

Fibromyalgia Testing

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I. Policy Description

Fibromyalgia is a chronic diffuse pain condition and the most common cause of chronic widespread musculoskeletal pain.¹ It is also known by “diffuse myofascial pain syndrome,” “fibromyalgia-fibromyositis syndrome,” or “fibromyalgia syndrome.”² FM has The etiology and pathophysiology of FM is generally unknown, but it can be found with “fatigue, cognitive disturbance psychiatric symptoms, and multiple somatic symptoms;” however, presentation may vary from patient to patient.^{1,3} Controversy has arisen regarding the disease origin, as it has been considered to be psychogenic or psychosomatic, but recent research indicates it as a disorder of pain regulation, a form of “central sensitization.”¹

Terms such as male and female are used when necessary to refer to sex assigned at birth.

II. Related Policies

Policy Number	Policy Title
AHS-G2155	General Inflammation Testing

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the “Applicable State and Federal Regulations” section of this policy document.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual’s illness.

- 1) For the diagnosis of fibromyalgia or chronic pain syndromes, the following tests **DO NOT MEET COVERAGE CRITERIA**:
 - a) Genetic testing (e.g., mutation analysis, copy number variants, epigenetic analysis, mRNA expression, miRNA expression).
 - b) Biomarker panel testing with proprietary algorithms and/or index scores (e.g., FM/a[®], NutrEval FMV[®]).

IV. Table of Terminology

Term	Definition
5HT	Serotonin
5-HT2A	Serotonin 2A
A1AT	Alpha-1 antitrypsin
AAPT	American Pain Society Pain Taxonomy
ACE I/D	<i>Angiotensin-converting enzyme I/D polymorphism</i>
ACR	American College of Rheumatology
ACTTION	Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks
ADRA1A	<i>Adrenoreceptor alpha 1A gene</i>
ADRB2	<i>Adrenoreceptor beta 2 gene</i>
ADRB3	<i>Adrenoreceptor beta 3 gene</i>
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ANS	Autonomic nervous system
APS	American Pain Society
BDNF	<i>Brain derived neurotrophic factor gene</i>
CB-1	Cannabinoid receptor type 1
CLIA '88	Clinical Laboratory Improvement Amendments Of 1988
CMS	Centers for Medicare and Medicaid Services
CNR1	<i>Cannabinoid receptor 1 gene</i>
CNS	Central nervous system
CNV	Copy number variant
COMT	<i>Catecholamine o-methyl transferase gene</i>
CRA	Canadian Rheumatology Association
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CWP	Chronic widespread pain
DNA	Deoxyribonucleic acid
DRD3	<i>Dopamine receptor D3 gene</i>
EDN1	<i>Endothelin 1 gene</i>
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
FIQ	Fibromyalgia-Impact Questionnaire
FM	Fibromyalgia
GABRB3	<i>Gamma-aminobutyric acid receptor subunit beta-3 gene</i>
GBP1	<i>Guanylate binding protein 1 gene</i>
GCH1	<i>Guanosine triphosphate (GTP) cyclohydrolase 1 gene</i>
GERD	Gastroesophageal reflux disease
GRIA4	<i>Glutamate ionotropic receptor AMPA type subunit 4 gene</i>
HLA-DRB1	<i>Human leukocyte antigen DR beta 1 gene</i>
HTR2A	<i>5-Hydroxytryptamine Receptor 2A gene</i>
HTR3A	<i>5-Hydroxytryptamine Receptor 3A gene</i>
HTR3B	<i>5-Hydroxytryptamine Receptor 3B gene</i>
IBS	Irritable bowel syndrome

