I. POLICY

Biochemical Markers for Diagnosis of Alzheimer’s Disease
Measurement of cerebrospinal fluid biomarkers of Alzheimer’s disease, including but not limited to tau protein, amyloid beta peptides, or neural thread proteins, is considered investigational.

Measurement of urinary biomarkers of Alzheimer’s disease is considered investigational, including but not limited to neural thread proteins.

Genetic Testing for Diagnosis of Alzheimer’s Disease
Genetic testing for the diagnosis or risk assessment of Alzheimer’s disease is considered investigational. Genetic testing includes, but is not limited to, testing for the apolipoprotein E epsilon 4 allele, presenilin genes, amyloid precursor gene, or TREM2.

There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with the above procedures.

Policy Guidelines
Genetic testing for Alzheimer’s disease may be offered along with cerebral spinal fluid (CSF) levels of the Tau protein and AB-42 peptide. This group of tests may be collectively referred to as the ADmark™ Profile, offered by Athena Diagnostics (Worcester, Mass.).

Cross-references: None
II. PRODUCT VARIATIONS

This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

FEP PPO*


III. DESCRIPTION/BACKGROUND

Genetic Testing for Alzheimer Disease

Alzheimer disease (AD) is commonly associated with a family history; 40% of patients with AD have a least 1 other afflicted first-degree relative. Numerous genes have been associated with late-onset AD, while mutations in chromosomes 1, 14, and 21 have been associated with early onset familial AD.¹

**Susceptibility Polymorphism at the Apolipoprotein E Gene**

The apolipoprotein E (APOE) lipoprotein is a carrier of cholesterol produced in the liver and brain glial cells. The APOE gene has 3 alleles—ε2, 3, and 4—with the epsilon 3 allele being the most common. Individuals carry 2 APOE alleles. The presence of at least 1 ε4 allele is associated with a 1.2- to 3-fold increased risk of AD, depending on the ethnic group. Among those homozygous for epsilon 4 (≈2% of the population), the risk of AD is higher than for those heterozygous for ε4. Mean age of onset of AD is at about age 68 years for ε4 homozygotes, about 77 years for heterozygotes, and about 85 years for those with no ε4 alleles. About half of patients with sporadic AD carry an ε4 allele. However, not all patients with the allele develop AD. The ε4 allele represents a risk factor for AD rather than a disease-causing mutation. In the absence of APOE testing, first-degree relatives of an individual with sporadic or familial AD are estimated to have a 2- to 4-fold greater risk of developing AD than the general population.²

There is evidence of possible interactions between ε4 alleles, other risk factors for AD (eg, risk factors for cerebrovascular disease such as smoking, hypertension, hypercholesterolemia, diabetes³), and a higher risk of developing AD. However, it is not clear that all risk factors have been taken into account in such studies, including the presence of polymorphisms in other genes that may increase the risk of AD.
**Genetic Mutations**

Individuals with early-onset familial AD (ie, before age 65 years but as early as 30 years) form a small subset of AD patients. AD within families of these patients may show an autosomal dominant pattern of inheritance. Pathogenic mutations in 3 genes have been identified in affected families: amyloid-beta precursor protein (APP) gene, presenilin 1 (PSEN1) gene, and presenilin 2 (PSEN2) gene. APP and PSEN1 mutations have 100% penetrance absent death from other causes, while PSEN2 has 95% penetrance. A variety of mutations within these genes has been associated with AD; mutations in PSEN1 appear to be the most common. While only 3% to 5% of all patients with AD have early-onset disease, pathogenic mutations have been identified in up to 70% or more of these patients. Identifiable genetic mutations are, therefore, rare causes of AD.

Testing for the APOE 4 allele among patients with late-onset AD and for APP, PSEN1, or PSEN2 mutations in the rare patient with early-onset AD have been investigated as an aid in diagnosis of patients presenting with symptoms suggestive of AD, or as a technique for risk assessment in asymptomatic patients with a family history of AD. Mutations in PSEN1 and PSEN2 are specific for AD; APP mutations are also found in cerebral hemorrhagic amyloidosis of the Dutch type, a disease in which dementia and brain amyloid plaques are uncommon.

**Susceptibility Testing at the Triggering Receptor Expressed on Myeloid Cells 2 Gene**

Recent studies identified rs75932628-T, a rare functional substitution for R47H of triggering receptor expressed on myeloid cells 2 (TREM2), as a heterozygous risk variant for late-onset AD. On chromosome 6p21.1, at position 47 (R47H), the T allele of rs75932628 encodes a histidine substitute for arginine in the gene that encodes TREM2.

TREM2 is highly expressed in the brain and is known to have a role in regulating inflammation and phagocytosis. TREM2 may serve a protective role in the brain by suppressing inflammation and clearing it of cell debris, amyloids, and toxic products. A decrease in the function of TREM2 would allow inflammation in the brain to increase and may be a factor in the development of AD. The effect size of the TREM2 variant confers a risk of AD that is similar to the APOE ε4 allele, although it occurs less frequently.

**Diagnosis of AD**

The diagnosis of AD is divided into 3 categories: possible, probable, and definite AD. A diagnosis of definite AD requires postmortem confirmation of AD pathology, documenting the presence of extracellular beta amyloid plaques and intraneuronal neurofibrillary tangles in the cerebral cortex. As a result, a diagnosis of definite AD cannot be made during life, and the diagnosis of probable or possible AD is made on clinical grounds. Probable AD dementia is diagnosed clinically when the patient meets core clinical criteria for dementia and has a typical clinical course for AD. Criteria for diagnosis of probable AD have been developed by the National Institute on Aging and the Alzheimer’s Association. These criteria require evidence of a specific pattern of cognitive impairment, a typical clinical course, and exclusion of other potential etiologies, as follows:

- Cognitive impairment
### Diagnostic Testing and Risk Assessment for Alzheimer’s Disease (Biochemical and Genetic)

<table>
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<th>Policy Title</th>
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<tr>
<td>Policy Number</td>
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- Cognitive impairment established by history from patient and a knowledgeable informant, plus objective assessment by bedside mental status examination or neuropsychological testing
- Cognitive impairment involving a minimum of 2 of the following domains:
  - Impaired ability to acquire and remember new information
  - Impaired reasoning and handling of complex tasks, poor judgment
  - Impaired visuospatial abilities
  - Impaired language functions
  - Changes in personality, behavior, or comportment
- Initial and most prominent cognitive deficits are one of the following:
  - Amnestic presentation
  - Nonamnestic presentations, either a language presentation with prominent word-finding deficits; a visuospatial presentation with visual cognitive defects; or a dysexecutive presentation with prominent impairment of reasoning, judgment, and/or problem solving.

#### Clinical course
- Insidious onset
- Clear-cut history of worsening over time
- Interference with ability to function at work or usual activities
- Decline from previous level of functioning and performing

#### Exclusion of other disorders
- Cognitive decline not explained by delirium or major psychiatric disorder
- No evidence of other active neurologic disease, including substantial cerebrovascular disease or dementia with Lewy bodies.
- Lack of prominent features of variant frontotemporal dementia or primary progressive aphasia.
- No medication use with substantial effects on cognition.

A diagnosis of possible AD dementia is made when the patient meets most of the AD criteria, but has an atypical course or an etiologically mixed presentation. This may consist of an atypical onset (e.g., sudden onset) or atypical progression. A diagnosis of possible AD is also made when there is another potentially causative systemic or neurologic disorder that is not thought to be the primary etiology of dementia.

Mild cognitive impairment (MCI) is a precursor of AD in many instances. MCI may be diagnosed when there is a change in cognition, but not sufficient impairment for the diagnosis of dementia. Features of MCI are evidence of impairment in 1 or more cognitive domains and preservation of independence in functional abilities. In some patients, MCI may be a predementia phase of AD. Patients with MCI may undergo ancillary testing (e.g., neuroimaging, laboratory studies, neuropsychological assessment) to rule out vascular, traumatic, and medical causes of cognitive decline and to evaluate genetic factors.
Biomarker evidence has been integrated into the diagnostic criteria for probable and possible AD for use in research settings. Other diagnostic tests for AD include CSF levels of tau protein or beta amyloid precursor protein, as well as positron emission tomography amyloid imaging. The CSF tests are considered separately in evidence review 2.04.14. PET amyloid imaging is considered in evidence review 6.01.55 (Beta Amyloid Imaging With Positron Emission Tomography for Alzheimer Disease).

