TESTING RECOMMENDATIONS FOR SUSPECTED ME/CFS
US ME/CFS Clinician Coalition
Version 1
February 20, 2021

Overview
People with ME/CFS may present with a range of symptoms that include a decreased level of functioning, debilitating fatigue, cognitive impairment, orthostatic intolerance, flu-like symptoms, a worsening of their symptoms following exertion, pain, and other symptoms. Patients often report symptoms started with a viral infection. Recently, some COVID-19 patients are reporting extended illness with symptoms similar to ME/CFS.

To help improve the speed and accuracy of diagnosis, the National Academy of Medicine established new diagnostic criteria for ME/CFS in 2015 that focus on the hallmark symptoms of the illness. While there are no specific diagnostic tests for ME/CFS, the clinician can rely on medical history, physical exam, laboratory testing results (used primarily to identify alternative diagnoses and comorbidities), and recognition of the hallmark symptoms to diagnose ME/CFS.

This document includes tests recommended to identify alternative and comorbid diagnoses and further characterize ME/CFS. These recommendations include a limited set of tests recommended for all people with suspected ME/CFS and additional tests to be ordered based on the patient's particular presentation. These recommendations are intended as general guidance for a diagnostic process that may extend over several office visits and involve referrals to specialists. The clinician will need to apply their own clinical judgment in deciding which tests to order and whether to refer to a specialist.

In addition to tests to support the diagnostic process, this document also includes recommendations for tests that can be used to help support disability claims and guide treatment decisions. The testing recommendations are broken into three tiers as follows:

Tier 1 *(Page 2)* More common diagnoses	• Tests recommended in all suspected patients and tests for specific presentation to identify more common alternative and comorbid diagnoses or fatal or easily treatable diagnoses. Many of these tests are normal in ME/CFS patients.
Tier 2 *(Page 7)* Followup	• Follow-up and/or more advanced tests for given presentation to identify less common alternative diagnoses and comorbidities
Tier 3 *(Page 11)* ME/CFS specific	• Tests to help characterize ME/CFS and to help document disability and guide treatment. These may require access to specialized labs

Each tier is further broken down by the system, describes the presentation that might indicate a given test, and suggests the next steps that might be taken if abnormalities are detected.

For more information on ME/CFS diagnosis and management and on terms of use for these recommendations, see the ME/CFS Clinician Coalition website and handout.
Website: https://mecfscliniciancoalition.org/
Handout: https://drive.google.com/file/d/1SG7hlJTCSDrDHqvioPMq-cX-rgRKXjfk/view
This handout summarizes the alternative diagnoses and comorbidities to be evaluated depending on presentation during the differential diagnosis.

Tier 1: Tests for All Suspected Patients and for Common Differential Diagnoses

Tier 1 includes tests recommended for all patients with suspected ME/CFS. Many of these tests may be normal in ME/CFS patients but help identify other diagnoses. The 4 point salivary cortisol can support a diagnosis of ME/CFS. For more information, see Tier 3.

Tier 1 also includes tests for more common alternative and comorbid diagnoses and diagnoses that could be fatal or are easily treated. The tests may be ordered by primary care providers or specialists as appropriate.

Test Category / Name	Who should get the test?	Examples of targeted diagnoses	Next steps if abnormalities are identified
All Suspected Patients			
CBC with differential	All suspected patients	Anemias, leukemias, hemoglobinopathies, platelet disorders, myelopathies, infection	Additional workup to identify underlying cause or referral to a specialist
Comprehensive metabolic panel (Chem20 Panel)	All suspected patents	Diabetes, renal insufficiency, liver disease, hypercalcemia, hepatitis, Hodgkin's lymphoma	Additional workup to identify underlying cause or referral to a specialist
Urinalysis	All suspected patients	Screen for infection, autoimmune disorders and malignancies	Additional workup to identify underlying cause or referral to a specialist
Ferritin	All suspected patients	Iron deficiency, hemochromatosis, restless legs syndrome	Low levels indicate iron deficiency, from some primary cause. Additional workup to identify underlying cause or referral to a specialist NOTE: High levels can indicate ongoing infection, inflammation

