Geisinger

Geisinger Health Plan Policies and Procedure Manual

Policy: MP350

Section: Medical Benefit Policy

Subject: Genetic and Biochemical Testing for Alzheimer's Disease and Dementia

Applicable Lines of Business

Commercial	**X**	**CHIP**	**X**
Medicare	**X**	**ACA**	**X**
Medicaid	**X**		

I. Policy: Genetic and Biochemical Testing for Alzheimer's Disease and Dementia

II. Purpose/Objective:

To provide a policy of coverage regarding Genetic and Biochemical Testing for Alzheimer's Disease and Dementia

III. Responsibility:

A. Medical Directors
B. Medical Management

IV. Required Definitions

1. Attachment – a supporting document that is developed and maintained by the policy writer or department requiring/authoring the policy.
2. Exhibit – a supporting document developed and maintained in a department other than the department requiring/authoring the policy.
3. Devised – the date the policy was implemented.
4. Revised – the date of every revision to the policy, including typographical and grammatical changes.
5. Reviewed – the date documenting the annual review if the policy has no revisions necessary.

V. Additional Definitions

Medical Necessity or Medically Necessary means Covered Services rendered by a Health Care Provider that the Plan determines are:

a. appropriate for the symptoms and diagnosis or treatment of the Member's condition, illness, disease or injury;
b. provided for the diagnosis, and the direct care and treatment of the Member's condition, illness disease or injury;
c. in accordance with current standards of good medical treatment practiced by the general medical community.
d. not primarily for the convenience of the Member, or the Member's Health Care Provider; and
e. the most appropriate source or level of service that can safely be provided to the Member. When applied to hospitalization, this further means that the Member requires acute care as an inpatient due to the nature of the services rendered or the Member's condition, and the Member cannot receive safe or adequate care as an outpatient.

Medicaid Business Segment

Medically Necessary — A service, item, procedure, or level of care that is necessary for the proper treatment or management of an illness, injury, or disability is one that:

- Will, or is reasonably expected to, prevent the onset of an illness, condition, injury or disability.
- Will, or is reasonably expected to, reduce or ameliorate the physical, mental or developmental effects of an

illness, condition, injury or disability.
- Will assist the Member to achieve or maintain maximum functional capacity in performing daily activities, taking into account both the functional capacity of the Member and those functional capacities that are appropriate for Members of the same age

DESCRIPTION:
Alzheimer disease is the most common cause of dementia. Alzheimer disease is a progressive, irreversible neurodegenerative disease. Individuals are typically classified into early-onset and late-onset disease using the age of 65 years as a cutoff. Genetic testing and biomarker testing has been proposed as a means to identifying a definitive diagnosis, improving understanding for the family, and allowing at-risk relatives to have predictive testing.

Genetic testing in the setting of neurological disorders lead to management changes primarily affecting the following areas of management: drug selection, drug repurposing, clinical trial eligibility, screening for non-neurologic comorbidities, and prognosis.

Studies of patients with early-onset Alzheimer's disease, both familial and apparently sporadic, have reported genetic testing yields of 5–13% when analyzing APP, PSEN1, and PSEN2. The clinical utility beyond familial risk remains unclear, and this testing is still not widely utilized. However, APOE genotyping has recently been used for dose stratification in experimental and emerging anti-amyloid therapeutics, and may impact prescribing decisions for lecanemab and other emerging amyloid-targeting agents.

Frontotemporal dementia (FTD) is an important cause of young-onset and non-autosomal dominant dementia. Three genes account for the majority of genetic FTD: MAPT, GRN, and C9orf72, though many other genes have been implicated. In those with FTD-ALS and family history of either condition, up to 88% have a C9orf72 pathogenic RE. Variants in GRN account for about 5% of all FTD and 20% of FTD with positive family history.

INDICATIONS:
Germline testing via panel sequencing as a first line test is covered and considered medically necessary in the in members meeting the following clinical criteria:

1.Diagnosis of Amyotrophic Lateral Sclerosis (ALS) at any age, regardless of family history AND is considering therapy with Tofersen
2. Diagnosis of frontotemporal dementia at any age, regardless of family history, when necessary to aid in establishing a diagnosis.