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Biochemical Markers for Diagnosis of Alzheimer’s Disease

The diagnosis of AD is divided into 3 categories: possible, probable, and definite AD. A diagnosis of definite AD requires postmortem confirmation of AD pathology, including the presence of extracellular beta amyloid plaques and intraneuronal neurofibrillary tangles in the cerebral cortex. Probable AD dementia is diagnosed clinically when the patient meets core clinical criteria for dementia and has a typical clinical course for AD. A typical clinical course is defined as an insidious onset, with the initial and most prominent cognitive deficits being either amnestic or nonamnestic (eg, language, visuospatial, or executive function deficits), and a progressively worsening cognition over time. A diagnosis of possible AD dementia is made when the patient meets core clinical criteria for AD dementia but has an atypical course or an etiologically mixed presentation.

MCI may be diagnosed when there is a change in cognition but insufficient impairment for the diagnosis of dementia. MCI is characterized by impairment in 1 or more cognitive domains but preserved functional independence. In some patients, MCI may be a predementia phase of AD. Patients with MCI or suspected AD may undergo ancillary testing (eg, neuroimaging, laboratory tests, neuropsychological assessment) to rule out vascular, traumatic, and medical causes of cognitive decline and to evaluate genetic factors. Because clinical diagnosis can be difficult, particularly early in the course of disease, there has been considerable interest in developing an accurate laboratory test for AD. Several potential biomarkers of AD are associated with AD pathophysiology (ie, -amyloid plaques and neurofibrillary tangles).

Elevated CSF levels of specific proteins have been found in patients with AD. These include tau protein, phosphorylated at AD-specific epitopes such as threonine 181 (P-tau) or total tau protein (T-tau), or an amyloid- peptide such as AB-42. Other potential CSF3,4 and serum5 peptide markers also 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. AB-42 is a subtype of amyloid-β peptide that is produced from metabolism of amyloid precursor protein. AB-42 is the key peptide deposited in amyloid plaques characteristic of AD. Low levels of AB-42 in the CSF have been associated with AD, perhaps because AB-42 is deposited in amyloid plaques instead of remaining in fluid. Investigators have suggested that the tau/AB-42 ratio may be a more accurate diagnostic marker than either alone.6 A variety of kits are commercially available to measure AB-42 and tau proteins. Between-laboratory variability in CSF biomarker measurement is large.7,8

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.

**Regulatory Status**

No biochemical marker tests for AD are currently approved by the U.S. Food and Drug Administration (FDA). Commercially available tests include:

- AlzheimAlert™ (Nymox Pharmaceutical Corp., Hasbrouck Heights, NJ)
- Innotest® assays for T-tau, P-tau, and AB-42 (Fujirebio [previously Innogenetics], Malvern, PA)
- AdMark® CSF analysis

These are laboratory-developed tests (LDTs). Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; LDTs must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). AlzheimAlert™ and AdMark® CSF analysis are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, FDA has chosen not to require any regulatory review of these tests.

Nymox Pharmaceutical Corp. previously offered AD7C testing as an LDT but no longer lists the test on its website.

**IV. RATIONALE**

*Genetic Testing for Alzheimer’s Disease*

The most recent update was performed through September 4, 2015. This review addresses BCBSA genetic testing category 3 on testing an asymptomatic individual to determine future risk of disease (see Appendix Table 1 for BCBSA genetic testing categories).
Genetic Testing for Late-Onset Alzheimer Disease

Analytic Validity
There is a lack of published evidence on the analytic validity of genetic testing for late-onset familial Alzheimer disease (AD). Analytic validity is expected to be high when current methods of sequencing are performed, ie, Sanger sequencing and/or next-generation sequencing.

Clinical Validity
Subsequent to the TEC Assessment, advances in genetic understanding of AD have been considerable, with associations between late-onset AD and more than 20 non-\textit{APOE} genes suggested.

In 2014, Naj et al published a genome-wide association study of multiple genetic loci in late-onset AD. Genetic data from 9162 white race participants with AD from the Alzheimer Disease Genetics Consortium were assessed for polymorphisms at 10 loci significantly associated with risk of late-onset AD. Analysis confirmed the association of \textit{APOE} with an earlier age of onset and found significant associations for \textit{CR1}, \textit{BIN1}, and \textit{PICALM}. \textit{APOE} contributed 3.7% of the variation in age of onset and the other 9 loci combined contributed 2.2% of the variation. Each additional copy of the \textit{APOE} ε4 allele reduced age of onset by 2.45 years.

\textbf{Susceptibility Testing at the Apolipoprotein E Gene}

The association of the \textit{APOE} ε4 allele with AD is significant; however, \textit{APOE} genotyping does not have high specificity or sensitivity, and is of little value in the predictive testing of asymptomatic individuals.

The American College of Medical Genetics and Genomics has concluded that \textit{APOE} genotyping for AD risk prediction has limited clinical utility and poor predictive value.

The association of \textit{APOE} genotype with response to AD therapy has been examined. The USA-1 Study group found \textit{APOE} genotype did not predict therapeutic response. Rigaud et al followed 117 individuals with AD over 36 weeks in an open-label trial of donepezil; 80 (68%) completed the trial. They found no statistically significant effect of \textit{APOE} genotype on change in cognition (assessed by Cognitive subscale of the Alzheimer's Disease Assessment Scale). However, the study was not designed to examine predictive therapeutic response, and there were baseline cognitive differences according to \textit{APOE} genotype. There is currently insufficient information to make treatment decisions based on \textit{APOE} subtype.

\textbf{Susceptibility Testing at the Triggering Receptor Expressed on Myeloid Cells 2 Gene}

Jonsson et al evaluated 3550 subjects with AD and found a genome-wide association with only 1 marker, the T allele of rs75932628 (excluding the \textit{APOE} locus and the A673T variant in \textit{APP11}). The frequency of rs75932628 (triggering receptor expressed on myeloid cells 2 [\textit{TREM2}]) was then tested in a general population of 110,050 Icelanders of all ages and was found to confer a risk of AD of 0.63% (odds ratio [OR], 2.26; 95% confidence interval [CI], 1.71 to 2.98; \(p=1.13\times10^{-8}\)). In the control population of 8888 patients 85 years of age or older without a diagnosis of AD, \textit{TREM2} frequency was 0.46% (OR=2.92; 95% CI, 2.09 to 4.09;
p=3.42×10^{-10}). In 1236 cognitively intact controls age 85 or older, the frequency of TREM2 decreased even further to 0.31% (OR=4.66; 95% CI, 2.38 to 9.14; p=7.39×10^{-6}). The decrease in TREM2 frequency in elderly patients who are cognitively intact supports the findings associating TREM2 with increasing risk of AD.

Guerriero et al also found a strong association of the R47H TREM2 variant with AD (p=0.001). Using 3 imputed data sets of genome-wide association AD studies, a meta-analysis found a significant association with the variant and disease (p=0.002). The authors further reported direct genotyping of R47H in 1994 AD patients and 4062 controls, and found a highly significant association with AD (OR=5.05; 95% CI, 2.77 to 9.16; p=9.0×10^{-9}).

**Clinical Utility**

The REVEAL study was designed to examine consequences of AD risk assessment by APOE genotyping. Of 289 eligible participants, 162 were randomized (mean age, 52.8 years; 73% female; average education, 16.7 years) to either risk assessment based on APOE testing and family history (n=111) or family history alone (n=51). During a 1-year follow-up, those undergoing APOE testing with a high-risk genotype were more likely than low-risk or untested individuals to take more vitamins (40% vs 24% and 30%, respectively), change diet (20% vs 11% and 7%, respectively), or change exercise behaviors (8% vs 4% and 5%, respectively). While in this well-educated sample of women there were some behavior changes, none can be considered a meaningful surrogate end point.

No studies were identified that addressed how the use of the TREM2 rs75932628-T variant might be incorporated into clinical practice.

