



Test Definition: PAVAL

Paraneoplastic, Autoantibody Evaluation,
Serum

Overview

Useful For

Serological evaluation of patients who present with a subacute neurological disorder of undetermined etiology, especially those with known risk factors for cancer

Directing a focused search for cancer

Investigating neurological symptoms that appear during, or after, cancer therapy and are not explainable by metastasis

Differentiating autoimmune neuropathies from neurotoxic effects of chemotherapy

Monitoring the immune response of seropositive patients during cancer therapy

Detecting early evidence of cancer recurrence in previously seropositive patients

Profile Information

Test Id	Reporting Name	Available Separately	Always Performed
PAINT	Interpretive Comments	No	Yes
AMPHS	Amphiphysin Ab, S	No	Yes
AGN1S	Anti-Glial Nuclear Ab, Type 1	No	Yes
ANN1S	Anti-Neuronal Nuclear Ab, Type 1	No	Yes
ANN2S	Anti-Neuronal Nuclear Ab, Type 2	No	Yes
ANN3S	Anti-Neuronal Nuclear Ab, Type 3	No	Yes
CRMS	CRMP-5-IgG, S	No	Yes
PCABP	Purkinje Cell Cytoplasmic Ab Type 1	No	Yes
PCAB2	Purkinje Cell Cytoplasmic Ab Type 2	No	Yes
PCATR	Purkinje Cell Cytoplasmic Ab Type Tr	No	Yes

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
AGNBS	AGNA-1 Immunoblot, S	No	No

AMIBS	Amphiphysin Immunoblot, S	No	No
AN1BS	ANNA-1 Immunoblot, S	No	No
AN2BS	ANNA-2 Immunoblot, S	No	No
CRMWS	CRMP-5-IgG Western Blot, S	Yes	No
PC1BS	PCA-1 Immunoblot, S	No	No
PCTBS	PCA-Tr Immunoblot, S	No	No
AGNTS	AGNA-1 Titer, S	No	No
APHTS	Amphiphysin Ab Titer, S	No	No
AN1TS	ANNA-1 Titer, S	No	No
AN3TS	ANNA-3 Titer, S	No	No
CRMTS	CRMP-5-IgG Titer, S	No	No
PC1TS	PCA-1 Titer, S	No	No
PC2TS	PCA-2 Titer, S	No	No
PCTTS	PCA-Tr Titer, S	No	No
AN2TS	ANNA-2 Titer, S	No	No

Testing Algorithm

If the immunofluorescence assay (IFA) patterns suggest antinuclear antibody-1 (AGNA-1) antibody, then AGNA-1 immunoblot and AGNA-1 IFA titer will be performed at an additional charge.

If the IFA patterns suggest amphiphysin antibody, then amphiphysin immunoblot and amphiphysin IFA titer will be performed at an additional charge.

If the IFA pattern suggests antineuronal nuclear antibody type 1 (ANNA-1), then ANNA-1 immunoblot (IB), ANNA-1 IFA titer, and ANNA-2 IB will be performed at an additional charge.

If the IFA pattern suggests ANNA-2 antibody, then ANNA-2 IB, ANNA-2 IFA titer, and ANNA-1 IB will be performed at an additional charge.

If the IFA pattern suggests ANNA-3 antibody, then ANNA-3 IFA titer will be performed at an additional charge.

If the IFA pattern suggests Purkinje cytoplasmic antibody type 1 (PCA-1) antibody, then PCA-1 IB and PCA-1 IFA titer will be performed at an additional charge.

If the IFA pattern suggests PCA-2 antibody, then PCA-2 IFA titer will be performed at an additional charge.

If the IFA pattern suggests PCA-Tr antibody, then PCA-Tr IB and PCA-Tr IFA titer will be performed at an additional charge.

If the collapsin response-mediator protein (CRMP) IFA is positive, then CRMP-5-IgG Western blot and CRMP-5-IgG IFA titer will be performed at an additional charge.

CRMP-5-IgG Western blot is also performed by specific request for more sensitive detection of CRMP-5-IgG. Testing should be requested in cases of subacute basal ganglionic disorders (chorea, parkinsonism), cranial neuropathies (especially loss of vision, taste, or smell), and myelopathies.

For more information see [Paraneoplastic Evaluation Algorithm-Serum](#).

