Test Definition: AD2AR

PrecivityAD2, Reflex to Apolipoprotein E, Plasma

Overview

Useful For

Assisting in the evaluation of adult patients, aged 50 years and older, with signs or symptoms of mild cognitive impairment or dementia who are being assessed for Alzheimer disease and other causes of cognitive decline

Determining APOE E4 status to aid in medical management and treatment decisions when the PrecivityAD2 blood test result is positive

This test **is not intended for** patients younger than 50 years, or for use as a screening test in patients without signs or symptoms of cognitive, or for serial testing for assessment of longitudinal changes.

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
C2NAP	Precivity-ApoE	No	No

Testing Algorithm

When this test result is positive, then apolipoprotein E testing will be performed at an additional charge.

Highlights

The PrecivityAD2 blood test measures amyloid beta (Abeta) 42/40 ratio and percent tau phosphorylated at threonine-217 (%p-tau217). The results are then combined and used in a proprietary statistical algorithm to calculate the Amyloid Probability Score 2 (APS2). The APS2, Abeta 42/40 ratio and %p-tau217 are reported, however, individual Abeta42, Abeta40, phosphorylated tau217 and non-phosphorylated tau217 concentrations are not reported. For patients who receive a positive PrecivityAD2 test result, additional testing is performed to measure the apolipoprotein E isoforms E2, E3, and E4.

Method Name

Immunoprecipitation/Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS)

NY State Available

Yes

Specimen

Specimen Type

Plasma

Ordering Guidance

Test Definition: AD2AR

PrecivityAD2, Reflex to Apolipoprotein E, Plasma

This blood test is intended for use in patients aged 50 and older with signs or symptoms of mild cognitive impairment or dementia who are undergoing evaluation for Alzheimer disease or other forms of cognitive decline, and who have not had prior apolipoprotein E proteotyping or *APOE* genotyping.

Shipping Instructions

1. Specimens must be shipped frozen on dry ice.
2. Place labeled aliquot tubes inside a larger tube or vial for transport.

Specimen Required

Supplies: Screw cap micro tube, 2 mL, PCR Performance Tested, Low protein-binding (T983)
Collection Container/Tube: 10 mL Purple top (K EDTA)
Submission Container/Tube: Two 2-mL screw cap micro tubes
Specimen Volume: 3 mL in 2 tubes, each containing 1.5 mL
Collection Instructions:
1. Centrifuge within two hours of collection.
2. Label two 2-mL screw-cap micro tubes.
3. Aliquot 1.5 mL of plasma into each labeled micro tube.
4. Freeze plasma (no longer than 2 hours after collection) at or below -20 degrees C.

Forms

If not ordering electronically, complete, print, and send a Neurology Specialty Testing Client Test Request (T732) with the specimen.

Specimen Minimum Volume

See Specimen Required

Reject Due To

Gross hemolysis	Reject
Gross lipemia	Reject
Gross icterus	Reject
Outside of age range Specimen collected outside of testing range (too long in storage before arrival to testing facility) Insufficient volume Incorrect	Reject

labeling	

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Plasma	Frozen		

Clinical & Interpretive

Clinical Information

Alzheimer disease (AD) is defined pathologically by the presence of amyloid plaques and neurofibrillary tangles in the brain. Clinical characteristics include gradual onset of Mild cognitive impairment (MCI), behavioral changes such as apathy, withdrawal, or agitation, and disease progression to middle and later stage dementia.(1,2) Currently, no test detects AD with 100% accuracy; definitive diagnosis occurs at brain autopsy.

Recent availability of anti-amyloid therapies increases the importance of detection of AD at an early stage.(3-5) MCI impacts 12% to 18% of people in the United States over age 60 and is often an initial clinical sign of AD.(6) Establishing or excluding an AD diagnosis with a high degree of certainty at first signs of memory decline may optimize medical management.

Brain amyloid pathology is detectable by amyloid positron emission tomography (PET) scan, cerebrospinal fluid testing, or liquid chromatography tandem mass spectrometry blood biomarker testing with high sensitivity and specificity in patients with MCI and early dementia.(7-12) In all testing modalities, healthcare professionals interpret test results in the context of the patient's clinical findings and other clinical work-up, as the neuropathological changes associated with AD can be seen in other forms of dementia and in unaffected individuals.(7,8,13)

The PrecivityAD2 test is an analytically and clinically validated blood test that aids healthcare professionals in ruling in or ruling out AD in patients presenting with MCI or dementia. This evaluation simultaneously quantifies specific plasma amyloid beta (Abeta) and tau peptide concentrations to calculate the Abeta42/40 ratio and percent tau phosphorylated at threonine-217 (% p-tau217).(12) The inclusion of plasma analyte ratios has been shown to mitigate the effects of confounding factors such as chronic kidney disease.(14,15) The ratios are combined into a proprietary statistical algorithm to calculate the Amyloid Probability Score 2 (APS2), a numerical value ranging from 0 to 100, that determines whether a patient is positive (has high likelihood) or negative (has low likelihood) for the presence of brain amyloid plaques by amyloid PET scan.

