Overview

Useful For

Investigating new onset cryptogenic epilepsy with incomplete seizure control and duration of fewer than 2 years using spinal fluid specimens

Investigating new onset cryptogenic epilepsy plus 1 or more of the following accompaniments:

-Psychiatric accompaniments (psychosis, hallucinations)

-Movement disorder (myoclonus, tremor, dyskinesias)

-Headache

-Cognitive impairment/encephalopathy

-Autoimmune stigmata (personal history or family history or signs of diabetes mellitus, thyroid disorder, vitiligo, premature graying of hair, myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus, idiopathic adrenocortical insufficiency) or "multiple sclerosis"

-History of cancer

-Smoking history (over 20 pack-years) or other cancer risk factors

-Investigating seizures occurring within the context of a subacute multifocal neurological disorder without an obvious cause, especially in a patient with a past or family history of cancer

Testing Algorithm

If client requests or if indirect immunofluorescence assay (IFA) patterns suggest collapsin response-mediator protein-5-IgG (CRMP-5-IgG), then CRMP-5-IgG Western blot is performed at an additional charge.

If IFA patterns suggest amphiphysin antibody, then amphiphysin immunoblot is performed at an additional charge.

If IFA pattern suggests antiglial nuclear antibody (AGNA)-1, then AGNA-1 immunoblot is performed at an additional charge.

If IFA pattern suggests antineuronal nuclear antibodies (ANNA)-1, then ANNA-1 immunoblot is performed at an additional charge.

If IFA pattern suggests ANNA-2 antibody, then ANNA-2 immunoblot is performed at an additional charge.

If IFA pattern suggests Purkinje cytoplasmic antibody (PCA-1), then PCA-1 immunoblot is performed at an additional charge.

If IFA pattern suggests PCA-Tr antibody, then PCA-Tr immunoblot is performed at an additional charge.

If IFA pattern suggests alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)-receptor antibody, and AMPA-receptor antibody cell-binding assay (CBA) is positive, then AMPA-receptor antibody IF titer assay is performed at an additional charge.

If IFA pattern suggests gamma-aminobutyric acid B (GABA-B)-receptor antibody, and GABA-B-receptor antibody is positive, then GABA-B-receptor antibody IF titer assay is performed at an additional charge.

If IFA pattern suggests glial fibrillary acidic protein (GFAP) antibody, then GFAP IFA titer and GFAP CBA are performed at an additional charge.

If IFA pattern suggests N-methyl-D-aspartate (NMDA)-receptor antibody, and NMDA-receptor antibody CBA is positive, then NMDA-receptor antibody IF titer assay is performed at an additional charge.

If IFA pattern suggests dipeptidyl-peptidase-like protein-6 (DPPX) antibody, then DPPX antibody CBA and DPPX titer are performed at an additional charge.

If IFA pattern suggests metabotropic glutamate receptor 1 (mGluR1) antibody, then mGluR1 antibody CBA and mGluR1 titer are performed at an additional charge.

For more information see Autoimmune/Paraneoplastic Epilepsy Evaluation Algorithm-Spinal Fluid

Special Instructions

- Autoimmune/Paraneoplastic Epilepsy Evaluation Algorithm-Spinal Fluid

Profile Information

Test Id	Reporting Name	Available Separately	Always Performed
AEPCI	Epilepsy, Interpretation, CSF	No	Yes
AMPCC	AMPA-R Ab CBA, CSF	No	Yes
AMPHC	Amphiphysin Ab, CSF	No	Yes
AGN1C	Anti-Glial Nuclear Ab, Type 1	No	Yes
ANN1C	Anti-Neuronal Nuclear Ab, Type 1	No	Yes
ANN2C	Anti-Neuronal Nuclear Ab, Type 2	No	Yes
ANN3C	Anti-Neuronal Nuclear Ab, Type 3	No	Yes
CS2CC	CASPR2-IgG CBA, CSF	No	Yes
CRMC	CRMP-5-IgG, CSF	No	Yes
DPPIC	DPPX Ab IFA, CSF	No	Yes
GD65C	GAD65 Ab Assay, CSF	Yes	Yes
GABCC	GABA-B-R Ab CBA, CSF	No	Yes
GFAIC	GFAP IFA, CSF	No	Yes
LG1CC	LGI1-IgG CBA, CSF	No	Yes
GL1IC	mGluR1 Ab IFA, CSF	No	Yes
NMDCC	NMDA-R Ab CBA, CSF	No	Yes
PCTRC	Purkinje Cell Cytoplasmc Ab Type Tr	No	Yes
PCA2C	Purkinje Cell Cytoplasmic Ab Type 2	No	Yes

