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CADTH Reference List

Antinuclear Antibody Testing

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Summary of Abstracts

CADTH

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Key Messages

- We found 3 non-randomized studies about the diagnostic test accuracy and clinical utility of antinuclear antibody testing in adults.
- We found 6 guidelines regarding antinuclear antibody testing.

Research Questions

1. What literature describes the diagnostic test accuracy and clinical utility of antinuclear antibody testing in adults?
2. What are the recommendations regarding antinuclear antibody testing?

Methods

Literature Search Methods

The report is based on a literature search strategy completed by an information specialist for a previous CADTH report: https://www.cadth.ca/ana-testing and run on October 28, 2022. It is also based on a grey literature search that was completed on February 1, 2023. The grey literature search was based on key resources, including the websites of Canadian and major international health technology agencies, as well as a focused internet search. The main search concept was antinuclear antibodies (ANA) testing. The search was limited to English-language documents published since January 1, 2012. Internet links were provided, where available.

Selection Criteria and Summary Methods

One reviewer screened literature search results (titles and abstracts) and selected publications according to the inclusion criteria presented in Table 1. Full texts of study publications were not reviewed. The Overall Summary of Findings was based on information available in the abstracts of selected publications. Open access full-text versions of guidelines were reviewed when available, and relevant recommendations were summarized.

Table 1: Selection Criteria

Criteria	Description
Population	Adult patients ≥ 18 years of age
Intervention	Antinuclear antibody testing using any method to test for a specific medical condition
Type of Information	Q1: Descriptions of findings related to diagnostic test accuracy (e.g., sensitivity, specificity, positive predictive value, negative predictive value) and clinical utility (e.g., time to treatment, morbidity, incidence of disease, mortality, quality of life) Q2: Recommendations regarding best practices for antinuclear antibody testing
Study designs	Q1. Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies Q2. No restriction of type of publication

Results

Nine relevant references were identified for this report.[1-9] Three non-randomized studies were identified regarding the diagnostic test accuracy and clinical utility of ANA testing in adults.[1-3] Six guidelines were identified about best practices for ANA testing.[4-9] No relevant health technology assessments, systematic reviews, or randomized controlled trials were identified.

Additional references regarding the relationship between the presence of ANA and medical conditions or diseases are provided in Appendix 1.

Overall Summary of Findings

Three non-randomized studies investigated the diagnostic test accuracy of ANA testing for rheumatic diseases (RD).[1-3] Two studies[1,2] reported predictive values of ANA testing for RDs, including systemic rheumatic diseases,[1] lupus,[2] and ANA-associated rheumatic diseases.[2] Another study[3] reported sensitivity and specificity of ANA for systemic lupus erythematosus (SLE) diagnosis using sera from healthy controls and patients with multiple medical problems. A detailed summary of the included non-randomized studies can be found in Table 2.

Six guidelines about ANA testing were identified.[4-9] Five guidelines recommend ANA testing for patients with symptoms suggestive of varying connective tissue diseases, including autoimmune liver disease,[6] lupus,[7] polymyositis/dermatomyositis,[6,8] scleroderma,[6,8] Sjögren's syndrome,[4,6,8] SLE,[6,8] and systemic rheumatic disease.[5] Of these, 2 guidelines[7,8] recommend against ANA testing for investigation of pain or fatigue without other clinical indications. The same guidelines[7,8] also recommend against repeating ANA testing, with the exception of significant clinical picture change.[7] In addition, 1 guideline[8] recommends against testing ANA to confirm a diagnosis of rheumatoid arthritis or osteoarthritis. Finally, 1 guideline[9]

recommends immunofluorescence ANA test using Human Epithelial type 2 substrate as the gold standard for ANA testing.

A detailed summary of the recommendations can be found in Table 3. Guidance documents were classified as evidence-based (i.e., recommendations were informed using a systematic search of the literature), consensus-based (i.e., recommendations were informed by expert opinion, with or without consideration for evidence collected using non-systematic methods), or as having unclear (i.e., not reported in detail) methodology.

