The PrecivityAD2® Test Clinician Brochure

Indication for Use

The PrecivityAD2® test is an in vitro device that uses immunoprecipitation followed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) to quantify β-Amyloid 1-42 (Aβ42) and β-Amyloid 1-40 (Aβ40) peptide concentrations, and phosphorylated and non-phosphorylated tau protein at amino acid threonine, position 217 (p-tau217 and np-tau217) peptide concentrations in human K2-EDTA plasma.

An algorithm combines the Aβ42/40 ratio and the p-tau217/np-tau217 ratio × 100 (%p-tau217) to generate the Amyloid Probability Score 2 (APS2) result, a numeric value ranging from 0 to 100.

The PrecivityAD2® test is indicated for use in adults aged 40 years and older who present with signs or symptoms of cognitive impairment undergoing evaluation for Alzheimer's disease or other forms of cognitive decline.

The PrecivityAD2® test is intended to be used in conjunction with clinical assessment to aid health care professionals experienced in the evaluation of cognitive impairment to identify patients with amyloid pathology associated with Alzheimer's disease.

The test is not intended as a screening or stand-alone diagnostic test.

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The PrecivityAD2® Test Overview

The PrecivityAD2® test is an in vitro diagnostic blood test intended to aid healthcare professionals in identifying brain amyloid pathology associated with Alzheimer's disease inadults aged 40 years and older who have signs or symptoms of cognitive impairment and are undergoing evaluation for Alzheimer's disease or other cause of cognitive decline.

The test uses high-resolution mass spectrometry to measure Aβ42/40 and %p-tau217 and combines these biomarkers using a proprietary algorithm to calculate the Amyloid Probability Score 2 (APS2), which indicates the likelihood of brain amyloid pathology. The PrecivityAD2® test demonstrated consistent, reliable diagnostic performance across the spectrum of cognitive impairment evaluated, with increasing age, and across 12 pre-specified chronic diseases commonly associated with aging.

Summary and Explanation of Test

The test uses a multianalyte assay with algorithmic analysis to measure plasma concentrations of four analytes:

β-Amyloid 1-42 (Aβ42)
β-Amyloid 1-40 (Aβ40)
Phosphorylated tau protein at amino acid Threonine 217 (p-tau217)
Non-phosphorylated tau protein at amino acid Threonine 217 (np-tau217)

From these absolute concentrations in pg/mL, two ratios are calculated:

Aβ42/40 ratio = [Aβ42]/[Aβ40]
%p-tau217 = ([p-tau217]/[np-tau217]) × 100

These ratios are combined in an algorithm to generate the Amyloid Probability Score 2 (APS2) result, which is evaluated against validated clinical cutoffs. The APS2 result indicates the likelihood of brain amyloid pathology, reported as Positive, Likely Positive, or Negative.

Protein Analytes

Amyloid Protein:
Studies have demonstrated the feasibility of quantifying plasma Aβ biomarkers using mass spectrometry and identifying amyloid deposition in the brain, a neuropathological hallmark of Alzheimer's disease (AD)[1-3]. Aβ42 is an established (Core 1) biomarker of amyloid plaque formation[4]. Studies have also demonstrated that ratios of Aβ biomarkers, such as Aβ42/40, show superior diagnostic performance than the individual Aβ biomarkers alone[5].

Tau Protein:
Phosphorylated tau at threonine 217 (p-tau217) in plasma is a specific and sensitive Core 1 biomarker for brain amyloid plaques[4]. Plasma levels of p-tau217 show strong correlations with β-amyloid deposition as measured by amyloid PET imaging[6-8]. Moreover, the ratio of p-tau217 to its non-phosphorylated counterpart (p-tau217/np-tau217, or %p-tau217) demonstrates greater diagnostic performance than p-tau217 concentration alone or other phosphorylated tau isoforms, offering improved specificity for underlying amyloid pathology, particularly in the presence of advancing age or various comorbidities such as chronic kidney disease, anemia or obesity [9-13].

Principles of the Test Procedure

The C2N-Aβ42/40 assay and the C2N-%p-tau217 Assay are used to generate input values for the APS2 algorithm. The C2N-Aβ42/40 Assay quantifies the concentrations of Aβ42 and Aβ40 in human plasma collected in K2-EDTA tubes (K2-EDTA plasma) and is used to calculate the Aβ42/Aβ40 ratio. The C2N-%p-tau217 Assay quantifies the concentration of p-tau217 and np-tau217 in K2-EDTA plasma and is used to calculate %p-tau217. The outputs of these assays are combined to form the result of the PrecivityAD2® test, the APS2 result. The APS2 result indicates the likelihood of brain amyloid pathology.

The C2N-Aβ42/40 Assay is performed as a single multiplexed LC-MS/MS assay. Total β-amyloid protein is purified directly from human K2-EDTA plasma by immunoprecipitation, and the protein is digested with Lys-N endoproteinase to generate C-terminal peptides that are specific for the Aβ42 and Aβ40 isoforms of β-amyloid protein. These peptides are detected and quantified; the quantity of each peptide in pg/mL is used to generate the Aβ42/Aβ40 ratio that is entered directly into the APS2 algorithm.