IFN- γ	Interferon- γ
IGHV1OR21-1	Immunoglobulin domain-containing like protein
IGLV3-25	Immunoglobulin lambda variable 3-25
IL-10	Interleukin-10
IL1RAP	Interleukin-1 receptor accessor protein
<i>IL-4</i>	<i>Interleukin-4 gene</i>
IL-5	Interleukin-5
IL-6	Interleukin-6
IL-8	Interleukin-8
LDTs	Laboratory-developed tests
<i>MAOA</i>	<i>Monoamine oxidase A gene</i>
MAPK	Mitogen-activated protein kinase
MCP-1	Monocyte chemoattractant protein-1
<i>MEFV</i>	<i>Mediterranean fever gene</i>
METTL18	Methyltransferase-like 18
MIP-1 β	Macrophage inflammatory protein-1 β
MSP	Multisite pain
<i>MTHFR</i>	<i>Methylenetetrahydrofolate reductase gene</i>
<i>MYT1L</i>	<i>Myelin transcription factor 1 like gene</i>
NA	Noradrenaline
<i>NRXN3</i>	<i>Neurexin 3 gene</i>
<i>OPRM1</i>	<i>Opioid receptor mu 1 gene</i>
PBMC	Plasma and peripheral blood mononuclear cells
PHA	Phytohemagglutinin
PMA	Phorbol-12-myristate-13-acetate
RA	Rheumatoid arthritis
<i>RGS4</i>	<i>Regulator of G protein signaling 4 gene</i>
SCL-90	Symptom Checklist-90 for Psychopathological Disorders
<i>SCN9A</i>	<i>Sodium voltage-gated channel alpha subunit 9 gene</i>
<i>SLC6A4</i>	<i>Solute carrier family 64 member 4 gene</i>
<i>SERPINA1</i>	<i>Serpin family A member 1 gene</i>
SLE	Systemic lupus erythematosus
SNPs	Single nucleotide polymorphisms
SS	Sjögren syndrome
<i>TAAR1</i>	<i>Trace amine-associated receptor 1 gene</i>
<i>TACR1</i>	<i>Tachykinin receptor 1 gene</i>
TMD	Temporomandibular joint disorder
TPC	Tender point count
TPQ	Tridimensional Personality Questionnaire
<i>TRPV2</i>	<i>Transient receptor potential vanilloid channel 2 gene</i>
<i>TRPV3</i>	<i>Transient receptor potential vanilloid channel 3 gene</i>
TSH	Thyroid stimulating hormone
<i>TSPO</i>	<i>Translocator protein gene</i>
WPI	Widespread pain index

V. Scientific Background

Fibromyalgia (FM) is a condition characterized by chronic and diffuse non-inflammatory musculoskeletal pain. FM is often accompanied by fatigue, cognitive disturbances (“fibro fog”), psychiatric symptoms, and multiple other nonspecific somatic symptoms.^{1,4} Aside from the secondary symptoms, patients may at times experience abdominal and chest wall pain, irritable bowel syndrome (IBS), gastroesophageal reflux disease (GERD), and symptoms of autonomic nervous system (ANS) dysfunction. Despite this, FM is generally of unknown etiology and pathophysiology. However, FM should be considered as a diagnosis in patients experiencing idiopathic chronic pain for at least three months and is solely confirmed by a clinical, symptom-based assessment.⁵

What adds to the controversial and mysterious nature of the condition is that it depends on subjective symptoms. On a normal physical examination, patients often appear well and do not show abnormalities other than “widespread soft tissue tenderness” with normal laboratory and radiologic studies, making it a common but elusive diagnosis. However, a history of other medical conditions that cause musculoskeletal pain can coexist with or mimic FM like rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and thyroid disease. Medical history can support a FM diagnosis.¹ FM is more commonly diagnosed in women than men. The prevalence of FM in the United States and other countries is about two to three percent and incidence tends to increase with age.⁶ FM can also be diagnosed in adolescents in the form of juvenile primary fibromyalgia, and it is confirmed mostly symptomatically but based on slightly different diagnostic criteria for research and epidemiological purposes.³