Vitamin B12	All suspected patients	Malabsorption syndromes, Celiac disease, primary Vitamin B12 deficiency, neuropathies	Additional workup or referral to a specialist. Consider oral supplementation and follow up
Vitamin D, 25-Dihydroxy	All suspected patients	Vitamin D deficiency	Supplement Vitamin D but also evaluate for causes of low Vitamin D such as inadequate intake (Vegan), malabsorption (Celiac), lack of sun exposure, etc
Erythrocyte Sedimentation Rate (ESR)	All suspected patents	Inflammation, autoimmune and connective tissue disorders, infections, malignancies	Additional workup to identify underlying cause or referral to a specialist. Consider: ● Creatine Kinase (if muscle pain or weakness is present) ● Malignancy evaluation ● Underlying chronic bacterial/mycobacterial or other infection (e.g., SBE, TB)
Antinuclear antibody (ANA)	All suspected patents	Autoimmune disease	Additional workup to identify underlying cause or referral to a specialist
Rheumatoid factor (RF)	All suspected patents	Autoimmune disease	Additional workup to identify underlying cause or referral to a specialist
C-reactive Protein (CRP)	All suspected patents	Inflammation, autoimmune and connective tissue disorders, infections, malignancies	Additional workup to identify underlying cause or referral to a specialist. Consider: ● Creatine Kinase (if muscle pain or weakness is present) ● Malignancy evaluation ● Underlying chronic bacterial/mycobacter

			ial or other infection (e.g., SBE, TB)
Thyroid stimulating hormone, free T4	All suspected patients	Hypothyroidism, hyperthyroidism, autoimmune thyroid disease	Additional workup or referral to a specialist. Consider: ● Thyroid peroxidase antibody (TPOAb) ● Thyroglobulin antibody (TgAb) ● TSH Receptor antibodies
AM cortisol	All suspected patients	Adrenal insufficiency	Cortrosyn stimulation test or referral to specialist
4-point salivary cortisol upon wakening, at noon, 4:00 PM, and bedtime	All suspected patients	Supportive of an ME/CFS diagnosis	Studies have demonstrated a flat cortisol curve in patients with ME/CFS. Treatment with hydrocortisone is not recommended.
Psychiatric screens	All suspected patients	Major depression, severe anxiety disorders, bipolar and psychotic disorders, eating disorders	Distinguish between primary and secondary mental health disorders. Mental health disorders are not exclusionary for ME/CFS. Additional workup or referral to a specialist
Autonomic Dysfunction			
10 minute NASA Lean Test or Stand Test (Note: may take up to 30 minutes to elicit neurally mediated hypotension	All patients with symptoms or signs suggesting intolerance for upright activity or orthostatic intolerance (dizziness, headache, cold hands and feet, palpitations, nausea, etc)	Orthostatic intolerance, orthostatic hypotension, Postural orthostatic tachycardia syndrome, (POTS), Neurally mediated hypotension (NMH)	Additional workup or referral to a specialist. NOTE: This test starts with BP and HR values in a relaxed supine position, followed by BP and HR every 1-2 minutes in a standing or leaning position for 10 minutes or more, based on patient response and tolerance
Tilt table test (usually 10-45 min)	Symptoms or signs suggesting orthostatic intolerance	Orthostatic Intolerance, orthostatic	Referral to a specialist