The C2N-%p-tau217 Assay is used to quantify the plasma concentrations of phosphorylated threonine-217 and non-phosphorylated threonine-217 within tau protein. This assay is performed as a single multiplexed LC-MS/MS assay that is processed separately from the C2N-Aβ42/40 Assay. In the C2N-%p-tau217 Assay, tau protein is purified directly from human K2-EDTA plasma by immunoprecipitation and the protein is digested with trypsin endoproteinase to generate two peptides: one peptide that is phosphorylated on amino acid threonine 217 (sequence TPSLP(p)TPPTR); and one peptide that is not phosphorylated on amino acid threonine 217 (sequence TPSLPTPPTR). These two peptides are detected and quantified; the quantity of each peptide in pg/mL is used to generate %p-tau217 that is entered directly into the APS2 algorithm.

The APS2 result is generated from the APS2 algorithm that combines Aβ42/Aβ40 ratio and %p-tau217. The APS2 is a whole number between 0 and 100 that is evaluated against clinical cutoffs to indicate whether an individual is likely to have brain amyloid pathology.

Specimen Collection/Preparation

The PrecivityAD2® test is a prescription-use-only test that must be ordered by a health care professional (HCP). Blood samples are collected from the patient and sent to C2N Diagnostics Laboratory. A sample may be collected through one of three routes:

- An HCP may order specimen collection tubes and instructions from C2N and the sample can be collected at the HCP's office; or
- A patient may visit one of several clinical sites within the U.S. that have contracted with C2N to collect samples for performing the PrecivityAD2® test; or
- An HCP may order the PrecivityAD2® test with specimen collection performed by a mobile phlebotomy service at the patient's home or another designated location.

In all scenarios, C2N provides the materials or specifies the materials that may be procured by the collection facility. C2N also provides the instructions required for specimen collection, processing, and shipment. Specimens may be shipped either refrigerated or frozen, as described below.

Procedure

The PrecivityAD2® test has four major steps – sample collection, sample processing, data processing, and result reporting. Samples are collected from each patient using a sample collection kit and/or procedure that is provided by C2N. Venous blood is processed to K2-EDTA plasma using FDA-cleared blood collection tubes. The plasma sample is frozen at the collection site and shipped overnight to C2N on dry ice or with cold packs. Upon arrival, samples are stored at −65 to −80 ºC until processed. All samples are analyzed at C2N Diagnostics' high complexity laboratory in St. Louis, MO USA.

Results: The APS2 Algorithm, Clinical Cutoffs and Clinical Interpretation

C2N has developed and validated an algorithm that combines the Aβ42/Aβ40 ratio and the %p-tau217 to produce a final value, the APS2 result. The two ratios incorporated into the algorithm are calculated from the two individual LC-MS/MS assays that measure the four individual analytes. Using a training data set of individuals from the intended use population, C2N established the APS2 algorithm and two clinical cutoffs for the APS2 value that indicate the likelihood that an individual will have brain amyloid pathology as determined by comparison to clinically validated amyloid pathology tests that include: FDA-approved β-amyloid PET imaging agents interpreted by visual read or CSF biomarkers using an FDA-authorized IVD product.

Table 1: APS2 Clinical Cutoffs and Test Result Interpretation

APS2 Value^	Result	Result Interpretation
APS2 > 66.5	Positive	An APS2 result > 66.5 is Positive and consistent with the presence of brain amyloid pathology. This result increases the likelihood that a patient's clinical presentation is due to Alzheimer's disease. The APS2 result alone does not establish a diagnosis of clinical Alzheimer's disease. Clinical correlation is recommended.
27.5 < APS2 < 66.5	Likely Positive	An APS2 result > 27.5 and < 66.5 is Likely Positive and likely consistent with the presence of brain amyloid pathology. The result increases the likelihood that a patient's clinical presentation is due to Alzheimer's disease. The APS2 result alone does not establish a diagnosis of clinical Alzheimer's disease. Additional evaluations and/or further testing may be appropriate.

APS2 Value^	Result	Result Interpretation
APS2 < 27.5	Negative	An APS2 result < 27.5 is Negative and not consistent with the presence of brain amyloid pathology. The result decreases the likelihood that a patient's clinical presentation is due to Alzheimer's disease. Other potential causes for the patient's cognitive symptoms should be considered.

APS2 = Amyloid Probability Score 2

^If APS2 cannot initially be calculated because one or more analyte results are outside the applicable Analytical Measuring Interval (AMI) (with the exception for p-tau217 below the limit of quantitation [LOQ]), the submitted specimen will not be retested and further recollection for APS2 testing is not recommended. If one or more mass spectrometry flags (i.e., ion ratio failure) are present, the submitted specimen will be retested. If the mass spectrometry flag persists upon retesting, an APS2 result cannot be determined. A new specimen may be collected and tested to address potential specimen-specific or pre-analytical factors.

Limitations

- The PrecivityAD2® test is for prescription use only.
- The PrecivityAD2® test is for in vitro diagnostic use: only performed at C2N Diagnostics Laboratory using qualified instruments and validated procedrures.
- This test is intended to be performed only on qualified, serial number-controlled instruments at C2N Diagnostics Laboratory. All instruments used for patient testing are controlled under C2N's Quality Management System and must successfully complete the required qualification and validation activities before implementation.
- Always interpret the PrecivityAD2® test in conjunction with the patient's medical history, clinical presentation, physical assessment, and other findings.
- The safety and effectiveness of the PrecivityAD2® test have not been established for:
    - Predicting development of dementia or other neurologic conditions
    - Monitoring responses to therapies
- The performance of the PrecivityAD2® test across racial subgroups has not been fully established because of the relatively small number of subjects who report racial categories other than white and the large proportion of subjects in the Pooled Validation Cohort with missing racial categorization. Results for these subgroups should be interpreted with caution.