Genoptying of APOE is covered and considered medically necessary ONLY in members meeting the following clinical criteria:
1. Clinical diagnosis of Alzheimer's disease AND
2. Required for eligibility to participate in clinical trial for anti-amyloid therapeutics

EXCLUSIONS:
The Plan considers testing of genetic markers APOE, TREM2, APP, PSEN1, and/or PSEN2 for the diagnosis of Alzheimer's disease to be **experimental, investigational or unproven** and therefore **NOT COVERED** as a diagnostic technique for individuals in:
- symptoms suggestive of Alzheimer's disease/ early-onset Alzheimer's disease(EOAD), or
- asymptomatic individuals with a family history of Alzheimer's disease/ early onset Alzheimer's disease.

There is insufficient evidence in the peer-reviewed medical literature to support APOE genotyping OR panel testing for Alzheimer disease-related gene variants. There is not sufficient data to support that this testing improves health outcomes or providers meaningful therapeutic opportunities for people diagnosed with Alzheimer's disease, dementia, or mild cognitive impairment unless otherwise specified in this policy.

The Plan considers measurements of serum, urinary, CSF or skin fibroblast biochemical markers (including but not limited to tau protein, AB-42, neural thread protein) to be **experimental, investigational or unproven** and therefore **NOT COVERED** as a diagnostic technique for individuals with symptoms suggestive of Alzheimer's disease. There is insufficient evidence in the peer-reviewed medical literature to support testing for Alzheimer disease-related biomarkers improves health outcomes for people diagnosed with Alzheimer's disease, dementia, or mild cognitive impairment.

The Plan considers genetic testing or measurements of biochemical markers as a screening technique in asymptomatic individuals with or without a family history of Alzheimer's disease to be **experimental, investigational or unproven** and

therefore **NOT COVERED.** There is insufficient evidence in the peer-reviewed medical literature to support testing for Alzheimer disease-related biomarkers improves health outcomes for people diagnosed with Alzheimer's disease, dementia, or mild cognitive impairment.

Medicaid Business Segment:

Any requests for services, that do not meet criteria set in the PARP, may be evaluated on a case by case basis.

Note: A complete description of the process by which a given technology or service is evaluated and determined to be experimental, investigational or unproven is outlined in MP 15 - Experimental Investigational or Unproven Services or Treatment.

CODING ASSOCIATED WITH: Genetic and Biochemical Testing for Alzheimer's Disease and Dementia
The following codes are included below for informational purposes and may not be all inclusive. Inclusion of a procedure or device code(s) does not constitute or imply coverage nor does it imply or guarantee provider reimbursement. Coverage is determined by the member specific benefit plan document and any applicable laws regarding coverage of specific services. Please note that per Medicare coverage rules, only specific CPT/HCPCS Codes may be covered for the Medicare Business Segment. Please consult the CMS website at www.cms.gov ***or the local Medicare Administrative Carrier (MAC) for more information on Medicare coverage and coding requirements.***

81401 Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) [when specified as the following]:

- APOE (apolipoprotein E) (eg, hyperlipoproteinemia type III, cardiovascular disease, Alzheimer disease), common variants (eg, *2, *3, *4)

81405 Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) [when specified as the following]:

- PSEN1 (presenilin 1) (eg, Alzheimer disease), full gene sequence

81406 Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) [when specified as the following]:

- APP (amyloid beta [A4] precursor protein) (eg, Alzheimer disease), full gene sequence
- PSEN2 (presenilin 2 [Alzheimer disease 4]) (eg, Alzheimer disease), full gene sequence

83520 Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified [when specified as tau protein, amyloid beta peptide testing]

84999 Unlisted chemistry procedure [when specified as tau protein, amyloid beta peptide or neural thread protein biochemical testing]

0206U Neurology (Alzheimer disease); cell aggregation using morphometric imaging and protein kinase C-epsilon (PKCe) concentration in response to amylospheroid treatment by ELISA, cultured skin fibroblasts, each reported as positive or negative for Alzheimer disease *{DISCERN™, NeuroDiagnostics, NeuroDiagnostics}*

0207U Neurology (Alzheimer disease); quantitative imaging of phosphorylated ERK1 and ERK2 in response to bradykinin treatment by in situ immunofluorescence, using cultured skin fibroblasts, reported as a probability index for Alzheimer disease *{DISCERN™, NeuroDiagnostics, NeuroDiagnostics}*

0289U Neurology (Alzheimer disease), mRNA, gene expression profiling by RNA sequencing of 24 genes, whole blood, algorithm reported as predictive risk score { *MindX Blood Test™* }

0358U Neurology (mild cognitive impairment), analysis of β-amyloid 1-42 and 1-40, chemiluminescence enzyme immunoassay, cerebral spinal fluid, reported as positive, likely positive, or negative {*Lumipulse G-Amyloid Ratio (1-42/1-40) Test}*

