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What the Absence of a Biomarker Does Not Mean

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Abstract

This article distinguishes the absence of a definitive biomarker from the absence of a basis for clinical judgment. The 2010 and 2016 fibromyalgia criteria structure patterns of pain distribution, symptom burden, and duration, but they do not establish a sole cause or define the entirety of a patient's condition. An individual's initial diagnosis requires a full medical evaluation that considers other and coexisting diagnoses, and a conclusion may be deferred when symptoms have been brief, are changing, or remain unclear. The current evidence does not provide a list of specific safety signals, a universal differential, a test panel, or a treatment rule. Nor can a particular negative test or QST result establish, beyond the target of the test, that pain is absent, an individual diagnosis is settled, or care is unnecessary.

Keywords: fibromyalgia biomarker · fibromyalgia diagnosis · negative test result · fibromyalgia differential diagnosis · quantitative sensory testing · QST · fibromyalgia pain · initial medical evaluation

What Is Absent?

The 2010 American College of Rheumatology preliminary diagnostic criteria paper described a central problem in fibromyalgia criteria as the absence of a gold standard or definitive case definition. The new criteria were not a test validated against an independent biological marker to distinguish true cases from false ones. The criteria proposed in that paper combined the distribution of pain with symptom burden. [2]

What is missing, then, is an external standard that can confirm an individual's diagnosis with a single test value. What is not missing is clinical information that can be assessed systematically: the distribution of pain over the previous week, fatigue, unrefreshing sleep, cognitive symptoms, and the duration of symptoms. [2,3] This information is not a set of measures that substitutes for a biomarker. It is a different kind of basis for judgment.

Missing this distinction produces errors in opposite directions. One is to say that no judgment is possible because there is no marker. The other is to say that a high symptom score establishes the cause and every coexisting condition. The current evidence supports neither conclusion.

Table 1. The Boundaries Between Biomarker Absence and Clinical Judgment

Observation or judgment	What this evidence supports	What it does not automatically mean	Judgment that remains
No definitive gold standard	Fibromyalgia criteria structure a clinical pattern of pain distribution, symptom burden, and duration. [2, 3]	It does not mean there is no basis for judgment, nor that symptom criteria establish a biological cause.	Interpret the clinical pattern together with the context of evaluation.
Criteria met	The specified clinical pattern fits the criteria. [3]	It does not establish the patient's entire condition, a sole cause, or the only or most important diagnosis.	Consider possible, alternative, and comorbid diagnoses together.
Another diagnosis or abnormal test finding	Another diagnosis or concomitant test abnormality does not automatically cancel the fibromyalgia pattern. [1, 3]	It does not mean that fibromyalgia excludes other clinically important illnesses.	Judge the meaning and importance of each condition in the patient's context.
Self-report criteria	They can be used in research. [3]	They do not independently establish an individual's clinical diagnosis.	Individual diagnosis requires physician-applied criteria and a full initial evaluation.
A particular negative test	Interpret its meaning in relation to what the test actually targeted. [2, 3]	The current evidence provides no general rule for interpreting negative results, and a negative result does not automatically prove that pain is absent or care is unnecessary.	Distinguish the scope of the test result from the scope of the full clinical judgment.
QST result	It records responses to controlled stimuli. [4]	It is not a definitive biomarker for an individual diagnosis or a verdict on whether pain is genuine.	Preserve the protocol, test site, test type, and patient context.

Note. Read the same finding by separating what it says from what it does not automatically mean. The table does not provide specific safety signals, a differential-diagnosis list, a test panel, or treatment or referral rules.

What the Criteria Do and Do Not Do

The 2016 revised criteria ask whether pain is present in at least four of five body regions, whether the combination of the number of painful areas and symptom severity crosses specified thresholds, and whether symptoms have persisted at a generally similar level for at least three months. [3] This is a rule for identifying a recurring clinical pattern in a consistent way.

Meeting the rule means that the pattern a person reports fits the criteria. It does not show which molecule, organ, or neural pathway is the sole cause of that pattern. The criteria structure the person's account of pain and the symptom pattern, but they are not a device that directly measures every mechanism of pain. [2, 3]

The criteria therefore show both the basis for making a positive clinical judgment and the limits of what that judgment establishes. Identifying a clinical pattern is not the same as obtaining an independent biomarker. The first boundary is to recognize the diagnostic pattern without overstating mechanistic certainty.

Other Diagnoses Are Not an Exclusion List

The 2016 revision states that a diagnosis of fibromyalgia can be valid irrespective of other diagnoses and that it does not exclude the presence of other clinically important illnesses. [3] The 1990 classification study likewise did not treat concomitant radiographic or laboratory abnormalities as automatic grounds for exclusion. [1]

This separates two ideas. Finding another illness does not automatically cancel a fibromyalgia pattern. At the same time, meeting fibromyalgia criteria does not end the search for other illnesses. The principle that two diagnoses can coexist means that neither should be used to erase the other. [1, 3]

The revision paper also drew a boundary around what the criteria mean: satisfying them does not define the entirety of a patient's medical condition, nor does it mean that fibromyalgia is the only or most important diagnosis. [3] Deciding which problem matters most now and what else should be assessed belongs to an evaluation of the patient's full situation, not to the criteria sheet itself.

