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The Low-Titer Antinuclear Antibody in Adults: A Scoping Review With Practical Guidance for Primary Care Physicians and Hospitalists

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ADMINISTRATIVE INFORMATION

Support - No support.

Review Stage at time of this submission - Formal screening of search results against eligibility criteria.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 22 September 2026 and was last updated on 22 September 2026.

INTRODUCTION

Review question / Objective Population: adults undergoing antinuclear antibody (ANA) testing. Concept: the meaning of a low-titer positive ANA, defined as a reported endpoint at or below 1:80, covering assay behavior and titer reporting, prevalence in health and by care setting, titer-specific diagnostic accuracy for systemic lupus erythematosus and other ANA-associated rheumatic diseases, outcome after a positive result, causes of a positive result other than rheumatic disease, and utilization and downstream harm. Context: primary care, general internal medicine, and hospital medicine. Objective: to map this evidence and convert it into a practical approach for the physician who orders the test.The review is complete: searches will be run in September 2026, and the manuscript has been submitted for publication. This record was registered after the review was conducted and is not a prospective protocol.

Background The ANA test is among the most frequently ordered immunologic investigations in general medicine and a common reason for rheumatology referral. It is a screening assay, read as a fluorescence pattern on HEp-2 cells and reported as an endpoint titer. Its sensitivity for systemic lupus erythematosus is high, which is why the 2019 EULAR/ACR classification criteria require a titer of 1:80 or above for entry, but its specificity is poor: in a multicenter study of healthy people, 31.7% were positive at 1:40 and 5.0% at 1:160. Positivity in the United States population has risen over three decades without a shift toward discriminating titers, and most tests are ordered outside rheumatology. A weak positive result is flagged by the laboratory and sits at the lupus entry threshold, so it appears meaningful, yet in most patients it is a normal population finding.

Rationale No synthesis tells the generalist how much weight a low-titer result deserves. The relevant evidence is spread across laboratory methodology statements, population prevalence

surveys, diagnostic accuracy meta-analyses, cohort studies, utilization audits, and studies of drug-, infection-, and treatment-associated positivity. Those designs cannot be pooled into a single estimate, which makes a scoping review, rather than a systematic review with meta-analysis, the appropriate method for mapping them.

METHODS

Strategy of data synthesis Narrative synthesis organized by six charting domains: assay behavior; prevalence in health and by care setting; titer-specific accuracy; outcome after a positive result; causes other than rheumatic disease; and utilization and downstream harm. No meta-analysis was performed. Positive and negative likelihood ratios and post-test probabilities at stated pretest probabilities were derived by the authors from published pooled sensitivity and specificity estimates, and are labeled as derived. Proportions are reported as n/N with the percentage where the source gives both; survey-weighted prevalence estimates are reported as published with their confidence intervals.

Eligibility criteria Included: sources addressing adults that reported classification criteria or laboratory methodology statements, population prevalence, titer-stratified diagnostic accuracy, outcome after a positive result, utilization or referral yield, or drug-, infection-, or treatment-associated positivity. Excluded: pediatric-only sources and sources confined to tertiary rheumatology populations. Only English-language sources were included; sources published after 1996, when the modern HEp-2 substrate became standard, were prioritized. No date limit was applied to the search.

Source of evidence screening and selection Two identification routes were used. A structured search of PubMed, Crossref, OpenAlex, Semantic Scholar, and ClinicalTrials.gov combined terms for low-titer, borderline, and indeterminate ANA with terms for interpretation, clinical significance, primary care, and inpatient management. It identified 225 records; 25 duplicates and 41 records without a retrievable abstract were removed, 159 were screened on title and abstract, 154 were excluded, and 5 were assessed in full text and included. A second route identified 193 records by hand-searching the reference lists of major reviews, classification criteria, and consensus statements, by citation chasing, and by retrieving society guidance (American College of Rheumatology, College of American Pathologists, International Consensus on ANA Patterns, Canadian Rheumatology Association, and provincial laboratory protocols). These were assessed directly at the full-record level, combining screening and eligibility in one step; 63 were excluded and 130 were included. In total, 135 sources were charted. Both authors screened sources and charted data independently and resolved disagreements between them.

Data management Data from included sources were charted into the six domains listed above. Bibliographic metadata for every cited source were verified against Crossref and PubMed records, and numerical claims were checked against the primary sources. This verification identified that a widely cited 2020 report of rising ANA prevalence had been retracted and replaced by a corrected 2022 analysis, which the review cites instead.

Reporting results / Analysis of the evidence Reported according to the PRISMA extension for scoping reviews (PRISMA-ScR), following the Arksey and O'Malley framework. Consistent with scoping review methodology, no formal risk-of-bias appraisal was undertaken. Findings are reported narratively by domain.

Presentation of the results A PRISMA-ScR flow diagram of source identification, screening, and charting; a table of titer-stratified sensitivity and specificity for systemic lupus erythematosus with derived likelihood ratios and worked post-test probabilities; a table of causes of a positive ANA other than systemic rheumatic disease; and a clinical algorithm for the approach to a positive ANA in adults, with modifications for the inpatient setting.

Language restriction English.

Country(ies) involved United States.

Keywords antinuclear antibody; low titer; systemic lupus erythematosus; diagnostic stewardship; pretest probability; primary care; hospital medicine.

Contributions of each author
Author 1 - Maria Carpintero.
Author 2 - Marco Ladino.