S3852 DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer's disease

0346U Beta amyloid, Aβ40 and Aβ42 by liquid chromatography with tandem mass spectrometry (LC-MS/MS), ratio, plasma*{QUEST AD-Detect™, Beta-Amyloid 42/40 Ratio, Plasma,}*

0412U Beta amyloid, Aβ42/40 ratio, immunoprecipitation with quantitation by liquid chromatography with tandem mass

spectrometry (LC-MS/MS) and qualitative ApoE isoform-specific proteotyping, plasma combined with age, algorithm reported as presence or absence of brain amyloid pathology *{ PrecivityAD® blood test}*

ICD-10 Diagnosis

- F03.90-F03.91 Unspecified dementia
- G30.0-G30.9 Alzheimer's disease
- G31.1 Senile degeneration of brain, not elsewhere classified
- R41.0 Disorientation, unspecified
- R41.3 Other amnesia (memory loss NOS)
- R41.81 Age-related cognitive decline

LINE OF BUSINESS:
Eligibility and contract specific benefits, limitations and/or exclusions will apply. Coverage statements found in the line of business specific benefit document will supersede this policy. For Medicare, applicable LCD's and NCD's will supercede this policy. For PA Medicaid Business segment, this policy applies as written.

REFERENCES:
Andreasen N, Blennow K. CSF biomarkers for mild cognitive impairment and early Alzheimer's disease. Clinical Neurol Neurosurg. 2005; 107:165-173.

Beecham GW, Martin ER, Li YJ, et al. Genome-wide association study implicates a chromosome 12 risk locus for late-onset Alzheimer disease. Am J Hum Genet. 2009; 84(1):35-43.

Chirila FV, Khan TK, Alkon DL. Fibroblast aggregation rate converges with validated peripheral biomarkers for Alzheimer's disease. J Alzheimers Dis. 2014; 42(4):1279-1294.

Hsuing GR, Sadovnick AD, Feldman H. Apolipoptrotein E 4 genotype as a risk factor for cognitive decline and dementia. Data from the Canadian Study of Health and Aging. CMAJ. 2004; 171:863-867.

Kapaki E, Liappas I. Paraskevas GP, et al. The diagnostic value of tau protein, beta-amyloid (1-42) and their ration for the discrimination of alcohol-related cognitive disorders from Alzheimer's disease in the early stages. Internat J Geriatric Psych. 2005; 20:722-729

Sinha S. The role of beta-amyloid in Alzheimer's disease. Med Clin North Am. 2002; 86(3): 629-639.

Teunissen CE, de Vente J, Steinbusch HW, De Bruijn C. Biochemical markers related to Alzheimer's dementia in serum and cerebrospinal fluid. Neurobiol Aging. 2002; 23(4):485-508

Ritchie C, Smailagic N, Noel-Storr AH, et al. Plasma and cerebrospinal fluid amyloid beta for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst Rev. 2014;6:CD008782.

Olsson B, Lautner R, Andreasson U, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet Neurol. Jun 2016;15(7):673-684.

Alexopoulos P, Werle L, Roesler J, et al. Conflicting cerebrospinal fluid biomarkers and progression to dementia due to Alzheimer's disease. Alzheimer's research & therapy. 2016;8(1):51.

van Maurik IS, Zwan MD, Tijms BM, et al. Interpreting Biomarker Results in Individual Patients With Mild Cognitive Impairment in the Alzheimer's Biomarkers in Daily Practice (ABIDE) Project. JAMA Neurol. 2017;74(12):1481-91.

Trombetta BA, Carlyle BC, Koenig AM, et al. The technical reliability and biotemporal stability of cerebrospinal fluid biomarkers for profiling multiple pathophysiologies in Alzheimer's disease. PloS one. 2018;13(3):e0193707.

Shaw, L. M., Arias, J., Blennow, K., Galasko, D., Molinuevo, J. L., Salloway, et al Appropriate use criteria for lumbar puncture and cerebrospinal fluid testing in the diagnosis of Alzheimer's disease. Alzheimers Dement, 2018;14(11), 1505-1521

Palmqvist, S., Janelidze, S., Stomrud, E., Zetterberg, H., Karl, J., Zink, et al. Performance of Fully Automated Plasma Assays as Screening Tests for Alzheimer Disease-Related β-Amyloid Status. JAMA Neurol, 2019; 76(9), 1060-1069

Hansson, O., Lehmann, S., Otto, M., Zetterberg, H., & Lewczuk, P. Advantages and disadvantages of the use of the CSF Amyloid β (Aβ) 42/40 ratio in the diagnosis of Alzheimer's Disease. Alzheimers Res Ther, 2019;11(1), 34

Fossati, S., Ramos Cejudo, J., Debure, L., et al. Plasma tau complements CSF tau and P-tau in the diagnosis of Alzheimer's disease. Alzheimers Dement 2019;11, 483-492.