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
AGNBC	AGNA-1 Immunoblot, CSF	No	No
AMPIC	AMPA-R Ab IF Titer Assay, CSF	No	No
AMIBC	Amphiphysin Immunoblot, CSF	No	No
AN1BC	ANNA-1 Immunoblot, CSF	No	No
AN2BC	ANNA-2 Immunoblot, CSF	No	No
CRMWC	CRMP-5-IgG Western Blot, CSF	Yes	No

DPPCC	DPPX Ab CBA, CSF	No	No
DPPTC	DPPX Ab IFA Titer, CSF	No	No
GABIC	GABA-B-R Ab IF Titer Assay, CSF	No	No
GFACC	GFAP CBA, CSF	No	No
GFATC	GFAP IFA Titer, CSF	No	No
GL1CC	mGluR1 Ab CBA, CSF	No	No
GL1TC	mGluR1 Ab IFA Titer, CSF	No	No
NMDIC	NMDA-R Ab IF Titer Assay, CSF	No	No
PC1BC	PCA-1 Immunoblot, CSF	No	No
PCTBC	PCA-Tr Immunoblot, CSF	No	No
PCA1C	Purkinje Cell Cytoplasmic Ab Type 1	No	No

Method Name

AGN1C, AMPHC, AMPIC, ANN1C, ANN2C, ANN3C, CRMC, DPPIC, DPPTC, GABIC, GFAIC, GFATC, GL1IC, GL1TC, NMDIC, PCA1C, PCA2C, PCTRC: Indirect Immunofluorescence Assay (IFA)

AMPCC, CS2CC, DPPCC, GABCC, GFACC, GL1CC, LG1CC, NMDCC: Cell-Binding Assay (CBA)

CRMWC: Western Blot (WB)

AGNBC, AMIBC, AN1BC, AN2BC, PC1BC, PCTBC: Immunoblot (IB)

GD65C: Radioimmunoassay (RIA)

NY State Available

Yes

Specimen

Specimen Type

CSF

Ordering Guidance

Multiple neuroimmunology profile tests are available. For testing that is performed with each profile, see Autoimmune

Neurology Antibody Matrix.

Necessary Information

Provide the following information:

-Relevant clinical information

-Ordering provider name, phone number, mailing address, and e-mail address

Specimen Required

Collection Container/Tube: Sterile vial

Specimen Volume: 4 mL

Forms

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

Reject Due To

Gross hemolysis	Reject
Gross lipemia	Reject
Gross icterus	Reject

Specimen Minimum Volume

2 mL

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
CSF	Refrigerated (preferred)	28 days	
	Frozen	28 days	
	Ambient		

Clinical & Interpretive

Clinical Information

Antiepileptic drugs (AED) are the mainstay of treatment for epilepsy, but seizures continue in one-third of patients despite appropriate AED therapeutic trials. The etiology of epilepsy often remains unclear. Seizures are a common symptom in autoimmune neurological disorders, including limbic encephalitis and multifocal paraneoplastic disorders. Seizures may be the exclusive manifestation of an autoimmune encephalopathy without evidence of limbic encephalitis.

Autoimmune epilepsy is increasingly recognized in the spectrum of neurological disorders characterized by detection of neural autoantibodies in serum or spinal fluid (CSF) and responsiveness to immunotherapy. The advent of more sensitive and specific serological detection methods is increasingly revealing previously underappreciated autoimmune epilepsies. Neural autoantibodies specific for intracellular and plasma membrane antigens aid the diagnosis of autoimmune epilepsy, but no single antibody is specific for this diagnosis.

Autoantibody specificities currently most informative for autoimmune epilepsies include leucine-rich glioma inactivated protein-1 (LGI1), glutamic acid decarboxylase-65 (GAD65), N-methyl-D-aspartate receptor (NMDA-R), alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPA-R), and gamma-aminobutyric acid type B receptor (GABA-B-R) antibodies.

Autoantibodies recognizing onconeural proteins shared by neurons, glia, or muscle (eg, antineuronal nuclear antibody, type 1 [ANNA 1]; collapsin response-mediator protein-5 neuronal [CRMP-5-IgG]; N-type calcium channel antibody), also serve as markers of paraneoplastic or idiopathic autoimmune epilepsies. A specific neoplasm is often predictable by the individual patient's autoantibody profile.