		hypotension, Postural orthostatic tachycardia syndrome, Neurally mediated hypotension	
Sleep Disorders References: Overnight Oximetry: https://intermountainhealthcare.org/ckr-ext/Dcmnt?ncid=520707915 AASM 2017 guidelines: https://aasm.org/resources/clinicalguidelines/diagnostic-testing-osa.pdf			
Overnight oximetry, Home Sleep Study, Polysomno-graphy	Consider in all adult ME/CFS with sleep disturbances	Nocturnal hypoxemia from varied causes. Sleep apneas. Periodic limb movement disorder	The type of test should be determined case by case based on clinical factors and judgement of the provider. Consider referral to a sleep specialist
Infectious Diseases			
Epstein-Barr virus antibody panel (VCA IgM, VCA IgG, EA, EBNA)	All patients who are at high risk (teenage/young adult) or whose ME/CFS followed acute EBV mono, or who are at high risk of, or have a clinical presentation consistent with EBV reactivation.	EBV mononucleosis or EBV reactivation	Consult with a specialist if EBV IgM and/or EBV-EA is still positive more than 9 months from known primary mononucleosis, or if early antigen (EA) or viral capsid antigen IgG titers are extremely high for unclear reasons
Cytomegalo-virus (CMV) antibody panel (IgM and IgG)	All patients at high risk for infection, reactivation, or with consistent clinical presentation. All immunocompromised patients	CMV mononucleosis, atypical CMV infection, or CMV reactivation	Consult with a specialist if CMV IgM is positive, or if CMV IgG is extremely high for unclear reasons
Human immuno-deficiency virus	CDC suggests screening everyone ages 13-65	Human immunodeficiency virus infection	Referral to a specialist
Hepatitis C antibody panel	CDC suggests screening everyone born between 1945-1965. Risk factors and abnormal liver tests	Hepatitis C infection	Referral to a specialist

	should prompt testing in others		
Hepatitis B antibody panel	Not needed if vaccinated; risk factors and abnormal liver tests should prompt testing	Hepatitis B infection	Referral to a specialist
PPD skin test, interferon gamma release assays	Night sweats, cough, hemoptysis, weight loss, known exposure to TB or other risk factors.	Mycobacterium tuberculosis	Referral to a specialist
Rapid plasma reagin, treponemal antibody test	Cognitive/ neurological signs, risk factors for syphilis exposure	Syphilis, including tertiary syphilis	Evaluate and treat as appropriate or refer to a specialist Note: The treponemal test is the preferred screening test. The Rapid plasma reagin can be used but can give false positive and false negative results and should be confirmed.
Vector-borne disease (Lyme, Dengue, Q-fever, Rocky Mountain Spotted Fever, etc)	Currently or previously living in endemic area; history of traveling to endemic areas; history of animal exposure, especially cats, dogs, and horses; history of scratches and bites; or suggestive symptoms and signs	Vector-borne disease (Lyme, Dengue, Q-fever, Rocky Mountain Spotted Fever, etc)	Referral to a specialist for additional workup
West Nile serum IgM and IgG antibody	High risk or endemic areas. Symptoms suggestive of West Nile virus infection such as cognitive dysfunction	West Nile virus infection / encephalitis	Referral to a specialist
Parvovirus B19 serum IgM and IgG	Onset with slapped cheeks rash, coryza, fever, headache, polyarthopathy	Parvovirus B19 infection	Referral to a specialist
Blood cultures	Patients with ongoing fevers, night sweats, elevated ESR, CRP,	Subacute bacterial endocarditis	Hospital admission/treat or refer to specialist

	abnormal urinalysis, cardiac murmur		
Rheumatological Disorders			
Creatine kinase	If muscle pain or weakness is present	Muscle inflammation, myositis, myopathy	Referral to rheumatology
Oncological Disorders			
Risk-factor appropriate cancer screening	Presenting symptoms and individual risk factors (age, sex, family history, exposures, etc.)	Common cancers - e.g. breast, prostate, colon, lung, cervical, endometrial, leukemia/lymphoma, melanoma, etc.	Additional workup or referral to a specialist
Cardiovascular and Pulmonary Disorders			
Chest X-ray	Cardiopulmonary symptoms or signs, risk factors for lung disease, night sweats	Post-acute COVID syndrome, Lung cancer, Chronic obstructive pulmonary disease (COPD), Congestive heart failure, asthma, pneumonia, pleural effusion, sarcoidosis	Additional workup or referral to a specialist
Computed tomography (CT) scan	Cough, dyspnea, shortness of breath, chest pain, suspected or known prior SARS-CoV2 infection	Post-acute COVID syndrome	Additional workup or referral to a specialist
Pulmonary function tests	Shortness of breath, exercise intolerance, pulmonary symptoms or signs, risk factors for lung disease, hypoxemia on overnight pulse oximetry	COPD, asthma, interstitial lung disease, pulmonary hypertension	Additional workup or referral to a specialist

