MAYO CLINIC LABORATORIES

Test Definition: DMNES

Peripheral Nervous System Demyelinating Neuropathy, Autoimmune Evaluation, Serum

Overview

Useful For

Evaluating patients with a suspected immune-mediated demyelinating peripheral neuropathy

Profile Information

Test Id	Reporting Name	Available Separately	Always Performed
DMNI	Demyelinating Neuropathy Interp, S	No	Yes
CONCS	Contactin-1 IgG CBA, S	No	Yes
GQ1ES	GQ1b-IgG ELISA, S	Yes	Yes
IGG_D	IgG Disialo. GD1b	No	Yes
IGM_D	IgM Disialo. GD1b	No	Yes
IGG_M	IgG Monos. GM1	No	Yes
IGM_M	IgM Monos. GM1	No	Yes
MAGES	MAG IgM, S	Yes	Yes
NF4FS	Neurofascin-155 IgG4, S	No	Yes

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
IGDTS	IgG Disialo GD1b Titer, S	No	No
IMDTS	IgM Disialo GD1b Titer, S	No	No
IGMTS	IgG Monos GM1 Titer, S	No	No
IMMTS	IgM Monos GM1 Titer, S	No	No

Testing Algorithm

Screening tests are performed for IgG and IgM antibodies to GM1 and GD1b. If positive, the appropriate titer assay will be performed at an additional charge.

For more information see:
-Demyelinating Neuropathy Evaluation Algorithm.
-Acquired Neuropathy Diagnostic Algorithm

To assess the probability of your patient having chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) vs mimic disorders, see the Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) calculator.

Special Instructions

- Demyelinating Neuropathy Evaluation Algorithm
- Acquired Neuropathy Diagnostic Algorithm

Method Name

DMNI: Technical Interpretation
CONCS: Cell-Binding Assay (CBA)
GQ1ES, IGG_D, IGM_D, IGG_M, IGM_M, IGDTS, IMDTS, IGMTS, IMMTS, MAGES: Enzyme-Linked Immunosorbent Assay (ELISA)
NF4FS: Flow Cytometry

NY State Available

Yes

Specimen

Specimen Type

Serum

Ordering Guidance

Multiple neurological phenotype-specific autoimmune/paraneoplastic evaluations are available. For more information as well as phenotype-specific testing options, refer to Autoimmune Neurology Test Ordering Guide.

For a list of antibodies performed with each evaluation, see Autoimmune Neurology Antibody Matrix.

Specimen Required

Patient Preparation: For optimal antibody detection, specimen collection is recommended to occur 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: 3 mL
Collection Instructions: Centrifuge and aliquot serum into a plastic vial.

Forms

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

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

Immune-mediated neuropathies refer to a group of disorders that share overlapping sensory, motor, and autonomic clinical, laboratory, and electrodiagnostic features. Testing for autoantibodies associated with immune-mediated neuropathies should be considered after a detailed history and physical examination is completed. In most situations, nerve conduction studies and electromyography are crucial in distinguishing between primary axonal, primary demyelinating, or mixed axonal and demyelinating neuropathies. This enables a more focused testing approach for disease-relevant autoantibodies. This evaluation focuses on persons with immune-mediated demyelinating neuropathies.

The antibody tests included in this evaluation aim to support the diagnosis of an immune-mediated demyelinating neuropathy as well as aid in distinguishing between the more common forms of immune-mediated demyelinating neuropathies that are associated with sensitive and specific antibody biomarkers.

Autoantibodies directed against myelin-associated glycoprotein (MAG) are associated with sensory motor demyelinating peripheral neuropathy. A distal acquired demyelinating symmetric (DADS) neuropathy phenotype is the most commonly associated presentation. This may mimic distal forms of chronic inflammatory demyelinating polyneuropathy (CIDP). Patients typically have a slowly progressive symmetric sensory ataxia with or without distal weakness and an IgM monoclonal gammopathy of undetermined significance. Nerve conduction studies typically demonstrate a characteristic progressive sensory-predominant mixed axonal and demyelinating neuropathy with reduced distal conduction velocities that are greater distally. In general, patients with a DADS neuropathy show limited treatment responses to intravenous immunoglobulin (IVIg), and more aggressive immunotherapy may be needed.