Fibromyalgia is categorized as a “disorder of pain regulation,” under “central sensitization.”⁷ This finding is supported by biochemical abnormalities that are oftentimes present in FM patients: low concentrations of metabolites of serotonin (5HT) and noradrenaline (NA), and high concentrations of substance P and nerve growth factors.⁸ Patients are more sensitive to central nervous system inputs of pain, and those with FM at times can experience symptoms like those suffering from other central pain disorders, like migraines, IBS, and temporomandibular joint disorder (TMD).⁷ Reduced 5HT and NA may actually account for the widespread pain symptoms by contributing to the dysfunction of endogenous systems that inhibit pain sensation.⁸

Contrary to the established findings published about FM, recent research has demonstrated that there is a possible genetic basis to the disease progression; up to 50% of disease risk can be attributed to candidate genes.⁵ There also appears to be a strong familial predisposition to FM, although it is suspected to have a more polygenic mode of inheritance.^{9,10} However, there is no singular definitive gene that directly causes FM; several genes under consideration include *SLC64A4*, *TRPV2*, *MYT1L*, and *NRXN3*.⁵ Single nucleotide polymorphisms (SNPs) in the *SLC64A4* gene, which encodes a sodium-dependent serotonin transporter, has been associated with both FM and TMD. *SLC64A4* mutations that cause increased serotonin reuptake have been associated with high levels of depression and psychological disorders, as well as “SCL-90 [Symptom Checklist-90 for psychopathological disorders] scores for somatic awareness and anger, TPQ [tridimensional personality questionnaire] harm avoidance trait, increased salivary cortisol level, [and] increased leukocyte count.”^{5,11} *TRPV2* (transient receptor potential vanilloid channel 2) gene is needed for not only cell cycle progression, growth, and differentiation of hematopoietic stem cells and innate immunity, but also the pain threshold due to its presence in the mechanoresponsive and thermo-responsive neurons in the dorsal root and trigeminal ganglia.^{5,12,13} Genetic correlations in FM between mutations in *SLC64A4* and *TRPV2*, which encodes a calcium-permeable channel that is heat-activated and modulates many cellular functions, are further

supported by linkage analysis done with FM to the chromosome 17p11.2-q11.2 region, which happens to house the two genes.^{14,15}

Docampo, et al. (2014) discovered that the rs11127292 polymorphism in the *MYT1L* (myelin transcription factor 1 like) gene, which is critical in the process of neuronal differentiation and has historically been associated with neuropsychiatric disorders, and an intronic CNV (copy number variant) in the *NRXN3* (neurexin 3) gene, which is involved in signal transmission by promoting synapse stability and function, affect the central nervous system (CNS) aspect of FM as well.¹⁶

Studies have also examined the differences in other allelic frequencies and influence of genetics on the sequelae of FM progression. Smith, et al. (2012) identified significant variations in allelic frequency of *GABRB3* (rs4906902), *TAAR1* (rs8192619), and *GBP1* (rs7911) between FM patients and controls. *TAAR1* was demonstrated to alter dopamine bioavailability and function, which may cause the increased pain sensitivity seen in FM. *RGS4*, *CNR1*, and *GRIA4* were implicated in other cohorts from the study by Smith, et al. (2012) and are genes primarily involved in mechanisms of analgesia and central sensitivity as well. *RGS4*, which is expressed in the CNS regions like the dorsal horn of the spinal cord and the locus coeruleus, influences opioid receptor function when overexpressed. *CNR1*, which encodes the CB-1 cannabinoid receptor, has been indirectly utilized in FM treatment by the cannabinoid receptor agonist nabilone. Low *CNR1* expression and thus low CB-1 receptor activity may pose as a strong candidate for future testing, as several FM patients have increased circulating anandamide, an endocannabinoid, which has been hypothesized to underlie the pain in conditions like FM. Alterations to the *GRIA4* gene affect AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors, which play roles in the pain and comorbidities associated with FM.¹⁷

