of AD pathophysiological process may be useful in three circumstances: investigational studies, clinical trials, and as optional clinical tools for use where available and when deemed appropriate by the clinician" (McKhann et al., 2011).

Alzheimer's Association (Mattsson et al., 2011; Shaw et al., 2018)

The Alzheimer's Association has initiated a quality control program for CSF markers, noting that "Measurements of CSF AD biomarkers show large between laboratory variability, likely caused by factors related to analytical procedures and the analytical kits. Standardization of laboratory procedures and efforts by kit vendors to increase kit performance might lower variability, and will likely increase the usefulness of CSF AD biomarkers" (Mattsson et al., 2011).

In 2013, the Alzheimer's Association published recommendations for operationalizing the detection of cognitive impairment in the primary care setting (Cordell et al., 2013). It stated that "the use of biomarkers (e.g., CSF tau and beta amyloid proteins, amyloid tracer positron emission tomography scans) was not considered as these measures are not currently approved or widely available for clinical use."

In 2018, a multidisciplinary group of the Alzheimer's Association published criteria for lumbar puncture and CSF testing in the diagnosis of AD The committee recommends CSF biomarker testing for six clinical indications deemed appropriate, as listed in the table below.

Table 1: Clinical indications for appropriate use of LP and cerebrospinal fluid testing in the diagnosis of AD (Shaw et al., 2018)

No.	Indication	Ratings
1	Cognitively unimpaired and within normal range functioning for age as established by objective testing; no conditions suggesting high risk and no SCD [subjective cognitive decline] or expressed concern about developing AD	Inappropriate
2	Cognitively unimpaired patient based on objective testing, but considered by patient, family informant, and/or clinician to be at risk for AD based on family history	Inappropriate
3	Patients with SCD (cognitively unimpaired based on objective testing) who are considered to be at increased risk for AD	**Appropriate**
4	Patients with SCD (cognitively unimpaired based on objective testing) who are not considered to be at increased risk for AD	Inappropriate
5	MCI that is persistent, progressing, and unexplained	**Appropriate**
6	Patients with symptoms that suggest possible AD	**Appropriate**
7	MCI or dementia with an onset at an early age (<65)	**Appropriate**
8	Meeting core clinical criteria for probable AD with typical age of onset	**Appropriate**
9	Symptoms of REM sleep behavior disorder	Inappropriate
10	Patients whose dominant symptom is a change in behavior (e.g., Capgras Syndrome, paranoid delusions, unexplained delirium,	**Appropriate**

	combative symptoms, and depression) and where AD diagnosis is being considered	
11	Use to determine disease severity in patients having already received a diagnosis of AD	Inappropriate
12	Individuals who are apolipoprotein E (APOE) ε4 carriers with no cognitive impairment	Inappropriate
13	Use of LP in lieu of genotyping for suspected ADAD mutation carriers	Inappropriate
14	ADAD mutation carriers, with or without symptoms	Inappropriate

Abbreviations: AD, Alzheimer's disease; LP, lumbar puncture; REM, rapid eye movement; SCD, subjective cognitive decline; ADAD, autosomal dominant Alzheimer's disease; MCI, mild cognitive impairment.

The workgroup has also identified several gray areas where more research is needed. The authors note that "One question that will need further data is whether measuring a ratio of CSF Aβ42/40 yields better diagnostic performance than measuring Aβ42 alone. Another question is how to characterize neurodegeneration using CSF biomarkers, and whether neurodegeneration in the absence of positive amyloid biomarkers predicts progression in persons with MCI" (Shaw et al., 2018). Further, the authors also state that "much more work is needed to document the potential impact of CSF AD biomarker testing on clinical outcomes in patients across the spectrum of AD" (Shaw et al., 2018).

Expert Working Group for the EU Joint Program—Neurodegenerative Disease Research (JPND) BIOMARKAPD Program (Herukka et al., 2017; Simonsen et al., 2017)

An expert working group, comprised of 28 international members, was convened to develop recommendations for CSF AD biomarkers in the diagnostic evaluation of dementia. "The working group recommended using the CSF biomarkers in MCI as an add-on to clinical evaluation alone for predicting functional decline or progression to AD dementia and, based on the available evidence, the recommendation was strong. However, in comparison with the outcome of using hippocampal atrophy as a biomarker, the working group issued a weak recommendation to incorporate CSF biomarkers in the diagnostic workup compared with hippocampal atrophy. Because of insufficient evidence, the working group could not recommend CSF biomarkers as an alternative to FDG-PET or amyloid-PET in predicting future decline or conversion. The working group recommended using CSF biomarkers to inform future disease management, but the strength of this recommendation was weak because of the small amount of evidence (Simonsen et al., 2017)."