There is a lack of interventions that can delay or mitigate late-onset AD. There is no evidence that early intervention for asymptomatic mutation carriers can delay or mitigate future disease. There are many actions patients may take following knowledge of a mutation. Changes in lifestyle factors (eg, diet, exercise) and/or incorporation of “brain training” exercises can be made, but there is no evidence that these interventions impact clinical disease.

Reproductive planning may be affected as well, but it is unclear whether outcomes would be improved. Testing for a disease that will not manifest for many decades includes uncertainty about whether treatments for AD will be available at that future time point. This leads to uncertainties about whether reproductive interventions now will reduce the future incidence or severity of disease.

**Section Summary: Genetic Testing for Late-Onset AD**

Both the APOE gene and the triggering receptor gene have shown strong statistical associations with AD, thus demonstrating some degree of clinical validity. However, the clinical sensitivity and specificity of APOE ε4 is poor, and there is a lack of evidence on the clinical sensitivity and specificity of the triggering receptor gene.

No studies were identified that address how the use of the APOE or TREM2 variant might be incorporated into clinical practice. It is not clear how management of asymptomatic patients with
these genes would change in a way that improves outcomes. Therefore, clinical utility has not been demonstrated for these tests.

**Genetic Testing for Early-Onset Familial AD**

**Analytic Validity**
There is a lack of published evidence on the analytic validity of genetic testing for early-onset familial AD. Analytic validity is expected to be high when current methods of sequencing are performed, ie Sanger sequencing and/or next-generation sequencing.

**Clinical Validity**
Genetic testing for presenilin 1 (PSEN1) detects 30% to 60% of familial early-onset AD. A number of mutations scattered throughout the PSEN1 gene have been reported, requiring sequencing of the entire gene when the first affected member of a family with an autosomal dominant pattern of AD inheritance is tested. Mutations in amyloid-beta precursor protein (APP) and presenilin 2 (PSEN2) genes account for only a small fraction of cases; it is likely that other causative genes will be discovered.

The nearly complete penetrance of a PSEN1 disease–associated mutation would change the probability of developing familial AD in an unaffected family member from 50% to either 0% or 100%. However, there is evidence that clinical expressivity is variable, ie, the presence of PSEN1 mutations is not useful in predicting age of onset (although it is usually similar to age of onset in affected family members), severity, type of symptoms, or rate of progression in asymptomatic individuals.

It is not uncommon to discover previously unreported PSEN1 mutations in an individual, and without additional family information, they may reflect mutations not associated with disease, or new causative mutations restricted to a single family (private mutation). Thus, interpretation of test results of asymptomatic individuals without identification of a mutation in affected family members may be inconclusive in a significant proportion of patients.

**Clinical Utility**
The potential clinical utility of testing is in early identification of asymptomatic patients who are at risk for developing early-onset AD. Genetic testing will in most cases lead to better risk stratification, distinguishing patients who will develop the disease from those who will not. If early identification of patients at risk leads to interventions to delay or mitigate clinical disease, then clinical utility will be established. Identification of asymptomatic, young adult carriers could impact reproductive planning. And clinical utility may be demonstrated if testing leads to informed reproductive planning that improves outcomes. Alternatively, clinical utility could be demonstrated if knowledge of mutation status leads to beneficial changes in psychological outcomes.

A systematic review on the psychological and behavioral impact of genetic testing for AD found few studies on the impact of testing for early-onset familial AD. The existing studies generally
have small sample sizes and retrospective designs, and the research was conducted in different countries, which may limit the generalizability of the findings.\(^{17}\)

There is no evidence that early intervention for asymptomatic mutation carriers can delay or mitigate future disease. There are many actions patients may take following knowledge of a mutation: changes in lifestyle factors (eg, diet, exercise) and incorporation of “brain training” exercises; but there is no evidence that these interventions impact clinical disease.

Reproductive planning may be affected as well, but it is unclear whether outcomes would be improved. Testing for a disease that will not manifest for more than several decades includes uncertainty about whether treatments for AD will be available. This leads to uncertainties about whether reproductive interventions now will reduce the future incidence or severity of disease.

Mihaesu et al\(^{18}\) cite the framework proposed by Khoury et al\(^{19}\) for the continuum of translational research that is required to move genomics research findings in AD into clinical and public health applications that benefit population health. The 4 phases of translation research include: (1) translation of basic genomics research into a potential health care application; (2) evaluation of the application for the development of evidence-based guidelines; (3) evaluation of the implementation and use of the application in health care practice; and (4) evaluation of the achieved population health impact. The authors concluded that genetic testing for AD is still in the first phase.

**Section Summary: Genetic Testing for Early-Onset AD**

A substantial percentage of patients with early-onset AD will have a pathogenic mutation; however, up to 40% will test negative. Therefore, the clinical sensitivity is suboptimal. The mutations are also found in some individuals who do not have a family history of familial AD, but the false-positive rate and clinical specificity is not well-defined.

For those from families with early-onset, familial AD, there are currently no known preventive measures or treatments that can mitigate the effect of the disease. It is not clear how management of asymptomatic patients with these genes would change in a way that improves outcomes. Therefore, clinical utility has not been demonstrated for these tests.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 1.
### Table 1. Summary of Key Trials

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<td>NCT 02564692</td>
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NCT: national clinical trial

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### Summary of Evidence

The evidence for genetic testing in individuals who are asymptomatic and at risk for developing Alzheimer disease (AD) includes studies on gene associations, test accuracy, and effects on health outcomes. Relevant outcomes are test accuracy, test validity, change in disease status, and health status measures. Many genes, including apolipoprotein E (APOE), CR1, BIN1, PICALM, and 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. For individuals with early-onset AD, mutations in the presenilin 1 (PSEN1) and amyloid-beta precursor protein (APP) genes are found in a substantial number of patients. However, there is no direct or indirect evidence to establish that clinical outcomes are improved as a result of genetic testing for these mutations. The current lack of effective methods to prevent the onset of AD or to target AD treatments based on genetic characteristics limits the clinical benefit for genetic testing. The evidence is insufficient to determine the effects of the technology on health outcomes.

### Practice Guidelines and Position Statements

**American College of Medical Genetics and Genomics**

The American College of Medical Genetics and Genomics lists genetic testing for APOE alleles as one of 5 recommendations in the Choosing Wisely initiative.\(^{13}\) 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 later-onset AD, the most common cause of dementia. These recommendations stated that “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.”

**American Academy of Neurology**

The American Academy of Neurology made the following recommendations\(^{20}\):

- Routine use of APOE genotyping in patients with suspected AD is not recommended at this time (Guideline).
There are no other genetic markers recommended for routine use in the diagnosis of AD (Guideline). This guideline is currently being updated as of October 6, 2015.

**European Federation of Neurological Sciences**

The European Federation of Neurological Sciences made the following recommendations:\(^21\)

Recommendations: genetic testing (level of evidence not reported)

Screening for known pathogenic mutations can be undertaken in patients with appropriate phenotype or a family history of an autosomal dominant dementia. Testing of patients with familial dementia and of unaffected at-risk-relatives should be accompanied by neurogenetic counseling and undertaken only after full consent and by specialist centers. Presymptomatic testing may be performed in at-risk members of family-carrying mutation. It is recommended that the Huntington’s disease protocol is followed for presymptomatic testing.

Routine Apo E genotyping is not recommended.

**Fourth Canadian Consensus Conference on Diagnosis and Treatment of Dementia**

The 2012 Canadian Consensus Conference on Diagnosis and Treatment of Dementia (CCCDTD) was held in May 2012 to update the third consensus guidelines referenced next. Previous recommendations were endorsed if there were no changes in the literature. Full articles written by CCCDTD workgroups providing complete background information for the consensus conference are available online (http://www.healthplexus.net/article/2012-canadian-consensus-conference-dementia).

A summary of consensus recommendations from the CCCDTD4 was published by Gauthier et al in 2012.\(^22\) It is noted in the summary that: “Despite a large number of important advances, the CCCDTD4 concluded that fundamental changes in dementia diagnosis and management have not yet arrived.” The 2012 CCCDTD4 summary recommends:

“Testing and longitudinal follow-up of asymptomatic individuals or patients with subjective cognitive impairments not meeting MCI [mild cognitive impairment] criteria, or at-risk individuals (e.g., gene mutation carriers, family history of AD, APOE epsilon 4) should be restricted to research.”