Warnings

- Erroneous results may occur due to improper specimen collection, handling, storage, shipping or unevaluated interfering substances.
- Hemoglobin concentration >150 mg/dL may interfere with analyte measurement and affect the APS2 result.

Reference Range

The reference range for the PrecivityAD2® test in cognitively normal individuals was evaluated in accordance with CLSI EP28-A3c[14]. The analysis was based on data from cognitively normal individuals who participated in three separate studies: the Bio-Hermes Cohort[15] (N=363); the PPAS008 study (N=74); and BioIVT[16] Normal Control study (N=27). In total, 470 cognitively normal individuals were enrolled across the three studies, of whom 464 had reportable APS2 results and were included in the analysis.

Table 2: Distribution of APS2 in All Subjects in Bio-Hermes, PPAS008 and BioIVT Healthy Control Cohorts

	All	Age			Gender		Race		
		40-59	60-69	70-85	Male	Female	White	African American	Other
n	464	93	188	183	187	277	402	46	16
	APS2								
Mean	20.67	9.28	17.63	29.57	21.52	20.09	21.72	13.63	14.31
SD	23.64	8.4	20.06	28.59	24.22	23.27	24.32	16.95	18.68
Median	11	6	10	16	11	10	11	8	8.5
Minimum	0	0	1	3	0	0	0	2	2
Maximum	100	48	99	100	100	99	100	84	80
2.5th Percentile	2	0	3.67	4	3	2	2	2.12	N/A*
97.5th Percentile	92	29.70	81	98	90.70	92.20	93.95	64.50	N/A*
	Aβ40								
Mean	482.65	425.31	470.24	524.53	471.84	489.94	486.06	466.13	444.31
SD	100.18	80.81	84.51	106.25	99.9	99.89	101.86	92.43	63.83
Median	470.40	418	464.72	509.22	458.87	476.46	472.84	444.28	430.27
Minimum	93.01	236.32	93.01	265.29	93.01	316.13	93.01	306.69	365.24
Maximum	954.05	905.69	954.05	951.06	795.35	954.05	954.05	786.10	630.87
2.5th Percentile	337.22	314.84	347.6	370.4	321.59	353.39	337.04	340.94	N/A*
97.5th Percentile	761.71	559.76	633.78	785.21	734.29	756.91	769.83	701.79	N/A*
	Aβ42								
Mean	48.60	47.44	47.54	50.27	46.89	49.75	48.56	49.77	46.21
SD	10.38	12.84	8.67	10.43	9.97	10.51	10.42	10.55	8.85
Median	47.53	44.37	46.86	49.1	45.87	48.39	47.6	49.69	44.68
Minimum	14.17	20.97	14.17	27.60	14.17	31.36	14.17	33.36	36.51
Maximum	90.51	85.73	83.93	90.51	83.93	90.51	90.51	83.93	68.07
2.5th Percentile	32.93	29.04	34.08	35.18	29.42	34.93	32.58	35.96	N/A*

97.5th Percentile	76.66	82.12	66.5	77.40	69.03	79.04	76.78	75.85	N/A*
	Aβ42/Aβ40 Ratio								
Mean	0.1014	0.111	0.1017	0.0961	0.1002	0.1022	0.1006	0.1071	0.1039
SD	0.0135	0.0186	0.0113	0.009	0.0127	0.014	0.0136	0.0108	0.0123
Median	0.1005	0.1081	0.102	0.096	0.0997	0.1009	0.0995	0.1061	0.1023
Minimum	0.075	0.075	0.0775	0.0764	0.075	0.0764	0.075	0.0809	0.0893
Maximum	0.19	0.19	0.1523	0.1277	0.19	0.1748	0.19	0.1358	0.1397
2.5th Percentile	0.0814	0.0831	0.082	0.0813	0.0817	0.0812	0.0813	0.0856	N/A*
97.5th Percentile	0.13	0.1696	0.12	0.1139	0.1195	0.1365	0.1266	0.1306	N/A*
	p-tau217								
Mean	10.99	0.81	3.31	1.8	12.77	9.79	10.28	15.32	16.56
SD	19.41	0.47	10.87	1.66	20.74	18.4	19.05	20.3	24.22
Median	1.35	0.68	0.65	0.65	1.53	0.65	1.34	1.67	1.1
Minimum	0.65	0.32	0.65	0.65	0.65	0.65	0.65	0.65	0.65
Maximum	86.34	3.59	85.71	7.70	81.44	86.34	86.34	63.72	60.33
2.5th Percentile	0.65	0.35	0.65	0.65	0.65	0.65	0.65	0.65	N/A*
97.5th Percentile	64.35	1.91	43.44	6.62	68.41	61.43	67.4	60.24	N/A*
	np-tau217								
Mean	37.98	44.63	44.47	50.22	35.51	39.66	38.85	30.28	38.49
SD	26.38	14.76	20.99	20.43	24.81	27.30	25.59	27.70	38.27
Median	40.13	41.61	42.67	45.02	39.29	40.65	40.44	33.27	41.57
Minimum	0.32	15.35	0.47	14.53	0.33	0.32	0.32	0.34	0.4
Maximum	201.72	86.34	164.21	201.72	116.21	201.72	201.72	116.21	149.4
2.5th Percentile	0.47	19.45	0.85	26.43	0.47	0.5	0.48	0.5	N/A*
97.5th Percentile	89.84	73.16	90.29	95.86	84.02	95.94	87.34	68.27	N/A*