Another gene commonly associated with FM is the *COMT* (catecholamine o-methyl transferase) gene. Though not directly affecting disease presentation, the *V158M* variant may contribute to subsequent depression, anxiety, and disability in many FM females.⁵ Mutations in the *COMT* gene are more closely linked to “pain catastrophizing, increased pain level during elevated pain attention, thermal and pressure sensitivity, psychological distress, increase number of tender points in TPC [tender point count], pain and positive affect interaction, and FIQ [fibromyalgia-impact questionnaire]-defined pain, fatigue, sleep, disturbance, morning stiffness, and disability.”¹¹ Similarly, mutations in the *HTR2A* (5-hydroxytryptamine receptor 2A) gene, which encodes for its receptor, 5-HT_{2A}, contributed to lower levels of total 5-HT in serum and CSF of FM patients.¹⁸ The phenotype in FM more closely relates to psychological facets of FM – including reduced perception of environmental quality, “increased SCL-90-R total score and subscales scores for somatic awareness, anxiety, psychosis, obsessive-compulsive behavior, hostility, global severity index, interpersonal sensitivity, phobic anxiety, [and] depression.”¹¹

Research has also demonstrated the role of epigenetics in FM phenotype and progression. Ciampi de Andrade, et al. (2017) investigated DNA methylation states in samples obtained from FM cases and healthy controls, and found that the majority (1042 genes, 65%) of the differently methylated genes between the two were mostly hypomethylated. These genes were involved in “transduction and calcium signaling, MAPK signaling pathway, regulation of actin cytoskeleton endocytosis, and neuroactive ligand-receptor interaction pathways,” and the sites that were identified were involved in DNA repair, immune system response and regulation, and membrane transport.⁵ Additionally, circulating miRNAs obtained from cerebrospinal fluid (CSF) and serum samples were found to be associated with many of the clinical symptoms of FM, including pain and fatigue, alterations in energy metabolism and growth, alterations in pain threshold, and sleep disturbance.^{20,21}

Proprietary Testing

Some researchers have opted for a proteomics approach to identify individuals with FM. Among females with FMS, Han, et al. (2020) discovered dysregulated proteins and mechanisms associated with an FM diagnosis. They propose a panel of methyltransferase-like 18 (METTL18), immunoglobulin lambda variable 3-25 (IGLV3-25), interleukin-1 receptor accessor protein (IL1RAP), and putative V-set and immunoglobulin domain-containing like protein (IGHV1OR21-1) to differentiate FM from healthy controls. This conclusion was drawn from using a decision tree model that yielded an accuracy of 0.97. Collectively, they offered 100% detection sensitivity in their training cohort, and a specificity of 88%.²²

Genova Diagnostics has also released the NutrEval FMV® Profile, which is a “blood and urine profile that evaluates over 125 biomarkers and assesses the body's functional need for 40 antioxidants, vitamins, minerals, essential fatty acids, amino acids, digestive support, and other select nutrients.” NutrEval® aims to provide insight into conditions such as depression, anxiety, certain inflammatory conditions, and chronic pain syndromes.²³ While there are no peer-reviewed studies published to confirm either the analytical or clinical utility of this particular proprietary test, researchers have delved into the biomarkers that comprise this assay. The aforementioned research on *COMT* proves relevant in the genomics component of this test. The clinical utility for the NutrEval® Profile is particularly pertinent to the chronic pain aspect. In patients with chronic pain, it was found that quinolinic acid, pyroglutamic acid (indicator of glutathione depletion), xanthurenic acid (indicator of vitamin B6 insufficiency), 3-hydroxypropyl mercapturic acid (acrolein metabolite), and methylmalonic acid (indicator of vitamin B12 deficiency) were all elevated to a certain degree among patients experiencing chronic pain. Seventy-seven percent of patients with chronic pain all had at least one abnormal biomarker.²⁴ This demonstrates that understanding the role of nutrition metabolism is necessary for delineating the underlying processes of FM, a chronic pain condition, but additional research is needed.