**Third Canadian Consensus Conference on Diagnosis and Treatment of Dementia**

The CCCDTD\(^23\) recommended the following predictive genetic testing for asymptomatic “at-risk” individuals with an apparent autosomal dominant inheritance and a family-specific mutation has been identified:

1. With appropriate pre- and post-testing counseling, predictive genetic testing (PGT) can be offered to “at-risk” individuals (Grade B, Level 2**). Examples:
   a) First-degree relatives of an affected individual with the mutation (e.g., children and siblings);
   b) First cousins of an affected individual if the common ancestors (parents who were
siblings) died before the average age of onset of dementia in the family;

c) Nieces and nephews of affected individuals whose parent (sibling of the affected individual) died well before the average age of onset of dementia in the family;

d) PGT in minors is not generally offered in Canada, but occasionally may be considered on a case-by-case basis by the relevant medical ethics committee(s);

e) Individuals who are not “at risk” for the inherited disease do not require testing.

2. In young persons (60 years or younger) presenting with an early onset dementia, it is sometimes worthwhile to test for the most common mutations based on the “best estimate” diagnosis (e.g., in early onset AD, one might test for the most common mutations in \( PS1 \), \( APP \)). (Grade B, Level 2**) If a mutation is identified, it would have direct implications for offspring of the individual (if a de novo mutation is assumed). Conversely, it would also be important to test other family members such as parents and siblings for possible non-penetrance of a mutation.

Genetic screening with \( APOE \) genotype in asymptomatic individuals in the general population is not recommended because of the low specificity and sensitivity. (Grade E, Level 2**)

Genetic testing with \( APOE \) genotype is not recommended for the purpose of diagnosing AD because the positive and negative predictive values are low. (Grade E, Level 2**)

** CCCDTD Evidence Ratings

Grade (B) There is fair evidence to support this maneuver.
Grade (E) There is good evidence to recommend against this procedure.
Level 2: (1) Evidence obtained from well-designed controlled trial without randomization,
or (2) Evidence obtained from well-designed cohort or case control analytic studies,
preferably from more than one center, or (3) Evidence obtained from comparisons between
times or places with or without intervention. Dramatic results in uncontrolled experiments
are included in this category.

American College of Genetics and National Society of Genetic Counselors

The American College of Genetics and the National Society of Genetic Counselors issued the following joint practice guidelines:

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 videoconference) 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 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 (available online at: 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.

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.
Stanford Program in Genomics, Ethics, and Society
In 1998, the Alzheimer Disease Working Group of the Stanford Program in Genomics, Ethics, and Society suggested that “predictive or diagnostic genetic testing for highly penetrant mutations (eg, APP, PSEN1, PSEN2) may be appropriate for individuals from families with a clear autosomal dominant pattern of inheritance, particularly those with a family history of early onset of symptoms.” Such families generally have 3 affected members in 2 generations. In the case of diagnostic testing of clearly symptomatic individuals, testing would do little to change diagnostic confidence; however, it might assist excluding other causes of early-onset dementia, as potentially treatable contributory causes would still require exploring. In cases of early detection of questionably symptomatic individuals (ie, those with mild cognitive impairment, MCI) mutation identification might secure a diagnosis and lead to early treatment. The possibility that earlier diagnosis might lead to improved outcomes, while plausible, is not based on current evidence. Pharmacologic interventions for MCI have not demonstrated benefit in reducing progression to AD.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination (NCD).

Biochemical Markers of Alzheimer’s Disease
The clinical purposes of testing for Alzheimer disease (AD)–related biomarkers are to improve diagnostic accuracy or to predict conversion from mild cognitive impairment (MCI) to AD. Evidence of health benefit or clinical utility from testing requires demonstrating:

- incremental improvement in diagnostic or prognostic accuracy over current practice and that incremental improvements lead to improved health outcomes (eg, by informing clinical management decisions) and generalizability.

A framework for evaluating evidence supporting health benefit from testing requires consideration of the following: appropriate reference standard; requirements for predicting conversion from MCI to AD; how better diagnostic accuracy or prediction of conversion would lead to improved health outcomes; appropriate data analysis, including assay cutoffs; patient sample composition (inclusion and exclusion criteria); and validation of accuracy or prediction in independent samples as evidence of generalizability.

Criterion Standard. Accuracy of clinical AD diagnostic criteria has been established by comparison with autopsy, the criterion standard. Therefore, comparison with autopsy is most appropriate to validly assess incremental diagnostic improvement of biomarkers.
Predicting Conversion From MCI to AD. Predicting conversion from MCI to AD may rely on clinical diagnosis, albeit with some attendant error and misclassification, because the prediction of interest is conversion and not the criterion standard diagnosis.

Incremental Diagnostic Improvement. Incremental diagnostic or prognostic improvement is best demonstrated by evidence that the proposed predictor can correctly reclassify patients with and without AD, or those with MCI who will and will not progress to AD. Alternative approaches such as classical receiver operating characteristic (ROC) analyses, while providing insight, do not allow one to directly translate improvements in diagnostic or prognostic accuracy to changes in health outcomes.

Test Cutoffs. Almost all studies employ optimal (data-driven) test cutoffs to define test accuracy (sensitivity and specificity). This approach is typically accompanied by a degree of optimism, in turn overstating test accuracy.

Sample Definition. Clear description of whether samples included consecutive patients or were selective is required to evaluate potential bias—including verification bias (exclusion of cases without postmortem autopsy)—and generalizability.

Validation. Validation in independent samples is required to establish generalizability of markers.

Relevant evidence and guidelines were identified by a MEDLINE search through July 30, 2015.

Diagnostic Accuracy of Cerebrospinal Fluid Markers Versus Clinical Diagnosis
Most studies have relied on clinically diagnosed AD as the criterion standard. These studies are described next; the results are summarized in Error! Reference source not found.

Rosa et al (2014) conducted a systematic review with meta-analysis of studies of cerebrospinal fluid (CSF) amyloid-β peptide-1-42 (AB-42) in patients with clinically diagnosed AD. Literature was searched to May 2013, and 41 prospective or retrospective, cohort, case-control, and cross-sectional studies were included (total N=5086; 2932 AD, 2154 nondemented controls). Patients with MCI were excluded. Seventy-six percent of studies satisfied all quality domains of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. Publication bias was detected. A summary ROC curve was generated from all reported thresholds. Pooled sensitivity and specificity were 84% (95% confidence interval [CI], 81 to 85) and 79% (95% CI, 77 to 81), respectively. Positive and negative likelihood ratios were 4.5 (95% CI, 3.7 to 5.4) and 0.18 (95% CI, 0.14 to 0.22), respectively, and their ratio, the diagnostic odds ratio, was 29 (95% CI, 21 to 40). Statistical heterogeneity was substantial ($I^2$=68%); studies varied in test cutoffs used and severity of AD across patient samples. Eleven studies (total N=1459; 830 AD, 629 controls) reported AB-42 CSF levels. Mean (SD) CSF AB-42 was 467 (189) pg/mL in patients with AD and 925 (414) pg/mL in controls (weighted mean difference, 450 pg/mL; 95% CI, -600 to -289; p<0.001). However, statistical heterogeneity was considerable ($I^2$=99%).

Ferreira et al (2014) published a meta-review of systematic reviews with meta-analyses to assess the use of CSF biomarker tests for AD after publication of revised AD diagnostic criteria in
2011. Literature was searched in September 2013, and 7 systematic reviews were included. None was published after introduction of the revised AD diagnostic criteria, so primary studies were searched. Twenty-six prospective or retrospective case-control, cross-sectional, or longitudinal studies were included. Most included studies used clinical criteria for AD diagnosis or did not specify. Results for both the systematic reviews and the individual studies are summarized in Error! Reference source not found.. For differentiating AD from nondemented controls, positive and negative likelihood ratios for all 3 biomarkers ranged from 4 to 8 and from 0.1 to 0.3, respectively. For differentiating AD from other dementias, 1 systematic review of 7 studies reported positive and negative likelihood ratios of 46 and 0.09, respectively, for differentiating AD (n=175) from Creutzfeldt-Jakob disease (n=110). With this systematic review excluded, positive and negative likelihood ratios ranged from 2 to 7 and from 0.15 to 0.4, respectively.