For patients with a positive PrecivityAD2 blood test result, apolipoprotein E (ApoE) proteotyping is performed to determine *APOE* E4 status.

ApoE is a component of several classes of lipoprotein particles, including chylomicron remnants, very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL) and high-density lipoprotein (HDL) and is highly expressed in the liver and brain.(16) The protein has seven isoforms (ApoE1-7), the most common of which are ApoE2, ApoE3 and ApoE4. ApoE isoforms are encoded by the *APOE* gene alleles E1-E7. The E3 allele, most frequent in all populations, has a

frequency range of 50% to 90%, whereas E4 and E2 allele frequencies range from 5% to 35% and 1% to 5%, respectively.(17)

ApoE isoforms differentially influence the buildup of amyloid beta plaques and tau neurofibrillary tangles in the brain. Determination of *APOE* proteotype/genotype status may aid in clinical evaluation for AD in symptomatic patients and can inform decision-making for optimal treatment pathways.(18-21) In recent clinical trials for amyloid-reducing therapies, the E4 allele showed an association with the development of amyloid-related imaging abnormalities (ARIA): cerebral edema (ARIA-E), and cerebral microhemorrhages (ARIA-H).(3,4)

Reference Values

Amyloid Probability Score 2 (APS2) (range of 0-100):
Negative: 0-47
Positive: 48-100

Abeta42/40 Ratio:
> or =0.095 Consistent with absence of amyloid plaques

Percent p-tau217:
<4.2% consistent with absence of brain amyloid plaques

ApoE Proteotype
E2/E2, E2/E3, E2/E4, E3/E3, E3/E4, E4/E4
-E3 is the most common allele.
-E4 allele is associated with increased risk of amyloid plaques.
-E2 allele is associated with lower risk of amyloid plaques.

Interpretation

The Amyloid Probability Score 2 (APS2) result is a composite score ranging from 0 to 100 that demonstrates the strongest correlation with brain amyloid pathology compared to the individual biomarkers (amyloid beta [Abeta] 42/40 ratio or percent tau phosphorylated at threonine-217 [%p-tau217]), considered separately. Discordance of the individual biomarkers can occur.

Table 1. Amyloid Probability Score and Interpretation

APS2		**Interpretation**
0-47	Negative	Consistent with a negative amyloid positron emission tomography (PET) scan; reflects a low likelihood of brain amyloid plaques and is therefore not consistent with a neuropathological diagnosis of Alzheimer disease (AD).
48-100	Positive	Consistent with a positive amyloid PET scan; reflects a high likelihood of brain amyloid plaques, one of the neuropathological findings of AD.

For apolipoprotein E (ApoE) testing, there are six possible allele combinations for AD risk interpretation.

ApoE proteotyping determines which ApoE protein types are present in the submitted sample. The protein types

detected determine the presence of E2, E3, and/or E4 alleles, corresponding to the patient's *APOE* genotype (see Table 2).

Table 2. Proteotype Interpretation

Proteotype result	Corresponding genotype	Interpretation
ApoE2/ApoE2	*APOE2/APOE2*	**E2/E2** homozygous individuals have a significantly decreased risk for AD compared to E3/E3 and E4 carriers.
ApoE2/ApoE3	*APOE2/APOE3*	**E2/E3** heterozygous individuals have a decreased risk for AD compared to E3/E3, and E4 carriers.
ApoE2/ApoE4	*APOE2/APOE4*	**E2/E4** heterozygous individuals have an increased risk for AD compared to E3/E3, E2/ E2, and E2/E3 proteotypes/genotypes.
ApoE3/ApoE3	*APOE3/APOE3*	**E3/E3** homozygous individuals are most common and have decreased risk for AD com- pared to E4 carriers, and increased risk compared to E2/E2 and E2/ E3 proteotypes/genotypes.
ApoE3/ApoE4	*APOE3/APOE4*	**E3/E4** heterozygous individuals have an approximately three-fold increased risk for AD compared to E4 noncarriers.
ApoE4/ApoE4	*APOE4/APOE4*	**E4/E4** homozygous individuals have an approximately eight- to twelve-fold increased risk for AD compared to E4 noncarriers.