The Evaluation That Still Precedes an Initial Diagnosis

The 2010 study removed the required tender-point count from the diagnostic criteria but retained the position that every patient being diagnosed should have a physical examination. [2] “One test is no longer required” and “no examination is needed” are entirely different statements.

The 2016 revision made this boundary more explicit. When physician-applied criteria are used for an individual's initial diagnosis, they must be accompanied by a full medical evaluation. Essential medical and social information should be gathered; possible, alternative, and comorbid diagnoses should be considered; and the criteria should be applied after an interview, physical examination, and required laboratory studies as the situation calls for. [3]

The scope of that evaluation is not defined by applying the same panel of tests to everyone. The paper notes that the amount of new information to collect varies with the care setting, the patient, and the information already available. [3] The current evidence supports the need for a process of evaluation, but it does not provide a universal test panel or an ordered differential for every patient.

How Far Can We Go in Naming Safety Signals?

The question behind this article includes which safety signals should be checked. The direct evidence available here, however, does not enumerate specific warning symptoms, vital-sign thresholds, test abnormalities, criteria for emergency escalation, or conditions for specialty referral. Filling such a list from common knowledge or memory would create clinical guidance without a source.

The safety principle that can be stated from the evidence is narrower. Necessary information should be gathered before an initial diagnosis; alternative diagnoses and comorbid illnesses should be considered; and the fibromyalgia criteria alone should not be used to explain the patient's entire condition. [3] The criteria also allow diagnosis to be deferred when symptoms have lasted less than three months, are still changing, or remain unclear. [3]

This article therefore does not conclude that there are no safety signals. It says only that this evidence cannot responsibly supply a named list of them. What is urgent in clinical care and which differential diagnoses require attention must be judged in light of current symptoms, examination, existing information, and the purpose of testing. That last sentence is not a rule directing a particular test or referral; it marks the boundary of the judgment this material permits.

What a Negative Test Can Say

The meaning of a negative result must remain tied to what the test actually targeted. The current evidence does not provide an interpretive rule that applies to negative results in general, nor does it show that any one such result directly measures whether a patient is in pain. This limit follows from the structure of fibromyalgia criteria, which operate through pain distribution and symptom burden without an independent gold standard. [2, 3]

Quantitative sensory testing (QST) does not fill this gap at once. A 2025 scoping review included 126 of 2,512 records, but reported no consistent common protocol as well as variation in test sites and test types. The authors cautioned that this heterogeneity could affect the integration of results and the reliability of QST as a biomarker. [4]

A particular negative test therefore cannot be translated into “there is no pain,” and a particular QST result cannot serve as the final verdict on an individual's diagnosis. [2, 3, 4] Conversely, this article does not say that a negative test has no meaning. Its meaning must remain tied to the target of the test and must not be automatically expanded into a verdict on the existence of pain or the patient's entire medical condition.

Why “No Treatment Is Needed” Does Not Follow

The direct evidence available here addresses the composition and application boundaries of diagnostic criteria and the methodological heterogeneity of QST. It does not consist of treatment studies comparing the benefits, harms, or conditions of use of specific treatments. [2, 3, 4] This material alone therefore cannot determine that a particular treatment is needed, nor can a negative test determine that treatment is unnecessary.

Separating the role of test results from decisions about care makes the logic clear. This evidence concerns diagnostic criteria and measurement methods; it does not provide a rule for deriving the need for treatment or support from a test result. It therefore does not predetermine decisions about care.

The statement “this test is negative, so there is no pain and no treatment is needed” contains two leaps: from the test's target to the existence of pain as a whole, and then from the existence of pain to the need for treatment. The explanation permitted by the current evidence is more restrained: “This result provides information about what this test examined. It does not decide in place of the reported pain, the full evaluation, or the care that may be needed.”

An Explanation That Neither Denies Nor Overstates

When explaining the situation to a patient, the first sentence should not set the test result against the patient's experience. Even without a definitive biomarker, clinicians can structure the distribution of pain, accompanying symptoms, and duration to identify a clinical pattern. [2, 3] This is not a provisional

phrase used merely to signal belief in pain. It accurately describes the kind of information the current criteria actually use.

The second sentence should state the ceiling of the judgment. Meeting the criteria does not establish a sole cause or every coexisting condition, and another diagnosis does not automatically erase the fibromyalgia pattern. [1, 3] A full evaluation is needed initially, and a conclusion can be deferred if symptoms have been brief, are changing, or remain unclear. [3]

The third sentence should narrow the scope of a negative test: “This result helps us understand what was tested, but it does not prove the absence of pain or that care is unnecessary.” Only then can what has been established, what remains unexplained, and what context is needed for further judgment be separated. This explanation neither rushes to diagnosis nor cancels experience. The conclusion of this article is that the space left by a missing biomarker should be filled by neither denial nor overstatement.

Declarations

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Ethics	Only public literature was used; no individual patient data or clinical intervention was involved. Any future human-participant research requires separate ethics review before it begins.

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