Clinical Utility and Validity

Currently, most, if not all, of the FM diagnoses are solely clinical. Judgment is made subjectively and dependent on guidelines to conclude if subjective symptoms translate to FM. The sensitivity and specificity of utilizing the 2016 ACR guidelines, when compared to the 1990 criteria in a referral care setting, are 71% and 60%, respectively, with a positive predictive value of 85% and a negative predictive value of 39%.²⁵ These statistical measures evidently prove that there need be more sensitive and specific measures beyond clinical symptoms for diagnosis of FM.

The clinical utility of an FM diagnosis extends beyond genetic testing and biomarkers; FM is also found concurrently among those with primary immunodeficiency and autoimmune diseases, such as RA, SLE, and Sjögren Syndrome (SS).^{22,26} Confirming an FM diagnosis could aid in explicating the additional complications found in RA and SLE, such as “alternating constipation and diarrhea, urinary frequency, diffuse paresthesias, and cognitive difficulties.” The converse also holds true – diagnoses of SS could prompt possible FM diagnoses as well, as seen in the cases of seeing sicca symptoms and TPC of six (though not necessary with 2016 ACR guidelines).²⁶

Janssen, et al. (2021) conducted a review that identified the polymorphisms related to FM and the respective clinical characteristics. From 27 articles, they found the relevant genes to be *MTHFR*, *RGS4*, *MYT1L*, *TACR1*, *SCN9A*, *DRD3*, *ADRB2*, *IL-4*, *HLA-DRB1*, *EDN1*, *CNR1*, *TAAR1*, *OPRM1*, *ADRA1A*, *ADRB3*, *BDNF*, *GRIA4*, *HTR3A*, *HTR3B*, *HTR2A*, *SERPINA 1* or *A1AT*, *NRXN3*, *GCH1*, *MEFV*, *TRPV3*, *SLC6A4*, *ACE I/D*, *TSPO*, *COMT*, and *MAOA*. Additionally, “73.33% of the genes related to FM were also associated with

some psychological disorders, such as anxiety, depression, schizophrenia, and obsessive and compulsive disorder, and 40.00% with pain sensitivity and/or migraine, besides other disorders associated (drug addiction, autoimmune disorders, circulatory problems, and metabolic alterations).” Of note, *SLC6A4*, *HTR3A*, *HTR3B*, and *HTRA* genes were associated with serotonergic regulation, chronic pain conditions, and anxiogenic situations; *COMT* was related to FM risk and increase in pain severity, increased likelihood of psychological disorders like depression, anxiety and schizophrenia, alcoholism, opioid addiction, and eating disorders; *BDNF* was associated with hyperalgesia in FM; and *TACR1* was related to dementia and fatigue. As for treating FM, Janssen, et al. (2021) also found that *TAAR1*, *RGS4*, *CNR1*, *GRIA4* may be considered as targets. These collective findings continue to demonstrate the comorbidities associated with FM, and how understanding the genetic bases may aid in preventing and treating additional sequelae.²⁷

Kendler, et al. (2022) studied the familial genetic risk for functional somatic disorders including internalizing disorders, chronic fatigue syndrome, IBS, and FM. The study included 5,829,186 individuals in Sweden. The authors used a novel method that assessed aggregated risk in first to fifth degree relatives and adjusted for cohabitation. “Patients with FM carry substantial genetic risks not only for FM, but also for pain syndromes and internalizing, autoimmune and sleep disorders.” Overall, patients with FM had a unique family risk genetic score with elevated genetic risk across other disorders; there was a similar but less marked pattern of genetic risks in patients of other functional somatic disorders. The authors suggest that the genetic risk score for FM differentiated it from classic autoimmune disorder and internalizing disorder.²⁸

VI. Guidelines and Recommendations

American Pain Society

The Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks (ACTTION) partnership with the Food and Drug Administration (FDA) and APS created the ACTTION-APS Pain Taxonomy (AAPT) to help standardize clinically useful and consistent diagnoses of chronic pain disorders. First and foremost, all patients must have chronic pain to be diagnosed with FM. The working group members raised a concern of defining FM-pain as by the 1990 ACR criteria (CWP – chronic widespread pain) or the ACR 2010/2016 criteria of multisite pain (MSP), which were distinguished in count (MSP) versus anatomical distribution (CWP) of pain.