	%p-tau217								
Mean	2.81	1.89	2.51	3.59	2.87	2.78	2.89	2.37	2.13
SD	2.4	0.90	1.98	3.02	2.54	2.31	2.49	1.68	1.81
Median	1.84	1.61	1.75	2.15	1.83	1.91	1.84	1.81	1.55
Minimum	0.44	0.60	0.44	0.68	0.77	0.44	0.60	0.95	0.44
Maximum	17.48	5.75	12.96	17.48	17.48	14.33	17.48	7.52	8.01
2.5th Percentile	0.94	0.78	0.92	1.05	0.93	0.95	0.96	1.02	N/A*
97.5th Percentile	10.26	4.03	8.10	12.34	10.01	10.26	10.5	7.40	N/A*
	APS2 % (n)								
Positive (APS2 > 66.5)	8.84% (41)	0% (0)	5.32% (10)	16.94% (31)	10.16% (19)	7.94% (22)	9.70% (39)	2.17% (1)	6.25% (1)
Likely Positive (27.5< APS2< 66.5)	11.64% (54)	4.30% (4)	10.64% (20)	16.39% (30)	10.70% (20)	12.27% (34)	12.44% (50)	8.70% (4)	0% (0)
Negative (APS2 < 27.5)	79.53% (369)	95.70% (89)	84.04% (158)	66.67% (122)	79.14% (148)	79.78% (221)	77.86% (313)	89.13% (41)	93.75% (15)
*Results listed as not applicable (N/A) are due to an insufficient number of samples to properly calculate the value.									

Aβ40 = β-Amyloid 1-40; Aβ42 = β-Amyloid 1-42; APS2 = Amyloid Probability Score 2; np-tau217 = non-phosphorylated tau protein at amino acid threonine, position 217; p-tau217 = phosphorylated tau protein at amino acid threonine, position 217

Ranges of Expected Values

The expected values for the PrecivityAD2® test in individuals with Alzheimer's disease-related neurological diseases and other medical conditions commonly observed in the intended use population were evaluated. The analysis is based on data from the BioIVT[16] cohort, which included 47 individuals. Data from individuals with AD-related neurological diseases and other medical conditions were analyzed to determine the expected values of the PrecivityAD2® test for each disease group.

Table 3: PrecivityAD2® Test Results by Disease in the BioIVT Cohort

Disease	APS2 Result						APS2 Result % (n)		
	n	Mean	SD	Median	Min, Max	2.5th Percentile, 97.5th Percentile	Positive (APS2 > 66.5)	Likely Positive (27.5< APS2< 66.5)	Negative (APS2 < 27.5)
Behavioral Frontotemporal Dementia	3	45	46.90	22	14, 99	N/A*, N/A*	33.30% (1)	0.0% (0)	66.70% (2)
Lewy Body Dementia	1	28	-	28	28, 28	N/A*, N/A*	0.0% (0)	100.0% (1)	0.0% (0)
Frontotemporal Dementia	3	12.70	11.50	13	1, 24	N/A*, N/A*	0.0% (0)	0.0% (0)	100.0% (3)
Parkinson's	40	32.20	26	23	5, 98	7, 97	12.50% (5)	35.00% (14)	52.50% (21)
*Results listed as not applicable (N/A) are due to an insufficient number of samples to properly calculate the value									

APS2 = Amyloid Probability Score 2

Analytical Performance

Analytical validation of the PrecivityAD2® test shows acceptable performance of the C2N-Aβ42/40 Assay and the C2N-%-p-tau217 Assay to quantify the four analytes, Aβ42, Aβ40, p-tau217, and np-tau217, and to generate the APS2 result. The studies demonstrate that the assays for each analyte and the resulting APS2 value have acceptable analytical performance characteristics.

Clinical Performance

The performance of the PrecivityAD2® test was assessed in plasma samples from 1,142 individuals with signs or symptoms of cognitive impairment from three cohorts. The reference standards for confirmation of presence or absence of brain amyloid pathology included amyloid positron emission tomography (PET) imaging or cerebrospinal fluid (CSF) analysis with the FDA-authorized Fujirebio Lumipulse G β-Amyloid Ratio (1-42/1-40) CSF test.

The clinical study population included individuals with subjective cognitive decline (SCD, 21.2%), mild cognitive impairment (MCI, 47.3%), or dementia (31.5%). The study population contained cohort data that included documentation of comorbidities.

The demographic and clinical characteristics of the study subjects according to diagnostic groups and amyloid status determined by amyloid PET visual read or CSF ratio test results are presented in Table 4.

Table 4: Demographic and Clinical Characteristics

		Clinical Presentation			Brain Amyloid Pathology		Total = 1142 n (%)
		SCD = 242 n (%)	MCI = 540 n (%)	Dementia = 360 n (%)	Present = 602 n (%)	Absent = 540 n (%)	
Sex	**Male**	121 (50%)	295 (54.6%)	183 (50.8%)	278 (46.2%)	321 (59.4%)	599 (52.5%)

