

KNOWLEDGE SUMMARY · APRIL 2026 · COMPILED FROM  
PEER-REVIEWED LITERATURE

# ME/*CFS*

## State of the Science

MYALGIC ENCEPHALOMYELITIS / CHRONIC FATIGUE SYNDROME  
· GENETICS · IMMUNOLOGY · METABOLISM · TREATMENT

### ABSTRACT

ME/CFS is a severe, multi-systemic chronic illness affecting an estimated 17–24 million people worldwide. Once dismissed as psychosomatic, the condition is now recognized as a complex neuroimmune and metabolic disorder. The overlap with Long COVID has accelerated research dramatically since 2023. As of early 2026, the field has moved from validating biological reality to mapping specific molecular mechanisms — though no FDA-approved disease-modifying therapy yet exists. This summary synthesizes the strongest findings across genetics, immunology, metabolism, muscle physiology, and emerging treatments.

**17–  
24M**  
ESTIMATED

**>60%**  
REMAIN  
UNDIAGNOSED

**15,000+**  
PARTICIPANTS IN  
DECODEME, THE

PATIENTS WORLDWIDE		LARGEST STUDY TO DATE
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01 / **Genetics**

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**DecodeME: The Largest Study Ever**

In 2025, the DecodeME study — involving over 15,000 UK participants whose DNA was compared against 250,000 controls — established that ME/CFS has a modest but real genetic heritability. The disease is highly polygenic, meaning risk is distributed across many genes each with small individual effects. Crucially, the strongest genetic signals point to the brain: genes like CA10, SHISA6, SOX6, LRRC7, and DCC are involved in neuronal development and inter-neuron communication. This strongly implicates the central nervous system in disease pathology.

**Stanford's Rare Mutation Study**

Mark Snyder's team at Stanford took a complementary approach, hunting for rare genetic variants with large effects rather than common variants. Using a neural network trained on protein interactions, they identified synaptic function — how neurons talk to each other — as a key affected network. This aligns closely with the DecodeME findings and reinforces a neurological model of ME/CFS.

*"Most of the genetic signals point to the brain — genes involved in neuronal development and communication. Theories on ME/CFS will need to*



## 02 / Mitochondria & Energy Metabolism

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### The WASF3 Discovery (NIH, 2023)

A landmark NIH study published in PNAS identified the WASF3 protein as a direct molecular cause of exercise intolerance. Endoplasmic reticulum stress triggers overproduction of WASF3, which then migrates to the mitochondria and physically disrupts the assembly of respiratory supercomplexes (Complex III and Complex IV of the electron transport chain). This blocks ATP production — the cell's energy currency — and explains why patients cannot generate adequate energy. Transgenic mice engineered to overexpress WASF3 displayed rapid-onset exercise intolerance, directly mimicking the human disease.

### Physical Damage to Mitochondrial Architecture

A 2024 study using high-resolution electron microscopy found that ME/CFS patients have structurally degraded mitochondria: the cristae — inner folds where energy generation actually occurs — were physically deteriorated. This is not merely a functional impairment but a morphological one, suggesting chronic oxidative stress destroys the organelles over time. It also explains why "pushing through" fatigue is biologically harmful.

### Columbia's Multi-Omics Immune-Metabolic Map (2025)

Ian Lipkin's team at Columbia University published a detailed map

showing that ME/CFS involves dysregulated immune responses to microbial stimuli that cascade into metabolic failure. Identified processes include altered mitochondrial  $\beta$ -oxidation of fatty acids, disrupted citric acid cycle function, amino acid metabolism abnormalities, and accumulation of triglycerides causing systemic inflammation. Microbial products from the gut also translocate into the bloodstream, triggering further immune activation. This study identifies potential biomarkers for distinct ME/CFS subtypes.

## 03 / Immunology

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### Natural Killer Cell Dysfunction

A 2024 meta-analysis in *Frontiers in Immunology* confirmed that Natural Killer (NK) cell cytotoxicity — the ability of these immune cells to destroy infected or diseased cells — operates at roughly half the capacity of healthy controls. This persistent immune dysfunction helps explain vulnerability to viral reactivations (such as Epstein-Barr Virus) and the feeling of fighting a constant low-grade infection. The dysfunction is linked to both genetic inhibitory alleles (particularly KIR3DL3\*002) and ATP starvation of white blood cells.