Table 2: Summary of Included Non-Randomized Studies

Study citation	Study design, population	Intervention and reference standard	Diagnostic test accuracy and/or clinical utility outcomes	Other relevant outcomes
Soto et al. (2015)[1]	**Study design:** Retrospective study **Population:** Patients tested for ANA[a] **Number of study participants:** NR	**Intervention:** ANA testing requested by different specialties **Reference standard:** NR	PPVs and NPVs for systemic rheumatic diseases	Relationship between coexistence of two or more autoimmune disorders and PPVs and NPVs of ANA test, prevalence of autoimmune disease
Abeles et al. (2013)[2]	**Study design**: Retrospective study **Population**: Patients with a positive ANA test result referred to a tertiary rheumatology clinic[a] **N =** 232	**Intervention**: ANA testing performed outside of the rheumatology setting **Reference standard**: NR	PPVs for lupus and any ANA-associated rheumatic disease	Prevalence of ANA-associated rheumatic disease in patients with ANA at a titre of < 1:160
Wichainun et al. (2013)[3]	**Study design**: Case-control study **Population**: Patients with SLE, patients with multiple medical problems, and healthy controls[a] **N =** 300	**Intervention**: ANA testing **Reference standard**: NR	Sensitivity and specificity of ANA at a titre of ≥ 1:80 and ≥ 1:160 for SLE	Prevalence of ANA at a titre of ≥ 1:80 and ≥ 1:160

ANA = antinuclear antibody; NPV = negative predictive value; NR = not reported; PPV = positive predictive value; SLE = systemic lupus erythematosus.
[a]Age of the population was unclear or unreported in the abstract.

Table 3: Summary of Recommendations in Included Guidelines

Summary of recommendations	Methodology[a]
Brazilian Society of Rheumatology (2019)[4]	
For patients with suspected SS Recommendation 15 (p. 10)	Evidence-based

Summary of recommendations	Methodology[a]
• "The levels of anti-HEp-2 antinuclear antibodies (ANAs), anti-Ro/SSA antibodies, anti-La/SSB antibodies and rheumatoid factor should be measured for all patients with suspected SS. These tests are useful for determining the diagnosis and prognosis."[b]	
Australian Rheumatology Association (2018)[5]	
For patients with suspected systemic rheumatic disease Recommendation 2 • "Do not order antinuclear antibody (ANA) testing without symptoms and/or signs suggestive of a systemic rheumatic disease." [b]	Consensus-based
Conlon et. al (2018)[6]	
For patients with suspected CTD Key Recommendations (p. 2) • "ANA testing is indicated when there are features suggestive of connective tissue diseases such as SLE, Sjogren's syndrome, scleroderma, polymyositis/dermatomyositis or autoimmune liver disease. If features of these conditions are not present an ANA test should not be ordered."[b]	Unclear
British Society of Rheumatology (2016)[7]	
For patients with suspected CTD Recommendation 1 • "Testing ANA and ENAs should be reserved for patients suspected to have a diagnosis of a connective tissue disease, e.g. lupus. Testing ANA and ENAs should be avoided in the investigation of widespread pain or fatigue alone. Repeat testing is not normally indicated unless the clinical picture changes significantly."[b]	Unclear
BC Guidelines (2013)[8]	
For patients with suspected CTD Key Recommendations (p. 1) • "ANA testing need only be ordered once." • "ANA testing is NOT indicated unless a connective tissue disease (e.g., systemic lupus erythematosus [SLE], scleroderma, Sjogren's syndrome, polymyositis/dermatomyositis) is a significant clinical possibility." • "ANA testing is NOT indicated as a screening test to evaluate fatigue, back pain, or other musculoskeletal pain without other clinical indications." • "ANA testing is NOT indicated to confirm a diagnosis of rheumatoid arthritis (RA) or osteoarthritis (OA)."	Unclear
American College of Rheumatology (2009)[9]	
Position 1 (p. 1) • "The ACR supports the immunofluorescence antinuclear antibody (ANA) test using Human Epithelial type 2 (Hep-2) substrate, as the gold standard for ANA testing."[b]	Unclear

ACR = American College of Rheumatology; ANA = antinuclear antibody; anti-Hep-2 = anti-human-epithelial-type-2; anti-La/SSB = anti-Sjögren's-syndrome-related antigen B; anti-Ro/SSA = anti-Sjögren's-syndrome-related antigen A; CTD = connective tissue disease; ENA = extractable nuclear antigen; OA = osteoarthritis; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; SS = Sjögren's syndrome.

