I. 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).

II. Scientific Background

Alzheimer disease (AD) is a devastating neurodegenerative disease with a strong genetic component, and the predominant form of dementia (50–75%)(M. Prince et al., 2013). In 2015, over 46 million people live 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).

Most patients develop clinical symptoms at 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 would seem to have potential utility in the early diagnosis of dementia(McDade & Peterson, 2017). 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).

A number of studies have examined the use of cerebrospinal fluid (CSF) markers for predicting conversion from MCI to dementia (Heister, Brewer, Magda, Blennow, & McEvoy, 2011; Riemschneider et al., 2002; Simonsen et al., 2007). The most replicated CSF biomarkers include: Increased levels of tau or tau protein phosphorylated at Thr 181 (Buerger et al., 2005; Buerger et al., 2002; De Meyer et al., 2010; Ewers et al., 2007; Hansson et al., 2006; Maruyama et al., 2004; Mattsson et al., 2009; Mitchell, 2009; van Rossum et al., 2012; Vemuri et al., 2009). Lower levels of amyloid beta 42 (Aß42) peptide, a low ratio of Aß42 to Aß40 levels, and a low ratio of Aß42 to tau...
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levels (De Meyer et al., 2010; Fagan et al., 2009; Graff-Radford et al., 2007; Landau et al., 2010; Li et al., 2007; Mattsson et al., 2009; Moonis et al., 2005; Petersen et al., 2010; Seppala et al., 2010; Shaw et al., 2009; Skoog et al., 2003; Snider et al., 2009; Vemuri et al., 2009; Visser et al., 2009) However, these tests are subject to variation in sensitivity (36 to 100 percent) and specificity (29 to 91 percent). In addition to concerns about low predictive value, a multicenter-study found that assays for CSF markers can vary (Ritchie et al., 2014), suggesting a need for better standardization of the assay (Mattsson et al., 2009). 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, 2017; Vemuri et al., 2010). Other biomarkers in CSF such as cargo proteins (chromogranin-B, α-synuclein, neuregulin-1, and nonamyloidogenic N-terminal fragment of APP (sAPPα 43 44), YKL-40 (chitinase-3 like-1, human cartilage glycoprotein-39, and chondrex), carnosinase I, chromogranin A, and NrCAM (neuronal cell adhesion molecule). 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).

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 presymptomatic 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, 2017).

III. 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
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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.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

Measurement of biochemical markers of Alzheimer disease is not covered. BCBSNC will not reimburse for non-covered services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member’s Benefit Booklet for availability of benefits. Member’s benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Biochemical Markers of Alzheimer Disease are covered

Not Applicable

When Biochemical Markers of Alzheimer Disease are not covered

Reimbursement is not allowed for the measurement of cerebrospinal fluid biomarkers of Alzheimer disease, including but not limited to tau protein, amyloid beta peptides, α-synuclein, or neural thread proteins.

Reimbursement is not allowed for the 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.

Reimbursement is not allowed for the measurement of urinary biomarkers of Alzheimer disease,
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including but not limited to neural thread proteins, amyloid beta peptides, and urinary extracellular vesicle analysis.

Reimbursement is not allowed for the use of multianalyte assays and/or algorithmic analysis for prognosis, diagnosis and/or management of Alzheimer disease or dementia.

Policy Guidelines

A. Guidelines and Recommendations

Wolk and Dickerson (2017) stated that there are several biomarkers that can support a diagnosis of Alzheimer’s disease, but are not yet recommended for routine diagnostic purposes. The authors further stated that “such testing can add incremental confidence to a clinical diagnosis of AD, however, and can be useful in certain circumstances, including early-onset dementia and atypical presentations of AD in which the differential diagnosis includes other non-amyloid neurodegenerative diseases such as frontotemporal dementia.” However, a role for these measurements in clinical practice has not been established.

Practice Guidelines and Position Statements

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
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scans) was not considered as these measures are not currently approved or widely available for clinical use.”

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."

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.”
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And 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)”

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: 81099, 83520, 86849

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


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Policy Implementation/Update Information

1/1/19 New policy developed. BCBSNC will not provide coverage for biochemical markers of alzheimers disease because it is considered to be investigational. BCBSNC does not provide coverage for investigational services. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (sk)

8/13/19 In the section “When Biochemical Markers of Alzheimers Disease are not covered”, the wording “is considered investigational” is changed to read: “is not covered.” Policy noticed 8/13/19 for effective date 10/15/19. (an)

10/29/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (gm)


12/10/19 Reviewed by Avalon 3rd Quarter CAB. Policy title changed from Biochemical Markers of Alzheimer’s Disease to Biochemical Markers of Alzheimer Disease and Dementia. Added α-synuclein to list of CSF biomarkers. Added amyloid beta peptides and extracellular vesicle analysis to list of urinary biomarkers. Added measurement of plasma and/or serum biomarkers to Not Covered section. Added use of multianalyte assays and/or algorithmic analysis to Not Covered section. (sk)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.