### Heightened Innate Immunity

Columbia University's Lipkin lab found that the innate immune cells of ME/CFS patients mount exaggerated cytokine responses when stimulated. The clearest abnormalities appeared in response to superantigens (broad immune activators), with some signal also from fungal antigen stimulation. This suggests a state of chronic immune over-readiness that may drive systemic inflammation and fatigue.

### B-Cell Repertoire Skewing

Two independent studies replicated an unusual pattern in ME/CFS B-cells: an increased use of the antibody building block IGHV3-30 in B-cell receptors. This skewing is normally a sign of a targeted immune response, but in ME/CFS patients the usual accompanying signs of active antibody refinement are absent — leaving its meaning unresolved. It was notably absent in the most severely ill patients.

## Plasmacytoid Dendritic Cells

Two 2025 studies (from De Vlaminck's Cornell lab and an Australian group) found an elevated proportion of plasmacytoid dendritic cells (pDCs) in ME/CFS patients. These cells produce large quantities of type I interferons in response to viral infection, and interferons are known to cause severe malaise and fatigue. This finding requires replication before firm conclusions can be drawn.

### ▲ CONTESTED TERRITORY: THE AUTOANTIBODY THEORY

Earlier reports by Carmen Scheibenbogen's group suggested elevated autoantibodies against G protein-coupled receptors (GPCRs), including beta-adrenergic receptors. However, a major 2025 study from Maureen Hanson's group at Cornell — using two state-of-the-art antibody profiling techniques against 6,183 extracellular proteins — found no significant differences in autoantibody levels between ME/CFS patients and controls. A Swedish study by Iwasaki's group also failed to replicate. The autoantibody theory remains unconfirmed and is an active area of investigation, with planned clinical trials that could provide a more definitive answer.

### ▲ CONTESTED TERRITORY: THE PATHOGEN HUNT

Despite initial hopes, 2025 research largely failed to find active

viral or bacterial infections driving ME/CFS. Ronald Davis's group found no excess viral RNA in patient blood compared to healthy controls. Iwasaki's group found no differences in pathogen exposure history. A Cornell RNA study looking for hidden viral signatures also came up empty. If a pathogen is involved, it is either completely cleared or extraordinarily difficult to detect.

## 04 / Gut Microbiome & Gut-Brain Axis

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### Butyrate Deficiency

Two 2023 multi-omics studies in *Cell Host & Microbe* revealed a severe deficiency in the gut's capacity to produce butyrate — a short-chain fatty acid critical for regulating intestinal inflammation, maintaining the gut lining, and supporting the gut-brain axis. The deficiency in butyrate-producing bacteria correlated directly with fatigue severity and cognitive dysfunction in patients.

### Leaky Gut and Systemic Immune Activation

Breakdown of the intestinal barrier allows microbial products to enter the bloodstream, triggering chronic systemic immune responses. In the most severely ill (housebound) patients, a 2024 study found a reduced capacity of IgG antibodies to react appropriately to gut microbes, suggesting a state of immune exhaustion from constant microbial leakage. This gut-driven inflammation is a prime suspect behind brain fog and cognitive symptoms.

## 05 / Muscle Physiology & Post-Exertional Malaise

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### ME/CFS Is Not Deconditioning

Dutch researcher Rob Wüst's team performed a landmark comparison in 2025: ME/CFS and Long COVID patients were compared to healthy volunteers who had undergone 60 days of strict bed rest (a NASA experiment). While bed rest caused severe whole-muscle atrophy, ME/CFS patients showed selective atrophy only in type I slow-twitch muscle fibers (used for endurance), not whole-muscle wasting. Capillary density patterns also differed. This proves that the muscle changes in ME/CFS are disease-specific, not the result of physical inactivity.

### Amyloid Deposits Post-Exercise

A 2024 study found amyloid-like deposits in the muscle tissue of ME/CFS patients following exercise — an abnormal accumulation of misfolded proteins. This provides a potential biological basis for post-exertional malaise (PEM) and suggests that exercise itself may cause structural tissue damage in susceptible patients.

## 06 / The NIH Deep-Phenotyping Study (2024)

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### Most Intensive Study Ever Conducted

Published in Nature Communications in February 2024, the NIH's \$8

million intramural study brought post-infectious ME/CFS patients to the NIH Clinical Center for days of exhaustive testing: spinal taps, muscle biopsies, fMRI scans, and metabolic chamber evaluations. The results provided the most detailed biological portrait of ME/CFS to date, confirming central nervous system dysfunction, immune exhaustion, and multi-system involvement. Functional MRI revealed abnormal brain activity patterns, and spinal fluid analysis identified neurological biomarkers absent in healthy controls.

