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Harmony Health Plan of Illinois, Inc.

Missouri Care, Inc.

*'Ohana Health Plan, a plan offered by
WellCare Health Insurance of Arizona, Inc.*

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WellCare of Texas, Inc.

WellCare Prescription Insurance, Inc.

Windsor Health Plan

Windsor Rx Medicare Prescription Drug Plan

Genetic Testing for Alzheimer's Disease

Policy Number: HS-055

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**Revised Date(s): 11/11/2009;
11/12/2010; 10/6/2011; 11/1/2012;
11/7/2013; 8/7/2014**

APPLICATION STATEMENT

The application of the Clinical Coverage Guideline is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations and state-specific Medicaid mandates, if any.

DISCLAIMER

The Clinical Coverage Guideline is intended to supplement certain standard WellCare benefit plans. The terms of a member's particular Benefit Plan, Evidence of Coverage, Certificate of Coverage, etc., may differ significantly from this Coverage Position. For example, a member's benefit plan may contain specific exclusions related to the topic addressed in this Clinical Coverage Guideline. When a conflict exists between the two documents, the Member's Benefit Plan always supersedes the information contained in the Clinical Coverage Guideline. Additionally, Clinical Coverage Guidelines relate exclusively to the administration of health benefit plans and are NOT recommendations for treatment, nor should they be used as treatment guidelines. The application of the Clinical Coverage Guideline is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations and state-specific Medicaid mandates, if any. *Note: The lines of business (LOB) are subject to change without notice; consult www.wellcare.com/Providers/CCGs for list of current LOBs.*

BACKGROUND

Alzheimer's disease (AD), which is the most common form of dementia, is a progressive, neurodegenerative disorder characterized by amyloid plaques and neurofibrillary tangles in the brain. Up to 4 million Americans currently suffer from AD, and the estimated lifetime risk of this disorder in the general population is 15%. Early onset AD, in which symptoms appear before age 60, is rare, while late-onset AD, which develops in people 60 years and older, is the most common form of the disease. Some early-onset AD runs in families and involves an autosomal dominant pattern of inheritance. Although rare familial forms of AD exist, most patients have no clear family history and are classified as having sporadic AD. Early diagnosis of AD can be difficult due to the heterogeneity in age of onset and clinical presentation, and the need to rule out other causes of dementia that can have a similar clinical appearance.¹

At the present time, definitive diagnosis of AD is made only by examination of brain tissue at autopsy and is based on neuropathologic criteria, such as the presence of intracellular neurofibrillary tangles and amyloid plaques. Clinical diagnosis of AD by an experienced physician can be made with up to 90% accuracy and involves patient history, physical and neurological examinations, laboratory tests, brain imaging, and neuropsychological testing to rule out other, sometimes treatable, causes of dementia. Molecular studies have identified mutations in four genes that either cause or increase susceptibility to AD. They are the amyloid precursor protein (*APP*) gene, the presenilin-1 (*PS-1*) gene, the presenilin-2 (*PS-2*) gene, and the apolipoprotein E (*APOE*) gene.¹

A 2010 Hayes report on genetic testing for early-onset familial Alzheimer's disease found a lack of validity to testing. Similarly, a 2009 Hayes report on genetic testing for late-onset familial Alzheimer's disease also found a lack of validity for testing.^{2,3}

The American College of Medical Genetics and the National Society of Genetic Counselors practice guidelines state the benefits of genetic testing.⁴

- Pediatric testing for AD should not occur and prenatal testing 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 videoconference) and support by someone with expertise in this area. Genetic counseling for symptomatic patients should be performed in the presence of the individual's legal guardian or family member. A protocol based on the International Huntington Association and World Federation of Neurology Research Group on Huntington's Chorea Guidelines is recommended for asymptomatic patients;
- 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 early onset AD (EOAD) or late onset AD (LOAD) 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 of 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; and
- 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 when:
 - A symptomatic individual with EOAD in the setting of a family history of dementia or in the setting of an unknown family history (e.g., adoption).
 - Autosomal dominant family history of dementia with one or more cases of EOAD.
 - A relative with a mutation consistent with EOAD (currently *PSEN1/2* or *APP*).

The Alzheimer Disease & Frontotemporal Dementia Mutation Database should be consulted (www.molgen.ua.ac.be/ADMutations/) 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.
- An affected family member should be tested first. If no affected family member is available 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.

