Lab Dept:	**Serology**
Test Name:	**ENCEPHALOPATHY AUTOIMMUNE/PARANEOPLASTIC EVALUATION, SERUM (>/= 18 y.o.)**

General Information

Lab Order Codes:	ENS1
Synonyms:	Autoimmune Encephalopathy Evaluation
CPT Codes:	83519 x3 – Immunoassay for analyte other than infectious agent antibody or infectious agent antigen, quantitative by radioimmunoassay 86255 x19 – Fluorescent noninfectious agent, antibody screen, each antibody 86341 – Islet cell antibody Possible reflex testing (at an additional charge): 84182 x7 – Western blot, with interpretation and report, each 86255 x7 – Fluorescent noninfectious agent, antibody screen, each antibody 86256 x8 – Fluorescent noninfectious agent, titer, each antibody 83519 x2 – Immunoassay for analyte, other than infectious agent antibody or infectious agent antigen, quantitative by radioimmunoassay
Test Includes:	See resources within reference lab test catalog (Mayo Code: ENS2)

Logistics

Test Indications:	This test is intended to be ordered for adult patients. If this test is ordered for a patient younger than 18 years of age, order Pediatric Autoimmune Encephalopathy/CNS Disorder Evaluation, Serum (PCDES). Evaluating new onset encephalopathy (noninfectious or metabolic) comprising confusional states, psychosis, delirium, memory loss, hallucinations, movement disorder, sensory or motor complaints, seizures, dyssonmnias, ataxias, nausea, vomiting, inappropriate antiduresis, coma, dysautonomias, or hypventialation in serum specimens. The following accompaniments should increase suspicion for autoimmune encephalopathy: ●Headache ●Autoimmune stigmata (personal or family history or signs of diabetes mellitus, thyroid disorder, vitiligo, poliosis [premature graying], myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus) ●History of cancer ●Smoking history or other cancer risk factors

●Inflammatory cerebral spinal fluid (or isolated protein elevation)
●Neuroimaging signs suggesting inflammation
●Evaluating limbic encephalitis (noninfectious)
●Directing a focused search for cancer
●Investigating encephalopathy appearing in the course or wake of cancer therapy and not explainable by metastasis or drug effect

Autoimmune encephalopathies extend beyond the classically recognized clinical and radiological spectrum of “limbic encephalitis”. They encompass a diversity of neurological presentations with subacute or insidious onset, including confusional states, psychoses, delirium, memory loss, hallucinations, movement disorders, sensory or motor complaints, seizures, dyssomnias, ataxias, eye movement problems, nausea, vomiting, inappropriate antiduresis, coma, dysautonomias, or hypoventilation. A diagnosis of autoimmune encephalopathy should be suspected on the basis of clinical course, coexisting autoimmune disorder (eg, thyroiditis, diabetes), serological evidence of autoimmunity, spinal fluid evidence of intrathecal inflammation, neuroimaging or electroencephalographic abnormalities, and favorable response to trial of immunotherapy.

Detection of one or more neural autoantibodies aids the diagnosis of autoimmune encephalopathy and may guide a search for cancer. Pertinent autoantibody specificities include: 1) neurotransmitter receptors and ion channels such as neuronal voltage-gated potassium channels (and interacting synaptic and axonal proteins, LGI1 and CASPR2), ionotropic glutamate receptors (NMDA and AMPA), metabotrophic GAGA-B recptors; 2) enzymes, signaling molecules, and RNA-regulatory proteins in the cytoplasm and nucleus of neurons (GAD65, CRMP-5, ANNA-1, and ANNA-2).

Importantly, autoimmune encephalopathies are reversible. Misdiagnosis as a progressive (currently irreversible) neurodegenerative conditions is not uncommon and has devastating consequences for the patient. Clinicians must consider the possibility of an autoimmune etiology in the differential diagnoses of encephalopathy. For example, a potentially reversible disorder justifies a trial of immunotherapy for the detection of neural autoantibodies in patients presenting with symptoms of personality change, executive dysfunction, and psychiatric manifestations.

A triad of clues helps to identifying patients with an autoimmune encephalopathy: 1) clinical presentation (subacute symptoms onset rapidlay progressive course and fluctuating symptoms) and radiological findings consistent with inflammation, 2) detection of neural autoantibodies in serum or cerebrospinal fluid (CSF), and 3) favorable respone to a trial of immunotherapy.

Detection of neural autoantibodies in serum or CSF informs the physician of a likely autoimmune etiology, and may heighten suspicion for a paraneoplastic basis and gude the search for cancer. Neurolgoical accompaniments of neural autoantibodies are generally not syndromic, but divers and multifocal. For example, neuronal voltage-gated potassium channel (VGKC)-complex antibodies were initially considered specific for autoimmune limbic encephalitis or disorders of peripheral nerve hyperexcitablilty. However, more diverse presentations are now recognized,

	including rapidly progressive cognitive decline mimicking frontotemporal dementia and Creutzfeldt-Jakob diseae. Comprehensive antibody testing is more informative then selective testing for 1 or 2 neural antibodies. Some antibodies strongly predict an underlying cancer. For example, small-cell lung carcinoma (ANN-1, CRMP-5-IgG, ovarian teratoma (NMDA-R) and thymoma (CRMP-5-IgG). An individual patient's profile autoantibody may be informative for a specific cancer type. For example, in a patient presenting with encephalitis who has CRMP 5 IgG, and subsequent reflex reveals muscle actylcholine receptor (AChR) binding antibody, the findings should raise a high suspicion from thymoma. 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 GFAP-IgG) because CSF testing is both more sensitive and specific. In contrast, serum testing for LGi1 antibody is more sensitive than CSF testing.
Lab Testing Sections:	Serology - Sendouts
Referred to:	Mayo Clinic Laboratories (Mayo Test: ENS2)
Phone Numbers:	MIN Lab: 612-813-6280 STP Lab: 651-220-6550
Test Availability:	Daily, 24 hours
Turnaround Time:	Results in 8-12 days
Special Instructions:	See Patient Preparation

