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**EVIDENCE-BASED CRITERIA  
SECTION: LABORATORY**

**ORIGINAL EFFECTIVE DATE: 12/06/22  
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## **EVALUATION OF BIOMARKERS FOR ALZHEIMER DISEASE**

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Non-Discrimination Statement and Multi-Language Interpreter Services information are located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Evidence-Based Criteria must be read in its entirety to determine coverage eligibility, if any.

This Evidence-Based Criteria provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Evidence-Based Criteria are subject to change as new information becomes available.

For purposes of this Evidence-Based Criteria, the terms "experimental" and "investigational" are considered to be interchangeable.

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## **EVALUATION OF BIOMARKERS FOR ALZHEIMER DISEASE (cont.)**

### **Description:**

Biochemical changes associated with the pathophysiology of Alzheimer disease (AD) are being evaluated to aid in the diagnosis of AD. This includes the potential use of biomarkers, such as amyloid beta peptide 1-42 and total or phosphorylated tau protein, in cerebrospinal fluid (CSF) and urine. Additionally, the potential correlation between CSF biomarkers and positron emission tomography (PET) amyloid scans may assist in selecting appropriate individuals for the initiation or discontinuation of amyloid beta plaque targeted therapy.

### **Alzheimer Disease**

Alzheimer Disease (AD) is a fatal neurodegenerative disease that causes progressive loss in memory, language, and thinking, with the eventual loss of ability to perform social and functional activities in daily life. Survival after a diagnosis of dementia due to AD generally ranges between 4 and 8 years; however, life expectancy can be influenced by other factors, such as comorbid medical conditions. It is estimated that 6.2 million Americans aged 65 and older are currently living with AD dementia, and the number is projected to reach over 12 million by 2050.

### **Biomarkers**

Several potential biomarkers of AD are associated with AD pathophysiology (eg, amyloid beta plaques, neurofibrillary tangles). Altered cerebrospinal fluid (CSF) levels of specific proteins have been found in individuals with AD. These include tau protein, phosphorylated at AD-specific epitopes such as phosphorylated threonine 181 or total tau protein, an amyloid beta peptide such as 1-42 (A $\beta$ 42), and the synaptic protein, neurogranin. Other potential CSF, urinary, and blood peptide markers have been explored. Tau protein is a microtubule-associated molecule found in neurofibrillary tangles that are typical of AD. Tau protein is thought to be related to degenerating and dying neurons and high levels of tau protein in the CSF have been associated with AD. Amyloid beta-42 is a subtype of amyloid beta peptide produced from the metabolism of the amyloid precursor protein. Amyloid beta-42 is the key peptide deposited in amyloid plaques characteristic of AD. Low levels of amyloid beta-42 in the CSF have been associated with AD, perhaps because amyloid beta-42 is deposited in amyloid plaques instead of remaining in the fluid. Investigators have suggested the tau/amyloid beta-42 ratio may be a more accurate diagnostic marker than either alone. Neurogranin is a dendritic protein and CSF measurement may serve as a biomarker for dendritic instability and synaptic degeneration. Elevated CSF neurogranin may predict prodromal AD in MCI and has been confirmed in AD dementia and prodromal AD in several studies.

A variety of kits are commercially available to measure amyloid beta-42 and tau proteins. Between-laboratory variability in CSF biomarker measurement is large. Neural thread protein is associated with neurofibrillary tangles of AD. Both CSF and urine levels of this protein have been investigated as a potential marker of AD. Urine and CSF tests for neural thread protein may be referred to as the AD7C test.

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## EVALUATION OF BIOMARKERS FOR ALZHEIMER DISEASE (cont.)

### Description: (cont.)

More recently, research has focused on blood as a new matrix for AD biomarkers that have already been validated in the CSF. As blood is more accessible than CSF, blood sampling would be preferable to CSF when taking samples to measure AD biomarkers, both for clinical diagnosis or screening. However, developing blood AD biomarkers has proven complex. While the CSF is continuous with the brain extracellular fluid, with a free exchange of molecules from the brain to the CSF, only a fraction of brain proteins enter the bloodstream. Examples of blood biomarkers that are currently under examination for use in AD include amyloid beta, tau protein, and neurofilament light. In a recent retrospective multicohort diagnostic performance study, both plasma tau phosphorylated at threonine 217 (p-tau217) and at threonine 181 (p-tau181) had excellent diagnostic performance for differentiating individuals with AD syndromes from other neurodegenerative disorders. At this time, although a growing area of research, blood AD biomarkers are not addressed in this review.

AlzheimAlert™ and AdMark® CSF analysis are examples of tests that may be available in Clinical Laboratory Improvement Amendments (CLIA) certified labs.

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### Criteria:

- Cerebrospinal fluid biomarker testing as an adjunct to clinical diagnosis in individuals with mild cognitive impairment is considered **experimental or investigational** when any **ONE** or more of the following criteria are met:
  1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
  3. Insufficient evidence to support improvement of the net health outcome; or
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, or
  5. Insufficient evidence to support improvement outside the investigational setting

These biomarkers include, *but are not limited to*:

- Amyloid beta peptides
- Tau protein
- Neural thread proteins



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## EVALUATION OF BIOMARKERS FOR ALZHEIMER DISEASE (cont.)