Electro-cardiogram	Consider in all patients with exercise intolerance, palpitations, shortness of breath, chest discomfort	Arrhythmias, Long QT, h/o ischemia, structural abnormalities	Additional workup or referral to a specialist
Trans-thoracic echocardio-graphy	Consider in patients with exercise intolerance, palpitations, shortness of breath, chest discomfort, syncope, orthopnea/ paroxysmal nocturnal dyspnea, abnormal cardiac exam or pedal edema	Post-acute COVID syndrome, Structural or functional changes of the heart, patent foramen ovale, pericarditis or pericardial effusion	Additional workup or referral to a specialist
24-hour or longer cardiac monitoring	Syncope, palpitations, dizziness,	Arrhythmias, dysautonomia	Additional workup or referral to a specialist
Exercise testing for coronary artery disease	Chest pain/ pressure/ sweating/ nausea/ vomiting with exertion, abnormal cardiac exam	Coronary artery disease, arrhythmias, and pulmonary diseases	Additional workup or referral to a specialist

Tier 2: Followup and/or Advanced Tests

Tier 2 tests include follow-up and/or more advanced tests to identify less common alternative diagnoses and comorbidities. These tests may be ordered by primary care providers or specialists as appropriate.

Test Category / Name	Who should get the test?	Examples of targeted diagnoses	Next steps
Vitamin B6 (pyridoxine)	Clinical concern for neuropathy. People taking B6 supplements	Peripheral or small fiber neuropathy from deficiency or overdose	Check level for overdose. Low values seen in vegans and in poor GI absorption e.g. Celiac disease)
Serum homocysteine	Patients who want to have genetic testing for MTHFR mutations. Patients with strong family history of vascular disease but no known risk factors	Vitamin B12, folate or pyridoxine deficiency. Genetic conditions. Certain medications and medical conditions may increase homocysteine	Treat the cause of high homocysteine after an appropriate workup
MTHFR mutations	Patients with high homocysteine or family history of MTHFR mutations		Supplement deficiencies in Vitamin B12, folate, pyridoxine. Consider L-methyl folate and methylcobalamin forms
Autonomic Dysfunction			
Capnography	Symptoms or signs suggesting orthostatic intolerance	Orthostatic intolerance, tachypnea, orthostatic hypocapnia	Additional workup or referral to a specialist NOTE: This test starts with RR and end tidal CO2 values in a relaxed supine position, followed by RR and eTCO2 every 1-2 minutes in a standing or leaning position for 10 minutes or more, based on patient response and tolerance
Neurological Disorders			
MRI of brain	Focal neurologic	Stroke, brain	Referral to a specialist for

(T2 weighted) or other appropriate imaging	symptoms, cognitive issues, a change in severity or nature of chronic headaches, abnormal neurologic examination, history of head trauma	tumors, aneurysm, multiple sclerosis, Chiari malformation, chronic subdural hematoma	additional workup
MRI of cervical spine (or other appropriate imaging)	Focal neurologic symptoms, or abnormal neurologic examination, chronic positional neck pain, orthostatic neurologic changes, hypermobility, history of head or neck trauma	Cervical spinal stenosis, syringomyelia, multiple sclerosis, cranio-cervical instability syndromes	Referral to a specialist for additional workup
MRI of lumbar spine (or other appropriate imaging)	Abnormal neurologic exam suggesting involvement of lumbar spine or nerve root compression: lower body weakness, low back or leg pain or sensory changes, bowel or bladder dysfunction, gait changes	Spinal stenosis, multiple sclerosis, spinal neoplasms, tethered cord, spina bifida occulta, ankylosing spondylitis, herniated disks	Referral to a specialist for additional workup
Lumbar puncture	A subset of patients with abnormal neurologic exam, photophobia, neck stiffness, meningeal signs, neurologic symptoms from upright posture	Infections of the CNS, multiple sclerosis, chronic spinal fluid leak syndromes	Prior to LP may need brain MRI to assess for brain tumor or increased intracranial pressure. Referral to a specialist for additional workup
Infectious Diseases			
Anti-streptolysin O (ASO) titer, Strep throat culture, Anti-DNaseB	Patients with recurrent strep infections / pharyngitis or suspected history of strep and lack of prior screening or treatment	Untreated chronic strep infections and associated conditions. Exposure to group A strep carrier (risk of transmission to others)	Consider appropriate treatment regimens for pharyngitis or to treat the carrier. Consider the possibility of transmission from a carrier
Immunological Disorders			
Histamine,	Patients with severe	Mast cell activation	Referral to a specialist

