MEDICAL COVERAGE POLICY

SERVICE:	**Biochemical Markers of Alzheimer's Disease**
Policy Number:	**029**
Effective Date:	**03/01/2024**
Last Review:	**12/29/2023**
Next Review:	**12/29/2024**

Important note: *Unless otherwise indicated, medical policies will apply to all lines of business. Medical necessity as defined by this policy does not ensure the benefit is covered. This medical policy does not replace existing federal or state rules and regulations for the applicable service or supply. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan documents. See the member plan specific benefit plan document for a complete description of plan benefits, exclusions, limitations, and conditions of coverage. In the event of a discrepancy, the plan document always supersedes the information in this policy.*

SERVICE: Biochemical Markers of Alzheimer's Disease

PRIOR AUTHORIZATION: Not Applicable

POLICY: Please review the plan's EOC (Evidence of Coverage) or Summary Plan Description (SPD) for details.

Note: Unless otherwise indicated (see below), this policy will apply to all lines of business.

For Medicare plans, please refer to appropriate Medicare NCD (National Coverage Determination) or LCD (Local Coverage Determination). Medicare NCD or LCD specific InterQual criteria may be used when available. If there are no applicable NCD or LCD criteria, use the criteria set forth below.

For Medicaid plans, please confirm coverage as outlined in the Texas Medicaid Provider Procedures Manual | TMHP (TMPPM). If there are no applicable criteria to guide medical necessity decision making in the TMPPM, use the criteria set forth below.

BSWHP considers the use of the following biomarkers, tests and measurements in the diagnosis and management of Alzheimer's Disease to be experimental and investigational and NOT medically necessary.

Biomarkers, tests and measurements not medically necessary include, but are not limited to:

- AB42 or AB42:AB40 ratio
- Apolipoprotein E
- ATP-binding cassette transporter
- Bcl-2 rs956572 polymorphism testing
- Beta amyloid 42 (BA-24, Aβ42) protein (cerebrospinal fluid and plasma)
- Beta-site amyloid precursor protein cleaving enzyme
- Cerebrospinal fluid (CSF) chitinase enzyme activity
- Circadian rhythm analysis
- CSF microRNAs (e.g., hsa-miR-27a-3p)
- CSF neurogranin
- CSF phosphorylated tau at threonine 181 (ptau181), tau/Aβ42, and ptau181/Aβ42
- CSF prion protein concentration

- CSF soluble amyloid precursor proteins (sAPP) level/CSF β-secretase activity
- CSF stathmin protein level
- CSF total tau (t-tau)
- CSF visinin-like protein-1 (VILIP-1) level
- Cognitive event-related potentials (cognitive evoked potentials)
- DNA methylation profiling (brain tissue or peripheral blood)
- Electronystagmography (in the absence of signs of vertigo or balance disorder)
- Genetic testing (e.g., presenilin-1 gene [PSEN1], presenilin-2 gene [PSEN2], apolipoprotein E epsilon 4 allele, amyloid precursor gene, etc.)
- Genetic variation of mitochondrial DNA
- Homocysteine (serum level)
- INNO-BIA AlzBio3 immunoassay kit (a multiplex immunoassay that allows simultaneous quantification of amyloid-beta, p-tau, and t-tau)
- Insulin degrading enzyme polymorphisms
- Long-term measurement of cortisol
- Macular thickness
- Microtubule-associated protein tau (MAPT)
- N-terminal pro-brain natriuretic peptide (NT-proBNP)
- Olfactory screening tests
- Plasma clusterin level
- Plasma prion protein concentration
- Plasma tau
- Pituitary adenylate cyclase-activating polypeptide (PACAP)
- Red blood cell omega-3 fatty acid level 06/06/2018
- Resting state eye-closed cortical electroencephalography
- Serum ceramides
- Serum insulin-like growth factor-1 (IGF-1 also known as somatomedin C)
- Serum microRNAs
- Serum neurofilament light concentration
- Tau protein, total tau, phosphor-tau
- Transforming growth factor-beta1 (TGF-β1)
- TREM2 (triggering receptor expressed on myeloid cells 2)
- Tympanometry (in the absence of hearing loss)
- Urinary AD7c-NTP (neuronal thread protein/neural thread protein)
- Videopupillography and tropicamide drop test

BACKGROUND:

Alzheimer's disease (AD) is an irreversible, progressive brain disorder that occurs gradually and results in memory loss, unusual behavior, personality changes, and a decline in thinking ability. The Alzheimer's Foundation of America (AFA) reports that there are between 4.2 and 5.8 million people affected with AD. The incidence of AD is expected to climb as the population ages. Additionally, the Alzheimer's Association (AA) reports that there are between 200,000 and 500, 000 people with early onset disease occurring before the age of 65. The mean duration from the onset of clinical symptoms to the death of the patient has been reported to be approximately 8.5 years.

Currently the diagnosis of AD is a clinical diagnosis, focusing on the exclusion of other causes of senile dementia. The United States Preventative task force continues to support the use of clinical findings in diagnosis. Psycho-behavioral instruments such as the Mini-Mental State Examination (MMSE) and the Functional Activities Questionnaire are in current use. The MMSE has a sensitivity that ranges from 71 to 96 percent and a specificity range from 56 to 72 percent for dementia. The task force also concluded that current therapies, primarily medication, could only slow AD progression two to seven months and had limited effects on activities of daily living. The benefits of early screening will not be fully realized until better treatment modalities are developed.