### Criteria: (cont.)

- Cerebrospinal fluid biomarker testing as an adjunct to clinical diagnosis in individuals with mild dementia due to Alzheimer disease is considered **experimental or investigational** when any **ONE** or more of the following criteria are met:

1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
3. Insufficient evidence to support improvement of the net health outcome; or
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, or
5. Insufficient evidence to support improvement outside the investigational setting

These biomarkers include, *but are not limited to*:

- Amyloid beta peptides
- Tau protein
- Neural thread proteins

- Cerebrospinal fluid biomarker testing as part of an evaluation for the initiation of amyloid beta targeting therapy in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease is considered **experimental or investigational** when any **ONE** or more of the following criteria are met:

1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
3. Insufficient evidence to support improvement of the net health outcome; or
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, or
5. Insufficient evidence to support improvement outside the investigational setting

These biomarkers include, *but are not limited to*:

- Amyloid beta peptides
- Tau protein
- Neural thread proteins

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## EVALUATION OF BIOMARKERS FOR ALZHEIMER DISEASE (cont.)

### Criteria: (cont.)

- Cerebrospinal fluid biomarker testing as part of an evaluation for the continuation of amyloid beta targeting therapy in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease is considered **experimental or investigational** when any **ONE** or more of the following criteria are met:
1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
  3. Insufficient evidence to support improvement of the net health outcome; or
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, or
  5. Insufficient evidence to support improvement outside the investigational setting

These biomarkers include, *but are not limited to*:

- Amyloid beta peptides
- Tau protein
- Neural thread proteins

- Measurement of urinary and blood biomarkers as an adjunct to clinical diagnosis in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease is considered **experimental or investigational** when any **ONE** or more of the following criteria are met:

1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
3. Insufficient evidence to support improvement of the net health outcome; or
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, or
5. Insufficient evidence to support improvement outside the investigational setting

These biomarkers include, *but are not limited to*:

- Neural thread proteins

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### Resources:

Literature reviewed 12/06/22. We do not include marketing materials, poster boards and non-published literature in our review.

Resources prior to 12/06/22 may be requested from the BCBSAZ Medical Policy and Technology Research Department.

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## **EVALUATION OF BIOMARKERS FOR ALZHEIMER DISEASE (cont.)**

### **Resources:** (cont.)

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## **EVALUATION OF BIOMARKERS FOR ALZHEIMER DISEASE (cont.)**

### **Resources:** (cont.)

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## **EVALUATION OF BIOMARKERS FOR ALZHEIMER DISEASE (cont.)**

### **Resources:** (cont.)

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## **EVALUATION OF BIOMARKERS FOR ALZHEIMER DISEASE (cont.)**

### **Resources: (cont.)**

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## **EVALUATION OF BIOMARKERS FOR ALZHEIMER DISEASE (cont.)**

### **Resources: (cont.)**

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## **EVALUATION OF BIOMARKERS FOR ALZHEIMER DISEASE (cont.)**

### **Coding:**

CPT: 81099, 83520, 86849

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### **History:**

### **Date:**

### **Activity:**

Medical Policy Panel

12/06/22

Approved guideline

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### **Policy Revisions:**



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## EVALUATION OF BIOMARKERS FOR ALZHEIMER DISEASE (cont.)

### Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ's Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, [crc@azblue.com](mailto:crc@azblue.com). You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ's Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at <https://ocrportal.hhs.gov/ocr/portal/lobby.jsf>, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1-800-368-1019, 800-537-7697 (TDD). Complaint forms are available at <http://www.hhs.gov/ocr/office/file/index.html>

### Multi-Language Interpreter Services:

Spanish: Si usted, o alguien a quien usted está ayudando, tiene preguntas acerca de Blue Cross Blue Shield of Arizona, tiene derecho a obtener ayuda e información en su idioma sin costo alguno. Para hablar con un intérprete, llame al 602-864-4884.

Navajo: Dii kwe'é atah nilinigií Blue Cross Blue Shield of Arizona haada yit'éego bina'idilkidgo éi doodago Háida bíjá anilyeedigií t'áadoo le'é yina'idilkidgo beehaz'ánii hóloq dii t'áa hazaadk'ehjí háká a'doowolgo bee haz'á doo baqah ilinígóo. Ata' halne'ígíí kojí' bich'í' hodílnih 877-475-4799.

Chinese: 如果您，或是您正在協助的對象，有關於插入項目的名稱 Blue Cross Blue Shield of Arizona 方面的問題，您有權利免費以您的母語得到幫助和訊息。洽詢一位翻譯員，請撥電話 在此插入數字 877-475-4799。

Vietnamese: Nếu quý vị, hay người mà quý vị đang giúp đỡ, có câu hỏi về Blue Cross Blue Shield of Arizona quý vị sẽ có quyền được giúp và có thêm thông tin bằng ngôn ngữ của mình miễn phí. Để nói chuyện với một thông dịch viên, xin gọi 877-475-4799.

Arabic:

إن كان لديك أو لدى شخص تساعد أسئلة بخصوص Blue Cross Blue Shield of Arizona، فلديك الحق في الحصول على المساعدة والمعلومات الضرورية بلغتك من دون أية تكلفة. للتحدث مع مترجم اتصل بـ 877-475-4799.