To facilitate identifying FM in clinical practice and in research, the AAPT core diagnostic criteria for FM are as follows:

1. “MSP defined as 6 or more pain sites from a total of 9 possible sites [head; left arm; right arm; chest; abdomen; upper back and spine; lower back and spine, including buttocks; left leg; and right leg]
2. Moderate to severe sleep problems OR fatigue
3. MSP plus fatigue or sleep problems must have been present for at least 3 months.”⁹

This guideline did not mention genetic testing for FM.⁹

American College of Rheumatology (ACR)

In 2016, the ACR published revisions to their 2010/2011 guidelines on preliminary diagnostic criteria for fibromyalgia and measurements of symptom severity. To satisfy a diagnosis of fibromyalgia, a patient must have:

1. “Widespread pain index (WPI) ≥ 7 and symptom severity (SS) scale score ≥ 5 or WPI 4-6 and SS scale score ≥ 9 .
2. Generalized pain, defined as pain in at least 4 or 5 regions, must be present. Jaw, chest, and abdominal pain are not included in generalized pain definition.
3. Symptoms have been present at a similar level for at least 3 months.
4. A diagnosis of fibromyalgia is valid irrespective of other diagnoses. A diagnosis of fibromyalgia does not exclude the presence of other clinically important illnesses.”

The table below obtained from the ACR’s publication regarding ascertainment of WPI and SS is shown.

Ascertainment		
(1) WPI: note the number of areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Score will be between 0 and 19		
<i>Left upper region (Region 1)</i>	<i>Right upper region (Region 2)</i>	<i>Axial region (Region 5)</i>
Jaw, left*	Jaw, right*	Neck
Shoulder girdle, left	Shoulder girdle, right	Upper back
Upper arm, left	Upper arm, right	Lower back
Lower arm, left	Lower arm, right	Chest*
		Abdomen*
<i>Left lower region (region 3)</i>	<i>Right lower region (Region 4)</i>	
Hip (buttock, trochanter), left	Hip (buttock, trochanter), right	
Upper leg, left	Upper leg, right	
Lower leg, left	Lower leg, right	
(2) Symptom severity scale (SSS) score		
Fatigue		
Waking unrefreshed		
Cognitive symptoms		
For the each of the 3 symptoms above, indicate the level of severity over the past week using the following scale:		
0 = No problem		
1 = Slight or mild problems, generally mild or intermittent		
2 = Moderate, considerable problems, often present and/or at a moderate level		
3 = Severe: pervasive, continuous, life-disturbing problems		
The symptom severity scale (SSS) score: is the sum of the severity scores of the 3 symptoms (fatigue, waking unrefreshed, and cognitive symptoms) (0-9) plus the sum (0-3) of the number of the following symptoms the patient has been bothered by that occurred during the previous 6 months:		
(1) Headaches (0-1)		
(2) Pain or cramps in lower abdomen (0-1)		
(3) And depression (0-1)		
The final symptom severity score is between 0 and 12		
The fibromyalgia severity (FS) scale is the sum of the WPI and SSS		

The FS scale is also known as the polysymptomatic distress (PSD) scale.

* Not included in generalized pain definition.