*"We understand pathophysiology of ME much better than we used to, including the central role of neuroinflammation and the interaction of abnormalities in the autonomic nervous system, circulatory, immune, endocrine, and energy metabolism systems — continuously feeding each other in a vicious cycle."*

DR. LUIS NACUL, IACFS/ME BOARD MEMBER, 2025 INTERNATIONAL CONFERENCE



07 /

## Emerging Treatments & Clinical Trials

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No FDA-approved disease-modifying treatment for ME/CFS currently exists. However, multiple targeted trials are underway based on the mechanisms now identified. Below is the current landscape:

TREATMENT	STATUS & NOTES
Daratumumab	Immunoadsorption



#### PROMISING PILOT

Anti-CD38 drug targeting plasma cells (antibody-producing B-cells). In a pilot of 10 patients, 6 showed significant improvement in physical function at 12–24 months. Larger trials planned.

### Rituximab

#### PHASE 3 NEGATIVE

B-cell depleting drug. Failed its primary endpoint (fatigue reduction at 2 years) in a large RCT, largely attributed to patient heterogeneity in the study sample.

### BCo07

#### ONGOING

Targets functional autoantibodies. Being trialed in post-COVID syndrome (reCOVer trial) with potential relevance to ME/CFS.

#### PROMISING (SUBSET)

Filtering antibodies from blood. Showed significant symptom improvement in 20 post-COVID ME/CFS patients with elevated beta-adrenergic receptor antibodies. A sham-controlled trial is underway.

### Low-Dose Naltrexone

#### ONGOING TRIALS

Thought to modulate neuroinflammation. Widely used by patients off-label; formal controlled trial evidence is still limited but actively being gathered.

### Ampligen (Rintatolimod)

#### FINAL RESULTS 2024–25

Immunomodulatory drug. AIM ImmunoTech published final results of the AMP-518 study. Modest benefit in some patients; not yet FDA-approved for ME/CFS.

*Candidate targets from Columbia's biomarker study include IL-37, the mTOR inhibitor rapamycin, and metformin for patients with innate immune hypersensitivity. These have not yet entered ME/CFS-specific trials.*

### **Graded Exercise Therapy (GET) as Treatment**

The biological evidence now firmly contradicts the deconditioning model that justified GET as a primary treatment. Muscle biopsy data, mitochondrial findings, and the WASF3 mechanism collectively demonstrate that patients cannot safely increase exercise capacity by forcing exertion. The amyloid deposit findings suggest exercise may cause tissue damage. Clinical guidelines in the UK and elsewhere have been updated to remove GET as a recommended treatment.

### **Psychosomatic / "Fear of Exercise" Framing**

The NIH's deep-phenotyping study, the WASF3 discovery, and extensive immune/metabolic profiling have conclusively demonstrated that ME/CFS is a biological disease with measurable, reproducible pathophysiology. The psychological framing — which led to decades of misdiagnosis, inadequate care, and harmful treatments — is not supported by the current evidence base.

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### **What triggers the illness in the first place?**

ME/CFS most commonly follows a viral infection (post-infectious onset), but a clear single causative pathogen has not been found. It may be that multiple viruses can act as initial triggers that set off a

common downstream biological cascade, rather than one virus being responsible.

### **Is it one disease or several?**

Growing evidence suggests ME/CFS may be heterogeneous — a collection of related conditions sharing a symptom profile but with different underlying mechanisms. Columbia's subtype biomarker work supports this. Stratified treatment approaches (matching treatment to biological subtype) may be necessary for clinical success.

### **Do autoantibodies play a causal role?**

The autoantibody hypothesis remains unresolved despite large-scale testing. Upcoming trials targeting antibody-producing plasma cells (Daratumumab) and antibody filtration (immunoadsorption) will provide critical evidence. The DecodeME HLA-region results — expected in the next phase of analysis — may also clarify the autoimmune question.

### **How does the gut-brain axis perpetuate symptoms?**

The mechanisms by which gut dysbiosis, leaky gut, and neuroinflammation interact and sustain one another are not yet fully characterized. Understanding this feedback loop may open additional therapeutic avenues.

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SOURCES: NIH, NATURE COMMUNICATIONS, PNAS, FRONTIERS IN IMMUNOLOGY, CELL HOST & MICROBE, ME/CFS SCIENCE ANNUAL REVIEW 2025, IACFS/ME 2025 CONFERENCE, MEDSCAPE, COLUMBIA UNIVERSITY CII, MEDRXIV PREPRINTS

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