FEP Medical Policy Manual

FEP 2.04.13 Genetic Testing for Alzheimer Disease

Annual Effective Policy Date: April 1, 2024

Original Policy Date: December 2023

Related Policies:

2.04.14 - Evaluation of Biomarkers for Alzheimer Disease
5.60.052 - Aducanumab for Alzheimer Disease
6.01.55 - Selected Positron Emission Tomography Technologies for Evaluation of Alzheimer Disease

Genetic Testing for Alzheimer Disease

Description

Description

Alzheimer disease (AD) is the most common cause of dementia in elderly patients. For late-onset AD , there is a component of risk that runs in families, suggesting the contribution of genetic factors. Early-onset AD is much less common but can occur in non-elderly individuals. Early-onset AD has a stronger component of family risk, with clustering in families, thus suggesting an inherited genetic disease-causing variant.

OBJECTIVE

The objective of this evidence review is to determine whether genetic testing improves the net health outcome in individuals who are asymptomatic and at risk for developing Alzheimer disease, and to guide initiation or management of a U.S. Food and Drug Administration-approved amyloid-beta targeting therapy.

POLICY STATEMENT

Targeted genetic testing for a known familial variant in the presenilin (PSEN) genes or amyloid-beta precursor protein (APP) gene associated with autosomal dominant early-onset Alzheimer disease may be considered **medically necessary** in an asymptomatic individual to determine future risk of disease when the following criteria are met:

- The individual has a close relative (i.e., first- or second-degree relative) with a known familial variant associated with autosomal dominant early-onset Alzheimer disease (see Policy Guidelines) AND
- Results of testing will inform reproductive decision making.

Genetic testing for variants in presenilin (PSEN) genes or amyloid-beta precursor protein (APP) gene associated with autosomal dominant early-onset Alzheimer disease may be considered **medically necessary** in an asymptomatic individual to determine future risk of disease when the following criteria are met:

- The individual has a family history of dementia consistent with autosomal dominant Alzheimer disease for whom the genetic status of the affected family members is unavailable AND
- Results of testing will inform reproductive decision making.

Genetic testing for the risk assessment of Alzheimer disease in asymptomatic individuals is considered **investigational** in all other situations. Genetic testing includes but is not limited to, testing for the apolipoprotein E (*APOE*) epsilon 4 allele or triggering receptor expressed on myeloid cells 2 (*TREM2)*.

Genetic testing to guide initiation or management of a U.S. Food and Drug Administration-approved amyloid-beta targeting therapy (e.g., aducanumab) is considered **investigational**. Genetic testing includes but is not limited to, testing for the *APOE* epsilon 4 allele.

POLICY GUIDELINES

Genetic testing for Alzheimer disease (AD) may be offered along with analysis of cerebral spinal fluid levels of the tau protein and amyloid-beta peptide 1-42 (see evidence review 2.04.14). This group of tests may be collectively referred to as the ADmark™ Profile, offered by Athena Diagnostics.

Testing Strategy

The 2011 guidelines from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors recommended that genetic testing for early-onset, autosomal dominant AD should only occur in the context of genetic counseling with support by someone expert in the area. In asymptomatic patients, a testing protocol based on the 1994 International Huntington Association and World Federation of Neurology Research Group on Huntington's Chorea guidelines has been recommended. Consultation of the Alzheimer Disease & Frontotemporal Dementia Mutation Database has also been recommended before disclosure of genetic test results.

A family history of autosomal dominant AD is suggested by 3 affected members in 2 generations. Testing for genes associated with early-onset autosomal dominant AD is appropriate for symptomatic individuals with early-onset Alzheimer disease in the setting of a family history of dementia, the setting of an unknown family history (eg, adoption), or for guiding testing of unaffected family members making reproductive decisions. In individuals at risk of early-onset, autosomal dominant AD, ideally, an affected family member should be tested first to identify the familial variant. Additionally, targeted testing of the parents of a proband with early-onset autosomal dominant AD and a confirmed genetic variant to identify mode of transmission (germline versus *de novo*) may be considered appropriate in some families, such as families with unaffected parents and no affected closely related family members. If no affected family member is available for testing and an asymptomatic individual remains interested in testing to inform reproductive decision making, then in-depth sequencing of the 3 genes (*APP*, *PSEN1*, *PSEN2*) associated with autosomal dominant AD may be indicated.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in deoxyribonucleic acid (DNA) and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology-"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"-to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing.

