Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Diagnosis and Management: The Basics and Beyond

Epidemiology and Science of ME/CFS

Diagnostic Criteria for ME/CFS

Physical Exam and Laboratory Workup

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Thursday October 6, 2011

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ME/CFS Overview

- A complex fatiguing disorder of unknown etiology that persists for a minimum of six months
- Acute or gradual onset
- The debilitating fatigue is accompanied with multiple symptoms, such as:
  - Cognitive problems
  - Sleep disturbances
  - Headaches
  - Depression
  - Muscle and joint pain
  - Low-grade fever
  - Recurrent sore throat
- No diagnostic test available
- No known cure

Prevalence of ME/CFS

- Prevalence in the USA
  - Estimated 400/100,000 = over 1 million patients (CDC 2007)
- Prevalence in Sweden
  - Estimated 40,000 Swedes diagnosed

What is Known About Patients with ME/CFS World Wide

- High degree of activity limitation
  - Need help with tasks
- Experience socio-economic disadvantage
  - Permanently unable to work
  - Personal income under $15,000
  - Food insecurity
  - Very weak sense of belonging to the community
  - Experience difficulty in social situations
- Insufficient care
  - Unmet medical care needs
  - Unmet home care needs

Annual Economic Loss Due to CFS/ME

- $ 9 billion USD
- $ 61 billion Swedish Kronor

Activity Limitation

Question	Canadians with ME/CFS	Canadians in General
Need help preparing meals	17%	3%
Need help getting to appointments and running errands	32%	3%
Need help doing housework	35%	5%
Need help with heavy household chores	56%	12%
Need help with personal care	9%	2%
Need help moving about both inside and outside the house	8%	1%

2005 Canadian Community Health Survey

Insufficient Care

Question	Canadians with ME/CFS	Canadians in General
Unmet healthcare needs over the previous 12 months	30%	11%
Unmet home care needs over the previous 12 months (ages 18+)	14%	2%

Socio-Economic Disadvantage

Question	Canadians with ME/CFS	Canadians in General
Permanently unable to work (ages 15-74)	18%	2%
Annual personal income <$15K (ages 15+)	44%	29%
Food insecure	17%	5%
Weak sense of community belonging	19%	10%
Experience difficulty in social situations	27%	5%

2005 Canadian Community Health Survey

ME/CFS Diagnostic Criteria

Classification and Definitions

History of "CFS"

Pre 1980 global

Outbreaks of a disease that caused debilitating fatigue, mental confusion, sleep dysfunction, pain, memory problems
Ramsey coined the term ME and described the disease

1980s to early 90s In the US

Focus on Fatigue *(in Definitions and Classification)*
Incline Village and Lyndonville outbreak
CFS label designated; Holmes case definition
CFS added to ICD-9-CM under "Signs and Symptoms/Malaise and Fatigue"
Fukuda Case Definition for CFS

Mid 90s to 2011

Focus on Neurological, Immunological, Endocrine, Post-exertional Malaise
ICD-10 released. CFS was added to ICD-10 at G93.3 - Nervous System Diseases
Canadian Case Criteria for ME/CFS issued (2003)
2004 and 2011 CFSAC recommendation to classify CFS as neurological in ICD-10-CM
CFSAC recommends ME/CFS for all HHS programs (2011)
ME International Consensus Criteria (ME-ICC) published (2011)

Classification

- International Classification of Disease (ICD)
  - ME/CFS is classified as a neurologic disease in the World Health Organizations ICD
- Do not confuse chronic fatigue with ME/CFS
  - The “fatigue” of ME/CFS is a pathophysiological exhaustion and is only one of many symptoms

Useful ICD 9 CM Diagnostic Codes

ICD 9 CM Diagnosis Code	Description
780.71	Chronic Fatigue Syndrome
078.5	Cytomegaloviral disease
079.5	Retrovirus
780.79	Other malaise and fatigue: Asthenia NOS, Lethargy, Postviral (asthenic) syndrome, Tiredness
279.06	Common variable immunodeficiency Dysgammaglobulinemia (acquired) (congenital) (primary) Hypogammaglobulinemia: acquired primary, congenital non-sex-linked, sporadic
729.1	Myalgia and myositis, unspecified Fibromyositis NOS
058.21	HHV-6 encephalitis
058.81	HHV-6 infection
058.12	HHV-7 infection
202.80	Other malignant lymphomas unspecified site

ICD-10 Code Recommendations from leaders in the field:

- ***Before ICD-10-CM is implemented in 2013:***

- Move CFS from “Signs and Symptoms/Chronic Fatigue Unspecified” to G93.3 under “Diseases of the Nervous System”
- Do not split ME/CFS cases into ME for viral triggers and CFS for bacterial or other pathogens. Use the same code for ME and CFS.

ME/CFS Definitions

- Center for Disease Control (CDC)
  - The 1988 CFS Research Case Definition
  - The 1994 International Case Definition (Fukuda)
- Canadian Consensus Document (2003)
- ME International Consensus (2011)

CDC - The 1994 International Case Definition (Fukuda)

- This document provides a comprehensive, systematic, and integrated approach for the evaluation, classification, and study of persons with ME/CFS and other fatiguing illnesses
- Two criteria must be met:
  1. Clinically evaluated, unexplained, persistent or relapsing chronic fatigue that is of new or definite onset, is not the result of ongoing exertion, is not substantially alleviated by rest, and results in substantial reduction in previous levels of occupational, educational, social, or personal activities
  2. Concurrently have four or more of the following symptoms:
     - Post-exertional malaise
     - Impaired memory or concentration
     - Unrefreshing sleep
     - Muscle pain
     - Multi-joint pain without redness or swelling
     - Tender cervical or axillary lymph nodes
     - Sore throat
     - Headache
- The symptoms must have persisted or recurred during six or more consecutive months of illness and must not have predated the fatigue

Fukudama et al, *Annals of Internal Medicine*, Vol. 121, December 15, 1994, pp. 953-959.

Canadian Consensus Document ME/CFS Clinical Case Definition

A patient with ME/CFS will meet the following criteria:

1. Fatigue
2. Post-exertional malaise and/or fatigue
3. Sleep dysfunction
4. Pain
5. Neurological/cognitive manifestations (two or more)
6. At least one symptom from two of the following categories:
   - Autonomic manifestations
   - Neuroendocrine manifestations
   - Immune manifestations
7. Illness duration > 6 months with a distinct onset

Carruthers , et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. Journal of Chronic Fatigue Syndrome, Vol. 11(1) 2003.

ME International Consensus 2011: The four components

- Post-Exertional Neuroimmune Exhaustion
- Neurological Impairments
- Immune Impairments
- Energy Production / Transport Impairments

Carruthers, et al (2011), Myalgic encephalomyelitis: International Consensus Criteria. Journal of Internal Medicine, 270: 327–338. doi: 10.1111/j. 1365-2796.2011.02428.x

Post-Exertional Neuroimmune Exhaustion (2011 Consensus)

- The inability to produce sufficient energy on demand with prominent symptoms in the neruoimmune regions. Characteristics are:
  - Rapid physical and/or cognitive fatigability in response to exertion
  - Post-exertional symptom exacerbation: including flu-like symptoms, pain, and worsening of other symptoms
  - Post-exertional exhaustion that may occur right after exertion or be delayed for hours or days.
  - Recovery period is prolonged (usually 24 hours or greater)
  - Low threshold of physical and mental fatigability.

Carruthers, et al (2011), Myalgic encephalomyelitis: International Consensus Criteria. Journal of Internal Medicine, 270: 327–338. doi: 10.1111/j.1365-2796.2011.02428.x

Neurological Impairments: At least one symptom from three of the following four categories (2011 Consensus)

- Neurocognitive Impairment
- Pain
- Sleep Disturbance
- Neurosensory, Perceptual and Motor Disturbances

Carruthers, et al (2011), Myalgic encephalomyelitis: International Consensus Criteria. Journal of Internal Medicine, 270: 327–338. doi: 10.1111/j.1365-2796.2011.02428.x

Immune, Gastro-intestinal and Genitourinary Impairments
At least one symptom from three of the following five categories (2011 Consensus)

1) Flu-like symptoms that may be chronic or recurrent and are worse following exertion.
2) Viral susceptibility with prolonged recovery
3) Gastro-intestinal tract discomfort and dysfunction
4) Genitourinary dysfunction
5) New or increased sensitivities to food medication, odors, and chemicals

Carruthers, et al (2011), Myalgic encephalomyelitis: International Consensus Criteria. Journal of Internal Medicine, 270: 327–338. doi: 10.1111/j.1365-2796.2011.02428.x

Energy Production/Transport Impairments: At least one at least one of the following symptoms. (2011 Consensus)

1) Cardiovascular: orthostatic intolerance, neurally mediated hypotension, POTS, palpitations with or without cardiac arrhythmias, light headedness/ dizziness.
2) Respiratory: Labored breathing, fatigue of chest walls and muscles of respiration.
3) Loss of thermostatic stability
4) Intolerance of extreme temperatures

Carruthers, et al (2011), Myalgic encephalomyelitis: International Consensus Criteria. Journal of Internal Medicine, 270: 327–338. doi: 10.1111/j.1365-2796.2011.02428.x

Canadian Consensus Document ME/CFS Clinical Case Definition (2003): "A Tried and Trusted Working Clinical Model"

A patient with ME/CFS will meet the following criteria:

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Carruthers , et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. Journal of Chronic Fatigue Syndrome, Vol. 11(1) 2003.