A 2011 meta-analysis included 119 studies on biomarkers and diagnostic imaging in AD. Sensitivity and specificity were calculated for distinguishing AD from nondemented controls, and for distinguishing AD from non-AD dementias with and without MCI, if available. Included studies of CSF biomarkers used a variety of thresholds, with clinical diagnosis or autopsy as the reference standard. Twenty studies of the AB-42 CSF marker were included; pooled analysis resulted in sensitivity of 76% and specificity of 77%. CSF total tau was evaluated in 30 studies with a resulting sensitivity of 79% and specificity of 85%. CSF P-tau was evaluated in 24 studies resulting in a pooled sensitivity of 78% and specificity of 81%. Six studies evaluated CSF P-tau as a biomarker to distinguish AD patients from patients with MCI, with a pooled sensitivity of 73% and specificity of 69%. The combination of total tau and AB-42 was evaluated in 12 studies with a pooled sensitivity of 80% and specificity of 76%. In a comparison of CSF biomarkers, area under the ROC curve was highest for P-tau alone (0.85). Study heterogeneity was due to use of different test thresholds and different assay kits. Sensitivity analysis including studies that used autopsy as the reference standard for P-tau resulted in slightly higher sensitivity (82%) and lower specificity (57%).
In a 2006 review of studies using clinical diagnosis as the criterion standard, Formichi et al identified studies examining diagnostic accuracy of the following CSF markers for AD: total tau protein (T-tau) (41 studies; 2287 AD patients, 1384 controls; sensitivity, 52%-100%; specificity, 50%-100%), phosphorylated tau protein (P-tau) (12 studies; 760 AD patients, 396 controls; sensitivity, 37%-100%; specificity, 80%-100%), and amyloid-β peptide 1 to 42 (AB-42) (14 studies; 688 AD patients, 477 controls; sensitivity, 55%-100%; specificity, 80%-100%). Although primarily a descriptive review, test accuracies varied widely and only 1 study included a majority of autopsy-confirmed AD diagnoses.

**Section Summary: Diagnostic Accuracy of Cerebrospinal Fluid Markers Versus Clinical Diagnosis**

Several studies have examined the diagnostic performance of CSF biomarkers for distinguishing probable AD from nondemented controls and from patients with other types of dementia. The range of reported sensitivities and specificities is broad; in systematic reviews with meta-analyses, sensitivity and specificity were 80% to 82% and 82% to 90%, respectively, for differentiating AD from nondemented controls, and 73% and 67%, respectively, for differentiating AD from other dementias. Positive and negative likelihood ratios were 2 to 8 and 0.2 to 0.4, respectively, in either setting. This evidence does not indicate that CSF biomarkers improve the accuracy of clinical diagnostic criteria.

**Diagnostic Accuracy of CSF Markers With AD Autopsy Confirmation**

Engelborghs et al (2008) assayed P-tau and AB-42 in banked CSF. Samples were examined from 100 patients with and 100 without dementing illness seen between 1992 and 2003. All dementia diagnoses were autopsy-proven (67 pure AD, 6 mixed, 27 non-AD dementias). Details of the sample selection were not provided; whether CSF testing was routine or selective was not
indicated. Of those with dementia, 76 were evaluated in a memory clinic and the remainder in referring centers; all underwent clinical, neuropsychological, and imaging evaluations. The nondemented group was substantially younger (mean age, 47 years vs 76 years). Laboratory technicians performing assays were blinded to clinical diagnoses. Samples from 52 patients required retesting due to unreliable results. Sensitivity and specificity of clinical evaluation for a pure AD diagnosis was 83% and 75%, respectively, and of P-tau and AB-42 in combination, 80% and 93%, respectively. In logistic regression models, CSF biomarkers did not provide incremental diagnostic accuracy over clinical diagnosis; as the authors stated: “[A]lthough biomarkers did not perform significantly better comparing all unique clinical diagnoses, they were also not significantly worse, and could therefore add certainty to an established diagnosis.”

Four of 7 listed authors were employees of the test manufacturer (Innogenetics [now Fujirebio], Ghent, Belgium).

Clark et al (2003) examined CSF from 106 patients with autopsy-confirmed dementia who were evaluated at 10 referral clinics, and 73 controls (4 pathologically examined). Laboratory technicians were blinded to clinical diagnoses. An optimal cutoff of 234 pg/mL for total tau had sensitivity and specificity of 85% and 84%, respectively, for distinguishing those with AD (n=73) from cognitively normal people (n=74); AB-42 offered no incremental diagnostic value to total tau in ROC analyses. An optimal cutoff for total tau of 361 pg/mL had sensitivity and specificity of 72% and 69%, respectively, for distinguishing AD (n=74) from frontotemporal dementia (FTD) (n=3) and dementia with Lewy bodies (DLB) (n=10).

Bian et al (2008) assembled from 2 institutions a sample of 30 patients with FTD (19 autopsy-proven, 11 with known causal genetic mutations) and autopsy-proven AD (n=19). Using an optimal cutoff of 403 pg/mL, total tau had sensitivity and specificity of 68% and 90%, respectively, for distinguishing FTD from AD. A tau/AB-42 ratio of 1.06 had 97% specificity for distinguishing FTD from AD.

Cure et al (2014) conducted a systematic review with meta-analysis of CSF and imaging studies for the diagnosis of definite AD (autopsy-confirmed). Literature was searched in January 2012, and 3 studies of CSF markers (P-tau, T-tau, AB-42, AB-40) were identified (total N=337). Pooled sensitivity of all CSF tests was 82% (95% CI, 72 to 92), and pooled specificity was 75% (95% CI, 60 to 90). Statistical heterogeneity was not reported, but studies varied in AD definitions, controls (nondemented patients or patients with dementia due to other causes), and test thresholds. Area under the summary ROC curve constructed using multiple test thresholds was 0.84.

Section Summary: Diagnostic Accuracy of CSF Markers With AD Autopsy Confirmation
There is limited evidence examining incremental diagnostic accuracy of CSF biomarkers for AD diagnosis employing autopsy as a criterion standard. Current evidence does not demonstrate improvement over a clinical diagnosis, or whether diagnosis using CSF biomarkers would lead to improved health outcomes.
CSF Markers in Combination

As previously noted, for patients with clinically diagnosed AD, some have suggested that the tau/AB-42 ratio is a more accurate predictor than either alone. For example, using optimal cutoffs, de Jong et al (2006) reported sensitivity and specificity of 95% and 90% in a sample with clinically diagnosed AD (n=61) and vascular dementia (VaD) (n=61). In contrast, Le Bastard et al (2007) found the P-tau/AB-42 ratio lacked specificity to distinguish AD from VaD in a sample of 85 patients (VaD [n=64], AD [n=21]; 76/85 autopsy-confirmed diagnoses); specificity was 52% and sensitivity ranged from 91% to 95%.

CSF AB-42 level normalized to CSF AB-40 (ie, the AB-42/AB-40 ratio) is being investigated as a marker for patients with uncertain clinical diagnosis. Because AB-40 is not incorporated into amyloid plaques, CSF levels are more stable than those of AB-42. Sauvee et al (2014) examined the AB-42/AB-40 ratio in 122 patients with atypical dementia who had discordant CSF biomarker results (ie, tau, P-tau, AB-42). Using 0.05 as the ratio threshold, biological profiles were clarified in 72 (59%) of 122 patients with the addition of the AB-42/AB-40 ratio. However, of 35 patients diagnosed with AD by biological profile, 9 (26%) did not meet clinical criteria for AD or mixed dementia.

Section Summary: CSF Markers in Combination

The clinical utility of CSF biomarkers used in combination has not been demonstrated.