Six clinical questions were asked by Simonsen et al. (2017):

1. "In patients with MCI, will CSF biomarkers (alone or in combination) compared with (A) clinical measures alone and/or (B) other imaging biomarkers identify or exclude AD as the cause of MCI?"
    a. Final recommendation: N/A
2. "In patients with MCI, will CSF biomarkers (alone or in combination) compared with (A) clinical measures alone and/or (B) other imaging biomarkers predict conversion to AD dementia within 3 years?"
    a. Final recommendation: Yes, strong

3. "In patients with MCI, will CSF biomarkers (alone or in combination) compared with (A) clinical measures alone and/or (B) other imaging biomarkers predict functional or cognitive decline?"
    a. Final recommendation: Yes, strong
4. "In patients with MCI, will CSF biomarkers (alone or in combination) compared with (A) clinical measures alone and/or (B) other imaging biomarkers change disease management?"
    a. Yes, weak
5. "In patients with MCI, will CSF biomarkers (alone or in combination) compared with (A) clinical measures alone and/or (B) other imaging biomarkers improve patient well-being?"
    a. Yes, weak
6. "In patients with MCI, will CSF biomarkers (alone or in combination) compared with (A) clinical measures alone and/or (B) other imaging biomarkers reduce health care costs?"
    a. No, weak

Additional recommendations were made by Herukka et al. (2017) for CSF AD biomarkers in the diagnostic evaluation of mild cognitive impairment. The same six clinical questions were asked as above by Herukka et al. (2017):

1. "In patients with MCI, will CSF biomarkers (alone or in combination) compared with (A) clinical measures alone and/or (B) other imaging biomarkers identify or exclude AD as the cause of MCI?"
    a. Final recommendation: N/A
2. "In patients with MCI, will CSF biomarkers (alone or in combination) compared with (A) clinical measures alone and/or (B) other imaging biomarkers predict conversion to AD dementia within 3 years?"
    a. Final recommendation: Yes, strong
3. "In patients with MCI, will CSF biomarkers (alone or in combination) compared with (A) clinical measures alone and/or (B) other imaging biomarkers predict functional or cognitive decline?"
    a. Final recommendation: Yes, strong
4. "In patients with MCI, will CSF biomarkers (alone or in combination) compared with (A) clinical measures alone and/or (B) other imaging biomarkers change disease management?"
    a. Yes, weak
5. "In patients with MCI, will CSF biomarkers (alone or in combination) compared with (A) clinical measures alone and/or (B) other imaging biomarkers improve patient well-being?"
    a. Yes, weak
6. "In patients with MCI, will CSF biomarkers (alone or in combination) compared with (A) clinical measures alone and/or (B) other imaging biomarkers reduce health care costs?"
    a. No, weak

National Institute on Aging (NIA, NIH) and Alzheimer's Association (Albert et al., 2011; Jack et al., 2018)

In 2011, the National Institute on Aging and Alzheimer's Association workgroups published guidelines for the diagnosis of AD. The authors also note that "Two fundamental issues about individuals with MCI may be answered by the use of biomarkers: (1) To establish support for the underlying etiology of the clinical syndrome in an individual with MCI, which will have major importance for choosing the correct therapy, when effective treatments are available. (2) To determine the likelihood of cognitive and functional progression for an individual MCI patient to a more severe stage of MCI or to dementia, and the likelihood that this progression will occur within a defined period (Albert et al., 2011)." The authors also note that "in these recommendations, CSF tau is considered to be a strong marker of the neuronal injury associated with AD. However, the two biomarkers in combination are extremely informative. Together with low CSF Aβ42, elevated CSF tau provides a high likelihood of progression to AD in patients with MCI; however, because many biochemical events may be associated with AD, the authors confirm that "Additional work in this area is needed to know how useful these markers will be" (Albert et al., 2011).