1. Fatigue

- Significant degree of physical and cognitive fatigue
  - New onset
  - Unexplained
  - Persistent
  - Recurrent
- Fatigue substantially reduces activity level
  - Activity level is reduced by approximately 50% or more
  - Some can be housebound or bedridden

Carruthers , et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. Journal of Chronic Fatigue Syndrome, Vol. 11(1) 2003.

2. Post-Exertional Malaise and/or Fatigue

- Inappropriate loss of physical and mental endurance
- Rapid muscular and cognitive fatigability
- Tendency for other associated symptoms to worsen after activity
- Pathologically slow recovery period – usually 24 hours or longer

Carruthers , et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. Journal of Chronic Fatigue Syndrome, Vol. 11(1) 2003.

3. Sleep Dysfunction

- Unrefreshed sleep, or
- Sleep quantity, or
- Rhythm disturbances, such as reversed or chaotic diurnal sleep rhythms

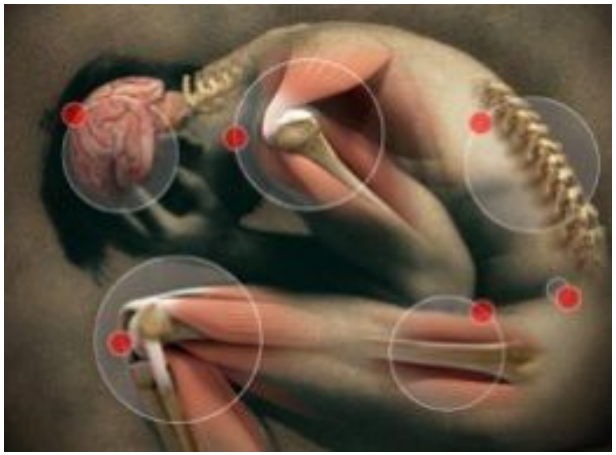
A small number of patients have no sleep dysfunction

Carruthers , et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. Journal of Chronic Fatigue Syndrome, Vol. 11(1) 2003.

4. Pain

- Significant degree of myalgia
- Pain in the muscles and/or joints, often widespread and migratory in nature
- Significant headach pattern, or severity

A small number of patients have no pain



Carruthers , et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. Journal of Chronic Fatigue Syndrome, Vol. 11(1) 2003.

5. Neurological/Cognitive Manifestations

- **Two or more** of the following should be present:
  - Confusion
  - Impairment of concentration and short term memory consolidation
  - Disorientation
  - Difficulty with information processing, categorizing and word retrieval
  - Perceptual and sensory disturbances (spatial instability, disorientation, inability to focus vision)
  - Ataxia, muscle weakness, and fasciculations
  - Overload phenomena: cognitive, sensory, emotional

Carruthers , et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. Journal of Chronic Fatigue Syndrome, Vol. 11(1) 2003.

6. Additional Symptoms

At least **one** symptom from **two** of the following categories:

Autonomic Manifestations

- Orthostatic intolerance - NMH, POTS delayed postural hypotension
- Light-headedness
- Extreme pallor
- Nausea and irritable bowel syndrome
- Urinary frequency and bladder dysfunction
- Palpitations with or without cardiac arrhythmias
- Exertional dyspnea

Neuroendocrine Manifestations

- Loss of thermostatic stability
- Marked weight change
- Loss of adaptability and worsening of symptoms with stress

Immune Manifestations

- Tender lymph nodes
- Recurrent sore throat
- Recurrent flu-like symptoms
- General malaise
- New sensitivities to food, medications, and/or chemicals

Carruthers , et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. Journal of Chronic Fatigue Syndrome, Vol. 11(1) 2003.

7. Illness Duration

- Illness persists for at least 6 months
- Usually a distinct onset, although it may be gradual
- Preliminary diagnosis may be possible earlier than 6 months
- Illness duration of 3 months is appropriate for children

Some patients may have been unhealthy for other reasons prior to onset of ME/CFS and lack detectable triggers, and/or have more gradual or insidious onset

Carruthers , et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. Journal of Chronic Fatigue Syndrome, Vol. 11(1) 2003.

Exclusions

- All active disease processes that explain major symptoms
  - Specific diseases:
    - Addison's disease
    - Cushing's disease
    - Hypo- or hyperthyroidism
    - Iron deficiency or iron overload syndrome
    - Other treatable forms of anemia
    - Diabetes mellitus
    - Cancer
  - Treatable sleep disorders
  - Rheumatological disorders
  - Immune disorders
  - Neurological disorders
  - Infectious diseases
  - Primary psychiatric disorders
  - Substance abuse

Carruthers , et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. Journal of Chronic Fatigue Syndrome, Vol. 11(1) 2003.

Co-morbid Entities

- Fibromyalgia Syndrome (FMS)
- Myofascial Pain Syndrome (MPS)
- Temporomandibular Joint Syndrome (TMJ)
- Irritable Bowel Syndrome (IBS)
- Interstitial Cystitis
- Irritable Bladder Syndrome
- Raynaud's Phenomenon
- Prolapsed Mitral Valve
- Depression
- Migraine
- Allergies
- Multiple Chemical Sensitivities
- Hashimoto's Thyroiditis
- Sicca Syndrome

Carruthers , et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. Journal of Chronic Fatigue Syndrome, Vol. 11(1) 2003.

Idiopathic Chronic Fatigue

- If a patient has unexplained fatigue for longer than 6 months and does not meet the diagnostic criteria for ME/CFS, classify as idiopathic chronic fatigue

Carruthers , et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. Journal of Chronic Fatigue Syndrome, Vol. 11(1) 2003.

Definition Comparison

- Jason, et al compared patients meeting the Canadian clinical criteria and Fukuda criteria for ME/CFS against control patients with chronic fatigue due to depression
- In summary, patients meeting the Canadian criteria appear to have more symptoms, more physical functional impairment, and less psychopathology compared to those in the CF-psychiatric group
- In addition, the Canadian criteria identifies patients with more fatigue/ weakness, neurological and neuropsychiatric symptoms than the Fukuda CFS criteria

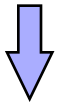
Jason L, et al. Comparing the Fukuda et al. Criteria and the Canadian Case Definition for Chronic Fatigue Syndrome. Journal of Chronic Fatigue Syndrome, Vol. 12(1) 2004. 37-52.

Epidemiology and Science of ME/CFS

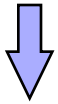
Infectious, Immune, Endocrine, Autonomic, Exercise, and Sleep Research

Model of ME/CFS Pathogenesis

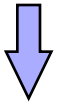
Genetic Predisposition



Triggering event / infection



Mediators (Immune, endocrine, neuroendocrine, psychosocial, viral reactivation or persistence)



ME/CFS

NKlimas-2007 Immunology and Infection

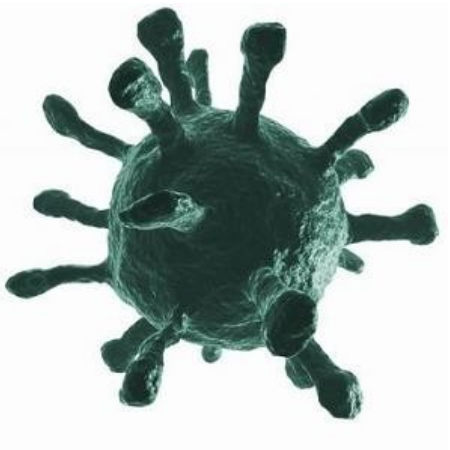
Summary of Genetic Predisposition Research for ME/CFS

- HLA DR haplotypes in 112 South Florida CFS patients, compared to 5,000 regional and national controls [1]
- 4 to 6 fold increased relative risk for DR4, DR3 and DQ3 (Keller et al. 1992)
- Seattle CFS Cooperative Research Center Twin study - genetic predisposition, hereditability estimate of 51% (2nd World Conf); similar results in Sweden, Australian studies