In 1988, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's and Related Disorders Association (ADRDA) published clinical criteria for the diagnosis of AD. These organizations defined three categories: Possible AD, Probable AD and Definite AD.

The only difference between Probable and Definite AD is that the Definite AD category requires a brain biopsy confirming the presence of characteristic neurofibrillary tangles. While Definite AD is invariably only confirmed at autopsy, in approximately 85% of those with a diagnosis of Probable AD, pathological findings are found to be consistent.

The clinical criteria currently used for AD in patients with probable AD provide a sensitivity of approximately 85% when compared to autopsy confirmed cases (Definite AD). Therefore, a biomarker should have a sensitivity approaching or exceeding this value. A biomarker should have a specificity of 75% to 85% or greater, and the positive predictive value should be 80% or more.

There are currently no biomarkers that meet the above criteria. To date, all studies have focused on the use of biomarkers with Probable AD. The clinical utility of biomarkers may be greatest in patients with Possible AD, where the diagnosis is more uncertain. Few studies have focused on the use of biomarkers in patients with Possible AD with any follow up to determine the sensitivity and specificity of these markers in earlier stages of the disease.

The use of biomarkers will continue to be of interest to distinguish early AD from other causes of mild cognitive impairment, such as normal aging, vascular dementia or alcohol-related cognitive disorders. Research in patients with incipient AD is challenging because of the long follow-up required, and the

possibility that any control group will also have patients with unrecognized incipient AD. There are inadequate data to determine how the results of these tests could be used to improve patient management, particularly given the limited treatment options. If ongoing research developing drugs targeting early stages of AD comes to fruition, then biomarkers to identify treatment candidates may have an impact on patient management.

The Alzheimer's Association and the National Institute on Aging (NIA), an agency of the U.S. National Institutes of Health (NIH), agree there are currently no validated biomarkers for Alzheimer's disease. They have jointly issued four new criteria and guidelines to diagnose Alzheimer's disease. Three of the four new criteria and guidelines that came out as a result of the research that the Alzheimer's Association and the National Institute on Aging (NIA) completed in April 2011 focus on three stages of Alzheimer's disease: 1) dementia due to Alzheimer's, 2) mild cognitive impairment (MCI) due to Alzheimer's, and 3) preclinical (presymptomatic) Alzheimer's. The 4th guideline updates criteria for documenting and reporting Alzheimer's related changes observed during an autopsy.

According to the research completed by these two agencies in 2011 "In the future, biomarker evidence may provide additional diagnostic certainty, but much more research is needed to identify the most accurate biomarkers and confirm their usefulness. " Please see http://www.alz.org/research/diagnostic_criteria/ for more information.

There are several widely investigated biomarkers (AB42 or AB42:AB40 ratio, total tau, phosphor-tau) for the molecular and degenerative process of AD that appear to be supportive of a diagnosis of AD but are not yet recommended as clinical tools to diagnose, predict or monitor the progress of AD.

MANDATES: None

CODES:
Important note: *Due to the wide range of applicable diagnosis codes and potential changes to codes, an inclusive list may not be presented, but the following codes may apply. Inclusion of a code in this section does not guarantee that it will be reimbursed, and patient must meet the criteria set forth in the policy language.*

CPT Codes:		
CPT Not Covered:	For this indication: 83015, 83018, 83520, 83825	
HCPCS Codes:		
ICD-10 Codes:	F01.50 - F03.91	Dementia
	F07.0 - F07.9	Personality and behavioral disorders due to known physiological condition
	G30.0 - G30.9	Alzheimer's disease
	Z13.858	Encounter for screening for other nervous system disorders (screening for dementia)

POLICY HISTORY:

Status	Date	Action
New	12/6/2010	New policy
Reviewed	12/6/2011	Reviewed.
Reviewed	10/25/2012	Reviewed.
Reviewed	10/3/2013	Checked for updated Hayes rating.
Reviewed	07/24/2014	No changes
Reviewed	08/11/2015	No changes
Reviewed	08/18/2016	No changes
Reviewed	07/18/2017	Updated "Overview" section and coding.
Reviewed	05/29/2018	No changes
Reviewed	08/22/2019	Added list of studies not medically necessary
Reviewed	09/24/2020	Re-formatted for SWHP/FirstCare
Reviewed	09/23/2021	No changes
Reviewed	09/22/2022	No changes
Updated	12/29/2023	Updated Overview section with updated investigational biomarkers not yet recommended for clinical use. Formatting changes, added hyperlinks to NCD and TMPPM, beginning and ending note sections updated to align with CMS requirements and business entity changes.

REFERENCES:

The following scientific references were utilized in the formulation of this medical policy. BSWHP will continue to review clinical evidence related to this policy and make modifications based upon the evolution of the published clinical evidence. Should additional scientific studies become available, and they are not included in the list, please forward the reference(s) to BSWHP so the information can be reviewed by the Medical Coverage Policy Committee (MCPC) and the Quality Improvement Committee (QIC) to determine if a modification of the policy is in order.

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