Antinuclear Antibody (ANA) Testing

Effective Date:

Scope

This guideline describes the appropriate use of antinuclear antibody (ANA) testing in the diagnosis of connective tissue disease (CTD) in adults aged ≥ 19 years. The guideline does NOT address ANA testing in the investigation of unexplained infertility, adverse pregnancy outcomes, liver disease or thrombotic disorders.

Key Recommendations

- 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 suspected fibromyalgia, 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).

Epidemiology

The autoimmune connective tissue diseases (CTDs) are rare conditions that disproportionately affect women.[1] The prevalence and incidence of these conditions varies by age, sex and ethnicity. Examples of CTDs include conditions such as Systemic Lupus Erythematosus (SLE), Systemic Sclerosis (Scleroderma), Sjogren's Syndrome and Dermatomyositis. Antinuclear antibody testing is often used to investigate these conditions, and the epidemiology and relative rarity of these conditions should be considered when ordering an ANA. Apart from female predominance, other epidemiological considerations include increased incidence and prevalence of the CTDs, particularly SLE and Scleroderma, in our Canadian Indigenous peoples (approximately two times increased risk.[2 4]

Incidence of select CTDs in Canada

Disease	Prevalence	Incidence
Systemic Lupus Erythematosus (SLE)[1]	32-51/100 000	3/100 000/year
Systemic Sclerosis (Scleroderma)[2]	23/100 000	1.92/100,000/year[5] *
Dermatomyositis[3]	28.6/100 000*	2.8/100 000/year**

*British Columbia data, Canadian data not available

**Alberta data, Canadian data not available

In Partnership with SASK Guidelines Provincial Committee, Ministry of Health, and Saskatchewan Health Authority

Saskatchewan Health Authority

Saskatchewan

Based on six months (2017) ANA utilization data from Saskatchewan Provincial lab and estimated population the lab covers (~500K)
Saskatchewan Annual Testing Rate: 1700-1800/100 000 • close to 5000 ANA tests have been ordered to make the diagnosis of Systemic autoimmune rheumatic diseases (SARD) in less than 200 new cases. • 10% of ANA orders were repeat testing. • close to 30% of repeat testing were ordered in less than 10 days and 2/3 of repeat orders occur within 2 months. • 2/3 of ANA tests ordered for hospitalized patients did not meet the criteria for any clinical indication.

Testing

ANA are autoantibodies directed against a variety of components of the cell nucleus.[6 7] Detection of ANA is a diagnostic adjunct in patients with suspected CTD.[6 8] The usefulness of the ANA test results depends on the clinical situation. If the clinical history and physical examination reveal symptoms or signs suggestive of SLE, scleroderma, Sjögren's syndrome or polymyositis/ dermatomyositis, then ordering ANA is appropriate and a positive test contributes to the diagnosis.[9 12] ANA testing is not indicated for diagnosis of RA or OA.

Such CTD patients typically present with at least one of the following clinical findings unexplained by other causes:

- arthritis
- pleurisy or pericarditis
- photosensitive rash
- laboratory evidence of renal disorder
- hemolytic anemia, immune thrombocytopenia or neutropenia
- clinical and laboratory evidence of myositis
- Raynaud's phenomenon
- skin changes of scleroderma, dermatomyositis or vasculitis

In the absence of such symptoms and signs, a positive ANA test only confounds the diagnosis because positive ANA are commonly found in the normal population. The prevalence of ANA in healthy individuals is about 3-15%.[13] The production of these autoantibodies is strongly age-dependent, increasing to 10-37% in healthy persons over the age of 65.

Positive ANA tests may also be seen in a wide range of diseases other than CTD where they have no diagnostic or prognostic value.[7 8 14] Individuals with viral infections can have positive ANA for a short time. Some medications (e.g., Procainamide and Hydralazine) and conditions, (e.g., cancer and auto immune thyroid disease), can also cause a positive ANA.[16 17 18 19]

The higher the ANA titre, the more likely that a CTD is present.[9] However, there is no role for serial monitoring of ANA and repeat ANA testing is rarely indicated. Atypical clinical presentations of CTD do occur and clinical judgment should guide ANA testing in these cases. CTD is uncommon, occurs almost exclusively in women, and typically presents at less than fifty years of age.