[a]Guidance documents were classified as evidence-based (i.e., recommendations were informed using a systematic search of the literature), consensus-based (i.e., recommendations were informed by expert opinion, with or without consideration for evidence collected using non-systematic methods), or as having unclear (i.e., not reported in detail) methodology.

[b]Age of the population of interest was unclear or unreported.

References

Health Technology Assessments

No literature identified.

Systematic Reviews

No literature identified.

Randomized Controlled Trials

No literature identified.

Non-Randomized Studies

Medical Condition Not Specified

1. Soto ME, Hernandez-Becerril N, Perez-Chiney AC, et al. Predictive value of antinuclear antibodies in autoimmune diseases classified by clinical criteria: Analytical study in a specialized health institute, one year follow-up. *Results Immunology*. 2015;5:13-22. PubMed

RD

2. Abeles AM, Abeles M. The clinical utility of a positive antinuclear antibody test result. *Am J Med*. 2013 Apr;126(4):342-348. PubMed

SLE or Multiple Medical Problems

3. Wichainun R, Kasitanon N, Wangkaew S, Hongsongkiat S, Sukitawut W, Louthrenoo W. Sensitivity and specificity of ANA and anti-dsDNA in the diagnosis of systemic lupus erythematosus: a comparison using control sera obtained from healthy individuals and patients with multiple medical problems. *Asian Pac J Allergy Immunol*. 2013 Dec;31(4):292-298. PubMed

Guidelines and Recommendations

4. Trevisani VFM, Pasoto SG, Fernandes M, et al. Recommendations from the Brazilian Society of Rheumatology for the diagnosis of Sjogren's syndrome (Part I): glandular manifestations (systematic review). Adv Rheumatol. 2019 12 18;59(1):58. PubMed
Refer to: Recommendation 15 (page 10)

5. Australian Rheumatology Association. Recommendations. 2. Do not order antinuclear antibody (ANA) testing without symptoms and/or signs suggestive of a systemic rheumatic disease. In: Choosing Wisely Australia. 2018; https://www.choosingwisely.org.au/recommendations/ara2. Accessed 2023 Feb 8.
Refer to: Recommendation 2

6. Conlon NP, Tormey V, Feighery C, Khalib K, Keogan M, National Clinical Programme for Pathology. Laboratory testing for antinuclear antibodies. (National laboratory handbook). Dublin (Ireland): Beaumont Hospital; [2018]: http://www.beaumont.ie/media/Guideline21.pdf. Accessed 2023 Feb 8.
Refer to: Key Recommendations (page 2)

7. British Society of Rheumatology. Recommendation 1. In: Choosing Wisely UK. Recommendations for clinicians 2016/18, 2019 archive. [2016]; https://choosingwisely.co.uk/recommendations-archive/#1572879061091-6c332449-706b. Accessed 2023 Feb 8.
Refer to: British Society of Rheumatology, Recommendation 1

8. Antinuclear antibody (ANA) testing protocol. BC Guidelines.ca. Victoria (BC): British Columbia Ministry of Health; 2013: https://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/ana.pdf. Accessed 2023 Feb 8.
Refer to: Key Recommendations

9. American College of Rheumatology. Position statement: methodology of testing for antinuclear antibodies. Atlanta (GA): American College of Rheumatology; 2009 (updated 2019): https://www.rheumatology.org/Portals/0/Files/Methodology%20of%20Testing%20Antinuclear%20Antibodies%20Position%20Statement.pdf. Accessed 2023 Feb 8.
Refer to: Position Statement 1 (page 1)

Appendix 1: References of Potential Interest

Previous CADTH Reports

Antinuclear antibody testing for autoimmune disorders. (CADTH rapid response: reference list). Ottawa (ON): CADTH; 2022: https://www.cadth.ca/sites/default/files/pdf/htis/2022/RA1237%20ANA%20Testing%20Final.pdf. Accessed 2023 Feb 8.