		Clinical Presentation			Brain Amyloid Pathology		Total = 1142 n (%)
		SCD = 242 n (%)	MCI = 540 n (%)	Dementia = 360 n (%)	Present = 602 n (%)	Absent = 540 n (%)	
	Female	121 (50%)	245 (45.4%)	177 (49.2%)	324 (53.8%)	219 (40.6%)	543 (47.5%)
Age (years)	**40-49**	3 (1.2%)	10 (1.9%)	1 (0.3%)	2 (0.3%)	12 (2.2%)	14 (1.2%)
	50–59	34 (14%)	41 (7.6%)	7 (1.9%)	18 (3%)	64 (11.9%)	82 (7.2%)
	60–69	77 (31.8%)	109 (20.2%)	38 (10.6%)	81 (13.5%)	143 (26.5%)	224 (19.6%)
	70–79	92 (38%)	253 (46.9%)	178 (49.4%)	303 (50.3%)	220 (40.7%)	523 (45.8%)
	≥80	36 (14.9%)	127 (23.5%)	136 (37.8%)	198 (32.9%)	101 (18.7%)	299 (26.2%)
	Mean	69.4	72.8	76.7	75.9	70.4	73.3
	Median	70	75	78	77	72	75
	Min.	43	40	49	48	40	40
	Max.	89	90	91	91	90	91
Race	**White**	0 (0%)	32 (5.9%)	9 (2.5%)	34 (5.6%)	7 (1.3%)	41 (3.6%)
	Black or African American	0 (0%)	2 (0.4%)	0 (0%)	2 (0.3%)	0 (0%)	2 (0.2%)
	Asian or America Indian or Alaska Native or More than one	0 (0%)	1 (0.2%)	0 (0%)	1 (0.2%)	0 (0%)	1 (0.1%)
	Unknown	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Not reported	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Missing	242 (100%)	505 (93.5%)	351 (97.5%)	565 (93.9%)	533 (98.7%)	1098 (96.1%)
MMSE	**<18**	3 (1.2%)	21 (3.9%)	64 (17.8%)	65 (10.8%)	23 (4.3%)	88 (7.7%)
	18–23	9 (3.7%)	77 (14.3%)	155 (43.1%)	165 (27.4%)	76 (14.1%)	241 (21.1%)
	24–30	210 (86.8%)	411 (76.1%)	116 (32.2%)	338 (56.1%)	399 (73.9%)	737 (64.5%)

		Clinical Presentation			Brain Amyloid Pathology		Total = 1142 n (%)
		SCD = 242 n (%)	MCI = 540 n (%)	Dementia = 360 n (%)	Present = 602 n (%)	Absent = 540 n (%)	
	Missing	20 (8.3%)	31 (5.7%)	25 (6.9%)	34 (5.6%)	42 (7.8%)	76 (6.7%)
Apolipo protein E (ApoE) Status	**ε2/ε2**	1 (0.4%)	5 (0.9%)	2 (0.6%)	3 (0.5%)	5 (0.9%)	8 (0.7%)
	ε2/ε3	22 (9.1%)	42 (7.8%)	16 (4.4%)	16 (2.7%)	64 (11.9%)	80 (7%)
	ε2/ε4	6 (2.5%)	14 (2.6%)	11 (3.1%)	22 (3.7%)	9 (1.7%)	31 (2.7%)
	ε3/ε3	124 (51.2%)	241 (44.6%)	149 (41.4%)	182 (30.2%)	332 (61.5%)	514 (45%)
	ε3/ε4	77 (31.8%)	194 (35.9%)	143 (39.7%)	296 (49.2%)	118 (21.9%)	414 (36.3%)
	ε4/ε4	12 (5%)	40 (7.4%)	38 (10.6%)	80 (13.3%)	10 (1.9%)	90 (7.9%)
	Missing	0 (0%)	4 (0.7%)	1 (0.3%)	3 (0.5%)	2 (0.4%)	5 (0.4%)
Years of Education	**<13**	98 (40.5%)	295 (54.6%)	244 (67.8%)	336 (55.8%)	301 (55.7%)	637 (55.8%)
	≥13	140 (57.9%)	233 (43.1%)	109 (30.3%)	252 (41.9%)	230 (42.6%)	482 (42.2%)
	Missing	4 (1.7%)	12 (2.2%)	7 (1.9%)	14 (2.3%)	9 (1.7%)	23 (2%)
Brain Amyloid Pathology	**Present**	58 (24%)	291 (53.9%)	253 (70.3%)	602 (100%)	0 (0%)	602 (52.7%)
	Absent	184 (76%)	249 (46.1%)	107 (29.7%)	0 (0%)	540 (100%)	540 (47.3%)

MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; SCD = subjective cognitive decline

Overall Test Performance

The performance of the PrecivityAD2® test, described by the predictive value (PV), likelihood ratio, and frequency of test results, is summarized in Table 5. The positive predictive value (PPV) for Positive and Likely Positive results corresponds to the PV while the negative predictive value (NPV) for Negative results can be calculated as 100% PV. At the calculated amyloid prevalence of 52.7%, the PPV for APS2 Positive subjects is 97.6% and the NPV for APS2 Negative subjects is 93.1%. The likelihood ratio for APS2 Positive subjects is 37.05 and 0.07 for APS2 Negative subjects.

Table 5: Clinical Performance of the PrecivityAD2® Test in the Pooled Validation Cohort at the Calculated Amyloid Prevalence of 52.7%

PrecivityAD2® Test	Brain Amyloid Pathology			Predictive Value [n/N] (95% CI)	Frequency [n/N]	Likelihood Ratio
	Present	Absent	Total			
Positive (APS2>66.5)	413	10	423	97.6% [413/423] (95.7%; 98.7%)	37.0% [423/1142]	37.05 (20; 68.62)
Likely Positive (27.5<APS2<66.5)	153	45	198	77.3% [153/198] (70.9%; 82.6%)	17.3% [198/1142]	3.05 (2.23; 4.16)
Negative (APS2<27.5)	36	485	521	6.9% [36/521] (5.0%; 9.4%)	45.6% [521/1142]	0.07 (0.05; 0.09)
Total	602	540	1,142	Prevalence = 52.7% [602/1142]		

APS2 = Amyloid Probability Score 2

Test Performance Across Clinical Comparators

The performance of the PrecivityAD2® test across clinical comparators is shown in Tables 6 and 7. The performance of the PrecivityAD2® test is similar across clinical comparators, providing evidence of the poolability of the data from the two clinical comparators into the Pooled Validation Cohort.