Suspicion for autoimmune epilepsy on clinical grounds justifies comprehensive evaluation of CSF and serum for neural autoantibodies. Selective testing for individual autoantibodies is not advised because each is individually rare, and a timely diagnosis is critical. Collectively, the antibodies tested for in the autoimmune epilepsy evaluations represent a broad spectrum of treatable disorders, some of which are associated with occult cancer. Testing of CSF for autoantibodies is particularly helpful when serum testing is negative, though in some circumstances testing both serum and CSF simultaneously is pertinent. Testing of CSF is recommended for some antibodies in particular (such as NMDA-R antibody and glial fibrillary acidic protein [GFAP]-IgG) because CSF testing is both more sensitive and specific. In contrast, serum testing for LGI1 antibody is more sensitive than CSF testing. Failure to detect a neural antibody does not exclude the diagnosis of autoimmune epilepsy when other clinical clues exist. A trial of immunotherapy is justifiable in those cases.

Reference Values

Test ID	Reporting Name	Methodology*	Reference Value
AEPCI	Epilepsy, Interpretation, CSF	Medical interpretation	NA
AMPCC	AMPA-R Ab CBA, CSF	CBA	Negative
AMPHC	Amphiphysin Ab, CSF	IFA	<1:2
AGN1C	Anti-Glial Nuclear Ab, Type 1	IFA	<1:2
ANN1C	Anti-Neuronal Nuclear Ab, Type 1	IFA	Negative at <1:2
ANN2C	Anti-Neuronal Nuclear Ab, Type 2	IFA	<1:2
ANN3C	Anti-Neuronal Nuclear Ab, Type 3	IFA	<1:2

CS2CC	CASPR2-IgG CBA, CSF	CBA	Negative
CRMC	CRMP-5-IgG, CSF	IFA	<1:2
DPPIC	DPPX Ab IFA, CSF	IFA	Negative
GABCC	GABA-B-R Ab CBA, CSF	CBA	Negative
GD65C	GAD65 Ab Assay, CSF	RIA	< or =0.02 nmol/L Reference values apply to all ages.
GFAIC	GFAP IFA, CSF	IFA	Negative
LG1CC	LGI1-IgG CBA, CSF	CBA	Negative
GL1IC	mGluR1 Ab IFA, CSF	IFA	Negative
NMDCC	NMDA-R Ab CBA, CSF	CBA	Negative
PCTRC	Purkinje Cell Cytoplasmic Ab Type Tr	IFA	<1:2
PCA2C	Purkinje Cell Cytoplasmic Ab Type 2	IFA	<1:2

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Test ID	Reporting Name	Methodology*	Reference Value
AGNBC	AGNA-1 Immunoblot, CSF	IB	Negative
AMPIC	AMPA-R Ab IF Titer Assay, CSF	IFA	<1:2
AMIBC	Amphiphysin Immunoblot, CSF	IB	Negative
AN1BC	ANNA-1 Immunoblot, CSF	IB	Negative
AN2BC	ANNA-2 Immunoblot, CSF	IB	Negative
CRMWC	CRMP-5-IgG Western Blot, CSF	WB	Negative
DPPCC	DPPX Ab CBA, CSF	CBA	Negative
DPPTC	DPPX Ab IFA Titer, CSF	IFA	<1:2
GABIC	GABA-B-R Ab IF Titer Assay, CSF	IFA	<1:2
GFACC	GFAP CBA, CSF	CBA	Negative
GFATC	GFAP IFA Titer, CSF	IFA	<1:2
GL1CC	mGluR1 Ab CBA, CSF	CBA	Negative
GL1TC	mGluR1 Ab IFA Titer, CSF	IFA	<1:2
NMDIC	NMDA-R Ab IF Titer Assay, CSF	IFA	Negative at <1:2
PC1BC	PCA-1 Immunoblot, CSF	IB	Negative
PCTBC	PCA-Tr Immunoblot, CSF	IB	Negative
PCA1C	Purkinje Cell Cytoplasmic Ab Type 1	IFA	<1:2

*Methodology abbreviations:

Immunofluorescence assay (IFA)

Cell-binding assay (CBA)

Western blot (WB)

Radioimmunoassay (RIA)

Immunoblot (IB)

Neuron-restricted patterns of IgG staining that do not fulfill criteria for ANNA-1, ANNA-2, ANN3C, PCA-1, PCA-2, or PCA-Tr 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 1:2 are detectable by recombinant CRMP-5 Western blot analysis. CRMP-5 Western blot analysis will be done on request on stored spinal fluid (held for 4 weeks). This supplemental testing is recommended in cases of chorea, vision loss, cranial neuropathy, and myelopathy. Call the Neuroimmunology Laboratory at 800-533-1710 to request CRMP-5 Western blot.