tryptase and chromo-granin A	allergies, intolerances, reactions to exposures; sudden changes in symptoms in different environments. At least two systems must be affected: upper or lower respiratory, cardiovascular, gastrointestinal, or dermatologic	syndrome	for additional workup and treatment
Allergy skin tests or RAST tests	Patients with chronic allergies and reactions; history of hayfever, asthma, skin allergies, anaphylaxis (swelling, hypotension, rashes)	Chronic allergies and responses. Immune dysregulation	Referral to an allergy/immunologist for testing and treatment
Immune testing: Total immuno-globulins, IgG subclasses	Patients with frequent or prolonged infections	Common variable immunodeficiency, other immune deficiency disorders	Referral to a specialist for testing and treatment
Rheumatological Disorders			
Early Sjogren's panel, SSA, SSB	Dry eyes, dry mouth	Sjogren's Syndrome	Referral for lip biopsy or other diagnostic testing
Acetylcholine Receptor (AChR) antibodies	Clinical picture of muscle weakness that worsens with repetitive motion or worsens throughout the day	Rule out myasthenia gravis and related conditions. Create treatment options	Refer to a specialist if positive
Endocrine/Metabolic Disorders			
Hemoglobin A1C	If evidence of elevated glucose or suspicion of diabetes, metabolic syndrome	Prediabetes or borderline diabetes	Additional treatment and consider referral if not responding
Parathyroid hormone (PTH) and ionized calcium	Middle-aged or older patient with fatigue, arthralgia, myalgia, diminished bone density and elevated calcium	Hyperparathyroidis m	Referral to a specialist

Follicle stimulating hormone	Patients who might be peri- or post-menopausal.	Peri- or post-menopause	Consider the risk/benefit of estrogen and/or progesterone replacement regimens for symptom management
Free and total Testosterone	Male patients with complaints of fatigue, muscle weakness, erectile dysfunction, on opioids or have metabolic syndrome	Hypogonadism, primary or secondary	Referral to a specialist for symptom management
Adreno-corticotropic hormone (ACTH)	Patients with low blood pressure, orthostatic intolerance, fatigue, weakness, weight gain, bruisability	Adrenal insufficiency or Cushings	Additional workup or referral to a specialist
Gastrointestinal Disorders			
Esophago-gastro-Duodeno-scopy (EGD)	Upper abdominal pain, persistent heartburn, nausea, early satiety, unintended significant weight loss, melena	Gastritis, gastroparesis, Celiac disease, H. pylori, cancer	Referral to a specialist for additional workup and treatment
Colonoscopy	Persistent constipation, diarrhea, melena, hematochezia, steatorrhea, unintended significant weight loss, family history of colon cancer or polyposis	Colon cancer, inflammatory bowel disease, diverticulosis/itis, confirmation of irritable bowel syndrome	Additional workup or referral to a specialist
Food sensitivity tests	Patients with reports of significant food sensitivities		Referral to a specialist for additional testing and treatment
Pain			
Small punch skin biopsies	Patients with peripheral neuropathy, patchy neuropathy, autonomic neuropathy, widespread hyperalgesia, risk factors for neuropathy	Small fiber neuropathy	Additional workup or referral to a specialist

Tier 3: Tests to Support ME/CFS Diagnosis and Disability and/or Guide Treatment

Tier 3 includes tests specific to ME/CFS. This section is broken into three subsections:

A. Tests to help confirm diagnosis
B. Tests used to document disability
C. More advanced tests to further characterize ME/CFS or guide treatment. These tests may require access to specialized labs and/or referrals to specialists