Table 6: Clinical Performance of the PrecivityAD2® Test Using Amyloid PET Visual Read as the Clinical Comparator

PrecivityAD2® Test	PET Visual Read			Predictive Value [n/N] (95% CI)	Frequency [n/N]	Likelihood Ratio
	Positive	Negative	Total			
Positive (APS2 > 66.5)	67	7	74	90.5% [67/74] (81.7%; 95.3%)	35.4% [74/209]	11.27 (5.43; 23.37)
Likely Positive (27.5 < APS2 < 66.5)	23	17	40	57.5% [23/40] (42.2%; 71.5%)	19.1% [40/209]	1.59 (0.91; 2.8)
Negative (APS2 < 27.5)	6	89	95	6.3% [6/95] (2.9%; 13.1%)	45.5% [95/209]	0.08 (0.04; 0.17)
Total	96	113	209	Prevalence = 45.9% [96/209]		

APS2 = Amyloid Probability Score 2

Table 7: Clinical Performance of the PrecivityAD2® Test Using CSF Lumipulse as the Clinical Comparator

PrecivityAD2® Test	Lumipulse G β-Amyloid Ratio (1-42/1-40)			Predictive Value [n/N] (95% CI)	Frequency [n/N]	Likelihood Ratio
	Positive	Negative	Total			
Positive (APS2 > 66.5)	346	3	349	99.1% [346/349] (97.5%; 99.7%)	37.4% [349/933]	97.33 (31.47; 301.04)
Likely Positive (27.5 < APS2 < 66.5)	130	28	158	82.3% [130/158] (75.6%; 87.4%)	16.9% [158/933]	3.92 (2.66; 5.77)
Negative (APS2 < 27.5)	30	396	426	7.0% [30/426] (5.0%; 9.9%)	45.7% [426/933]	0.06 (0.05; 0.09)
Total	506	427	933	Prevalence = 54.2% [506/933]		

APS2 = Amyloid Probability Score 2

Test Performance by Sex

The performance of the PrecivityAD2® test in males and females is shown in Table 8. The prevalence of brain amyloid pathology is higher in females (59.7%) than in males (46.4%). This leads to a slightly higher PPV for APS2 Positive subjects in females (98.3%) than in males (96.7%). The NPV for APS2 Negative subjects is slightly lower in females (91.2%) than in males (94.4%), and this difference is expected to diminish if amyloid prevalence between females and males is adjusted to be equivalent. Taken together, the performance of the PrecivityAD2® test is similar in female and male subjects.

Table 8: Clinical Performance of the PrecivityAD2® Test in the Pooled Validation Cohort: Subgroup Analysis – Sex

Sex	PrecivityAD2® Test	Brain Amyloid Pathology			Predictive Value [n/N] (95% CI)	Frequency [n/N]
		Present	Absent	Total		
Female	Positive (APS2 > 66.5)	238	4	242	98.3% [238/242] (95.8%; 99.4%)	44.6% [242/543]
	Likely Positive (27.5 < APS2 < 66.5)	67	18	85	78.8% [67/85] (69.0%; 86.2%)	15.7% [85/543]
	Negative (APS2 < 27.5)	19	197	216	8.8% [19/216] (5.7%; 13.3%)	39.8% [216/543]
	Total	324	219	543	Prevalence = 59.7% [324/543]	

Male	Positive (APS2 > 66.5)	175	6	181	96.7% [175/181] (93.0%; 98.5%)	30.2% [181/599]
	Likely Positive (27.5 < APS2 < 66.5)	86	27	113	76.1% [86/113] (67.5%; 83.0%)	18.9% [113/599]
	Negative (APS2 < 27.5)	17	288	305	5.6% [17/305] (3.5%; 8.7%)	50.9% [305/599]
	Total	278	321	599	Prevalence = 46.4% [278/599]	

APS2 = Amyloid Probability Score 2

Test Performance by Age Category

The performance of the PrecivityAD2® test in age subgroups is shown in Table 9. The predictive values in the Pooled Validation Cohort are comparable across all age groups, with the PPV for APS2 Positive subjects varying between 97.0% and 100%. For APS2 Negative subjects, NPV ranged between 89.4% and 100% and was similar across the age spectrum, decreasing with age as the observed prevalence of brain amyloid pathology expectedly increased.