1. NKlimas-2007 Immunology and Infection

Summary of ME/CFS Infectious Research

- Viral infections associated with ME/CFS:
  - Epstein-Barr Virus [1]
  - Cytomegalovirus [1]
  - Human Herpesvirus-6 [1]
  - Human Herpesvirus-7 [1]
  - Enteroviruses [1]
  - Parvovirus B19 [1]
  - XMRV [4]
- Dysregulation of the 2-5A synthetase/ribonuclease L (RNase pathway in monocytes [2]
- Bacterial infections associated with ME/CFS:
  - Chlamydia [3]
  - Mycoplasma [3]



ME/CFS Infectious References

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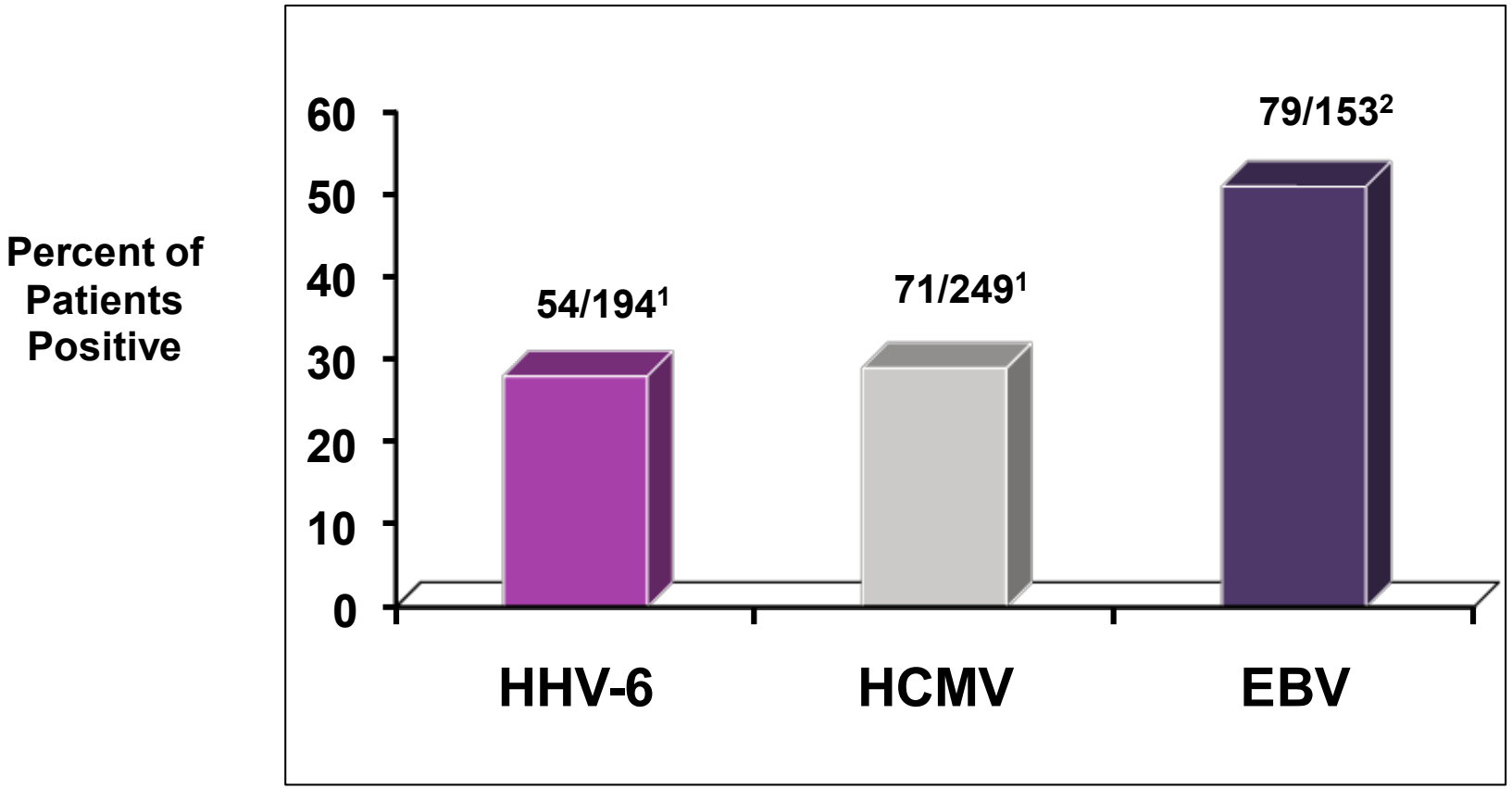
2. Klimas NG, Koneru AO. Chronic fatigue syndrome: inflammation, immune function, and neuroendocrine interactions. Curr Rheumatol Rep. 2007 Dec;9 (6):482-7.
3. Nicolson GL, et al. Diagnosis and integrative treatment of intracellular bacterial infections in chronic fatigue and fibromyalgia syndromes, Gulf War illness, rheumatoid arthritis and other chronic illnesses. *Clin Pract Altern Med* 2000;1(2):42-102.
4. V. C. Lombardi et al. Detection of an Infectious Retrovirus, XMRV, in Blood Cells of Patients with Chronic Fatigue SyndromeScience 326, 585 (2009).
5. Knox, K., et al. Systemic Leukotropic Herpesvirus Infections and. Reston, VA. Autoantibodies in Patients with Myalgic Encephalomyelitis – Chronic Fatigue Syndrome. 7th International Conference on HHV-6 and 7. March 1, 2011

ME/CFS Infectious Research

Herpesvirus Infections in Blood Samples from Clinic Patients with ME/CFS



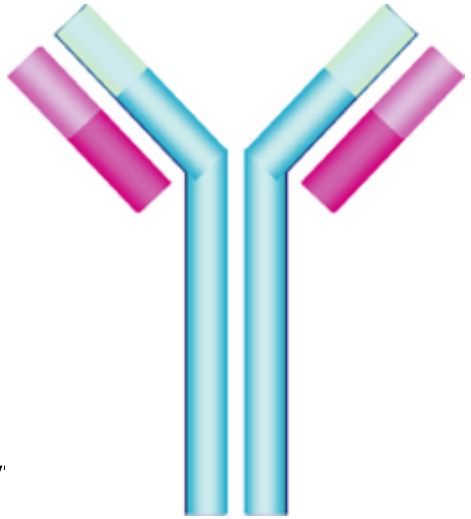
[1] Positive antigenemia or culture

[2] EBNA-1 IgG titer >4000 units/ml

Knox, K., et al. Systemic Leukotropic Herpesvirus Infections and. Reston, VA. Autoantibodies in Patients with Myalgic Encephalomyelitis – Chronic Fatigue Syndrome. 7th International Conference on HHV-6 and 7. March 1, 2011