Systematic Reviews

SLE

Leuchten N, Hoyer A, Brinks R, et al. Performance of antinuclear antibodies for classifying systemic lupus erythematosus: a systematic literature review and meta-regression of diagnostic data. Arthritis Care Res (Hoboken). 2018 03;70(3):428-438. PubMed

Recurrent Miscarriage

Cavalcante MB, Cavalcante C, Sarno M, da Silva ACB, Barini R. Antinuclear antibodies and recurrent miscarriage: systematic review and meta-analysis. Am J Reprod Immunol. 2020 03;83(3):e13215. PubMed

Non-Randomized Studies

Recurrent Miscarriage

Sakthiswary R, Rajalingam S, Norazman MR, Hussein H. Antinuclear antibodies predict a higher number of pregnancy loss in unexplained recurrent pregnancy loss. *Clin Ter*. 2015;166(2):e98-101. PubMed

Obstetrical Complications

Koubi M, Rossi P, Arcani R, et al. Relevance of systematic anti-nuclear antibodies testing after obstetrical complications. J Reprod Immunol. 2021 11;148:103437. PubMed

Liver Diseases

Lin L, Lin B, Lan Q, et al. Presence of serum antinuclear antibodies does not impact outcomes in HBY-related acute-on-chronic liver failure. *Can J Gastroenterol Hepatol*. 2022;2022:7981338. PubMed

Weber S, Benesic A, Buchholtz ML, Rotter I, Gerbes AL. Antimitochondrial rather than antinuclear antibodies correlate with severe drug-induced liver injury. *Dig Dis*. 2021;39(3):275-282. PubMed

Kirdar S, Sener AG, Cenglz M, Aydin N. The prevalence of autoantibody and its relationship with genotypes of hepatitis C virus in patients with chronic hepatitis C virus infection. *APMIS*. 2016 Nov;124(11):979-984. PubMed

Khairy M, El-Raziky M, El-Akel W, et al. Serum autoantibodies positivity prevalence in patients with chronic HCV and impact on pegylated interferon and ribavirin treatment response. *Liver Int*. 2013 Nov;33(10):1504-1509. PubMed

Mauss S, Berger F, Schober A, et al. Screening for autoantibodies in chronic hepatitis C patients has no effect on treatment initiation or outcome. *J Viral Hepat*. 2013 Apr;20(4):e72-77. PubMed

Infectious Diseases

Brianza-Padilla M, Juarez-Vicuna Y, Springall R, Gonzalez-Flores J, Patlan M, Amezcua-Guerra LM. Antinuclear antibodies detected by Enzyme-Linked Immunosorbent Assay (ELISA) in severe COVID-19: clinical and laboratory associations. Eur Rev Med Pharmacol Sci. 2022 07;26(14):5307-5310. PubMed

Im JH, Chung MH, Park YK, et al. Antinuclear antibodies in infectious diseases. Infect Dis. 2020 03;52(3):177-185. PubMed

RD

Paknikar SS, Crowson CS, Davis JM, Thanarajasingam U. Exploring the role of antinuclear antibody positivity in the diagnosis, treatment, and health outcomes of patients with rheumatoid arthritis. *ACR Open Rheumatol*. 2021 Jun;3(6):422-426. PubMed

Silvy F, Bertin D, Bardin N, et al. Antinuclear antibodies in patients with psoriatic arthritis treated or not with biologics. *PLoS ONE* [Electronic Resource]. 2015;10(7):e0134218. PubMed

Takase K, Horton SC, Ganesha A, et al. What is the utility of routine ANA testing in predicting development of biological DMARD-induced lupus and vasculitis in patients with rheumatoid arthritis? Data from a single-centre cohort. *Ann Rheum Dis*. 2014 Sep;73(9):1695-1699. PubMed

Sakthiswary R, Rajalingam S, Norazman MR, Hussein H. Antinuclear antibodies in primary osteoarthritis of the knee: a case-control study. *EXCLI j*. 2012;11:624-631. PubMed

Cancer

Skare TL, Neppel A, Machoski MCC, Maestri CA, Messias-Reason I, Nisihara R. Antinuclear antibodies in patients with cervical lesions and invasive cervical cancer. *Immunol Lett*. 2019 04;208:8-10. PubMed

Lang J, Ma K, Guo J, Zhang J, Wang Q, Sun H. Clinical significance of elevated antinuclear antibodies in patients with diffuse large B-cell lymphoma: A single center study. *J Cancer Res Ther*. 2018 Jan;14(1):213-219. PubMed