In November 2017, the 23andMe Personal Genome Service (PGS) Test with Genetic Health Risk Report for Late-onset Alzheimer Disease was granted a de novo classification by the U.S. Food and Drug Administration (class II with general and special controls, FDA product code: PTA). This is a direct-to-consumer test that has been evaluated by the FDA for accuracy, reliability, and consumer comprehension. This test reports whether an individual has variants associated with late-onset AD by detecting the presence of the *APOE* ε4 (rs429353) gene variant.

In June 2021, aducanumab (Aduhelm; Biogen) was approved by the FDA for treatment of AD. This indication was approved under accelerated approval based on reduction in amyloid-beta plaques observed in patients treated with aducanumab. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

In July 2021, FDA amended the approved label to emphasize the disease stages studied in the clinical trials. The amended label states, "Treatment with aducanumab should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied."

The FDA, under the accelerated approval regulations (21 CFR 601.41), requires that Biogen conduct a randomized, controlled trial to evaluate the efficacy of aducanumab-avwa compared to an appropriate control for the treatment of AD. The trial should be of sufficient duration to observe changes on an acceptable endpoint in the patient population enrolled in the trial. The expected date of trial completion is August 2029 with final report submission to the FDA by February 2030.

Aducanumab is reviewed separately in evidence review BCBSA reference policy 5.01.38.

RATIONALE

Summary of Evidence

For individuals who are asymptomatic and at risk for developing late-onset Alzheimer disease (AD) who receive genetic testing, the evidence includes studies on gene associations, test accuracy, and effects on health outcomes. Relevant outcomes are test accuracy and validity, change in disease status, health status measures, and quality of life. Many genes, including apolipoprotein E (*APOE)* , *CR1*, *BIN1*, *PICALM*, and triggering receptor expressed on myeloid cells 2 (*TREM2)*, are associated with late-onset AD. However, the sensitivity and specificity of genetic testing for indicating which individuals will progress to AD is low, and numerous other factors can affect progression. Overall, genetic testing has not been shown to add value to the diagnosis of AD made clinically. The current lack of effective methods to prevent the onset of AD limits the clinical benefit for genetic testing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic, at risk for developing early-onset, autosomal dominant AD, and have a known familial variant who receive targeted genetic testing, the evidence includes studies on gene associations and test accuracy. Relevant outcomes are test accuracy and validity, change in disease status, change in reproductive decision making, health status measures, and quality of life. Variants in the presenilin 1 (*PSEN1)* and presenilin 2 (*PSEN2)* and amyloid-beta precursor protein (*APP)* genes are known to cause early-onset AD in an autosomal dominant pattern with almost complete penetrance. The clinical validity for autosomal dominant early-onset AD will be nearly certain when a familial pathogenic variant has previously been identified. Outside the reproductive setting when used for prognosis or prediction, there is insufficient evidence to draw conclusions on the benefits of genetic testing for pathogenic variants. Testing a prospective parent, when performed in conjunction with genetic counseling, provides more accurate information to guide reproductive planning than family history alone. Therefore, the clinical utility for the purposes of reproductive decision making has been demonstrated for these tests. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic, at risk for developing early-onset, autosomal dominant AD, and have no known familial variant who receive genetic testing, the evidence includes studies on gene associations and test accuracy. Relevant outcomes are test accuracy and validity, change in disease status, change in reproductive decision making, health status measures, and quality of life. Variants in the *PSEN1*, *PSEN2*, and *APP* genes are known to cause early-onset AD in an autosomal dominant pattern with almost complete penetrance. The clinical validity for autosomal dominant early-onset AD will be reasonably certain when a variant found in the database of pathogenic *PSEN1*, *PSEN2*, and *APP* variants are identified. Outside the reproductive setting when used for prognosis or prediction, there is insufficient evidence to draw conclusions on the benefits of genetic testing for pathogenic variants. Testing a prospective parent, when performed in conjunction with genetic counseling, provides more accurate information to guide reproductive planning than family history alone. Therefore, the clinical utility for the purposes of reproductive decision making has been demonstrated for these tests. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with a clinical diagnosis of mild cognitive impairment or mild dementia associated with AD who are considering initiation or discontinuation of an U.S. Food and Drug Administration (FDA)-approved amyloid-beta targeting therapy who receive genetic testing, the evidence includes 2 randomized clinical trials. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, functional outcomes, health status measures, quality of life, and treatment-related morbidity and mortality. The incidence of amyloid-related imaging abnormalities (ARIA) following treatment with the amyloid-beta targeting therapy aducanumab was 23% higher for ARIA-edema in *APOE* ε4 carriers compared to non-carriers, requiring dose modifications in 45% of carriers exposed to a full 10 mg/kg dose. Carriers and non-carriers had similar rates of radiographic severity and symptomatic status. While the *APOE* status of patients may identify those at higher risk for ARIA, the clinical benefit of aducanumab has not been established. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Medical Genetics and Genomics et al