Summary of ME/CFS Immune Research

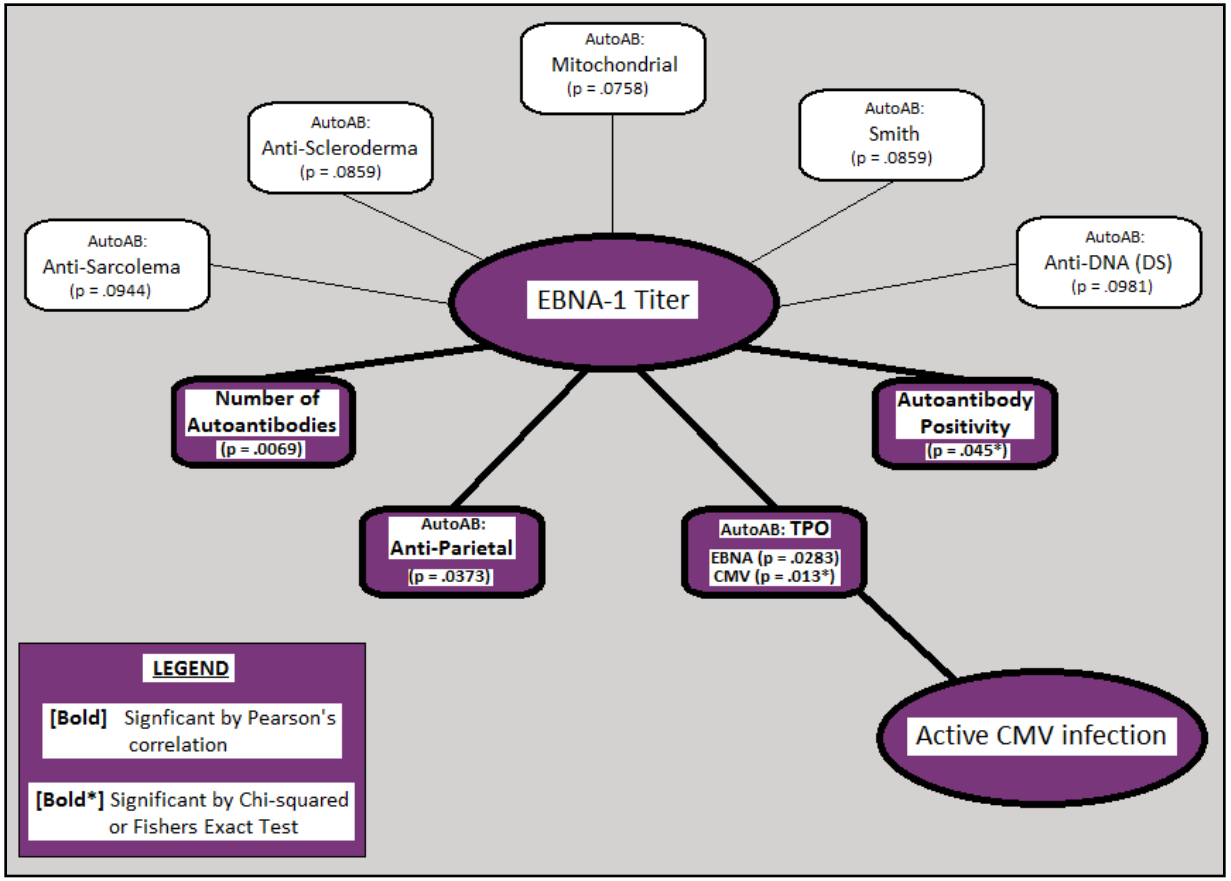
- Functional defects
  - Antiviral enzyme (RNase L) dysfunction
  - Low natural killer (NK) cell numbers and function
  - CD8 abnormalities
  - Decreased perforins and granzymes
  - Macrophage abnormalities
  - Antibody production
- Immune activation
  - Increased numbers of activated T cells
  - Increased production of inflammatory cy chemokines
  - DR, CD26 expression



Klimas NG, Koneru AO. Chronic fatigue syndrome: inflammation, immune function, and neuroendocrine interactions. Curr Rheumatol Rep. 2007 Dec;9(6):482-7.

ME/CFS Immune Research

Evaluation of HHV-6, CMV, EBV infections and autoantibodies in 90 ME/CFS patients



Knox, K., et al. Systemic Leukotropic Herpesvirus Infections and Autoantibodies in Patients with Myalgic Encephalomyelitis – Chronic Fatigue Syndrome. 7th International Conference on HHV-6 and 7. March 1, 2011. Reston, VA.

Summary of ME/CFS Endocrine Research

- Hormonal alterations in adolescent ME/CFS[1]
  - Plasma ADH was significantly decreased
  - Increased serum osmolality and plasma renin activity
- Hypothalamic-Pituitary-Adrenal Axis Function[2]
  - Despite contradicting studies, there is evidence of mild hypocortisolism, blunted ACTH responses and enhanced negative glucocorticoid feedback in a portion of patients with ME/CFS

1. Wyller VB, Evang JA, Godang K, Solhjell KK, Bollerslev J. Hormonal alterations in adolescent chronic fatigue syndrome. Acta Paediatr. 2010 May;99(5):770-3. Epub 2010 Mar 1.
2. Van Den Eede F, Moorkens G, Van Houdenhove B, Cosyns P, Claes SJ. Hypothalamic-pituitary-adrenal axis function in chronic fatigue syndrome. Neuropsychobiology. 2007;55(2):112-20

Summary of ME/CFS GI Research

- Patients with ME/CFS are likely to report a previous diagnosis of irritable bowel syndrome (IBS) and experience IBS-related symptoms [1]
- Altered gut microbiota [2]
- Increased gut-intestinal permeability [3]
  - Translocation of LPS provokes immune response increasing serum IgA and IgM antibodies
- Altered fecal microbiota [4,5]
- High levels of H2S caused by intestinal overgrowth may play a major role in ME/CFS and lead to a series of reactions that leave cells devoid of oxygen and energy[6]

ME/CFS GI References

1. Aaron LA, et al. Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. Arch Int Med 2000, 160:221-227.
2. Logan A, Rao V, Irani D. Chronic fatigue syndrome: lactic acid bacteria may be of therapeutic value. Med Hypotheses 2003, 60:915-923.
3. Maes, et al. Increased serum IgA and IgM against LPS of enterobacteria in chronic fatigue syndrome (CFS): indication for the involvement of gram-negative enterobacteria in the etiology of CFS and for the presence of an increased gut-intestinal permeability.J Affect Disord. 2007 Apr;99(1-3):237-40.
4. Sheedy JR, et al. Increased d-lactic acid intestinal bacteria in patients with chronic fatigue syndrome. In Vivo 2009, 23:621-628
5. Butt HL, et al. Bacterial colonosis in patients with persistent fatigue. Proceedings of the AHMF international clinical and scientific conference Sydney, Australia 2001.
6. Kenny De Meirleir

Summary of ME/CFS Cardiovascular Research

- A characteristic repetitively oscillating T-wave inversions and/or T-wave flattening during 24 hour monitoring [1,2]
- Decreased vagal activity [3]
- Orthostatic Intolerance [4, 5, 6]
  - POTS [7]
  - Neurally mediated hypotension [8, 9]
- Decreased total blood volume [10]
- Lower blood pressure and abnormal diurnal blood pressure regulation [11]
- Reduced cardiac stroke volume and cardiac output [12]

ME/CFS Cardiovascular References

1. Lerner AM, et al. Repetitively negative T waves at 24-h electrocardiographic monitors in patients with the Chronic Fatigue Syndrome. Chest 1993, Nov;104(5):1417-142
2. Lerner AM, et al. Cardiac involvement in patients with chronic fatigue syndrome as documented with Holter and biopsy data in Birmingham, Michigan, 1991-1993. Infect Dis Clin Pract1997;6:327-333
3. Codero DL, et al. Decreased vagal power during treadmill walking in patients with chronic fatigue syndrome. Clin Auton Res 1996 Dec;6(6):329-333
4. Rowe PC, Calkins H. Neurally mediated hypotension and chronic fatigue syndrome. Am J Med 1998;105 (3A):15S-21S
5. De Becker P, et al. Autonomic testing in patients with chronic fatigue syndrome. Am J of Med 1998; 105(3A):22S-26S
6. Schondorf R, Freeman R. The importance of orthostatic intolerance in the chronic fatigue syndrome. Am J Med Sci 1999;317:117-123
7. Hoad A, Spickett G, Elliott J, Newton J. Postural orthostatic tachycardia syndrome is an under recognized condition in chronic fatigue syndrome. QJM. 2008 Dec;101(12):961-5. Epub 2008 Sep 19.
8. Bou-Holaigah I, Rowe PC, Kan J,Calkins H. The relationship between neurally mediated hypotension and the chronic fatigue syndrome. JAMA. 1995 Sept 27;274(12): 961-967
9. Rowe PC, Bou-Holaigah I, Kan JS, Calkins H. Is neurally mediated hypotension an unrecognised cause of chronic fatigue? Lancet 1995;345:623-624
10. Streeten DHP, Bell DS. Circulating blood volume in chronic fatigue syndrome. J CFS 1998;4(1): 3-11
11. Newton JL, Sheth A, Shin J, Pairman J, Wilton K, Burt JA,Jones DE. Lower ambulatory blood pressure in chronic fatigue syndrome. Psychosom Med. 2009 Apr;71(3):361-5. Epub 2009 Mar 17.
12. Hurwitz BE et al. Chronic fatigue syndrome: illness severity, sedentary lifestyle, blood volume and evidence of diminished cardiac function. Clin Sci (Lond). 2009 Oct 19;118(2):125-35.