A. Tests Used to Support a Diagnosis of ME/CFS

- Endocrine/metabolic/HPA
  - 4-point salivary cortisol in all suspected patients (upon wakening, at noon, 4:00 PM, and bedtime). Studies have demonstrated a flat cortisol curve in patients with ME/CFS (Nater). This test is supportive of an ME/CFS diagnosis, but treatment with hydrocortisone is not recommended.
    Note: This test is also listed in Tier 1 for all suspected patients
- Autonomic Dysfunction and Orthostatic intolerance
  - 10 - 20 minute passive standing test (NASA Lean test) for all suspected patients
  - Tilt Table Test (For those patients with abnormal passive standing test when clarification needed, high suspicion for delayed near-syncope or syncope, NMH)

References:

- Nater U et al. Alterations in Diurnal Salivary Cortisol Rhythm in a Population-Based Sample of Cases With Chronic Fatigue Syndrome. Psychosom Med 2008. https://pubmed.ncbi.nlm.nih.gov/18378875/
- Bateman Horne Center. 10 Minute Lean Test | Instructions for Providers. http://batemanhornecenter.org/wp-content/uploads/2016/09/NASA-LeanTest-Instructions-April-2018.pdf
- Rowe, P. General Information Brochure On Orthostatic Intolerance And Its Treatment. March 2014. https://www.dysautonomiainternational.org/pdf/RoweOIsummary.pdf

B. Tests to Support Disability Application

Objective tests are a critical part of a successful disability case. Two tests that have been particularly helpful include:

- Neuropsychological evaluation to evaluate neurocognitive impairment
- 2-day cardiopulmonary exercise testing to evaluate functional Impairment and post-exertional malaise (Stevens)

Note that these tests have distinctive findings for ME/CFS and need to be interpreted by someone knowledgeable about both the test and ME/CFS. These tests are expensive, can trigger an episode of post-exertional malaise, and may not be covered by insurance. But the tests are objective and have been successfully used in disability cases when other parts of the medical record were questioned. Other objective tests that have been used as evidence in disability cases include Tilt Table test, EEGs, QEEGs, SPECT scans, PET scans, and MRIs (Podell).

References:
- Stevens S, Snell C, Stevens J, Keller B, VanNess JM. Cardiopulmonary exercise test methodology for assessing exertion intolerance in myalgic encephalomyelitis/chronic fatigue syndrome. Front Pediatr. 2018 Sep 4;6:242
- Podell R, Dimmock ME, Comerford BB. Documenting disability in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Work. 2020;66(2):339-352. doi: 10.3233/WOR-203178

C. Advanced Tests to Further Characterize ME/CFS or Guide Treatment

Note: These tests may require specialized labs and/or collection procedures

Test Category / Name	Who should get the test?	Why use - e.g. guide treatment	Additional details on what to order, what labs, etc
Autonomic Dysfunction and Orthostatic intolerance			
Skin biopsy for small fiber neuropathy	All with clinical presentation of peripheral neuropathy, autonomic dysregulation, widespread pain and sensory amplification	Small fiber polyneuropathy (SFPN) Objective evidence of illness. Leads to additional testing for causes of SFPN. Consider treatment with IVIG - refer to specialist	The differential of SFPN causes is nicely outlined in: Scientific Advances in and Clinical Approaches to Small-Fiber Polyneuropathy: A Review. Oaklander AL, Nolano M. JAMA Neurol. 2019 Sep 9. doi: 10.1001/jamaneurol.2019.2917
Infections - pathogens associated with onset of post-viral or post-infectious syndromes			
Epstein Barr Virus panel	Mono-like onset or clinical presentation of EBV reactivation	A rationale for trying chronic antiviral therapy	Order EBV VCA IgG, VCA IgM, Early Ag ab, Nuclear Ag ab--- all quantitative. Reactivation or chronic infection may be associated with positive EBV PCR, persistent or recurrent IgM and high levels of Early Ag IgG, very high VCA IgG. Treatment is not FDA approved nor scientifically proven in trials to be effective
Cyto-	Mono-like or flu-like onset of ME/CFS with	Complications of CMV infection,	Ideally CMV IgM should be identified in early