Neural Thread Protein

Zhang et al (2014) conducted a systematic review and meta-analysis of urinary AD-associated neural thread protein for diagnosing AD in patients with suspected AD. Nine studies were included (total N=841 patients with probable or possible AD, 37 patients with MCI, 992 non-AD demented or nondemented controls). For probable AD, pooled sensitivity and specificity were 89% (95% CI, 86 to 92) and 90% (95% CI, 88 to 92), respectively. Pooled positive and negative likelihood ratios were 8.9 (95% CI, 7.11 to 11.1) and 0.12 (95% CI, 0.09 to 0.16), respectively.

Kahle et al (2000) reported on the diagnostic potential of CSF levels of total tau protein and neural thread protein in a group of 35 patients with dementia (30 with probable or definite AD), 5 patients with DLB, 29 patients with Parkinson disease, and 16 elderly healthy control patients. Levels of both tau and neural thread protein were elevated in patients with AD compared with controls; sensitivity and specificity were 63% and 93%, respectively, for tau, and 70% and 80%, respectively, for neural thread protein.

In a prospective multicenter study conducted at 8 sites, Goodman et al (2007) enrolled 168 patients with recent referrals to memory clinics. The Urinary Neural Thread Protein Test was 91.4% sensitive for a diagnosis of probable AD (32/35) and 90.1% specific among healthy patients. However, it was unclear whether the marker changed management or what the potential consequences of a 9.9% false-positive rate might be.
Section Summary: CSF Markers in Combination
Data on neural thread protein as a marker for AD are limited. In 2 studies and 1 meta-analysis, estimated sensitivity and specificity ranged from 70% to 91% and from 80% to 90%, respectively. The clinical utility of neural thread protein testing has not been demonstrated.

CSF Markers and Progression of MCI
Studies also have evaluated the prognostic value of markers for progression of MCI and conversion to clinically manifest AD.

Ritchie et al (2014) published a Cochrane review of CSF amyloid-β protein (primarily AB-42) for detecting which patients with MCI would progress to AD or other dementias. Literature was searched in December 2012, and 14 prospective or retrospective cohort studies of AD, including 1 discussed next, were included (total N=1349 patients with MCI). Studies that enrolled patients younger than 50 years of age or with less than 2 years of follow-up were excluded. Risk of bias was moderate to high in most studies. AD, diagnosed by clinical criteria, developed in 436 (32%) of 1349 patients. Sensitivity ranged from 36% to 100%, and specificity from 29% to 91%. Due to heterogeneity of thresholds used, summary sensitivity and specificity were not calculated. However, a summary ROC curve was generated using the median specificity of 64%; pooled sensitivity was 81% (95% CI, 72 to 87). Positive and negative likelihood ratios were 2.2 (95% CI, 2.0 to 2.5) and 0.31 (95% CI, 0.21 to 0.48), respectively. Analysis of the pre- and posttest probabilities of conversion to AD among patients with MCI in primary and secondary care settings showed little incremental value of AB-42 testing in either setting.

The 2014 meta-review of systematic reviews by Ferriera et al (previously discussed) included studies of CSF biomarkers for differentiating patients with MCI who progress to AD from those who do not. In systematic reviews with meta-analyses, sensitivity and specificity of AB-42 were 67% (95% CI, 59 to 75) and 71% (95% CI, 65 to 78), respectively; for T-tau, 82% (95% CI, 76 to 86) and 70% (95% CI, 65 to 85), respectively; and for P-tau, 81% (95% CI, 69% to 91%) and 65% to 76%, respectively. Positive and negative likelihood ratios for all 3 tests ranged from 2 to 3 and from 0.3 to 0.5, respectively.

Mattsson et al (2009) recruited from 12 U.S. and European centers patients with MCI (n=750) or AD (n=529) and controls (n=304). Those with MCI were followed a minimum of 2 years or to disease progression. Development of probable AD was associated with lower CSF AB-42 and higher T-tau and P-tau. Using cutoffs defined in the AD and control groups for a diagnostic sensitivity of 85%, combining AB-42/P-tau and T-tau yielded sensitivity for AD conversion of 83% (95% CI, 78 to 88); specificity, 72% (95% CI, 68 to 76); positive predictive value, 62%; and negative predictive value, 88%. Type of MCI (amnestic or nonamnestic) was not specified.

Herukka et al (2007) reported on a sample of 106 patients evaluated at a university neurology department and 33 patients “from an ongoing prospective population-based study”; selection criteria other than agreeing to a lumbar puncture were not further described. Seventy-nine patients were diagnosed with MCI, 47 with amnestic type, and 33 converting to dementia; 60 patients were included as controls. Average follow-up was 3.5 years (MCI converters), 3.9 years
### MEDICAL POLICY

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(controls), and 4.6 years (stable MCI). CSF AB-42, P-tau, and total tau were measured. Graphical representation of AB-42, P-tau, and total tau suggested considerable overlap between controls, those with stable MCI, and progressive MCI. Test accuracy was not reported.

Hansson et al (2006) obtained 137 CSF samples from a larger group of 180 consecutive patients with MCI who were evaluated at a referral memory clinic between 1998 and 2001. CSF also was obtained from 39 controls. In the analytical sample (n=137), patients were 50 to 86 years of age at baseline, and 55% were female. Median follow-up was 5.2 years; 57 (42%) progressed to AD. Using a predictor comprising T-tau and AB-42/P-tau with optimal cutoffs, sensitivity and specificity for progression to clinical AD were 95% (95% CI, 86 to 98) and 87% (95% CI, 78 to 93), respectively. Patients were not categorized by the presence of amnestic MCI conferring increased risk of conversion to AD.

From 4 international clinical research centers, Ewers et al (2007) retrospectively assembled a sample of 88 patients with amnestic MCI based on both the availability of CSF samples and at least 1 follow-up visit between 1 and 3 years after initial evaluation; 57 healthy controls with baseline evaluations only also were included. Forty-three patients (49%) in the MCI group converted to AD over an average 1.5-year follow-up. Using a cutoff of 27.3 pg/mL, sensitivity and specificity of P-tau for conversion were 87% (95% CI, 73 to 93) and 73% (95% CI, 55 to 84), respectively. It should be noted that the conversion rate to AD in the sample was between 2- and 3-fold higher than the typical 15% found in amnestic MCI.

Andreasen et al (2005) studied 32 controls and 44 patients with MCI who, after a 1-year follow-up, had progressed to probable AD. At the start of the study, investigators evaluated total and P-tau and AB-42 levels. At baseline, 79.5%, 70.4%, and 77.3% had abnormal levels of total tau, P-tau, and AB-42, respectively. These results would have been more informative if patients with MCI who did not progress to AD were included for comparison.

Bouwman et al (2007) followed 59 patients with MCI for a mean of 19 months (range, 4-45), obtaining baseline CSF AB-42 and tau. Abnormal AB-42 (<495 pg/mL) and total tau (>356 pg/mL) were accompanied by increased, but imprecise, relative risks for progression to AD (5.0 [95% CI, 1.4 to 18.0] and 5.3 [95% CI, 1.5 to 19.2], respectively).

Parnetti et al (2006) examined 55 patients with MCI. Baseline CSF AB-42, total tau, and P-tau were measured; 38% had abnormal values. After 1 year, 4 (12%) of 33 stable patients had abnormal markers. Of 11 patients who progressed to AD, DLB, or familial FTD, 10 (91%) had 2 or more abnormal markers. Although results from these studies are consistent with potential prognostic utility of markers, sample sizes were small. Additionally, the type of MCI (amnestic or nonamnestic) was not specified but has important predictive value for progression to dementia.

**Section Summary: CSF Markers and Progression of MCI**

Evidence suggests that biomarker testing may identify increased risk of conversion from MCI to AD. Evidence that earlier diagnosis leads to improved health outcomes through delay of AD onset or improved quality of life is lacking.
Alzheimer Disease Neuroimaging Initiative

In 2003, the Alzheimer Disease Neuroimaging Initiative (ADNI) initiated a public-private effort designed to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as to lessen the time and cost of clinical trials. Participants have been recruited across the United States and Canada with follow-up every 6 months for approximately 10 years. Participants undergo neuropsychological testing, imaging, and biomarker evaluations to determine whether these measures can be combined to monitor the progression of MCI and AD. Ongoing results from several studies span diagnostic and prognostic questions addressed here.