Interpretation

Antibodies specific for neuronal, glial, or muscle proteins are valuable serological markers of autoimmune epilepsy and a patient's immune response to cancer. These autoantibodies are not found in healthy subjects and are usually accompanied by subacute neurological symptoms and signs. It is not uncommon for more than 1 of the following autoantibodies to be detected in patients with autoimmune epilepsy:

-Plasma membrane antibodies (N-methyl-D-aspartate [NMDA] receptor; 2-amino-3-[5-methyl-3-oxo-1,2-oxazol-4-yl] propanoic acid [AMPA] receptor; gamma-aminobutyric acid [GABA-B] receptor). These autoantibodies are all potential effectors of dysfunction.

-Neuronal nuclear autoantibody, type 1 (ANNA-1) or type 3 (ANNA-3).

-Neuronal or muscle cytoplasmic antibodies (amphiphysin, Purkinje cell antibody-type 2 [PCA-2], collapsin response-mediator protein-5 neuronal [CRMP-5-IgG], or glutamic acid decarboxylase [GAD65] antibody).

A rising autoantibody titer in a previously seropositive patient suggests cancer recurrence.

Cautions

Negative results do not exclude autoimmune epilepsy or cancer.

This evaluation does not detect Ma2 antibody (alias MaTa). Ma2 antibody has been described in patients with brainstem and limbic encephalitis in the context of testicular germ cell neoplasms. Scrotal ultrasound is advisable in men who present with unexplained subacute encephalitis.

Clinical Reference

1. Quek AL, Britton JW, McKeon A, et al: Autoimmune epilepsy: clinical characteristics and response to immunotherapy.

Arch Neurol. 2012 May;69(5):582-593. doi: 10.1001/archneurol.2011.2985

2. Yu Z, Kryzer TJ, Griesmann GE, Kim K, Benarroch EE, Lennon VA: CRMP-5 neuronal autoantibody: marker of lung cancer and thymoma-related autoimmunity. Ann Neurol. 2001 Feb;49(2):146-154

3. Pittock SJ, Yoshikawa H, Ahlskog JE, et al: Glutamic acid decarboxylase autoimmunity with brainstem, extrapyramidal, and spinal cord dysfunction. Mayo Clin Proc. 2006 Sep;81(9):1207-1214. doi: 10.4065/81.9.1207

4. Klein CJ, Lennon VA, Aston PA, et al: Insights from LGI1 and CASPR2 potassium channel complex autoantibody subtyping. JAMA Neurol. 2013 Feb;70(2):229-234. doi: 10.1001/jamaneurol.2013.592

5. Lancaster E, Martinez-Hernandez E, Dalmau J: Encephalitis and antibodies to synaptic and neuronal cell surface proteins. Neurology. 2011 Jul;77(2):179-189. doi: 10.1212/WNL.0b013e318224afde

Performance

Method Description

Indirect Immunofluorescence Assay:

Before testing, patient's specimen is pre-diluted. After applying to a composite substrate of frozen mouse tissues (brain, kidney, and gut) and washing, fluorescein-conjugated goat-antihuman IgG is applied to detect the distribution and pattern of patient IgG binding.(Pittock SJ, Kryzer TJ, Lennon VA: Paraneoplastic antibodies coexist and predict cancer, not neurological syndrome. Ann Neurol. 2004 Nov;56:715-719. doi: 10.1002/ana.20269; Honorat JA, Komorowski L, Josephs KA, et al: IgLON5 antibody: Neurological accompaniments and outcomes in 20 patients. Neurol Neuroimmunol Neuroinflamm. 2017 Jul 18;4(5):e385. doi: 10.1212/NXI.0000000000000385)

Radioimmunoassay:

Duplicate aliquots of patient specimen are incubated with (125)I-labeled antigen. Immune complexes, formed by adding secondary (goat) antihuman immunoglobulin, are pelleted by centrifugation and washed. Gamma emission from the washed pellet is counted, and mean counts per minute (cpm) are compared with results yielded by high positive and negative control sera. Specimen yielding cpm higher than the background cpm yielded by normal human specimens are retested to confirm positivity and titrated as necessary to obtain a value in the linear range of the assay. The antigen binding capacity (nmol per liter) is calculated from the cpm precipitated at a dilution yielding a linear range value.(Griesmann GE, Kryzer TJ, Lennon VA: Autoantibody profiles of myasthenia gravis and Lambert-Eaton myasthenic syndrome. In: NR Rose, RG Hamilton, eds. Manual of Clinical and Laboratory Immunology. 6th ed. ASM Press; 2002:1005-1012; Walikonis JE, Lennon VA: Radioimmunoassay for glutamic acid decarboxylase [GAD65] autoantibodies as a diagnostic aid for stiff-man syndrome and a correlate of susceptibility to type 1 diabetes mellitus. Mayo Clin Proc. 1998 Dec;73[12]:1161-1166; Jones AL, Flanagan EP, Pittock SJ, et al: Responses to and outcomes of treatment of autoimmune cerebellar ataxia in adults. JAMA Neurol. 2015 Nov;72[11]:1304-1312. doi: 10.1001/jamaneurol.2015.2378)

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 February;49[2]:146-154; Dubey D, Jitprapaikulsan J, Bi H, et al: Amphiphysin-IgG autoimmune neuropathy: A recognizable clinicopathologic syndrome. Neurology. 2019 Nov 12;93[20]:e1873-e1880 . doi: 10.1212/WNL.0000000000008472)

Immunoblot:

All steps are performed at ambient temperature (18-28 degrees C) utilizing the EUROBlot One instrument. Diluted patient specimen (1:12.5) is added to test strips (strips containing recombinant antigen manufactured and purified using biochemical methods) in individual channels and incubated for 30 minutes. Positive specimens will bind to the purified recombinant antigen and negative specimens will not bind. Strips are washed to remove unbound antibodies and then incubated with antihuman IgG antibodies (alkaline phosphatase-labeled) for 30 minutes. The strips are again washed to remove unbound antihuman IgG antibodies and nitroblue tetrazolium chloride/5-bromo-4-chloro-3-indolyl phosphate (NBT/BCIP) 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 Apr 4;6[3]:e552 doi: 10.1212/NXI.0000000000000552)

Cell-Binding Assay:

Patient specimen is applied to a composite slide containing transfected and nontransfected HEK-293 cells. After incubation and washing, fluorescein-conjugated goat-antihuman IgG is applied to detect the presence of patient IgG binding.(Package insert: : IIFT: Neurology Mosaics, Instructions for the indirect immunofluorescence test. EUROIMMUN; FA_112d-1_A_UK_C13, 02/2019)

PDF Report

No

Specimen Retention Time

28 days

Performing Laboratory Location

Rochester

Fees & Codes

Test Classification

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

CPT Code Information

86255x16

86341 x1

84182-AGNBC (if appropriate)

86256-AMPIC (if appropriate)

84182-AMIBC (if appropriate)

84182-AN1BC (if appropriate)

84182-AN2BC (if appropriate)

84182-CRMWC (if appropriate)

86255-DPPCC (if appropriate)

86256-DPPTC (if appropriate)

86256-GABIC (if appropriate)

86255-GFACC (if appropriate)

86256-GFATC (if appropriate)

86255-GL1CC (if appropriate)

86256-GL1TC (if appropriate)

86256-NMDIC (if appropriate)

84182-PC1BC (if appropriate)

84182-PCTBC (if appropriate)

86255-PCA1C (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
EPC2	Epilepsy, Autoimm/Paraneo, CSF	In Process

Result ID	Reporting Name	LOINC®
89079	AGNA-1, CSF	94355-5
5906	Amphiphysin Ab, CSF	94354-8
3852	ANNA-1, CSF	94356-3
36429	Reflex Added	77202-0
7472	ANNA-2, CSF	94357-1
21633	ANNA-3, CSF	94358-9
21650	CRMP-5-IgG, CSF	94706-9
21632	PCA-2, CSF	94364-7
21631	PCA-Tr, CSF	94362-1
21702	GAD65 Ab Assay, CSF	94359-7
61513	NMDA-R Ab CBA, CSF	93502-3
61514	AMPA-R Ab CBA, CSF	93491-9
61515	GABA-B-R Ab CBA, CSF	93426-5
34258	Epilepsy, Interpretation, CSF	69048-7
64280	LGI1-IgG CBA, CSF	94288-8
64282	CASPR2-IgG CBA, CSF	94286-2
64929	DPPX Ab IFA, CSF	82989-5
64927	mGluR1 Ab IFA, CSF	94361-3
605156	GFAP IFA, CSF	94360-5