In 2018, guidelines were published by the National Institute on Aging and Alzheimer's Association for the preclinical, mild cognitive impairment, and dementia stages of AD, and are intended for use in observational and interventional research, not routine clinical care. These guidelines state that "there is now a growing consensus that application of biomarkers should be harmonized conceptually across the disease continuum and that biomarkers of neurodegeneration are not equivalent to those reflecting amyloid and pathologic tau accumulation" (Jack et al., 2018). Further, regarding the guidelines noted above from 2011, the authors state that "Studies published since 2011 have reinforced the idea that certain imaging and CSF biomarkers are valid proxies for neuropathologic changes of AD…. additional research has highlighted the fact that measures of neurodegeneration or neuronal injury that are commonly used in AD research—magnetic resonance imaging (MRI), fluoro-deoxyglucose (FDG) PET, and CSF total tau (T-tau)—are not specific for AD but rather are nonspecific indicators of damage that may derive from a variety of etiologies, for example, cerebrovascular injury (Jack et al., 2018)." The authors also state that the "data firmly establish that more advanced disease defined by biomarkers predicts greater likelihood of and more rapid cognitive decline. Thus, a solid evidence base exists proving that combinations of biomarker abnormalities are useful for staging the Alzheimer's continuum" (Jack et al., 2018).

Global Biomarker Standardization Consortium (GBSC) (GBSC, 2019)

The GBSC of the Alzheimer's Association has noted that before biomarkers can be used in clinical practice, they "must be standardized and validated on a global scale" (GBSC, 2019).

American Academy of Neurology (AAN) (Petersen et al., 2018)

This guideline was issued as an update to the 2001 AAN guideline on mild cognitive impairment (MCI) and endorsed by the Alzheimer's Association. The panel determined that the field of biomarkers is rapidly evolving. And, according to the panel, there are no biomarkers that that could clearly predict progression in patients with MCI. They have provided the following recommendations:

Recommendation A7a

"For patients and families asking about biomarkers in MCI, clinicians should counsel that there are no accepted biomarkers available at this time (Level B)."

Recommendation A7b

"For interested patients, clinicians may discuss the option of biomarker research or refer patients or both, if feasible, to centers or organizations that can connect patients to this research (e.g., subspecialty centers, Trial Match, ClinicalTrials.gov) (Level C)."

In 2001, the Quality Standards Committee of the American Academy of Neurology issued a "Practice parameter: Diagnosis of dementia (an evidence-based review)." Relevant statements to the current policy include the following:

"...no laboratory tests have yet emerged that are appropriate or routine use in the clinical evaluation of patients with suspected AD. Several promising avenues genotyping, imaging and biomarkers are being pursued, but proof that a laboratory test has value is arduous. Ultimately, the putative diagnostic test must be administered to a representative sample of patients with dementia who eventually have pathologic confirmation of their diagnoses. A valuable test will be one that increases diagnostic accuracy over and above a competent clinical diagnosis."

"There are no CSF or other biomarkers recommended for routine use in determining the diagnosis of AD at this time" (Knopman et al., 2001)

Dementia with Lewy Bodies (DLB) Consortium (McKeith et al., 2017)

The DLB Consortium published a consensus report on the diagnosis and management of dementia with Lewy bodies, which are characteristic of Alzheimer's Disease and other neurological conditions. The Consortium states that "direct biomarker evidence of LB-related pathology is not yet available for clinical diagnosis" (McKeith et al., 2017).

Consensus of the Task Force on Biological Markers in Psychiatry of the World Federation of Societies of Biological Psychiatry (Lewczuk et al., 2018)

The Federation published an update on cerebrospinal fluid (CSF) and blood biomarkers for neurodegenerative dementias. The Federation considers blood-based biomarkers to "offer an ideal complementary step to advanced CSF and neuroimaging biomarkers and can serve as the first-step in a multi-stage process", although these biomarkers still require validation and "a great deal of additional work" (Lewczuk et al., 2018).

International Working Group (IWG) (Dubois et al., 2014)

In 2014, Dubois et al. (2014) published a position paper which presents a new diagnostic algorithm for AD which states: "Aβ1–42 and tau (T-tau or P-tau) should be used in combination, and the CSF AD signature, which combines low Aβ1 and high T-tau or P-tau concentrations, significantly increases the accuracy of AD diagnosis even at a prodromal stage. This combination reaches a sensitivity of 90–95% and a specificity of about 90% in AD. CSF biomarkers cannot be used as standalone tests and should be interpreted in a larger clinical context with confounding factors taken into account. An important concern is the large variability in CSF measures between laboratories and across techniques, and the lack of agreement on cutoff thresholds. These variations have made direct comparison of study results difficult. Several programmes of standardisation, including the Alzheimer's Association Quality Control programme for CSF biomarkers, initiatives within the Joint Program for Neurodegenerative Diseases, and the Global Biomarker Standardisation Consortium, and by industry, will minimise between-laboratory variations in the future and allow identification of uniform cutoff levels."