For families in which autosomal dominant AD is unlikely:

- Inform them why their family history is consistent with familial or sporadic AD;
- Discuss that both sporadic and familial cases can be due to a genetic susceptibility. Risk estimates are only available for first-degree relatives of an affected individual in sporadic or familial cases;
- Genetic testing for susceptibility loci (e.g., *APOE*) is not clinically recommended due to limited clinical utility and poor predictive value. If a patient wishes to pursue testing despite genetic counseling and recommendations to the contrary, testing may be considered at the clinician's discretion. Testing performed should follow the HD genetic testing guidelines, with emphasis on genetic counseling with a qualified clinician. As such, DTC genetic testing is not advised;
- Motives and considerations for pursuing genetic testing should be explored. This counseling should be an exploration of personal experiences, value and beliefs, and personal and family needs. Genetic testing should be discussed within the context of adapting to familial risk and when clients feel compelled to learn a more refined estimate of their risks to enhance their quality of life. As part of this, it is helpful to lead the individual through the scenario of receiving a positive test result and a negative test result, having them assess the ways these results would positively or adversely impact their psyche, life plans, and relationships;
 - Symptomatic patients: Because genetic testing of a symptomatic individual is typically requested by a relative concerned about his risk, the counselor must remain alert to any potential conflicts of interest, such as lack of interest of the symptomatic patient or of other at-risk family members. If the symptomatic patient gives any inclination of being averse to testing, it is not recommended. Instead, DNA banking should be explored. If there is disagreement within the family regarding whether testing should be performed, a family meeting is strongly encouraged (with or without the genetic counselor

present). A family meeting would allow all interested parties to discuss the potential impact of the genetic testing on the family, how test results will be communicated, and how to respect the rights of those family members who do not wish to know the results.

- Genetic testing: In the event testing is chosen, the following is recommended:
 - Asymptomatic patients should receive a neurologic examination to assess for signs of dementia and to establish a baseline.
 - Assess patient's and any accompanying family member's psychological state of mind. In the case of presymptomatic testing, a consultation with a psychologist/psychiatrist may be recommended for the patient as part of the HD testing approach.
 - If the patient seems to suffer from, or is potentially at risk for significant psychological/psychiatric problems, consider a psychotherapy referral before testing.
 - If the psychological assessment suggests testing is not in the person's current best interest (e.g., untreated depression or recent death), these reservations should be shared openly, and an agreement should be made to revisit testing once the underlying condition and/or stressors have diminished. A referral for psychotherapy may also be appropriate.
 - Assess and review the psychosocial impact of testing on the patient and his/her family.
 - Reinforce results cannot be "taken back" (although an individual can decide not to learn his or her test results after having the test performed.)
 - Discuss testing logistics, associated costs, and possible outcomes.
 - For EOAD genes, determine best approach to testing for patient (i.e., stepwise testing beginning with *PSEN1* as the most likely gene or ordering a panel).
 - Discuss where results will be kept (e.g., medical record).
 - Determine who will accompany the patient to the result session for support.
 - Discuss possible test outcomes (positive, negative, or variant of uncertain significance). If testing for *APOE*, consider whether you will report other disease risk implications. If so, these should be included in the discussion of test outcomes with the patient. Also, it should be reiterated that *APOE* is a susceptibility gene and is not a predictive test. Thus, individuals with no copies of the ϵ_4 allele still face a 2–4-fold increased lifetime risk of developing AD if they have a first-degree relative with AD.
 - Assist the patient and participating family members with informed decision making regarding whom, if anyone, they plan to share the results with and how. Inform about the importance of discretion when discussing genetic testing and results.
 - Discuss the potential impact of genetic test results on insurance, and the benefits and limitations of existing state and federal genetic discrimination legislation.
 - Obtain informed consent for all genetic testing for AD.
 - After results disclosure, revisit the individual's plans regarding with whom and how the results will be shared.
 - Arrange for a follow-up plan to "check in" with the patient and, if relevant, participating family member, and determine whether another genetic counseling session would be beneficial to the patient and/or the patient's partner/family members/friends.
- Discuss the availability and status of AD research and/or DNA banking.

POSITION STATEMENT

Applicable To:

- Medicaid – Hawaii, Kentucky*
- Medicare – Easy Choice Health Plan, Hawaii, Kentucky*

For markets noted below, please refer to Care Core National Lab Management criteria available at www.wellcare.com/provider/CCGs.

- Medicaid – Florida, Georgia, Illinois, New Jersey, New York, South Carolina
- Medicare – Connecticut, Florida, Georgia, Illinois, Louisiana, Missouri, New Jersey, New York, Texas, Windsor

Predictive and diagnostic genetic testing for Alzheimer's Disease **is considered experimental and investigational and NOT a covered benefit.**

CLINICAL EVIDENCE

While gene testing and predictive gene testing may be of benefit in suspected familial early-onset AD, **the value to diagnosing late-onset AD and efficacy of treatment is minimal.**⁵ Genetic testing for familial early-onset AD may be carried out, with the patient's permission, to determine if there are mutations in APP, PSEN1, or PSEN2 which would confirm the diagnosis of familial early-onset AD. If a demented person has a PSEN1 mutation and has a MRI scan that is supportive, then the diagnosis is AD. DNA banking, for future analysis, should be provided as an option for those who do not currently want a test or those who may lack a known mutation.