Table 9: Clinical Performance of the PrecivityAD2® Test in the Pooled Validation Cohort: Subgroup Analysis – Age

Age	PrecivityAD2® Test	Brain Amyloid Pathology			Predictive Value [n/N] (95% CI)	Frequency [n/N]
		Present	Absent	Total		
40-49	Positive (APS2 > 66.5)	2	0	2	100.0% [2/2] (34.2%; 100.0%)	14.3% [2/14]
	Likely Positive (27.5 < APS2 < 66.5)	0	1	1	0.0% [0/1] (0.0%; 79.3%)	7.1% [1/14]
	Negative (APS2 < 27.5)	0	11	11	0.0% [0/11] (0.0%; 25.9%)	78.6% [11/14]
	Total	2	12	14	Prevalence = 14.3% [2/14]	
50-59	Positive (APS2 > 66.5)	14	0	14	100.0% [14/14] (78.5%; 100.0%)	17.1% [14/82]
	Likely Positive (27.5 < APS2 < 66.5)	3	3	6	50.0% [3/6] (18.8%; 81.2%)	7.3% [6/82]
	Negative (APS2 < 27.5)	1	61	62	1.6% [1/62] (0.3%; 8.6%)	75.6% [62/82]
	Total	18	64	82	Prevalence = 22.0% [18/82]	

60-69	Positive (APS2 > 66.5)	56	1	57	98.2% [56/57] (90.7%; 99.7%)	25.4% [57/224]
	Likely Positive (27.5 < APS2 < 66.5)	21	5	26	80.8% [21/26] (62.1%; 91.5%)	11.6% [26/224]
	Negative (APS2 < 27.5)	4	137	141	2.8% [4/141] (1.1%; 7.1%)	62.9% [141/224]
	Total	81	143	224	Prevalence = 36.2% [81/224]	
70-79	Positive (APS2 > 66.5)	197	6	203	97.0% [197/203] (93.7%; 98.6%)	38.8% [203/523]
	Likely Positive (27.5 < APS2 < 66.5)	85	22	107	79.4% [85/107] (70.8%; 86.0%)	20.5% [107/523]
	Negative (APS2 < 27.5)	21	192	213	9.9% [21/213] (6.5%; 14.6%)	40.7% [213/523]
	Total	303	220	523	Prevalence = 57.9% [303/523]	
≥80	Positive (APS2 > 66.5)	144	3	147	98.0% [144/147] (94.2%; 99.3%)	49.2% [147/299]
	Likely Positive (27.5 < APS2 < 66.5)	44	14	58	75.9% [44/58] (63.5%; 85.0%)	19.4% [58/299]
	Negative (APS2 < 27.5)	10	84	94	10.6% [10/94] (5.9%; 18.5%)	31.4% [94/299]
	Total	198	101	299	Prevalence = 66.2% [198/299]	

APS2 = Amyloid Probability Score 2

Test Performance by Race

The performance of the PrecivityAD2® test across racial subgroups has not been fully established because of the relatively small number of subjects who report racial categories other than white and the large proportion of subjects in the Pooled Validation Cohort with missing racial categorization. Results for these subgroups should be interpreted with caution.

Test Performance in Subpopulations of SCD, MCI, and Dementia

The performance of the PrecivityAD2® test in the clinical presentation subgroups of SCD, MCI and dementia is shown in Table 10.

The observed amyloid positivity prevalence differs between the disease stage categories of SCD (24.0%), MCI (53.9%) and dementia (70.3%), consistent with previously published clinical and population-based data. Despite the lower underlying amyloid prevalence, the PrecivityAD2® test performance in the SCD category is similar to that of the Pooled Validation Cohort and the other diagnostic subgroups with more advanced disease.

Table 10: PrecivityAD2® Test Performance Across Clinical Disease Stages

PrecivityAD2® Test	Disease Stage			
	SCD (n = 242)	**MCI (n = 540)**	**Dementia (n = 360)**	**All (N = 1,142)**
Positive Results PV [n/N] (95% CI)	90.3% [28/31] (75.1%; 96.7%)	97.9% [187/191] (94.7%; 99.2%)	98.5% [198/201] (95.7%; 99.5%)	97.6% [413/423] (95.7%; 98.7%)
Likely Positive Results PV [n/N] (95% CI)	67.6% [23/34] (50.8%; 80.9%)	79.8% [83/104] (71.1%; 86.4%)	78.3% [47/60] (66.4%; 86.9%)	77.3% [153/198] (70.9%; 82.6%)
Negative Results PV [n/N] (95% CI)	4.0% [7/177] (1.9%; 7.9%)	8.6% [21/245] (5.7%; 12.7%)	8.1% [8/99] (4.2%; 15.1%)	6.9% [36/521] (5.0%; 9.4%)
Prevalence [n/N]	24.0% [58/242]	53.9% [291/540] (49.7%; 58.1%)	70.3% [253/360]	52.7% [602/1142]
Frequency of Likely Positive Results [n/N]	14.0% [34/242]	19.3% [104/540]	16.7% [60/360]	17.3% [198/1142]

Note: Positive = APS2 > 66.5; Likely Positive = 27.5 < APS2 < 66.5; Negative = APS2 < 27.5
APS2 = Amyloid Probability Score 2; MCI = mild cognitive impairment; SCD = subjective cognitive decline; PV = predictive value

Test Performance in Subjects with Comorbidities

The performance of the PrecivityAD2® test in 12 different documented comorbidities as well as in subjects with one, two, or three or more of these comorbidities, was evaluated. Not all studies reported all 12 different comorbidities. Thus, it was not possible to evaluate the clinical performance of the PrecivityAD2® test in subjects with no comorbidities since it is not clear that the absence of a reported comorbidity for an individual is evidence of the absence of that specific comorbidity. The data depicted in Tables 11 and 12 demonstrate that the clinical performance of the PrecivityAD2® test is similar in all subjects regardless of the presence of any single comorbidity or multiple number of comorbidities.