Nisihara R, Machoski MCC, Neppel A, Maestri CA, Messias-Reason I, Skare TL. Anti-nuclear antibodies in patients with breast cancer. Clin Exp Immunol. 2018 08;193(2):178-182. PubMed

Zou HY, Gu X, Yu WZ, Wang Z, Jiao M. Detection of serum antinuclear antibodies in lymphoma patients. *Genet Mol Res*. 2015 Dec 11;14(4):16546-16552. PubMed

Oral Diseases

Thongprasom K, Prapinjumrune C, Kanjanabuch P, Youngnak-Piboonratanakit P, Preuksrisakul T. Correlation of serum ANA and direct immunofluorescence studies in elderly Thai patients with red and white oral lesions. *J Oral Pathol Med*. 2016 Nov;45(10):797-802. PubMed

Prucktrakul C, Youngnak-Piboonratanakit P, Kanjanabuch P, Prueksrisakul T, Thongprasom K. Oral lichenoid lesions and serum antinuclear antibodies in Thai patients. *J Oral Pathol Med*. 2015 Jul;44(6):468-474. PubMed

Dermatomyositis and/or Polymyositis

Hoesly PM, Sluzevich JC, Jambusaria-Pahlajani A, Lesser ER, Heckman MG, Abril A. Association of antinuclear antibody status with clinical features and malignancy risk in adult-onset dermatomyositis. *J Am Acad Dermatol*. 2019 May;80(5):1364-1370. PubMed

Park EH, Hwang WC, Lee Y, et al. Raynaud's phenomenon and anti-nuclear antibody are associated with pulmonary function decline in patients with dermatomyositis and polymyositis. *Int J Rheum Dis*. 2019 Mar;22(3):507-515. PubMed

Psychosis

Spies MC, Gutjahr-Holland JA, Bertouch JV, Sammel AM. Prevalence of neuropsychiatric lupus in psychosis patients who have tested positive for antinuclear antibodies. Arthritis Care Res (Hoboken). 2022 03;74(3):427-432. PubMed

Mantovani C, Louzada-Junior P, Nunes EA, de Figueiredo FP, Oliveira GR, Del-Ben CM. Antinuclear antibodies testing as a routine screening for systemic lupus erythematosus in patients presenting first-episode psychosis. *Early Interv Psychiatry*. 2012 Aug;6(3):322-325. PubMed

Isolated Inflammatory Eye Diseases

Sumethkul K, Urailert I, Kitumnuaypong T, Angthararak S, Silpa-Archa S. The incidence, risk factor, and time to develop rheumatologic diseases after isolated inflammatory eye diseases: a 12-year cohort study. *Clin Rheumatol*. 2022 Apr;41(4):1003-1012. PubMed

Interstitial Lung Disease

Ghrairi N, Aouadi S, Elhechmi YZ, Ben Saad S, Ben Ali I, Yalaoui S. Antinuclear antibodies in interstitial lung disease: prevalence and clinical significance. *Tunis Med*. 2019 Nov;97(11):1240-1245. PubMed

Lv H, Liu J, Pan Q, Cai R, Zhang J. Clinical retrospective analysis of interstitial lung disease patients associated with pulmonary hypertension. *Med Sci Monit*. 2019 Oct 16;25:7763-7769. PubMed

Chronic Lymphocytic Leukemia

Sun Q, Wang L, Zhu HY, et al. Presence of serum antinuclear antibodies correlating unfavorable overall survival in patients with chronic lymphocytic leukemia. *Chin Med J*. 2019 Mar 05;132(5):525-533. PubMed

Hidradenitis Suppurativa

Mulani S, McNish S, Jones D, Shanmugam VK. Prevalence of antinuclear antibodies in hidradenitis suppurativa. *Int J Rheum Dis*. 2018 May;21(5):1018-1022. PubMed

Multiple Sclerosis

Szmyrka-Kaczmarek M, Pokryszko-Dragan A, Pawlik B, et al. Antinuclear and antiphospholipid antibodies in patients with multiple sclerosis. *Lupus*. 2012 Apr;21(4):412-420. PubMed