A subset of patients with suspected CIDP have been identified with autoantibodies targeting nodal-paranodal proteins. These patients share common immunopathological mechanisms of disease, clinical features, and treatment responses that are distinct from classic CIDP. A common target of these autoantibodies is the neurofascin-155 (NF155)-contactin-1 (CNTN1) adhesion complex, which is critical in maintaining the paranodal myelin-axon junction. NF155 is expressed at the paranodal loops of Schwann cells where it interacts with CNTN1 expressed on adjacent axons. This interaction stabilizes and allows the proper organization of the paranodal axoglial junction. Antibody-mediated disruption of this interaction in animal models recapitulates the pathophysiology observed in humans.

Neurofascin-155 IgG antibodies are present in approximately 5% to 10% of patients with CIDP-like presentations and, more rarely, in those with more acute forms of demyelinating polyradiculoneuropathy. NF155 IgG positive cases are more likely to present with distal weakness, gait disturbance, tremor, and dysarthria as compared to classic CIDP. Most patients who are seropositive for NF155 IgG have been reported to be refractory to IVIg therapy and often require second-line treatment that includes B-cell depleting therapies, such as rituximab. The detection of NF155 IgG4 is a highly specific finding and has not been reported in other disease mimics, such as hereditary neuropathies, distal acquired demyelinating symmetric neuropathy, and motor neuron disease.

Contactin-1 IgG antibodies are present in approximately 2% of patients with CIDP-like presentations. CNTN1 IgG-positive cases are more likely to present with neuropathic pain, sensory ataxia, and subacute progressive demyelinating polyradiculoneuropathy or polyradiculopathy. The majority of seropositive patients have been reported to be refractory to treatment with IVIg. However, some of these patients respond well to B-cell depleting therapies, such as rituximab. Up to half of CNTN1 IgG-positive patients with CIDP or CIDP-like presentations have been reported to develop membranous nephropathy; thus, screening for proteinuria may be warranted.

Autoantibodies targeting ganglioside GQ1b are associated with a group of disorders that includes Miller Fisher syndrome (MFS), Bickerstaff brainstem encephalitis (BBE), and classic Guillain-Barre syndrome (GBS) with ophthalmoplegia. Collectively these are referred to as GQ1b IgG-related syndromes, which reflects the diverse clinical presentations associated with these autoantibodies. The prevalence of GQ1b IgG in MFS and BBE is high and has been reported to be greater than 80% in well-defined clinical cohorts. GQ1b IgG may occur in patients with GBS but generally with a lower prevalence.

Autoantibodies targeting ganglioside GD1b antibodies frequently occur in sensory ataxic conditions such as chronic, ataxic, neuropathy, ophthalmoplegia, IgM gammopathy, cold agglutinins, and disialosyl antibodies (CANOMAD), acute sensory ataxic neuropathy (ASAN), and chronic ataxic neuropathy with disialosyl antibodies (CANDA).

Autoantibodies targeting ganglioside GM1 more commonly occur in patients with multifocal motor neuropathy (MMN), multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy, and motor-predominant Guillain-Barre syndrome.

Reference Values

Contactin-1 IgG CBA: Negative
GQ1b-IgG ELISA: Negative
IgG Disialo. GD1b: Negative
IgM Disialo. GD1b: Negative
IgG Monos. GM1: Negative
IgM Monos. GM1: Negative
MAG IgM: <1500 Buhlmann titer unit
Neurofascin-155 IgG4: Negative

Reflex Information:
IgG Disialo GD1b Titer: <1:2000
IgM Disialo GD1b Titer: <1:2000
IgG Monos GD1b Titer: <1:2000

IgM Monos GD1b Titer: <1:4000

Interpretation

The presence of specific autoantibodies or combinations of antibodies in this panel provides supportive evidence of an immune-mediated demyelinating peripheral neuropathy. However, these results must be interpretated in the appropriate clinical context. A negative result does not exclude the possibility of an immune-mediated demyelinating peripheral neuropathy.

Cautions

Negative results do not exclude a diagnosis of an immune-mediated demyelinating neuropathy. Autoantibody results should always be correlated with the clinical phenotype.

The use of immunotherapy prior to sample collection may result in either false-positive or false-negative results.