In a 2011 report, Gomar et al evaluated the value of neuropsychological testing, neuroimaging, and biomarkers (CSF AB and tau) for diagnosing AD in all participants in the ADNI database who had a lumbar puncture. This included 105 normal controls, 179 patients with MCI, and 91 patients with AD. Neuropsychological testing and magnetic resonance imaging (MRI) were found to be the most informative techniques, with 84% and 82% correct classification, respectively. CSF assessments had 73% correct classification and did not add diagnostic information when all techniques were combined. CSF assessments were less informative in patients aged 75 years and older (70% correct classification vs 77% for patients ≤75 years).

Two reports from 2009 compared MRI scans and CSF biomarkers for diagnosis and prognosis among 399 participants undergoing both exams (109 normal, 192 amnestic MCI, 98 AD). In ROC analyses, C statistics for MRI as diagnostic of probable AD compared with normal and for P-tau/AB-42 were 0.90 and 0.84, respectively. In longitudinal evaluation, both MRI and biomarkers were associated with conversion to AD; c-indices were 0.69 for MRI and 0.62 for T-tau/AB-42. Reclassification measures were not reported. In these studies, MRI appeared to provide greater diagnostic (for probable AD) and prognostic information.

In a 2012 report, Schmand et al evaluated the value of neuropsychological testing, neuroimaging, and biomarkers (AB and tau in CSF) for predicting conversion to AD in 175 patients with MCI. With a mean follow-up of 2.7 years (range, 0.5-4.6), 81 patients (46%) converted to AD. Neuropsychological testing and MRI predicted conversion with 63% to 67% classification success both in patients younger and older than 75 years. CSF biomarkers correctly classified 64% of patients younger than 75 years and 60% of patients 75 years of age or older. Difference in prediction for markers in combination (70%) was not significantly better than for individual markers.

Landau et al (2010) examined predictors of conversion to clinically diagnosed AD and cognitive decline in 85 patients with amnestic MCI in the ADNI. Twenty-eight patients developed AD over a mean 1.9-year follow-up. In multivariate models, CSF markers (P-tau, T-tau, P-tau/AB-42, T-tau/AB-42) were not associated with conversion to AD.

De Meyer et al (2010) developed a model using biomarkers (CSF AB-42/P-tau) in the U.S.-ADNI sample (114 cognitively normal, 200 MCI, 102 AD patients). Sensitivity and specificity in the development set were 90% and 64%, respectively; one-third of cognitively normal people had false-positive results. The model was then validated in a Belgian data set of 73 patients with...
autopsy-confirmed dementia and correctly identified 64 (94%) of 68 AD patients. In a separate data set of 57 patients with MCI, the model identified all patients who progressed to AD.

Ewers et al (2012) evaluated CSF AB-42, amyloid PET, fluorodeoxyglucose-positron emission testing (FDG-PET), and MRI in 211 ADNI patients with at least 1 detected amyloid biomarker. Using the most recent diagnostic criteria, in 92 patients undergoing all tests, AB-42 had 94% sensitivity for a positive FDG-PET or MRI. The authors concluded, “[m]ore correlation and validation studies of biomarkers in the AD population will be essential to understand biomarker performance and correlation with autopsy data.”

In 181 ADNI patients with MCI, Richard et al (2013) found neither MRI nor CSF biomarkers improved classification of patients who developed AD compared with a brief memory test. Net reclassification improvement obtained by adding MRI results to the memory test were 1.1% and for CSF AB-42/P-tau, 2.2%.

**Improved Health Outcomes (Clinical Utility)**

Although not without controversy because of modest efficacy, cholinesterase inhibitors are used to treat mild-to-moderate AD. Memantine, an N-methyl-d-aspartate receptor antagonist, appears to provide a small benefit in those with moderate-to-advanced disease. Given available therapies, in principle, more accurate diagnosis might allow targeting treatment to those most likely to benefit. However, clinical trial entry criteria and benefit have been based on clinical diagnosis. While the possibility that more accurate diagnosis may lead to improved outcomes is plausible, it is not based on current evidence. Pharmacologic interventions for MCI have not demonstrated benefit in reducing progression to AD.

**Ongoing and Unpublished Clinical Trials**

A search of ClinicalTrials.gov in June 2015 did not identify any ongoing or unpublished trials that would likely influence this review.

**Summary of Evidence**

The evidence for testing for Alzheimer disease (AD)–related biomarkers in patients who have dementia or mild cognitive impairment includes systematic reviews, meta-analyses, and case series. Relevant outcomes are test accuracy, test validity, symptoms, change in disease status, morbid events, quality of life, medication use, and resource utilization. Most studies derive from select patient samples and define optimal test cutoffs without validation; thus, generalizability of results is uncertain. For the diagnosis of AD, evidence does not demonstrate incremental improvement in diagnostic accuracy over clinical testing. For predicting conversion from mild cognitive impairment (MCI) to AD, limited evidence, including that from the Alzheimer Disease Neuroimaging Initiative, suggests that testing may define increased risk. Whether earlier diagnosis leads to improved health outcomes through delay of AD onset or improved quality of life is unknown. Therefore, the evidence is insufficient to determine the effects of the technology on health outcomes.
Practice Guidelines and Position Statements

National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer Disease and Related Disorders Association

In 1984, National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and Alzheimer Disease and Related Disorders Association (ADRDA) developed clinical criteria for the diagnosis of AD. Although evidence to date has used NINCDS/ADRDA’s AD classification, in 2011, the National Institute on Aging and the Alzheimer’s Association workgroup revised diagnostic criteria for dementia due to AD.

In the 1984 guidelines, diagnostic categories were defined as follows.

**Possible Alzheimer Disease**

Clinical diagnosis of possible AD:

A. May be made on the basis of the dementia syndrome in the absence of other neurological, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, the presentation, or the clinical course.

B. May be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia.

C. Should be used in research studies when a single gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

**Probable Alzheimer Disease**

Criteria for the clinical diagnosis of probable AD included:

A. Dementia, established by clinical examination and documented by the Mini-Mental State Examination, the Blessed Dementia Scale, or some similar examination and confirmed by neuropsychological tests;

B. Deficits in 2 or more areas of cognition;

C. Progressive worsening of memory and other cognitive functions;

D. No disturbance of consciousness;

E. Onset between ages 40 and 90 years, most often after the age of 65 years; and

F. Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

The diagnosis of probable AD is supported by:

A. Progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);

B. Impaired activities of daily living and altered patterns of behavior;

C. Family history of similar disorders, particularly if confirmed neuropathologically; and

D. Laboratory results: normal lumbar puncture as evaluated by standard techniques, normal pattern or nonspecific changes in the electroencephalogram (EEG), and evidence of cerebral atrophy on computed tomography (CT) scanning with progression documented by serial observation.
Other clinical features consistent with the diagnosis of probable AD, after exclusion of causes of dementia other than AD, include

A. Plateaus in the course of progression of the illness;
B. Associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, sexual disorders, weight loss, and catastrophic verbal, emotional, or physical outbursts;
C. Other neurological abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder; and
D. Seizures in advanced disease CT normal for age.

Features that make the diagnosis of probable AD uncertain or unlikely include:

A. Sudden apoplectic onset;
B. Focal neurological findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and
C. Seizures or gait disturbances at the onset or very early in the course of the illness.

Definite Alzheimer Disease
Criteria for diagnosis of definite AD are:

A. Clinical criteria for probable Alzheimer disease; AND
B. Histopathologic evidence obtained from a biopsy or autopsy.

National Institute on Aging and the Alzheimer’s Association
As of 2011, probable AD is defined by the National Institute on Aging and the Alzheimer’s Association workgroup according to the following diagnostic criteria:

“Meets criteria for dementia…and in addition, has the following characteristics:

A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;
B. Clear-cut history of worsening of cognition by report or observation; and
C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories.
   a. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text.
   b. Nonamnestic presentations: Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present. Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present. Executive dysfunction: The
most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.