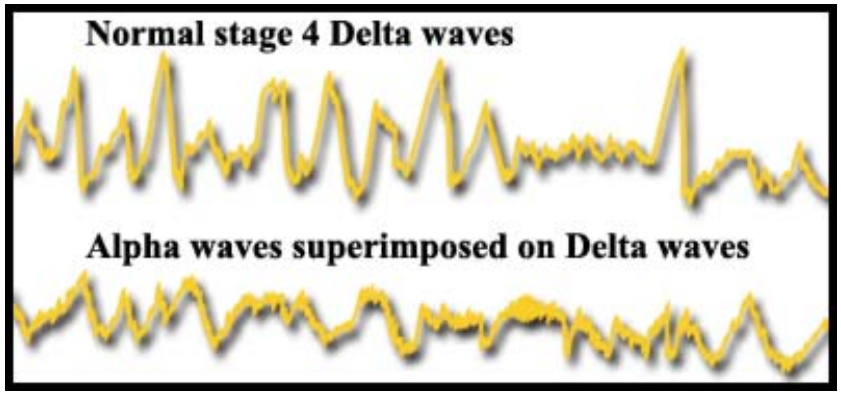
Summary of ME/CFS Exercise Research

- Symptom exacerbation [1]
- Elevated resting heart rate [1]
- Reduced heart rate at maximum workload [1]
- Reduced oxygen uptake [1]
- Decreased cerebral blood flow [1]
- Decreased body temperature [1]
- Breathing irregularities [1]
- Gait abnormalities [1]
- Cognitive function/reaction time is prolonged in post-exertional state [2]
- Increased recovery period [3]

1. Carruthers , et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. Journal of Chronic Fatigue Syndrome, Vol. 11(1) 2003.
2. Snell et al, 2007 3. Stevens et al, 2007

Summary of ME/CFS Sleep Research

- Decrease in the length of periods of uninterrupted sleep [1]
- Alpha intrusion into delta sleep [2]



1. Togo F, et al. Sleep structure and sleepiness in chronic fatigue syndrome with or without coexisting fibromyalgia. Arthritis Res Ther. 2008;10(3):R56.
2. Van Hoof, et al. Defining the occurrence and influence of alpha-delta sleep in CFS. Am J Med Sci. 2007 Feb. 333(2):78-84

Diagnosing ME/CFS

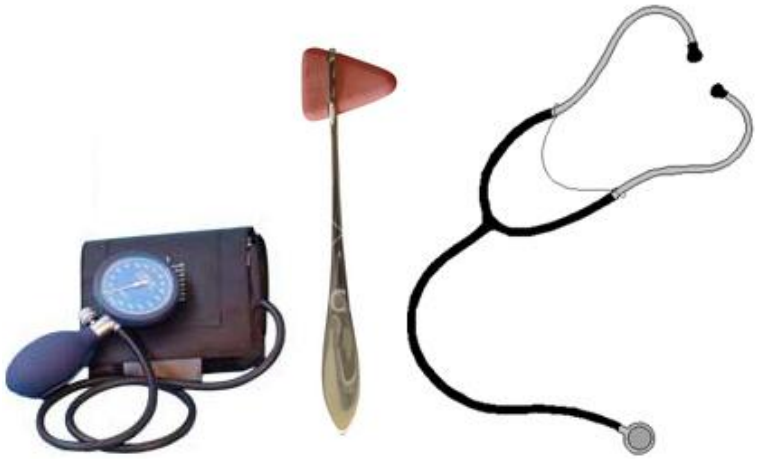
Physical Examination and Laboratory Workup

Diagnosing ME/CFS

- Diagnosis of ME/CFS is primarily one of exclusion
- A detailed and thorough medical history are necessary for the diagnosis
  - Written assessment tools can be given to the patient to fill out ahead of time and reviewed before the patient's first visit
- A vital part of the diagnostic process are the physical exam and laboratory testing

Physical Examination

- Conduct a standard PE with specific attention to:
  - Musculoskeletal system
  - CNS
  - Endocrine system
  - Cardiovascular system
  - GI system
  - Immune system



PE - Musculoskeletal System

- FMS tender point exam
  - Pain on palpation in 11 or more of the 18 designated tender point sites meets FMS diagnosis
- Check joints for inflammation, hypermobility, and restricted movement
- Document muscle strength

PE - CNS

- Reflex examination
- Tandem walk
- Romberg test
- Evaluate cognitive symptoms
  - Ability to remember questions
  - Cognitive fatigue
    - Serial 7 subtraction
  - Cognitive interface
    - Serial 7 subtraction and tandem done simultaneously

PE – Endocrine System

- Examine for signs of dysfunction in the following:
  - Thyroid
  - Adrenal
  - Pituitary

PE – GI System

- Check for the following:
  - Increased bowel sounds
  - Abdominal bloating
  - Abdominal tenderness

PE – Cardiovascular System

- Arrhythmias
- BP
  - Lying down
  - Immediately after standing

PE – Immune System

- Recurrent flu symptoms
- Sore throat
- Crimson crescents in tonsillar fossa
  - Red crescents are demarcated along the margins of both anterior pharyngeal pillars
  - They will assume a posterior position in the oropharynx in patients without tonsils
- Tenderness in the following lymph nodes:
  - Cervical
  - Axillary
  - Inguinal
- General malaise
- Examine for splenomegaly

ME/CFS Laboratory Workup

- Screening Diagnostic Tests
- Specific Studies
- Highly Specific Studies
- Functional Studies
- Neuro Imaging
- Other Useful Studies
- Experimental and Investigational Studies

Screening Diagnostic Tests

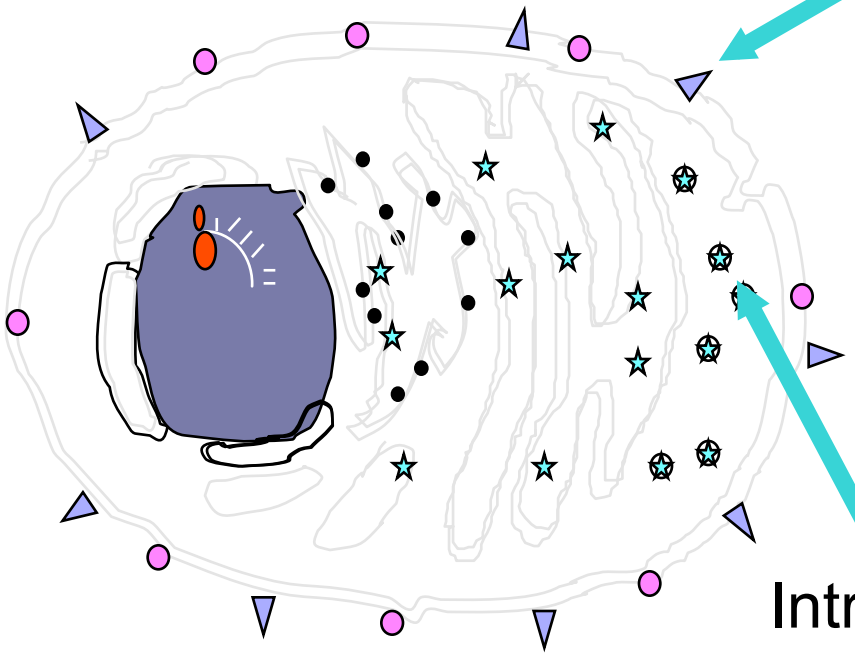
- Access previous lab diagnostics that have been performed
  - Repeat if greater than 3 months and reassess screening diagnostics for any diagnosable and treatable disorders
- Minimum diagnostic workup
  - CBC
  - Chemistry panel
  - UA
  - Thyroid panel
  - Sedimentation rate or equivalent
  - Testosterone
  - FSH and LH level II
- Additional diagnostics (depending on individual clinical presentation)
  - DHEA
  - Cortisol AM and PM
  - ACTH
  - Stool for WBC pathogens
  - Anitgliadin Ab
  - Iron
  - TIBC
  - Ferritin
  - Narcolepsy panel
  - Focused rheumatologic testing (ANA and rheumatoid factor)

Specific ME/CFS Studies

- **Natural killer cell numbers and function**
- Lymph enumeration panel
  - Specifically cytotoxic T cell testing
- B and T-cell function including:
  - IgG and IgG subclasses 1 - 4
  - IgA
  - IgM

Natural Killer Cell

Cell Surface Antigen:
CD56



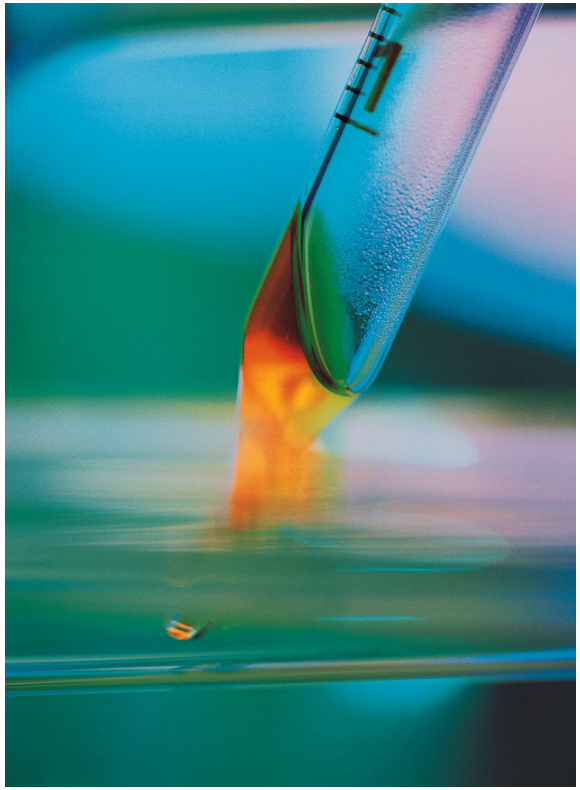
Intracellular
Cytolytic Granules:
* Perforin
* Granzyme A
* Granzyme B

Perforin is a molecule in cytotoxic lymphocytes necessary for killing of virus infected and tumor cells.