Table 11: Clinical Performance of the PrecivityAD2® Test by Comorbidity Category (Alphabetized)

PrecivityAD2® Test	Comorbidity		
	Atrial Fibrillation	**Autoimmune/ Inflammatory Disease**	**Chronic Heart Failure**
Positive Result PV [n/N] (95% CI)	100.0% [33/33] (89.6%; 100.0%)	91.8% [45/49] (80.8%; 96.8%)	100.0% [10/10] (72.2%; 100.0%)

Likely Positive Result PV [n/N] (95% CI)	66.7% [12/18] (43.7%; 83.7%)	75.0% [15/20] (53.1%; 88.8%)	42.9% [3/7] (15.8%; 75.0%)
Negative Result PV [n/N] (95% CI)	0.0% [0/27] (0.0%; 12.5%)	5.6% [2/36] (1.5%; 18.1%)	0.0% [0/10] (0.0%; 27.8%)
Prevalence [n/N]	57.7% [45/78]	59.0% [62/105]	48.1% [13/27]
Frequency of Likely Positive [n/N]	23.1% [18/78]	19.0% [20/105]	25.9% [7/27]
PrecivityAD2® Test	**Comorbidity**		
	Chronic Kidney Disease	**Coronary Heart Disease (CHD)**	**Depression**
Positive Result PV [n/N] (95% CI)	100.0% [97/97] (96.2%; 100.0%)	92.1% [35/38] (79.2%; 97.3%)	98.2% [54/55] (90.4%; 99.7%)
Likely Positive Result PV [n/N] (95% CI)	73.2% [30/41] (58.1%; 84.3%)	93.3% [14/15] (70.2%; 98.8%)	57.1% [16/28] (39.1%; 73.5%)
Negative Result PV [n/N] (95% CI)	1.8% [1/56] (0.3%; 9.4%)	0.0% [0/43] (0.0%; 8.2%)	1.9% [2/103] (0.5%; 6.8%)
Prevalence [n/N]	66.0% [128/194]	51.0% [49/96]	38.7% [72/186]
Frequency of Likely Positive [n/N]	21.1% [41/194]	15.6% [15/96]	15.1% [28/186]
PrecivityAD2® Test	**Comorbidity**		
	Diabetes	**Dyslipidemia**	**History of Cancer**
Positive Result PV [n/N] (95% CI)	100.0% [43/43] (91.8%; 100.0%)	95.2% [79/83] (88.3%; 98.1%)	95.5% [64/67] (87.6%; 98.5%)
Likely Positive Result PV [n/N] (95% CI)	73.5% [25/34] (56.9%; 85.4%)	72.1% [31/43] (57.3%; 83.3%)	64.0% [16/25] (44.5%; 79.8%)
Negative Result PV [n/N] (95% CI)	6.2% [4/65] (2.4%; 14.8%)	4.8% [5/104] (2.1%; 10.8%)	5.7% [3/53] (1.9%; 15.4%)
Prevalence [n/N]	50.7% [72/142]	50.0% [115/230]	57.2% [83/145]
Frequency of Likely Positive	23.9% [34/142]	18.7% [43/230]	17.2% [25/145]

[n/N]			
PrecivityAD2® Test	**Comorbidity**		
	History of Stroke or TIA	**Hypertension**	**Obesity**
Positive Result PV [n/N] (95% CI)	97.0% [32/33] (84.7%; 99.5%)	96.7% [147/152] (92.5%; 98.6%)	96.9% [31/32] (84.3%; 99.4%)
Likely Positive Result PV [n/N] (95% CI)	50.0% [10/20] (29.9%; 70.1%)	75.0% [54/72] (63.9%; 83.6%)	77.3% [17/22] (56.6%; 89.9%)
Negative Result PV [n/N] (95% CI)	2.3% [1/44] (0.4%; 11.8%)	5.7% [11/192] (3.2%; 10.0%)	8.5% [11/130] (4.8%; 14.5%)
Prevalence [n/N]	44.3% [43/97]	51.0% [212/416]	32.1% [59/184]
Frequency of Likely Positive [n/N]	20.6% [20/97]	17.3% [72/416]	12.0% [22/184]

Note: Positive = APS2 > 66.5; Likely Positive = 27.5 < APS2 < 66.5; Negative = APS2 < 27.5
APS2 = Amyloid Probability Score 2; PV = predictive value; TIA = transient ischemic attack

Table 12: Clinical Performance of the PrecivityAD2® Test by Number of Documented Comorbidities

PrecivityAD2® Test	**Number of Comorbidities**		
	One	**Two**	**Three or More**
Positive Result PV [n/N] (95% CI)	98.3% [118/120] (94.1%; 99.5%)	98.5% [67/68] (92.1%; 99.7%)	96.3% [104/108] (90.9%; 98.6%)
Likely Positive Result PV [n/N] (95% CI)	80.0% [44/55] (67.6%; 88.4%)	77.8% [21/27] (59.2%; 89.4%)	68.9% [42/61] (56.4%; 79.1%)
Negative Result PV [n/N] (95% CI)	8.3% [11/132] (4.7%; 14.3%)	3.8% [3/80] (1.3%; 10.5%)	4.6% [7/151] (2.3%; 9.3%)
Prevalence [n/N]	56.4% [173/307]	52.0% [91/175]	47.8% [153/320]
Frequency of Likely Positive [n/N]	17.9% [55/307]	15.4% [27/175]	19.1% [61/320]

Note: Positive = APS2 > 66.5; Likely Positive = 27.5 < APS2 < 66.5; Negative = APS2 < 27.5
APS2 = Amyloid Probability Score 2; PV = predictive value

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