D. The diagnosis of probable AD dementia should not be applied when there is evidence of:
   a. Substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or
   b. Core features of dementia with Lewy bodies other than dementia itself; or
   c. Prominent features of behavioral variant frontotemporal dementia; or
   d. Prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or
   e. Evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.”

All probable AD by NINCDS-ADRDA criteria are subsumed in the revised probable AD criteria. Revised criteria include a category of “Probable AD dementia with increased level of certainty” due to documented decline or having a causative AD genetic mutation. Additionally, a category “Probable AD dementia with evidence of the AD pathophysiological process” has been added. Evidence of the AD pathophysiological process is supported by detection of low cerebrospinal fluid (CSF) AB-42, positive positron emission tomography (PET) amyloid imaging, or elevated CSF tau, and decreased 18-F fluorodeoxyglucose uptake on PET in the temporoparietal cortex with accompanying atrophy by magnetic resonance imaging in relevant structures. Detection of the “pathophysiological process” is further divided according to when in the disease natural history markers are expected to be detectable.

Note on Revised AD Criteria and Biomarkers
The biomarkers considered in this evidence review included in a category among revisions to the 2011 updated AD diagnostic criteria, “probable AD dementia with evidence of the AD pathophysiological process.” However, the diagnostic criteria workgroup noted that

“we do not advocate the use of AD biomarker tests for routine diagnostic purposes at the present time. There are several reasons for this limitation: 1) the core clinical criteria provide very good diagnostic accuracy and utility in most patients; 2) more research needs to be done to ensure that criteria that include the use of biomarkers have been appropriately designed, 3) there is limited standardization of biomarkers from one locale to another, and 4) access to biomarkers is limited to varying degrees in community settings. Presently, the use of biomarkers to enhance certainty of AD pathophysiological process may be useful in 3 circumstances: investigational studies, clinical trials, and as optional clinical tools for use where available and when deemed appropriate by the clinician.”

Alzheimer’s Association
In 2009, the Alzheimer’s Association (AA) initiated a quality control program for CSF markers, noting that “Measurements of CSF AD biomarkers show large between laboratory variability, likely caused by factors related to analytical procedures and the analytical kits. Standardization
of laboratory procedures and efforts by kit vendors to increase kit performance might lower variability, and will likely increase the usefulness of CSF AD biomarkers." In 2012, the Alzheimer's Biomarkers Standardization Initiative published consensus recommendations for standardization of preanalytical aspects (eg, fasting, tube types, centrifugation, storage time, temperature) of CSF biomarker testing.

In 2013, AA published recommendations for operationalizing the detection of cognitive impairment during the Medicare annual wellness visit in primary care settings. The recommended algorithm for cognitive assessment was based on “current validated tools and commonly used rule-out assessments.” Guideline authors noted that use of biomarkers (eg, CSF tau and β-amyloid proteins) “was not considered as these measures are not currently approved or widely available for clinical use.”

**The 4th Canadian Consensus Conference on Diagnosis and Treatment of Dementia**

The 4th Canadian Consensus Conference on Diagnosis and Treatment of Dementia published updated evidence-based consensus recommendations in 2012. There was consensus that plasma AB-42 measurement is unreliable and is not recommended for clinical practice. There was lack of consensus for measurement of CSF AB-42 and tau levels in patients with atypical dementia. Conference participants concluded that “for now, measurement of CSF AB1-42 and tau have no clinical utility in Canada, although they are part of research protocols in observational and therapeutic studies.”

**European Federation of Neurological Societies and European Neurological Society**

In 2012, European Federation of Neurological Societies and European Neurological Society published updated evidence-based consensus guidelines on the diagnosis and management of disorders associated with dementia. A level B recommendation (probably effective based on class 3 [unblinded] evidence) that CSF AB-42/tau/p-tau assessment helps to differentiate AD was included.

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

There is no national coverage determination (NCD).

**V. DEFINITIONS**

**Allele** refers to one of two or more different genes containing specific inheritable characteristics that occupy corresponding positions (loci) on paired chromosomes.

**Autosomal Dominant Inheritance** refers to a pattern of inheritance in which the transmission of a dominant allele on an autosome causes a trait to be expressed.
**BIOCHEMICAL MARKER** refers to any biochemical compound such as an antigen, antibody, abnormal enzyme, or hormone that is sufficiently altered in a disease to serve as an aid in diagnosing or in predicting susceptibility to disease.

**FIRST-DEGREE RELATIVE** refers to parent, sibling, or child.

**GENE** is the basic unit of heredity, made of DNA, the code for a specific protein.

**LIPOPROTEIN** refers to conjugated chemicals in the bloodstream consisting of simple proteins bound to fat. Cholesterol, phospholipids and triglycerides are all fatty components of lipoproteins.

**NEUROFIBRIL** refers to any of the many tiny fibrils that extend in every direction of the nerve cell body. They extend into the axon and dendrites of the cell.

**NEURON** refers to a nerve cell, the structural and functional unit of the nervous system.

### VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member’s contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

### VII. DISCLAIMER

*Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.*
VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore not covered when used for genetic testing and/or biochemical markers for the diagnosis or risk assessment of Alzheimer’s disease:

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| HCPCS Codes | Description |  |
|-------------|-------------|
| S3852       | DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer's disease |  |

IX. REFERENCES

Genetic Testing for Alzheimer’s Disease

<table>
<thead>
<tr>
<th>POLICY TITLE</th>
<th>DIAGNOSTIC TESTING AND RISK ASSESSMENT FOR ALZHEIMER’S DISEASE (BIOCHEMICAL AND GENETIC)</th>
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<td>MP- 2.050</td>
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Biochemical Markers of Alzheimer’s Disease

<table>
<thead>
<tr>
<th>Policy Title</th>
<th>Diagnostic Testing and Risk Assessment for Alzheimer’s Disease (Biochemical and Genetic)</th>
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<td>Policy Number</td>
<td>MP- 2.050</td>
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X. POLICY HISTORY

| POLICY NUMBER | CAC 5/27/03 | CAC 4/26/05 | CAC 6/28/05 | CAC 5/30/06 | CAC 4/24/07 Consensus |
## Policy Title
**Diagnostic Testing and Risk Assessment for Alzheimer’s Disease (Biochemical and Genetic)**

## Policy Number
MP- 2.050

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<td>CAC 5/25/10</td>
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<td>02/27/2013-</td>
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<td>Consensus review. For genetic testing for diagnosis of alzheimer’s disease, TREM2 added as another example of a test considered investigational. References and rationale updated. Codes reviewed.</td>
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*Health care benefit programs issued or administered by Capital BlueCross and/or its subsidiaries, Capital Advantage Insurance Company®, Capital Advantage Assurance Company® and Keystone Health Plan® Central. Independent licensees of the BlueCross BlueShield Association. Communications issued by Capital BlueCross in its capacity as administrator of programs and provider relations for all companies.*
Appendix Table 1. Categories of Genetic Testing Addressed in Genetic Testing for Alzheimer’s Disease

<table>
<thead>
<tr>
<th>Category</th>
<th>Addressed</th>
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<tbody>
<tr>
<td>1. Testing of an affected individual’s germline to benefit the individual</td>
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<tr>
<td>1a. Diagnostic</td>
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<tr>
<td>1b. Prognostic</td>
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<tr>
<td>1c. Therapeutic</td>
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<tr>
<td>2. Testing cancer cells from an affected individual to benefit the individual</td>
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<tr>
<td>2a. Diagnostic</td>
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</tr>
<tr>
<td>2b. Prognostic</td>
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<tr>
<td>2c. Therapeutic</td>
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<tr>
<td>3. Testing an asymptomatic individual to determine future risk of disease</td>
<td>X</td>
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<tr>
<td>4. Testing of an affected individual’s germline to benefit family members</td>
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<tr>
<td>5. Reproductive testing</td>
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<tr>
<td>5a. Carrier testing: preconception</td>
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<tr>
<td>5b. Carrier testing: prenatal</td>
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<tr>
<td>5c. In utero testing: aneuploidy</td>
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<tr>
<td>5d. In utero testing: mutations</td>
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<tr>
<td>5e. In utero testing: other</td>
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</tr>
<tr>
<td>5f. Preimplantation testing with in vitro fertilization</td>
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