Special Instructions

- [Paraneoplastic Evaluation Algorithm-Serum](#)

Method Name

PAINT: Technical Interpretation

AGN1S, AGNTS, AMPHS, APHTS, ANN1S, ANN2S, ANN3S, AN2TS, AN3TS, CRMS, CRMTS, PCABP, PC1TS, PCAB2, PC2TS, PCATR, PCTTS, AN1TS: Indirect Immunofluorescence Assay (IFA)

CRMWS: Western Blot (WB)

AGNBS, AMIBS, AN1BS, AN2BS, PC1BS, PCTBS: Immunoblot (IB)

NY State Available

Yes

Specimen**Specimen Type**

Serum

Ordering Guidance

On June 1st, this test will become obsolete. To provide focused patient care, consider ordering a comprehensive neurological phenotype-specific autoimmune/paraneoplastic evaluation (eg, encephalopathy, movement disorders, myelopathy, axonal neuropathy). For more information, consult the [autoimmune neurology evolution web page](#).

This test **no longer contains all known, clinically relevant antibodies** for patients suspected of autoimmune neurological disorders. Instead, consider a comprehensive neurological phenotype-specific autoimmune/paraneoplastic evaluation (eg, encephalopathy, movement disorders, myelopathy, axonal neuropathy). For more information as well as phenotype-specific testing options, refer to [Autoimmune Neurology Test Ordering Guide](#) or the [Neurology specialty website](#).

This test **should not be requested** for patients who have recently received radioisotopes, therapeutically or diagnostically, because of potential assay interference. The specific waiting period before specimen collection will depend on the isotope administered, the dose given, and the clearance rate in the individual patient. Specimens will be

screened for radioactivity prior to analysis. Radioactive specimens received in the laboratory will be held 1 week and assayed if sufficiently decayed or canceled if radioactivity remains.

Necessary Information

Provide the following information:

- Relevant clinical information
- Ordering healthcare professional's name, phone number, mailing address, and email address

Specimen Required

Patient Preparation: For optimal antibody detection, specimen collection is recommended before starting immunosuppressant medication or intravenous immunoglobulin (IVIg) treatment.

Supplies: Sarstedt Aliquot Tube, 5 mL (T914)

Collection Container/Tube:

Preferred: Red top

Acceptable: Serum gel

Submission Container/Tube: Plastic vial

Specimen Volume: 4 mL

Collection Instructions: Centrifuge and aliquot serum into a plastic vial.

Specimen Minimum Volume

2 mL

Reject Due To

Gross hemolysis	Reject
Gross lipemia	Reject
Gross icterus	Reject

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Serum	Refrigerated (preferred)	28 days	
	Ambient	72 hours	
	Frozen	28 days	

Clinical & Interpretive

Clinical Information

Paraneoplastic autoimmune neurological disorders reflect a patient's humoral and cellular immune responses to cancer. The cancer may be new or recurrent, is usually limited in metastatic volume, and is often occult by standard imaging procedures. Autoantibodies specific for onconeural proteins found in the plasma membrane, cytoplasm, and nucleus of neurons, glia, or muscle are generated in this immune response and serve as serological markers of paraneoplastic

autoimmunity. Cancers recognized in this context most commonly are small-cell lung carcinoma, thymoma, ovarian (or related Mullerian) carcinoma, breast carcinoma, and Hodgkin lymphoma. Pertinent childhood neoplasms recognized thus far include neuroblastoma, thymoma, Hodgkin lymphoma, and chondroblastoma. An individual patient's autoantibody profile can predict a specific neoplasm with 90% certainty but not the neurological syndrome. It should be noted that this evaluation is considered to be limited and not comprehensive (see Cautions).

Three classes of autoantibodies are recognized in this evaluation:

- Antineuronal nuclear antibodies (ANNA-1, ANNA-2, ANNA-3)
- Anti-glial/neuronal nuclear antibodies (AGNA-1; also known as Sox1)
- Neuronal and glial cytoplasmic antibodies (Purkinje cytoplasmic antibody [PCA]-1, PCA-2, PCA-Tr, collapsin response-mediator protein [CRMP]-5, and amphiphysin)

Patients who are seropositive usually present with subacute neurological signs and symptoms such as encephalopathy, cerebellar ataxia, myelopathy, nerve (including radiculopathy, plexopathy, sensory/sensorimotor, or autonomic) or neuromuscular junction disorders. Initial signs may be subtle, but a subacute multifocal and progressive syndrome usually evolves.

Cancer risk factors include previous or family history of cancer, history of smoking, or social or environmental exposure to carcinogens. Early diagnosis and treatment of the neoplasm favor less neurological morbidity and offer the best hope for survival.