Specimen

Specimen Type:	Blood
Container:	SST (Marble, gold or red)
Draw Volume:	12 mL (Minimum: 7 mL) blood
Processed Volume:	4 mL (Minimum: 2.5 mL) serum
Collection:	Routine blood collection
Special Processing:	Lab Staff: Centrifuge specimen, remove serum from cells, aliquot into a screw-capped round bottom vial. Store and ship at refrigerated temperatures. Specimen stable refrigerated (preferred) or frozen for 28 days, ambient for 72 hours.

Patient Preparation:	For optimal antibody detection, specimen collection is recommended prior to initiation of immunosuppressant medication. This test should not be requested in patients who have recently received radioisotopes, therapeutically or diagnostically, because of potential 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 assayed if sufficiently decayed, or canceled if radioactivity remains. Patient should have no general anesthetic or muscle-relaxant drugs in previous 24 hours.
Sample Rejection:	Gross hemolysis or lipemia; grossly icteric; mislabeled or unlabeled specimens

Interpretive

Reference range:

Test ID	Reporting name	Methodology *	Reference value
AEESI	Encephalopathy, Interpretation	Medical interpretation	NA
AMPCS	AMPA-R Ab CBA, S	CBA	Negative
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
CS2CS	CASPR2-IgG CBA, S	CBA	Negative
CRMS	CRMP-5-IgG, S	IFA	Negative
DPPIS	DPPX Ab IFA, S	IFA	Negative
GABCS	GABA-B-R Ab CBA, S	CBA	Negative
GD65S	GAD65 Ab Assay, S	RIA	< or =0.02 nmol/L Reference values apply to all ages.
GFAIS	GFAP IFA, S	IFA	Negative
IG5IS	IgLON5 IFA, S	IFA	Negative
LG1CS	LGI1-IgG CBA, S	CBA	Negative
GL1IS	mGluR1 Ab IFA, S	IFA	Negative
NCDIS	Neurochondrin IFA, S	IFA	Negative
NIFIS	NIF IFA, S	IFA	Negative
NMDCS	NMDA-R Ab CBA, S	CBA	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
SP7IS	Septin-7 IFA, S	IFA	Negative

Reflex Information:

Test ID	Reporting name	Methodology *	Reference value
AGNBS	AGNA-1 Immunoblot, S	IB	Negative
AGNTS	AGNA-1 Titer, S	IFA	<1:240
AINCS	Alpha Internexin CBA, S	CBA	Negative
AMPIS	AMPA-R Ab IF Titer Assay, S	IFA	<1:240
APHTS	Amphiphysin Ab 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
CRMTS	CRMP-5-IgG Titer, S	IFA	<1:240
CRMWS	CRMP-5-IgG Western Blot, S	WB	Negative
DPPCS	DPPX Ab CBA, S	CBA	Negative
DPPTS	DPPX Ab IFA Titer, S	IFA	<1:240
GABIS	GABA-B-R Ab IF Titer Assay, S	IFA	<1:240
GFACS	GFAP CBA, S	CBA	Negative
GFATS	GFAP IFA Titer, S	IFA	<1:240
IG5CS	IgLON5 CBA, S	CBA	Negative
IG5TS	IgLON5 IFA Titer, S	IFA	<1:240
GL1CS	mGluR1 Ab CBA, S	CBA	Negative
GL1TS	mGluR1 Ab IFA Titer, S	IFA	<1:240
NCDCS	Neurochondrin CBA, S	CBA	Negative
NCDTS	Neurochondrin IFA Titer, S	IFA	<1:240
NFHCS	NIF Heavy Chain CBA, S	CBA	Negative
NIFTS	NIF IFA Titer, S	IFA	<1:240
NFLCS	NIF Light Chain CBA, S	CBA	Negative
NMDIS	NMDA-R Ab IF Titer Assay, S	IFA	<1:240
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
SP7CS	Septin-7 CBA, S	CBA	Negative
SP7TS	Septin-7 IFA Titer, S	IFA	<1:240

*Methodology abbreviations:
Immunofluorescence assay (IFA)
Cell-binding assay (CBA)
Western blot (WB)
Radioimmunoassay (RIA)
Immunoblot (IB)

Critical value: N/A

Limitations: Negative results do not exclude autoimmune encephalopathy or cancer.

This test does not detect Ma1 or Ma2 antibodies, which are sometimes associated with brainstem and limbic encephalitis in the context of testicular germ cell neoplasms. Scrotal ultrasound is advised for men who present with unexplained subacute encephalitis.

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

Methodology: See Reference range

References:	https://www.mayocliniclabs.com/test-catalog/ February 2023
Updates:	6/11/2019: Updated algorithm to enhance testing panel, new antibodies added. 5/14/2020: Updated algorithm and addition reflex testing per Mayo 4/28/2022: Updated name per Mayo 2/20/2023: Updated minimum volume, age guidance, added specimen stability, updated turnaround time, significant changes to reflex tests and reference ranges.