megalovirus IgG, IgM	severe widespread pain, neuropathic, encephalopathic or GI symptoms	unusual in the immunocompetent person, may warrant treatment with valganciclovir or other CMV drugs	stages of illness, otherwise very high CMV IgG in chronic setting might support (but not prove) a chronic or reactivating CMV infection
Human Herpesvirus 6 (HHV-6)	Past history of encephalitis-like illness, or MS-like illness, or seizures	Establish “load” of herpes virus exposure as justification for trial of antiviral drugs	IgG is positive in most people and is not diagnostic of ME/CFS. Consider PCR as an alternate way of evaluating for chronic infection or reactivation
Herpes Simplex 1 & 2 IgG	Clinical presentation of frequent outbreaks of HSV, or in combination with other herpes family virus reactivation	Indirect support for chronic viral reactivation and opportunity to treat with chronic antiviral therapies	Prolonged suppression of HSV outbreaks can improve quality of life and may reduce the immune activation associated with viral outbreaks. Chronic antiviral therapy indicated for frequent HSV outbreaks
Parvovirus B19 IgG, IgM	Illness onset with polyarthralgia or exposure to ParvoB19	Consideration of IVIG as a primary intervention	This would be off label use with weak scientific support in ME/CFS
Enterovirus panel: Coxsackie, Echovirus	ME/CFS with comorbid GI symptoms interested in pursuing non-FDA approved treatments	Consider a trial of oxymatrine (Equilibrant is one product)	Coxsackievirus B1-6 and Echovirus 6,7,9,11, 30 antibodies (ARUP labs); if any titer is higher than 1:320, any tissue biopsy can be stained by immunoassay for enterovirus protein and double-stranded RNA (available via John Chia lab)
West Nile Virus IgG, IgM	High risk or high suspicion of WNV infection or exposure	Objective evidence of underlying pathogen possibly contributing to cognitive symptoms	No specific treatments are available for acute WNV infection, but awareness of possible WNV neurologic complications could be helpful

Other infections: Chlamydia pneumoniae, Mycoplasma pneumoniae, Mycoplasma fermentans, Giardia, Coccidioides, Lyme, Bartonella, Brucella, etc	Patients with suggestive clinical presentation, geography, epidemiological risk factors	Identification of potentially treatable active or chronic infections	Consider appropriate treatment regimens
Immunological Aspects			
Total immuno-globulins: IgG, IgM, IgA, total IgE if clinically indicated; IgG subclasses 1-4	Clinical presentation of immune deficiency or chronic immune activation	Identify potential treatment with IVIG, estimate clinical risk, objective evidence of illness	Abnormalities may justify referral to an immunologist and/or insurance coverage of chosen treatments
Circulating immune complex panel	Useful only if highly sensitive radioimmunoassay used		
Natural Killer Cell function	Supporting evidence in most patients meeting criteria	Objective sign/support of chronic illness, but nonspecific	Run within 24 hours or less, room temp, requires a skilled lab. A few studies have demonstrated that Isoprinosine can improve NK cell function
Vaccine response testing to establish immunodefi-ciency	Clinical presentation suggesting immunodeficiency	Identify possible treatment options. Objective evidence of disease	These tests are typically done by immunologists. There are several protocols. They basically measure antibodies before and after a vaccine to determine the immune system's ability to respond normally
Neurological and Neurocognitive Aspects			

Single-photon emission computerized tomography (SPECT) scan	Clinical presentation of cognitive impairment or neurologic symptoms	Objective evidence of abnormal perfusion in the brain	Can help to further characterize ME/CFS but does not currently inform treatment decisions
Positron emission tomography (PET) scan	Clinical presentation of cognitive impairment or neurologic symptoms	Objective evidence of abnormal perfusion in the brain	Can help to further characterize ME/CFS but does not currently inform treatment decisions
Magnetic Resonance Spectroscopy (MRS)	Clinical presentation of cognitive impairment or neurologic symptoms	Objective evidence of abnormal perfusion in the brain	Can help to further characterize ME/CFS but does not currently inform treatment decisions