The American College of Medical Genetics and Genomics (ACMG) has listed genetic testing for apolipoprotein E (*APOE*) alleles as 1 of 5 recommendations in the Choosing Wisely initiative.[30,] The recommendation is "Don"t order APOE genetic testing as a predictive test for Alzheimer disease." The stated rationale is that *APOE* is a susceptibility gene for late-onset Alzheimer disease (AD), the most common cause of dementia: "The presence of an ε4 allele is neither necessary nor sufficient to cause AD. The relative risk conferred by the ε4 allele is confounded by the presence of other risk alleles, gender, environment and possibly ethnicity, and the APOE genotyping for AD risk prediction has limited clinical utility and poor predictive value."

In 2011, the ACMG, jointly with the National Society of Genetic Counselors issued the following joint practice guidelines:[2,]

- "Pediatric testing for AD should not occur. Prenatal testing for AD is not advised if the patient intends to continue a pregnancy with a mutation.
- Genetic testing for AD should only occur in the context of genetic counseling (in person or through video conference) and support by someone with expertise in this area.
    - Symptomatic patients: Genetic counseling for symptomatic patients should be performed in the presence of the individual"s legal guardian or family member.
    - Asymptomatic patients: A protocol based on the International Huntington Association and World Federation of Neurology Research Group on Huntington"s Chorea Guidelines is recommended.
- DTC [direct-to-consumer] *APOE* testing is not advised.
- A ≥3-generation family history should be obtained, with specific attention to the age of onset of any neurologic and/or psychiatric symptoms, type of dementia and method of diagnosis, current ages, or ages at death (especially unaffected relatives), and causes of death. Medical records should be used to confirm AD diagnosis when feasible. The history of additional relatives may prove useful, especially in small families or those with a preponderance of early death that may mask a history of dementia.
- A risk assessment should be performed by pedigree analysis to determine whether the family history is consistent with EOAD [early-onset AD] or LOAD [late-onset AD] and with autosomal dominant (with or without complete penetrance), familial, or sporadic inheritance.
- Patients should be informed that currently there are no proven pharmacologic or lifestyle choices that reduce the risk of developing AD or stop its progression.
- The following potential genetic contributions to AD should be reviewed:
    - The lifetime risk of AD in the general population is approximately 10-12% in a 75-80 year lifespan.
    - The effect(s) of ethnicity on risk is still unclear.

- Although some genes are known, there are very likely others (susceptibility, deterministic, and protective) whose presence and effects are currently unknown.

For families in which an autosomal dominant AD gene mutation is a possibility:

- Discuss the risk of inheriting a mutation from a parent affected with autosomal dominant AD is 50%. In the absence of identifying a mutation in apparent autosomal dominant families, risk to offspring could be as high as 50% but may be less.
- Testing for genes associated with early-onset autosomal dominant AD should be offered in the following situations:
  - A symptomatic individual with EOAD in the setting of a family history of dementia or the setting of an unknown family history (eg, adoption).
  - Autosomal dominant family history of dementia with one or more cases of EOAD.
  - A relative with a mutation consistent with EOAD (currently presenilin [*PSEN]1/2* or amyloid-beta precursor protein [*APP*]).

The Alzheimer Disease & Frontotemporal Dementia Mutation Database should be consulted before disclosure of genetic test results, and specific genotypes should not be used to predict the phenotype in diagnostic or predictive testing.