Cautions

This test is not a standalone test; positive or negative Amyloid Probability Score 2 (APS2) values alone neither rule in nor rule out a diagnosis of Alzheimer disease (AD).

Test results should be used in conjunction with other diagnostic tools such as neurological examination, neurobehavioral tests, imaging, and routine laboratory tests.

False-positive and false-negative test results may occur.

This test uses interpretive data that were derived from clinical studies in a predominantly White US population of patients with mild cognitive impairment or early dementia. The extent of the differences in results (if any) based on individuals of other racial and ethnic groups has not yet been firmly established.

Currently, there is insufficient evidence to support serial testing for the assessment of longitudinal changes in biomarkers, including monitoring response to therapy.

The results of other analyte tests using other methodologies cannot be interpreted in the context of the PrecivityAD2 test.

Apolipoprotein E
This test detects only peptides from E2, E3 and E4 proteins and does not detect peptides from rare apolipoprotein E (ApoE) phenotypes.

Although multiple epidemiological studies of diverse ethnic populations have demonstrated increased frequency of the E4 allele in late-onset AD cohorts, the extent of differences in individual risk estimates across different ethnicities has not been established.(22)

The E4 allele is neither necessary nor sufficient for the development of AD; thus, ApoE isoform/*APOE* allele status cannot be used alone for the diagnosis of AD.(18)

The Precivity-ApoE test provides a corresponding genotype based on the proteotype result. Be advised that submission of an order for this test constitutes certification to Mayo Clinic Laboratories by the ordering healthcare professional that they have obtained "Informed Consent" from the patient as required by any applicable state or federal laws with respect to the test ordered.

Clinical Reference

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Performance

Method Description

Plasma specimens undergo immunoprecipitation followed by liquid chromatography tandem mass spectrometry (LC-MS/MS) for the quantification of amyloid beta (Abeta) 42 and Abeta 40 peptide isoform concentrations and phosphorylated and non-phosphorylated tau at amino acid threonine, position 217 (p-tau271 and np-tau217) peptide concentrations. The percent tau phosphorylated at threonine-217 (%p-tau217) is calculated using the following equation: p-tau271/np-tau217*100. A statistical algorithm combines the Abeta42/40 and %p-tau217 to generate the Amyloid Probability Score 2 (APS2).(Meyer MR, Kirmess KM, Eastwood S, et al. Clinical validation of the PrecivityAD2 blood test: A mass spectrometry-based test with algorithm combining %p-tau217 and Abeta42/40 ratio to identify presence of brain amyloid. Alzheimers Dement. 2024;20[5]:3179-3192. doi:10.1002/alz.13764)

For the identification of apolipoprotein E (ApoE) peptides specific to ApoE2, ApoE3, ApoE4 isoforms, patient specimens undergo immunoprecipitation followed by LC-MS/MS. Specific combinations of 'present' and 'absent' peptides are used

to determine ApoE proteotype.

PDF Report
No

Day(s) Performed
Monday through Friday

Report Available
18 days post sample receipt from MCL

Specimen Retention Time
60 days

Performing Laboratory Location
C2N Diagnostics LLC

Fees & Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification
C2N Diagnostics has developed and determined the analytical and clinical validity performance characteristics of this Laboratory Developed Test (LDT). This assay has been validated pursuant to CLIA regulations and is used for clinical purposes. This assay has not been cleared or approved by the FDA.

CPT Code Information
0503U

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
AD2AR	PrecivityAD2 Reflex to ApoE	Not Provided

Result ID	Test Result Name	Result LOINC® Value
C2RG	Amyloid Probability Score 2 (APS2)	Not Provided
C2RH	APS2 Result Interpretation	Not Provided
C2RI	APS2 Result Reference Interval	Not Provided
C2RJ	APS2 Description	Not Provided
C2RK	Percent p-tau217	Not Provided

C2RL	Percent p-tau217 Reference Interval	Not Provided
C2RM	Abeta42/40 Ratio	Not Provided
C2RN	Abeta42/40 Ratio Reference Interval	Not Provided
C2RO	Test Description	Not Provided
C2RP	Limitations of Test Result	Not Provided
C2RQ	Methods and Assay Category	Not Provided
C2RR	References	Not Provided
C2RRF	Performing Site	Not Provided
C2RRC	Report Comment	Not Provided
C2RGF	APS2 Result	Not Provided
C2RLD	Percent p-tau217 Description	Not Provided
C2RND	Abeta42/40 Ratio Description	Not Provided