The IWG describes specific biochemical evidence in their definitions of AD:

"In-vivo evidence of Alzheimer's pathology (one of the following)

- Decreased Aβ1–42 together with increased T-tau or P-tau in CSF
- Increased tracer retention on amyloid PET
- AD autosomal dominant mutation present (in PSEN1, PSEN2, or APP)"

United States Preventive Services Task Force (USPSTF) (Owens et al., 2020)

In 2020, the USPSTF published a recommendations stating that "current evidence is insufficient to assess the balance of benefits and harms of screening for cognitive impairment in older adults" (Owens et al., 2020).

European Federation of Neurological Societies (EFNS) (Hort et al., 2010; Sorbi et al., 2012)

The EFNS published updated guidelines in 2012 for the diagnosis and management of disorders associated with dementia. These guidelines state that "Routine CSF analysis may help to rule out or rule in certain infectious causes (Good Practice Point). CSF abeta 1-42/tau/p-tau assessment helps to differentiate AD (Level B). Assessment of CSF total tau and 14-3-3 protein is recommended in rapidly progressive dementia when sCJD is suspected (Good Practice Point)" (Sorbi et al., 2012).

VI. State and Federal Regulations, as applicable

A search of the FDA Devices database on 07/12/2021 for the terms "peptide," "Alzheimer," "tau," "synuclein," "chromogranin," "neuregulin," "chitinase," "carnosinase," "apoE," and "thread protein" yielded no results pertaining to testing for AD.

On February 15, 2018, the FDA released a statement concerning the advancement of the development of novel treatments for neurological conditions, including Alzheimer's disease. FDA Commissioner Scott Gottlieb, M.D., states, "Symptoms and progression of neurological diseases can also vary significantly across patients, and even within patients, and across organ systems. Some diseases, like Alzheimer's, may progress invisibly for years. Once clinical symptoms become apparent, significant function may already be lost. These issues can make drug development more challenging for companies and are deeply frustrating for patients and caregivers living with these serious and life-threatening conditions. The FDA recognizes the urgent need for new medical treatments for many serious conditions including neurological disorders such as muscular dystrophies, amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), migraine and epilepsy. This requires us to become more nimble, collaborative and patient-focused. As part of our ongoing efforts to expand access to safe and effective treatment options across all disease areas and promote innovation, the FDA is modernizing multiple aspects of our drug regulatory programs – including how we communicate scientific and regulatory guidance for drug development (Gottlieb, 2018)." Concurrently, the FDA released a guidance for industry concerning AD for public comment for 90 days. Within the guidance, the FDA states, "FDA supports and endorses the use of diagnostic criteria that are based on a contemporary understanding of the pathophysiology and evaluation of AD… Important findings applicable to the

categorization of AD along its continuum of progression include the presence of pathophysiological changes as measured by biomarkers, the presence or absence of detectable abnormalities on sensitive neuropsychological measures, and the presence or absence of functional impairment manifested as meaningful daily life impact the present with subjective complaints or reliable observer reports (FDA, 2018)." The final draft of the guidance should be released in the future after the public comment period has concluded.

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

VII. Applicable CPT/HCPCS Procedure Codes

Code Number	Code Description
81099	Unlisted urinalysis procedure
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
0206U	Neurology (Alzheimer disease); cell aggregation using morphometric imaging and protein kinase C-epsilon (PKCe) concentration in response to amylospheroid treatment by ELISA, cultured skin fibroblasts, each reported as positive or negative for Alzheimer disease
0207U	Quantitative imaging of phosphorylated ERK1 and ERK2 in response to bradykinin treatment by in situ immunofluorescence, using cultured skin fibroblasts, reported as a probability index for Alzheimer disease (List separately in addition to code for primary procedure)

Procedure codes appearing in policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

VIII. Evidence-based Scientific References

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Revision History

Revision Date	Summary of Changes
01/01/2022	Initial Effective Date
05/20/2022	Updated background, guidelines, and evidence-based scientific references. Addition of CPT code 0206U, 0207U. Removed CPT 86949