Clinical Reference

1. Asati A, Kachurina O, Kachurin A. Simultaneous measurements of auto-immune and infectious disease specific antibodies using a high throughput multiplexing tool. PLoS One. 2012;7(8):e42681
2. Beecher G, Shelly S, Dyck PJB, et al. Pure motor onset and IgM-gammopathy occurrence in multifocal acquired demyelinating sensory and motor neuropathy. 2021;97(14):e1392-e1403
3. Dubey D, Honorat J, Shelly S, et al. Contactin-1 autoimmunity: Serologic, neurologic, and pathologic correlates. Neurol Neuroimmunol Neuroinflamm. 2020;7(4):e771
4. Klein CJ. Autoimmune-mediated peripheral neuropathies and autoimmune pain. Handb Clin Neurol. 2016;133:417-446
5. Klein CJ. Charcot-Marie-Tooth disease and other hereditary neuropathies [published correction appears in Continuum (Minneap Minn). 2021;27(1):289
6. Le Cann M, Bouhour F, Viala K, et al. CANOMAD: a neurological monoclonal gammopathy of clinical significance that benefits from B-cell-targeted therapies. Blood. 2020;136(21):2428-2436
7. Le Quintrec M, Teisseyre M, Bec N, et al. Contactin-1 is a novel target antigen in membranous nephropathy associated with chronic inflammatory demyelinating polyneuropathy. Kidney Int. 2021;100(6):1240-1249
8. Liberatore G, Giannotta C, Sajeev BP, et al. Sensitivity and specificity of a commercial ELISA test for anti-MAG antibodies in patients with neuropathy. J Neuroimmunol. 2020;345:577288
9. Martinez-Thompson JM, Snyder MR, Ettore M, et al. Composite ganglioside autoantibodies and immune treatment response in MMN and MADSAM. Muscle Nerve. 2018;57(6):1000-1005
10. Querol L, Nogales-Gadea G, Rojas-Garcia R, et al. Neurofascin IgG4 antibodies in CIDP associate with disabling tremor and poor response to IVIg. Neurology. 2014;82(10):879-886
11. Shahrizaila N, Yuki N. Bickerstaff brainstem encephalitis and Fisher syndrome: anti-GQ1b antibody syndrome. J Neurol Neurosurg Psychiatry. 2013;84(5):576-583
12. Shelly S, Klein CJ, Dyck PJB, et al. Neurofascin-155 Immunoglobulin Subtypes: Clinicopathologic Associations and Neurologic Outcomes. Neurology. 2021;97(24):e2392-e2403
13. Shelly S, Dubey D, Mills JR, Klein CJ. Paraneoplastic neuropathies and peripheral nerve hyperexcitability disorders. In: Giometto B, Pittock S, eds. Paraneoplastic Neurologic Disorders. Elsevier; 2024:chap 15 Handbook of Clinical Neurology, Vol 200
14. Svahn J, Petiot P, Antoine JC, et al. Anti-MAG antibodies in 202 patients: clinicopathological and therapeutic features. J Neurol Neurosurg Psychiatry. 2018;89(5):499-505
15. Yuki N, Uncini A. Acute and chronic ataxic neuropathies with disialosyl antibodies: a continuous clinical spectrum and

a common pathophysiological mechanism. Muscle Nerve. 2014;49(5):629-635

Performance

Method Description

Ganglioside Antibodies: IgG/IgM Disialo, GD1b; IgG/IgM Monos, GM1 Enzyme-Linked Immunosorbent Assays: Antiganglioside antibodies are detected by enzyme-linked immunosorbent assays (ELISA). Microwells are precoated with GM1 or GD1b antigen. The calibrator, controls, and diluted patient samples are added to the wells, and autoantibodies recognizing GM1 or GD1b bind during the first incubation. After washing the wells to remove all unbound proteins, purified alkaline phosphatase-conjugated antihuman IgG or IgM is added. The conjugated secondary IgG or IgM binds to the captured human autoantibody, and the excess unbound conjugated IgG or IgM is removed by a further wash step. The bound conjugated IgG or IgM is visualized with 4-nitrophenyl phosphate substrate, which gives a yellow reaction product, the intensity of which is proportional to a concentration of autoantibody in the sample. A base is added to each well to stop the reaction, and the final product is read at 405 nm. For screening assays, patient results are calculated by dividing the optical density (OD) of patient samples or controls by the average OD of the calibrator. Any sample with a ratio of patient to calibrator OD greater than 2.0 is considered positive. Any positive sample on screening is then titered. For titer assays, patient samples are diluted, and the last dilution where the ratio of patient to calibrator OD is greater than 2.0 is reported as the end-point titer.(Unpublished Mayo method)