Several cases previously deemed positive by the 2010/2011 criteria would be considered negative by the 2016 modified criteria, indicating a lower specificity. The current criteria also state patients can experience pain in 4-5 regions (four quadrants and axial), termed “generalized pain,” to distinguish from the 1990 guideline’s “widespread pain” definition. The 2016 ACR guidelines also now recognize spatial distribution of painful sites.⁹ It lastly modifies the language from the 2010 guidelines that discuss other disorders serving as the etiology of experienced pain, and assumes the 1990 ACR guideline criterion of possible comorbidities with fibromyalgia (#4).²⁹

After conducting an in-depth review of existing guidelines and literature, Heymann, et al. (2017) published recommendations based on the 2010 ACR guidelines, and endorse using the 2010 ACR criteria for diagnosis of FM. They stated:

1. “The presence of widespread pain is essential for the diagnosis of patients with suspected FM.

2. Tender points may be useful in the diagnosis of fibromyalgia when evaluated in combination with other functional disorders covered in the 2010 [ACR] criteria. The tender point count may be correlated with the intensity of some symptoms, particularly emotional stress.
3. Sleep disorders and changes in cognition and fatigue should be considered in the diagnosis of FM. They should also be considered in the assessment of severity of patients with FM.

We suggest the systematic measurement of mood disorders using validated instruments suitable to the healthcare level in which they are administered because they are highly important when assessing the severity of patients with FM.”³⁰

These guidelines did not mention genetic testing for FM.

Canadian Rheumatology Association (CRA)

The CRA released recommendations to the “identification, evaluation, and management” of those with FM after conducting a needs assessment. In relation to diagnosis of FM, the CRA recommends:

- “Fibromyalgia, a condition that can wax and wane over time, should be diagnosed in an individual with diffuse body pain that has been present for at least 3 months, and who may also have symptoms of fatigue, sleep disturbance, cognitive changes, mood disorder, and other somatic symptoms to variable degree, and when symptoms cannot be explained by some other illness [Level 5, Grade D].
- All patients with a symptom complaint suggesting a diagnosis of fibromyalgia should undergo a physical examination which should be within normal limits except for tenderness on pressure of soft tissues (i.e., hyperalgesia which is increased pain following a painful stimulus) [Level 4, Grade D].
- Fibromyalgia should be diagnosed as a clinical construct, without any confirmatory laboratory test, and with testing limited to simple blood testing including a full blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), creatine kinase, and thyroid stimulating hormone (TSH). Any additional laboratory or radiographic testing should depend on the clinical evaluation in an individual patient that may suggest some other medical condition [Level 5, Grade D].”³¹

This guideline did not mention genetic testing for FM.³¹

American Family Physician (AFP)

The AFP published a guideline in 2023 that outlines recommendations for Diagnosis and Management of Fibromyalgia. Recommendations related to diagnosis include:

- Fibromyalgia should be considered in patients that have chronic pain and a history of tissue injury or inflammation that has been present for more than three months; patients must also present with fatigue, mood issues, and sleep disturbances for more than three months.
- The following criteria are all acceptable methods of diagnosis: The 2011 ACR criteria, the 2016 ACR criteria, and the 2019 AAPT criteria.
- Fibromyalgia is a clinical diagnosis and laboratory testing is not needed as a routine measure. However, fatigue can arise from many origins, and providers may consider the following to eliminate other causes: a complete blood count to exclude anemia, a comprehensive metabolic

panel and a TSH test. Other tests, such as those for rheumatoid factor or antinuclear antibody levels are “not recommended” in individuals without suspected rheumatologic conditions because these tests can have high false-positive rates.³²

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website <https://www.cms.gov/medicare-coverage-database/search.aspx>. For the most up-to-date Medicaid policies and coverage, please visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VIII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
81479	Unlisted molecular pathology procedure
81599	Unlisted multianalyte assay with algorithmic analysis
84999	Unlisted chemistry procedure

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

IX. Evidence-based Scientific References

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X. Review/Revision History

Effective Date	Summary
07/01/2025	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria.
12/01/2024	Initial Policy Implementation