Predictive gene testing for mutations in APP, PSEN1, or PSEN2 in healthy adults should be conducted in a setting of adequate genetic counseling and confidentiality. This should consist of counseling regarding the purpose of performing testing, the meaning of positive or negative results, the implication of results for the patient and their family, alternative options, the benefits and risks, and reassurance that care will not be withdrawn as a result of not undergoing testing AD. Despite the lack of a cure for familial early-onset AD, there are some **benefits** to undergoing predictive gene testing. These include life-planning (e.g. whether or not to reproduce) and social planning (e.g. financial and social support) AD. The **risks** of predictive gene testing include depression, disruption to family and breach of confidentiality, which could lead to social stigmatization, job or health insurance loss in those found to have the mutation.⁵

For patients with sporadic late-onset AD genetic testing for APOE ε4, SORL1, CLU, CR1, or PICALM is not recommended as it does not provide clinically useful information. These risk factor genes do not improve the sensitivity or specificity of the diagnosis, nor do they alter the treatment. **Predictive gene testing for these risk factor genes is also not recommended as there is currently no potential for prevention or early-intervention.** Knowledge of APOE ε4 status in adults with a parent with Alzheimer's disease did not result in significant short-term psychological distress according to the REVEAL study conducted by Green and colleagues.⁵

Professional Societies and Organizations

The Quality Standards Subcommittee of the **American Academy of Neurology (AAN)** concluded that there are no laboratory tests (e.g., APOE genotyping, genetic markers or biomarkers) suitable for evaluating and diagnosing patients with AD; genotyping, biomarkers, and imaging are areas to conduct further research for diagnosis.⁶

According to the **American Psychiatric Association**, providing an Alzheimer's disease requires clinical symptomology and microscopic examination of the brain post-mortem; 70%–90% of clinical diagnoses match pathological diagnosis post-mortem.⁷

The **Alzheimer's Association** position on genetic testing applies to current tests for early-onset genes and to reliable tests that may eventually be developed to predict late-onset Alzheimer's.¹

- Having the APOE-e4 gene does not mean a person has or will develop AD.
- Because of possible social consequences or discrimination, anonymous testing should be available, thereby making the fact of and results of genetic testing for Alzheimer's disease invisible on an individual's medical records.

If performed, genetic testing for Alzheimer's should be done with pre- and post-test counseling, which includes a full discussion of the implication of the test and provides the individual with all information necessary to make an

informed decision. All genetic counseling and information should be provided in culturally and linguistically appropriate formats and should take into account an individual's literacy level.

The **United States Preventive Services Task Force (USPSTF)** concludes that the evidence is insufficient to recommend for or against routine screening for dementia in older adults.⁸

CODING

Non-Covered CPT® Codes

- 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; APOA (apolipoprotein E) (eg, hyperlipoproteinemia type III, cardiovascular disease, Alzheimer disease, common variants (eg, *2, *3, *4)
- 81405** 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; APOA (apolipoprotein E) (eg, hyperlipoproteinemia type III, cardiovascular disease, Alzheimer disease, common variants (eg, *2, *3, *4)
- 81406** Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons) – includes PSEN 1 (presenilin 1) (e.g., Alzheimer disease), full gene sequence

CPT Genetic Testing Modifier

- 7A** APOE or apolipoprotein E

ICD-9-CM Procedure Codes No applicable codes.

Non-Covered HCPCS® Codes

- S3852*** DNA analysis for apoe epsilon 4 allele for susceptibility to Alzheimer's disease
 - S3855*** Genetic testing for detection of mutations in the presenilin – 1 gene
- *Note: S-Codes are NON COVERED FOR MEDICARE – For Medicare, bill the appropriate CPT code.*

Non-Covered ICD-9-CM Diagnosis Codes (Include non-covered dx when applicable)

- 290.0 – 290.9** Dementias
- 294.10 – 294.11** Dementia in conditions classified elsewhere
- 310.1** Personality change due to conditions classified elsewhere
- 331.0** Alzheimer's disease
- 331.83** Mild cognitive impairment, so stated
- 780.93** Memory loss
- 781.1** Disturbances of sensation of smell and taste
- V17.2** Family history of other neurological diseases [family history of Alzheimer's disease]
- V80.0** Special screening for neurological conditions [screening for dementia]

Non-covered Draft 2014 ICD-10-CM Diagnosis Codes (Include non-covered dx when applicable)

- F03.090, F05** Unspecified dementia without behavioral disturbance
- F02.80, F023.81** Dementia in conditions classified elsewhere
- F07.0** Personality change due to conditions classified elsewhere
- G30.0** Alzheimer's disease with early onset
- G30.1** Alzheimer's disease with late onset
- G30.8** Other Alzheimer's disease
- G30.9** Alzheimer's disease, unspecified
- G31.84** Mild cognitive impairment

- R41.1, R41.2, R41.3** Memory loss
R43.0 – R43.9 Disturbances of sensation of smell and taste
Z03.89 Family history of other neurological diseases
Z13.858 Screening for neurological conditions

*Current Procedural Terminology (CPT) 2014 American Medical Association: Chicago, IL.®©

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MEDICAL POLICY COMMITTEE HISTORY AND REVISIONS

Date	Action
8/7/2014	<ul style="list-style-type: none"> • Approved by MPC. Clarified lines of business.
11/7/2013	<ul style="list-style-type: none"> • Approved by MPC. No changes.
11/1/2012	<ul style="list-style-type: none"> • Approved by MPC. No changes.
12/1/2011	<ul style="list-style-type: none"> • New template design approved by MPC.
10/6/2011	<ul style="list-style-type: none"> • Approved by MPC.