Reference Values

Test ID	Reporting name	Methodology*	Reference value
PAINT	Interpretive Comments	Medical interpretation	Not applicable
AMPHS	Amphiphysin Ab, S	IFA	Negative
AGN1S	Anti-Glial Nuclear Ab, Type 1	IFA	Negative
ANN1S	Anti-Neuronal Nuclear Ab, Type 1	IFA	Negative
ANN2S	Anti-Neuronal Nuclear Ab, Type 2	IFA	Negative
ANN3S	Anti-Neuronal Nuclear Ab, Type 3	IFA	Negative
CRMS	CRMP-5-IgG, S	IFA	Negative
PCABP	Purkinje Cell Cytoplasmic Ab Type 1	IFA	Negative
PCAB2	Purkinje Cell Cytoplasmic Ab Type 2	IFA	Negative
PCATR	Purkinje Cell Cytoplasmic Ab Type Tr	IFA	Negative

Reflex Tests:

Test ID	Reporting name	Methodology*	Reference value
AGNBS	AGNA-1 Immunoblot, S	IB	Negative
AGNTS	AGNA-1 Titer, S	IFA	<1:240
AMIBS	Amphiphysin Immunoblot, S	IB	Negative
AN1BS	ANNA-1 Immunoblot, S	IB	Negative
AN1TS	ANNA-1 Titer, S	IFA	<1:240
AN2BS	ANNA-2 Immunoblot, S	IB	Negative

AN2TS	ANNA-2 Titer, S	IFA	<1:240
AN3TS	ANNA-3 Titer, S	IFA	<1:240
APHTS	Amphiphysin Ab Titer, S	IFA	<1:240
CRMTS	CRMP-5-IgG Titer, S	IFA	<1:240
CRMWS	CRMP-5-IgG Western Blot, S	WB	Negative
PC1BS	PCA-1 Immunoblot, S	IB	Negative
PC1TS	PCA-1 Titer, S	IFA	<1:240
PC2TS	PCA-2 Titer, S	IFA	<1:240
PCTBS	PCA-Tr Immunoblot, S	IB	Negative
PCTTS	PCA-Tr Titer, S	IFA	<1:240

***Methodology abbreviations:**

Immunofluorescence assay (IFA)

Western blot (WB)

Immunoblot (IB)

Neuron-restricted patterns of IgG staining that do not fulfill criteria for amphiphysin, ANNA-1, ANNA-2, ANNA-3, AGNA-1, PCA-1, PCA-2, PCA-Tr, or CRMP-5-IgG may be reported as "unclassified antineuronal IgG." Complex patterns that include non-neuronal elements may be reported as "uninterpretable."

Note: CRMP-5 titers lower than 1:240 are detectable by recombinant CRMP-5 Western blot analysis. CRMP-5 Western blot analysis will be done on request on stored serum (held 4 weeks). This supplemental testing is recommended in cases of chorea, vision loss, cranial neuropathy, and myelopathy. Call 800-533-1710 to request CRMP-5 Western blot.

Interpretation

Antibodies directed at onconeural proteins shared by neurons, glia, muscle, and certain cancers are valuable serological markers of a patient's immune response to cancer. They are not found in healthy subjects and are usually accompanied by subacute neurological signs and symptoms. Several autoantibodies have a syndromic association, but no autoantibody predicts a specific neurological syndrome. Conversely, a positive autoantibody profile has 80% to 90% predictive value for a specific cancer. It is not uncommon for more than one paraneoplastic autoantibody to be detected, each predictive of the same cancer.

Cautions

Negative results do not exclude cancer.

Intravenous immunoglobulin (IVIg) treatment prior to specimen collection may cause a false-positive result.

Immunosuppressive treatments, including plasma exchange, may lead to false-negative results.

This evaluation does not include a broad number of antibodies pertinent to autoimmune neurological disorders, paraneoplastic and idiopathic autoimmune. Use of phenotype specific evaluations is recommended rather than the paraneoplastic evaluation (eg, autoimmune encephalopathy evaluation for suspected autoimmune encephalitis, or autoimmune movement disorders evaluation for suspected autoimmune ataxia). In particular, several high and medium risk paraneoplastic antibodies are not included such as AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic

acid) receptor IgG, gamma-aminobutyric acid (GABA) B receptor IgG, kelch-like protein 11- (KLHL11) IgG, Ma2-IgG, and N-methyl-D-aspartate (NMDA) receptor-IgG, among others.