Ganglioside GQ1b Antibody, IgG ELISA:
Microwells are precoated with GQ1b antigen. The calibrator, controls, and diluted patient samples are added to the wells, and autoantibodies recognizing GQ1b bind during the first incubation. After washing the wells to remove all unbound proteins, purified horseradish peroxidase-labeled anti-human IgG conjugate is added. The conjugated IgG binds to the captured human autoantibody, and the excess unbound conjugated IgG is removed by a further wash step. The bound conjugated IgG is visualized with 3,3',5,5'-tetramethylbenzidine substrate, which gives a blue reaction product, the intensity of which is proportional to a concentration of autoantibody in the sample. Acid is added to each well to stop the reaction. This produces a yellow end-product color, which is read at 450 nm. Patient results are calculated as a cutoff index (COI) by dividing the OD of patient samples or controls by the average OD of the calibrator. Any sample with a COI greater than or equal to 1.0 is considered positive. Any sample with a COI less than 1.0 is considered negative. Results are reported qualitatively as positive or negative.(Unpublished Mayo method)

Myelin-Associated Glycoprotein Autoantibodies, IgM ELISA:
Microwells are precoated with human myelin-associated glycoprotein (MAG) antigen. The calibrators, controls, and diluted patient samples are added to the wells, and autoantibodies recognizing the MAG antigen bind during the first incubation. After washing the wells to remove all unbound proteins, purified horseradish peroxidase-labeled anti-human IgM conjugate is added. The secondary antibody conjugate binds to captured human autoantibody, and the excess unbound conjugate is removed by a further wash step. The bound secondary antibody conjugate undergoes an enzymatic reaction with a chemical substrate to generate a colormetric reaction. Absorbance is measured on a plate reader and patient sample signal is compared to a calibration curve to generate Buhlmann titer units.(Package insert: anti-MAG Autoantibodies ELISA. Buhlmann Laboratories AG; 10/2018)

Contactin-1 IgG Cell-Binding Assay:

Patient sample is applied to a composite slide containing contactin-1 transfected and nontransfected EU90 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, 02/25/2019)

Neurofascin-155 IgG4 Flow Cytometry:
This cell-binding assay utilizes flow cytometry to detect neurofascin 155 (NF155) IgG4 antibodies in patient samples. Briefly, a stable HEK293 cell line expressing human NF155 on the cell surface is premixed with parental HEK293 cells that do not express human NF155. The two cell populations are distinguished using a green fluorescent protein marker, which is only expressed in NF155 expressing cells. The mixture of cells is incubated with diluted patient sample to allow antibodies present in the sample to bind target antigens. Next, the cells are incubated with a human IgG4 specific secondary antibody conjugated to AlexaFluor 647 to detect cell bound human IgG4 antibodies. The AlexaFluor 647 signal intensity of the different cell populations is measured using a flow cytometer. The IBI (IgG binding index) is then calculated as the median fluorescent intensity (MFI) of AlexaFluor 647 of the NF155 expressing cells divided by the MFI of the parental non-NF155 expressing cells. When the IBI is greater than or equal to 2.0 the result is considered positive for NF155 IgG4 antibodies.(Unpublished Mayo method)

PDF Report
No

Day(s) Performed
Monday through Sunday

Report Available
5 to 8 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

83516 x5
83520
86255 x2
83520 x4 (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
DMNES	Demyelinating Neuropathy Ab Eval, S	82455-7

Result ID	Test Result Name	Result LOINC® Value
4416	IgG Disialo. GD1b	94868-7
4412	IgG Monos. GM1	63243-0
4417	IgM Disialo. GD1b	94870-3
4413	IgM Monos. GM1	63247-1
607034	MAG IgM, S	39087-2
614591	Neurofascin-155 IgG4, S	100845-7
616442	Contactin-1 IgG CBA, S	101448-9
621107	GQ1b-IgG ELISA, S	63254-7
621104	Demyelinating Neuropathy Interpretation, S	69048-7