Fink HA, Linskens EJ, Silverman PC, et al. Accuracy of Biomarker Testing for Neuropathologically Defined Alzheimer Disease in Older Adults With Dementia. Ann Intern Med. 2020;172(10):669-77.

Hayes. Clinical Utility Evaluation. Genetic Testing for APP, PSEN1, and PSEN2 for Early-Onset Alzheimer Disease. 4/6/2021. Updated Mar 18, 2022

Hayes. Clinical Utility Evaluation. APOE Genetic Testing for Alzheimer Disease. 4/6/2021. Updated Mar 18, 2022

Dubois B, Villain N, Frisoni GB, et al. Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. Lancet Neurol. 2021; 20(6):484-496.

Roggenbuck J, Quick A, Kolb SJ. Genetic testing and genetic counseling for amyotrophic lateral sclerosis: an update for clinicians. Genetics in medicine 2017;19(3):267-274.

Ashton NJ, Pascoal TA, Karikari TK, et al. Plasma p-tau231: A new biomarker for incipient Alzheimer's disease pathology. Acta Neuropathol. 2021;141(5):709-724.

Wong, T. H., Seelaar, H., Melhem, S., et al Genetic screening in early-onset Alzheimer's disease identified three novel presenilin mutations. Neurobiol Aging, 2020;86, 201.e209-201.e214

Weintraub, S., Teylan, M., Rader, B., et al APOE is a correlate of phenotypic heterogeneity in Alzheimer disease in a national cohort. Neurology, 2020;94(6), e607-e612

Miller TM, Cudkowicz ME, et al. Trial of Antisense Oligonucleotide Tofersen for SOD1 ALS. NEJM 2022;387(12):1099-1110.

Ji AL, Zhang X, Chen WW, Huang WJ. Genetics insight into the amyotrophic lateral sclerosis/frontotemporal dementia spectrum. J Med Genet. 2017 Mar;54(3):145-154. doi: 10.1136/jmedgenet-2016-104271. Epub 2017 Jan 13. PMID: 28087719.

Huq AJ, Sexton A, Lacaze P, et al. Genetic testing in dementia-A medical genetics perspective. Int J Geriatr Psychiatry. 2021 Aug;36(8):1158-1170. doi: 10.1002/gps.5535. Epub 2021 Mar 28. PMID: 33779003.

Roggenbuck J, Fong JC. Genetic Testing for Amyotrophic Lateral Sclerosis and Frontotemporal Dementia: Impact on Clinical Management. Clin Lab Med. 2020 Sep;40(3):271-287. doi: 10.1016/j.cll.2020.05.002. Epub 2020 Jul 2. PMID: 32718499.

Roggenbuck J, Eubank BHF, Wright J, et al; ALS Genetic Testing and Counseling Guidelines Expert Panel. Evidence-based consensus guidelines for ALS genetic testing and counseling. Ann Clin Transl Neurol. 2023;10(11):2074-2091. doi:10.1002/acn3.51895

Dratch L, Azage M, Baldwin A, et al. Genetic testing in adults with neurologic disorders: indications, approach, and clinical impacts. J Neurol. Published online October 27, 2023. doi:10.1007/s00415-023-12058-6

This policy will be revised as necessary and reviewed no less than annually.
Devised: 11/21

Revised: 12/22 (clarified exclusion language); 12/23 (expand description, add indications)

Reviewed:

Geisinger Health Plan may refer collectively to health care coverage sponsors Geisinger Health Plan, Geisinger Quality Options, Inc., and Geisinger Indemnity Insurance Company, unless otherwise noted. Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

Coverage for experimental or investigational treatments, services and procedures is specifically excluded under the member's certificate with Geisinger Health Plan. Unproven services outside of an approved clinical trial are also specifically excluded under the member's certificate with Geisinger Health Plan. This policy does not expand coverage to services or items specifically excluded from coverage in the member's certificate with Geisinger Health Plan. Additional information can be found in MP015 Experimental, Investigational or Unproven Services.

Prior authorization and/or pre-certification requirements for services or items may apply. Pre-certification lists may be found in the member's contract specific benefit document. Prior authorization requirements can be found at https://www.geisinger.org/health-plan/providers/ghp-clinical-policies