Policy Description

Alzheimer’s 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).

Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request

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, is EXPERIMENTAL AND INVESTIGATIONAL.

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, is EXPERIMENTAL AND INVESTIGATIONAL.

3. Measurement of urinary biomarkers of Alzheimer disease is EXPERIMENTAL AND INVESTIGATIONAL, 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 for prognosis, diagnosis, and/or management of Alzheimer disease or dementia is EXPERIMENTAL AND INVESTIGATIONAL.

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 2015, over 46 million people lived with dementia worldwide, and this number is estimated to
increase to 131.5 million by 2050 (Martin Prince, 2016). The average lifetime risk of developing Alzheimer disease 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).

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, 2018). 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 (Aβ42) peptide, which may be represented by a low ratio of Aβ42 to Aβ40 levels, or a low ratio of Aβ42 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. Currently they are of marginal clinical utility and do not have an established role in the evaluation of patients in the clinical setting (McDade & Peterson, 2018; Wolk & Dickerson, 2018).

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, 2018).

Plasma levels of 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).

None of these tests is 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 (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, 2018).

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 Aβ42 to Aβ40 (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. 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 studied the correlation of tau protein levels (in plasma) with neuronal damage. 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 (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 compared the ratio of Aβ42/40 to just Aβ42 as measurements of clinical AD. 200 patients (150 PET-negative, 50 PET-positive for amyloid) were examined and compared to the 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 performed a meta-analysis on CSF Apolipoprotein E levels in AD patients. 24 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 sub group 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).

Wang et al 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. 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 performed a meta-analysis focusing on urinary Alzheimer-associated neuronal thread protein (AD7c-NTP)'s diagnostic ability for AD. 9 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).

Wang et al explored the potential of urinary extracellular vesicle (EV) biomarkers in neurological disorders, including AD, Parkinson’s Disease (PD), and Huntington’s 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, Kojima, Mobley, & West, 2019).”

Liu et al examined the urinary metabolic profile of β-amyloid 25-35 (Aβ 25-35)-injected rats. This was intended to establish Alzheimer’s Disease (AD) in the rats, and these rats’ impairment of spatial learning and memory was tested 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 studied the correlation of plasma tau with cerebrospinal fluid (CSF) tau and phosphorylated tau (P-tau). 97 subjects were included (68 healthy controls, 29 Alzheimer’s [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. 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 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 (r² = 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).

Guidelines and Recommendations

NINCDS and ADRDA

In 1984, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer’s Disease and Related Disorders Association (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

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.”

The Global Biomarker Standardization Consortium (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).

2017 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 (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 (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)**

In 2014, Dubois et al published a position paper (Dubois et al., 2014) which present 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)"

**State and Federal Regulations, as applicable**


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.

### Applicable CPT/HCPCS Procedure Codes

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<tr>
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<td>Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified</td>
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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

### Evidence-based Scientific References


**Policy Implementation/Update Information**

1/1/20   New Policy

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.