Klimas N. Miami VA Medical Center

Highly Specific ME/CFS Studies

- **Cytokine/Chemokine panel**
- **RNase L activity**
- Amino acid profile
- Carnitine panel
- Magnesium
- Mycoplasma panel
- Chlamydia panel
- Determine past viral infections
  - Herpes virus screening panel
    - EBV early antigenemia
    - HHV-6 IgG and IgM
  - Parvovirus IgG and IgM
- Determine active viral infections with viral culture antigenemia and PCR
  - EBV
  - CMV
  - HHV-6
  - HHV-7
  - Parvovirus



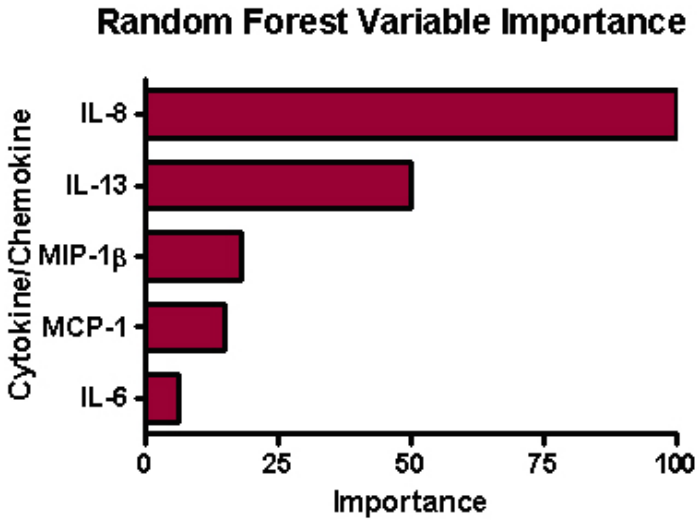
Cytokine & Chemokine Profiling in ME/CFS

- Chronic Innate Immune activation by pathogenic triggers in a genetically susceptible host mediate the pathogenesis through a cytokine/chemokine storm

- Multiplex cytokine arrays afford the opportunity to analyze the complex relationships between the cytokines and clinical disease and to determine if clinical subgroups of disease could be identified based on distinct cytokine profiles

Cytokine & Chemokine Profiling in ME/CFS

- ME/CFS patients can be distinguished from healthy controls with 94% accuracy by measuring 5 Cytokines and Chemokines



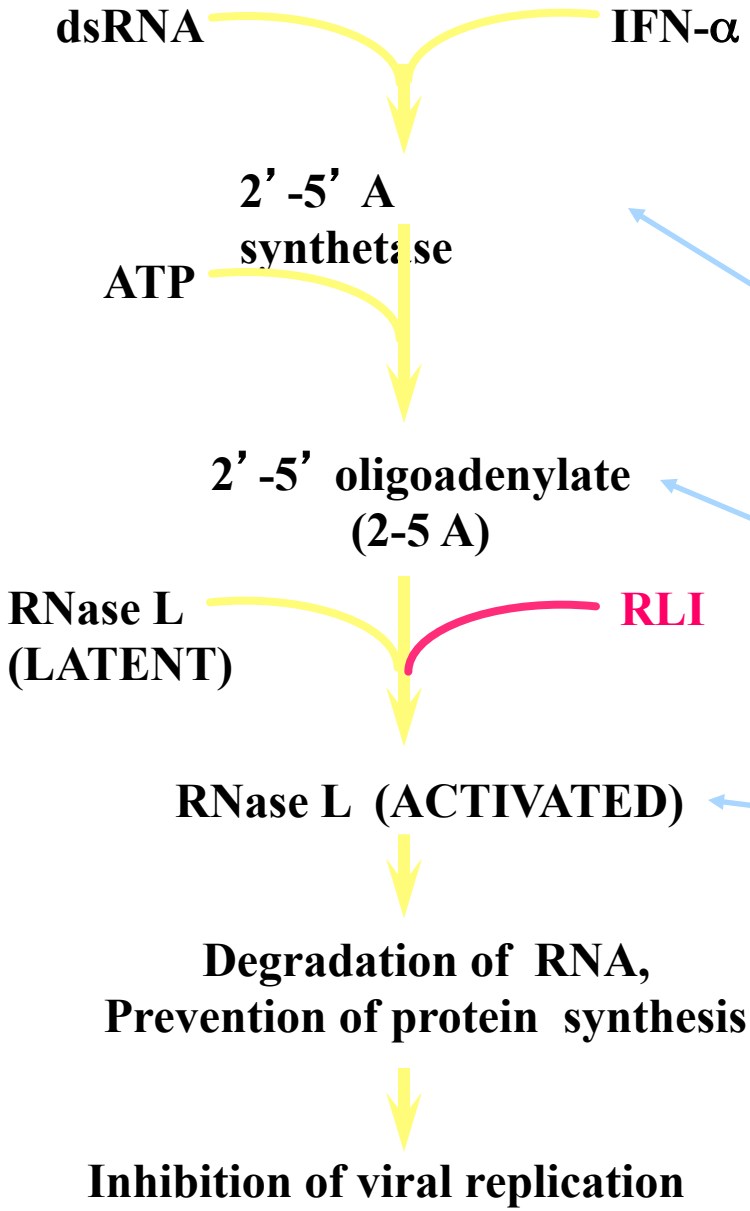
Random Forests Prediction Success

Actual Class	Total Cases	Percent Correct	Control N=141	Patient N=162
Control	138	93.48	129	9
Patient	118	94.92	6	112

2-5A / RNase L Pathway in ME/ CFS

- Positive Clinical Correlation
  - RNase L activity and MSQ score ($p < 0.01$)
    - MSQ = Metabolic Screening Questionnaire
- Negative Clinical Correlations
  - RNase L activity and KPS ($p < 0.002$)
  - Bioactive 2-5A and KPS ($p < 0.025$)
    - KPS = Karnofsky Performance Score

R. J. Suhadolnik et al., *J. Chronic Fatigue Syndromes* *5*, 223 (1999)



Status of the 2-5A synthetase / RNase L pathway in ME/CFS:

- 2-5 A synthetase is activated
- Bioactive 2-5 A is present
- RNase L is activated

Suhadolnik et al, *Clin. Inf. Dis.* 18: S96 (1994)
Suhadolnik et al, *In Vivo* 8: 599 (1994)
Shetzline & Suhadolnik, *J. Biol. Chem.* 276: 23707 (2001)

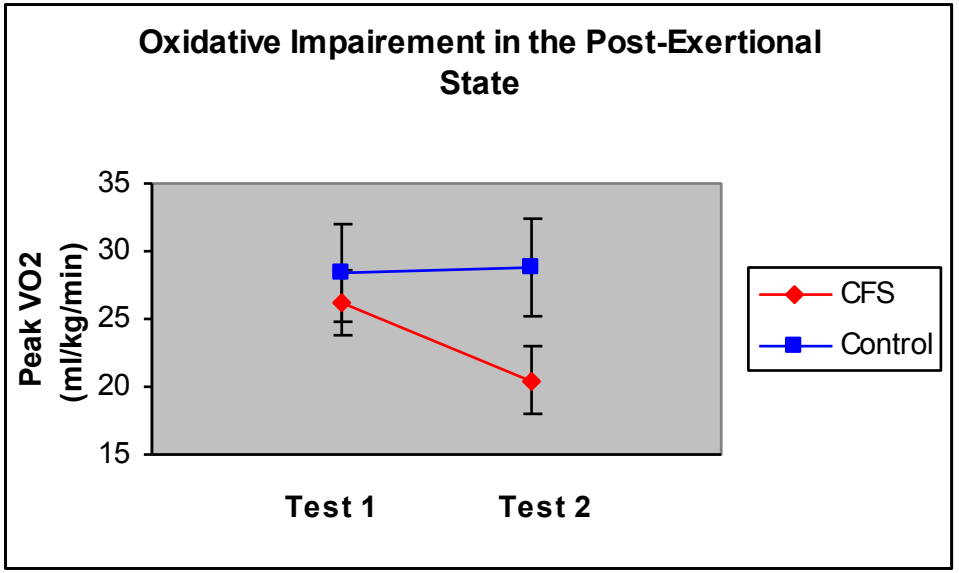
Functional studies

- Sleep study (if indicated)
- Nocturnal oxygen screen
- **Exercise tolerance testing with expired gas exchange**
- Neuropsychometric testing
- SF-36