Clinical Reference

1. McKeon A, Pittock SJ. Overview and diagnostic approach in autoimmune neurology. *Continuum (Minneap, Minn)*. 2024;30(4):960-994. doi:10.1212/CON.0000000000001447
2. Zekeridou A. Paraneoplastic neurologic disorders. *Continuum (Minneap, Minn)*. 2024;30(4):1021-1051. doi:10.1212/CON.0000000000001449

Performance

Method Description

Indirect Immunofluorescence Assay:

The patient's specimen is tested by a standardized immunofluorescence assay that uses a composite frozen section of mouse cerebellum, kidney, and gut tissues. After incubation with the specimen and washing, fluorescein-conjugated goat-antihuman IgG is applied. Neuron-specific autoantibodies are identified by their characteristic fluorescence staining patterns. Specimens that are scored positive for any neuronal nuclear or cytoplasmic autoantibody are titrated.

Interference by coexisting non-neuron-specific autoantibodies can usually be eliminated by serologic absorption. (Honorat JA, Komorowski L, Josephs KA, et al. IgLON5 antibody: Neurological accompaniments and outcomes in 20 patients. *Neurol Neuroimmunol Neuroinflamm*. 2017;4[5]:e385. Published 2017 Jul 18. doi:10.1212/NXI.0000000000000385)

Immunoblot:

All steps are performed at room temperature (18-28 degrees C) utilizing the EUROBlot One instrument. Diluted patient sample (1:101) is added to test strips (strips containing recombinant antigen manufactured and purified using biochemical methods) in individual channels and incubated for 30 minutes. Positive samples will bind to the purified recombinant antigen, and negative samples will not bind. Strips are washed to remove unbound antibodies and then incubated with anti-human IgG antibodies (alkaline phosphatase-labelled) for 30 minutes. The strips are again washed to remove unbound anti-human IgG antibodies, and nitroblue tetrazolium chloride/5-bromo-4-chloro-3-indolyl phosphate substrate is added. Alkaline phosphatase enzyme converts the soluble substrate into a colored insoluble product on the membrane to produce a black band. Strips are digitized via picture capture on the EUROBlot One instrument and evaluated with the EUROLineScan software. (O'Connor K, Waters P, Komorowski L, et al. GABAA receptor autoimmunity: A multicenter experience. *Neurol Neuroimmunol Neuroinflamm*. 2019;6[3]:e552. doi:10.1212/NXI.0000000000000552)

Western Blot:

Neuronal antigens extracted aqueously from adult rat cerebellum, full-length recombinant human collapsin response-mediator protein-5 (CRMP-5), or full-length recombinant human amphiphysin protein is denatured, reduced, and separated by electrophoresis on 10% polyacrylamide gel. IgG is detected autoradiographically by enhanced chemiluminescence. (Yu Z, Kryzer TJ, Griesmann GE, et al. CRMP-5 neuronal autoantibody: marker of lung cancer and thymoma-related autoimmunity. *Ann Neurol*. 2001;49[2]:146-154; Dubey D, Jitprapaikulsan J, Bi H, et al. Amphiphysin-IgG autoimmune neuropathy: A recognizable clinicopathologic syndrome. *Neurology*. 2019;93(20):e1873-e1880. doi:10.1212/WNL.00000000000008472)

PDF Report

No

Day(s) Performed

Profile tests: Monday through Sunday; Reflex tests: Varies

Report Available

10 to 17 days

Specimen Retention Time

28 days

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Main Campus

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

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

86255 x 9

84182-AGNBS (if appropriate)

86256-AGNTS (if appropriate)

84182-AMIBS (if appropriate)

86256-APHTS (if appropriate)

84182-AN1BS (if appropriate)

86256 AN1TS (if appropriate)

84182-AN2BS (if appropriate)

86256 AN2TS (if appropriate)

86256 AN3TS (if appropriate)

86256 CRMTS (if appropriate)

84182-CRMWS (if appropriate)

84182-PC1BS (if appropriate)

86256 PC1TS (if appropriate)

86256 PC2TS (if appropriate)

84182-PCTBS (if appropriate)

86256 PCTTS (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
PAVAL	Paraneoplastic Autoantibody Eval, S	43104-9

Result ID	Test Result Name	Result LOINC® Value
89080	AGNA-1, S	84927-3
81722	Amphiphysin Ab, S	72327-0
80150	ANNA-1, S	33615-6
80776	ANNA-2, S	43187-4
83137	ANNA-3, S	43102-3
83077	CRMP-5-IgG, S	72504-4
29347	Interpretive Comments	57771-8
618905	IFA Notes	48767-8
83138	PCA-2, S	84925-7
9477	PCA-1, S	84924-0
83076	PCA-Tr, S	84926-5