- Discuss the likelihood of identifying a mutation in *PSEN1*, *PSEN2*, or *APP*, noting that current experience indicates that this likelihood decreases with lower proportions of affected family members and/or older ages of onset.
- Ideally, an affected family member should be tested first. If no affected family member is available for testing and an asymptomatic individual remains interested in testing despite counseling about the low likelihood of an informative result (a positive result for a pathogenic mutation), he/she should be counseled according to the recommended protocol. If the affected relative, or their next of kin, is uninterested in pursuing testing, the option of DNA banking should be discussed."

In 2019, ACMG reaffirmed its position in the original document. However, an addendum was issued clarifying 2 points:[31,]

- Use of the phrase "pathogenic variant" should be adopted rather than the word "mutation" in discussing pathogenic variants related to autosomal dominant EOAD.
- Because the original document no longer meets the criteria for an evidence-based practice guideline by either the ACMG or National Society of Genetic Counselors, both societies have since reclassified it as a Practice Resource.

American Academy of Neurology

In 2001 (reaffirmed 2004), the American Academy of Neurology made the following guideline recommendations for the diagnosis of dementia:[32,]

- Routine use of *APOE* genotyping in patients with suspected AD is not recommended at this time.
- There are no other genetic markers recommended for routine use in the diagnosis of AD.

National Institute for Health and Care Excellence

In 2018, the National Institute for Health and Care Excellence (NICE) published guidelines on the assessment, management, and support of people living with dementia.[33,] The guidelines state that *APOE* genotyping should not be used to diagnose Alzheimer's disease.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES

1. Bird TD. Genetic aspects of Alzheimer disease. Genet Med. Apr 2008; 10(4): 231-9. PMID 18414205
2. Goldman JS, Hahn SE, Catania JW, et al. Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. Genet Med. Jun 2011; 13(6): 597-605. PMID 21577118
3. Caselli RJ, Dueck AC, Locke DE, et al. Cerebrovascular risk factors and preclinical memory decline in healthy APOE 4 homozygotes. Neurology. Mar 22 2011; 76(12): 1078-84. PMID 21325652
4. Jonsson T, Stefansson H, Steinberg S, et al. Variant of TREM2 associated with the risk of Alzheimer's disease. N Engl J Med. Jan 10 2013; 368(2): 107-16. PMID 23150908
5. Guerreiro R, Wojtas A, Bras J, et al. TREM2 variants in Alzheimer's disease. N Engl J Med. Jan 10 2013; 368(2): 117-27. PMID 23150934
6. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. May 2011; 7(3): 263-9. PMID 21514250
7. Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimers Dement. Jan 2012; 8(1): 1-13. PMID 22265587
8. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. May 2011; 7(3): 270-9. PMID 21514249
9. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Genetic Testing for Alzheimer's Disease: APOE Epsilon 4 Allele. TEC Assessments. 1999;Volume 14:Tab 7.
10. National Center for Biotechnology Information. GTR: Genetic Testing Registry. n.d.; https://www.ncbi.nlm.nih.gov/gtr/. Accessed September 12, 2022.
11. Slooter AJ, Cruts M, Hofman A, et al. The impact of APOE on myocardial infarction, stroke, and dementia: the Rotterdam Study. Neurology. Apr 13 2004; 62(7): 1196-8. PMID 15079025
12. Myers RH, Schaefer EJ, Wilson PW, et al. Apolipoprotein E epsilon4 association with dementia in a population-based study: The Framingham study. Neurology. Mar 1996; 46(3): 673-7. PMID 8618665
13. Bird TD. Alzheimer Disease Overview. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews. Seattle, WA: University of Washington; 2015.
14. Naj AC, Jun G, Reitz C, et al. Effects of multiple genetic loci on age at onset in late-onset Alzheimer disease: a genome-wide association study. JAMA Neurol. Nov 2014; 71(11): 1394-404. PMID 25199842
15. Lambert JC, Ibrahim-Verbaas CA, Harold D, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat Genet. Dec 2013; 45(12): 1452-8. PMID 24162737
16. Blue EE, Horimoto ARVR, Mukherjee S, et al. Local ancestry at APOE modifies Alzheimer's disease risk in Caribbean Hispanics. Alzheimers Dement. Dec 2019; 15(12): 1524-1532. PMID 31606368
17. Chao S, Roberts JS, Marteau TM, et al. Health behavior changes after genetic risk assessment for Alzheimer disease: The REVEAL Study. Alzheimer Dis Assoc Disord. Jan-Mar 2008; 22(1): 94-7. PMID 18317253
18. Green RC, Roberts JS, Cupples LA, et al. Disclosure of APOE genotype for risk of Alzheimer's disease. N Engl J Med. Jul 16 2009; 361(3): 245-54. PMID 19605829
19. Christensen KD, Roberts JS, Whitehouse PJ, et al. Disclosing Pleiotropic Effects During Genetic Risk Assessment for Alzheimer Disease: A Randomized Trial. Ann Intern Med. Feb 02 2016; 164(3): 155-63. PMID 26810768
20. Elias-Sonnenschein LS, Viechtbauer W, Ramakers IH, et al. Predictive value of APOE-4 allele for progression from MCI to AD-type dementia: a meta-analysis. J Neurol Neurosurg Psychiatry. Oct 2011; 82(10): 1149-56. PMID 21493755
21. Kowalska A, Wender M, Florczak J, et al. Molecular genetics of Alzheimer's disease: presenilin 1 gene analysis in a cohort of patients from the Poznan region. J Appl Genet. 2003; 44(2): 231-4. PMID 12817569
22. Janssen JC, Beck JA, Campbell TA, et al. Early onset familial Alzheimer's disease: Mutation frequency in 31 families. Neurology. Jan 28 2003; 60(2): 235-9. PMID 12552037
23. Giau VV, Bagyinszky E, Youn YC, et al. APP, PSEN1 , and PSEN2 Mutations in Asian Patients with Early-Onset Alzheimer Disease. Int J Mol Sci. Sep 25 2019; 20(19). PMID 31557888
24. Stoychev KR, Stoimenova-Popova M, Chumpalova P, et al. A Clinical Case of Patient Carrying Rare Pathological PSEN1 Gene Mutation (L424V) Demonstrates the Phenotypic Heterogenity of Early Onset Familial AD. Front Psychiatry. 2019; 10: 857. PMID 31920735
25. Cochran JN, McKinley EC, Cochran M, et al. Genome sequencing for early-onset or atypical dementia: high diagnostic yield and frequent observation of multiple contributory alleles. Cold Spring Harb Mol Case Stud. Dec 2019; 5(6). PMID 31836585
26. Rahman B, Meiser B, Sachdev P, et al. To know or not to know: an update of the literature on the psychological and behavioral impact of genetic testing for Alzheimer disease risk. Genet Test Mol Biomarkers. Aug 2012; 16(8): 935-42. PMID 22731638
27. Biogen. Highlights of Prescribing Information: ADUHELM (aducanumab-avwa) injection, for intravenous use. 2022; https://biogencdn.com/us/aduhelm-pi.pdf. Accessed on September 12, 2022.
28. Burkett P, Chalkias S, Umans K, et al. Considerations for the Real-World Management of ARIA from the Aducanumab Phase 3 Studies EMERGE and ENGAGE. Poster presented at: Alzheimer's Association International Conference; July 2021; Denver, Colorado. Available at: https://investors.biogen.com/static-files/7645a41f-4632-4ddd-a6b0-b2ea38cf5bda. Accessed on September 12, 2022.
29. Salloway S, Chalkias S, Barkhof F, et al. Amyloid-Related Imaging Abnormalities in 2 Phase 3 Studies Evaluating Aducanumab in Patients With Early Alzheimer Disease. JAMA Neurol. Jan 01 2022; 79(1): 13-21. PMID 34807243

30. American College of Medical Genetics and Genomics. Choosing Wisely. 2015; http://www.choosingwisely.org/societies/american-college-of-medical-genetics-and-genomics/. Accessed September 12, 2022.
31. Goldman JS, Hahn SE, Catania JW, et al. ADDENDUM: Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. Genet Med. Oct 2019; 21(10): 2404. PMID 31217590
32. Knopman DS, DeKosky ST, Cummings JL, et al. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. May 08 2001; 56(9): 1143-53. PMID 11342678
33. National Institute for Health and Care Excellence (NICE). Dementia: assessment, management and support for people living with dementia and their carers [NG97]. 2018; https://www.nice.org.uk/guidance/ng97. Accessed September 12, 2022.

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2023	New Policy	New Policy for FEP