Exercise Tolerance Testing with Expired Gas Exchange

- Measures cardiovascular, pulmonary and metabolic responses at rest and during exercise
- Used to rule out other cardiopulmonary disease processes

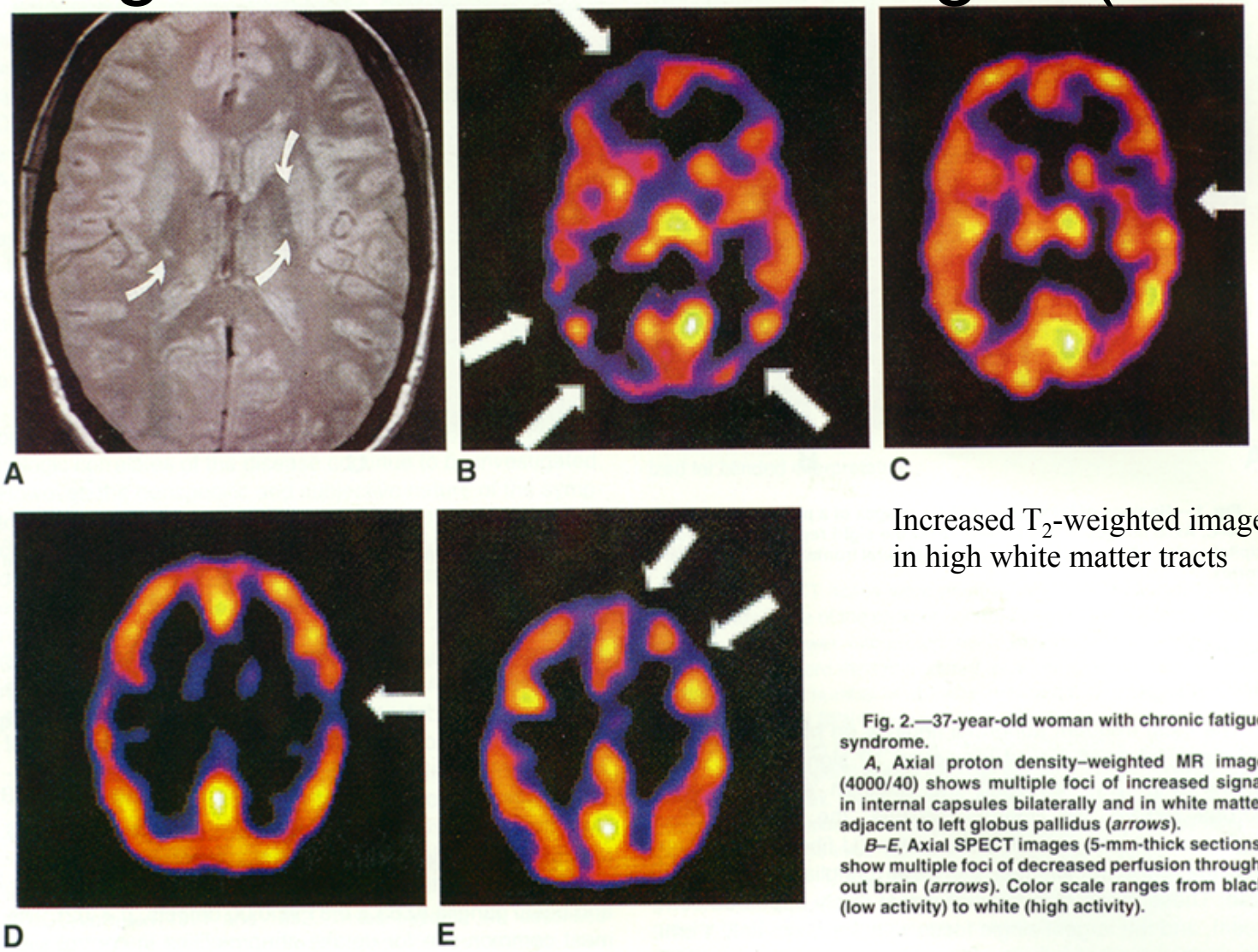
- Key measures:
  - Peak Oxygen Consumption (VO2)
  - Anaerobic Threshold (AT)
  - Heart Rate (HR)
  - Blood Pressure (BP)
  - Ventilation (VE)
- All ME/CFS patients demonstrate low VO2 max



Neuro Imaging

- **MRI with contrast**
- **Brain SPECT scan**
- PET scan

Magnetic Resonance Images (MRI)



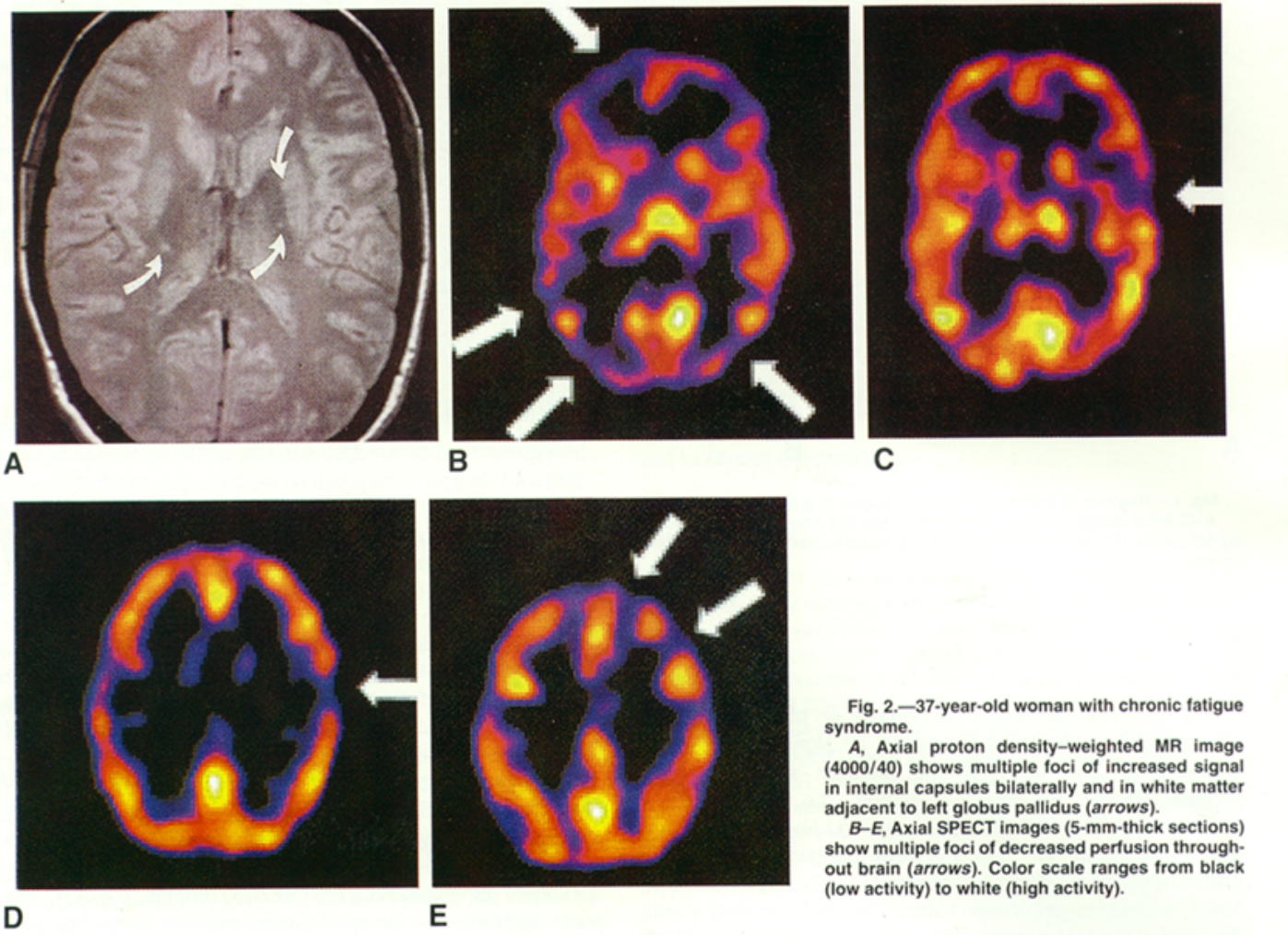
Increased T_2-weighted images in high white matter tracts

Fig. 2.—37-year-old woman with chronic fatigue syndrome.

A, Axial proton density–weighted MR image (4000/40) shows multiple foci of increased signal in internal capsules bilaterally and in white matter adjacent to left globus pallidus (*arrows*).

B–E, Axial SPECT images (5-mm-thick sections) show multiple foci of decreased perfusion throughout brain (*arrows*). Color scale ranges from black (low activity) to white (high activity).

Brain SPECT Scans:
Regional Hypoperfusion



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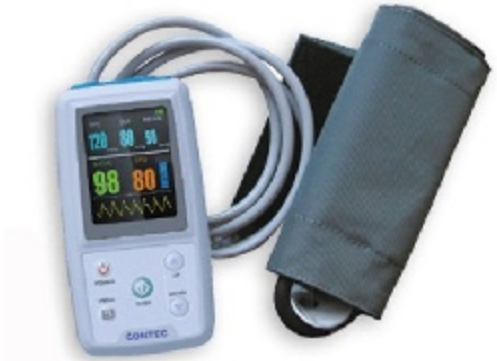
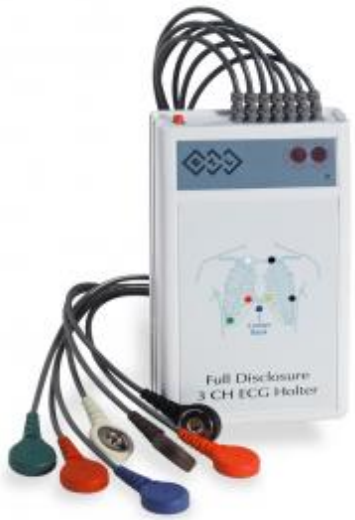
Other Useful Studies

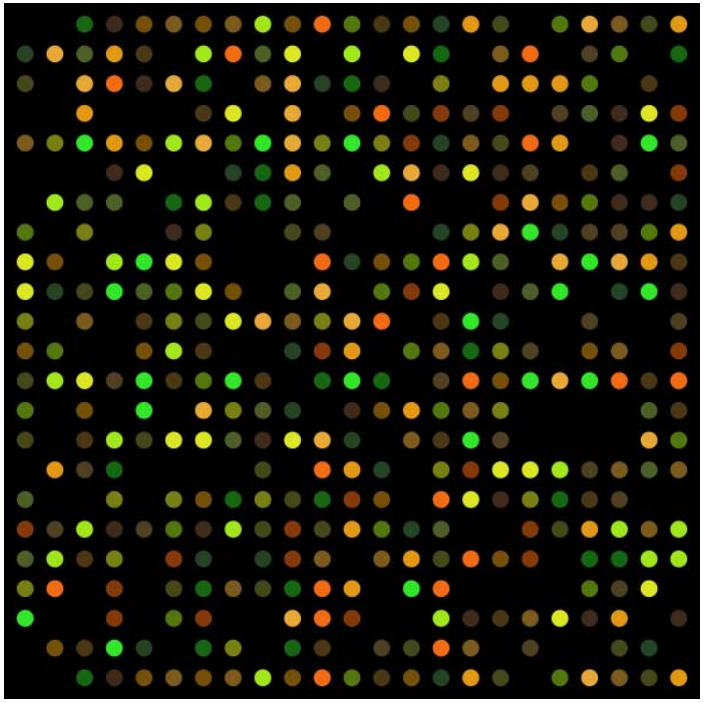
- Lumbar puncture
- 24-hour BP monitor
- Holter monitor





Experimental and Investigational Studies

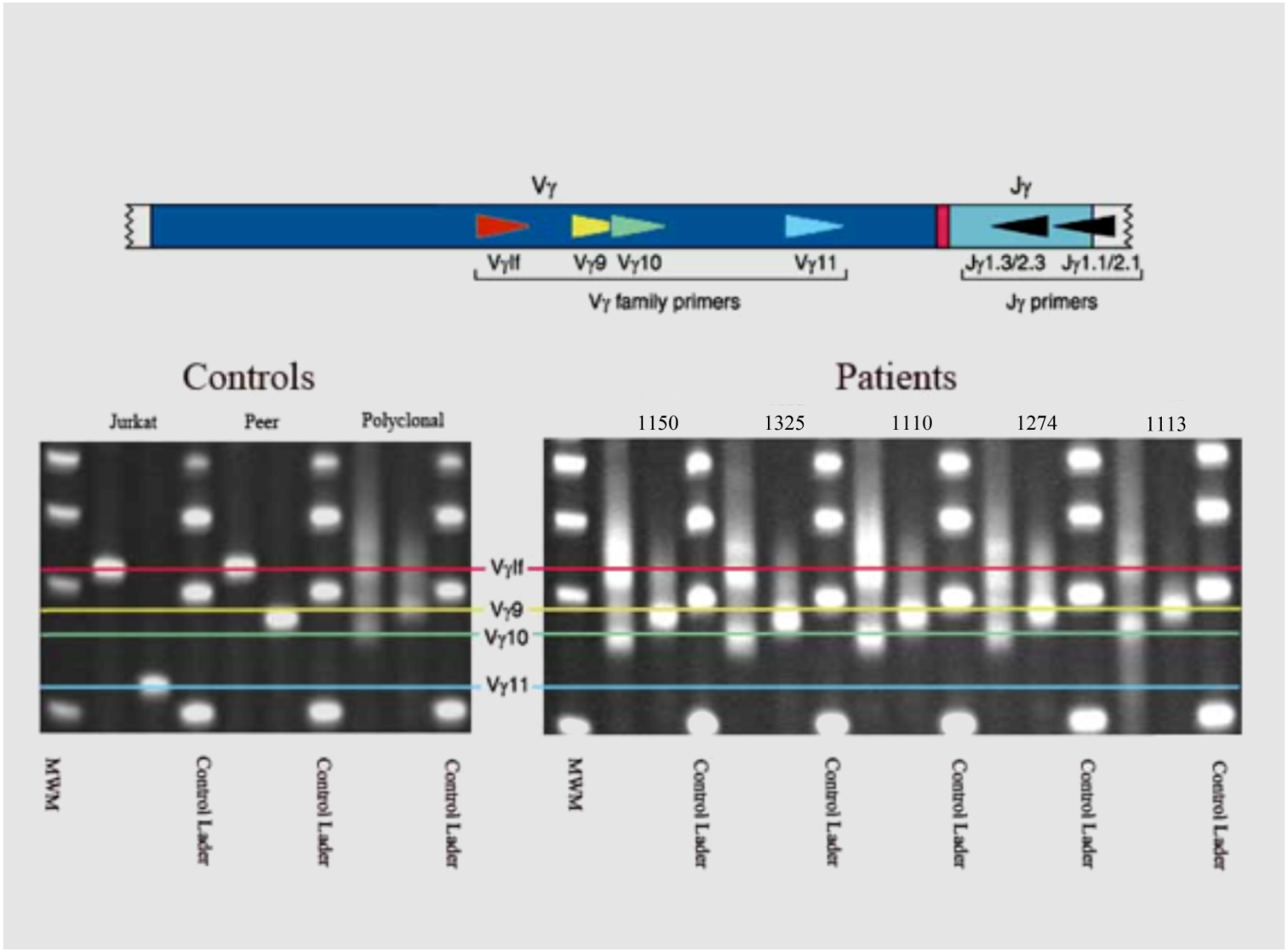
- **TCRγ Rearrangement**
- DNA array
- mRNA array
- Viral array/human pathogen array



Clonal TCRγ Rearrangement Testing

- What are γ T cells?:
  - Play active role in regulation and resolution of pathogen induced immune responses
  - Accumulate at sites of inflammation
  - Associated with Viral, Parasitic and bacterial Infections
  - Associated with autoimmune diseases
  - Upregulate MIP1α,B, TNFα, IL-10, IFNγ
- Rationale for testing:
  - Suggest chronic active infection particularly CMV
  - Predictive of lymphoma development
- Clinical Criteria for Testing:
  - Acute (viral) onset ME/CFS
  - Lymphadenopathy and/or splenomegaly

TCR γ Clonality in Nevada ME/CFS Cohort



Making the Diagnosis

- Making a Positive Diagnosis for ME/CFS
  - If the patient's presentation meets the diagnostic criteria for ME/CFS and no specified exclusions are present, classify the diagnosis as ME/CFS
  - If the patient has prolonged fatigue but does not meet the criteria for ME/CFS, classify the diagnosis as idiopathic chronic fatigue
- New Symptoms
  - ME/CFS patients can develop other medical problems during the course of treatment
  - New symptoms need to be appropriately investigated