ANA testing provides little useful information in the evaluation of complaints such as chronic fatigue or musculoskeletal pain in the absence of more specific symptoms or findings[9]

The very low specificity of a positive ANA in the absence of clinical findings of a CTD precludes its use as a screening test for disease in the general healthy population.[10]

- **ANA testing is NOT indicated:**
  - unless a CTD is a significant clinical possibility.
  - to confirm a diagnosis of rheumatoid arthritis or osteoarthritis.
  - to evaluate fatigue, back pain, or other musculoskeletal pain unless accompanied by one or more of the clinical findings listed above.
- **Repeat ANA testing is RARELY indicated:**
  - In general, ANA testing should only be ordered once.
  - Positive tests should not be repeated and there is no role for serial monitoring of ANA since changes in ANA titres do not correlate with disease activity.[6 10 14]
  - Negative tests should rarely be repeated except when there is a change in the patient's illness suggesting revision of diagnosis.

References

1. Carter EE, Barr SG, Clarke AE. The global burden of SLE: prevalence, health disparities and socioeconomic impact. Nat Rev Rheumatol 2016;12:605–20.
2. Calderon, L. & Pope, J. (2021). Scleroderma epidemiology update. Current Opinion in Rheumatology, 33 (2), 122-127. doi: 10.1097/BOR.0000000000000785
3. Osman, Mohammed, Karen J. B. Martins, Kai On Wong, Khanh Vu, Alexis Guigue, Jan Willem Cohen Tervaert, Robert Gniadecki, and Scott W. Klarenbach. "Incidence and Prevalence, and Medication Use among Adults Living with Dermatomyositis: An Alberta, Canada Population-based Cohort Study." Scientific Reports 13.1 (2023): 16444. Web.
4. Barnabe, C., Jones, C. A., Bernatsky, S., Peschken, C. A., Voaklander, D., Homik, J., ... Hemmelgarn, B. (2017). Inflammatory Arthritis Prevalence and Health Services Use in the First Nations and Non-First Nations Populations of Alberta, Canada. Arthritis Care & Research, 69(4), 467–474. doi: 10.1002/acr.22959
5. BC Stats. (n.d.). Retrieved from https://www2.gov.bc.ca/gov/content/data/about-data-management/bc-stats
6. Mongey, A. B., & Hess, E. V. (1991). Antinuclear antibodies and disease specificity. Advances in Internal Medicine, 36, 151-169.
7. Hilliquin, P. (1995). Biological markers in inflammatory rheumatic diseases. Cellular and Molecular Biology, 41(8), 993-1006.
8. Barland, P., & Lipstein, E. (1996). Selection and use of laboratory tests in the rheumatic diseases. The American Journal of Medicine, 100(Suppl 2A), 16S-23S.
9. Thomas, C., & Robinson, J. A. (1993). The antinuclear antibody test. When is a positive result clinically relevant? Postgraduate Medicine, 94(2), 55-66.
10. Metzger, A. L., & Morris, R. I. (1998). Appropriate laboratory testing in rheumatic diseases. Lippincott's Primary Care Practice, 2(1), 52-65.
11. Paraskevas, F., & Foerster, J. (1999). Immunodiagnosis. In G. R. Lee, J. Foerster, J. Lukens, F. Paraskevas, J. P. Greer, & G. M. Rodgers (Eds.), Wintrobe's Clinical Hematology (10th ed., pp. 45). New York: Lippincott, Williams & Wilkins, Inc.
12. Shojania, K. (2000). Rheumatology: 2. What laboratory tests are needed? CMAJ, 162(8), 1157-1163.
13. Tan, E. M., Feltkamp, T. E., Smolen, J. S., et al. (1997). Range of antinuclear antibodies in "healthy" individuals. Arthritis & Rheumatism, 40, 1601.

14. Slater, C. A., Davis, R. B., & Shmerling, R. H. (1996). Antinuclear antibody testing. A study of clinical utility. Archives of Internal Medicine, 156, 1421-1425.
15. Kavanaugh, A., Tomar, R., Reveille, J., Solomon, D. H., & Homburger, H. A. (2000). Guidelines for clinical use of the antinuclear antibody test and tests for specific autoantibodies to nuclear antigens. American College of Pathologists. Archives of Pathology & Laboratory Medicine, 124, 71-81.
16. Solhjoo, M., Goyal, A., & Chauhan, K. (2023). Drug-Induced Lupus Erythematosus. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK441889/
17. Araújo-Fernández, S., Ahijón-Lana, M., & Isenberg, D. A. (2014). Drug-induced lupus: Including anti-tumour necrosis factor and interferon induced. Retrieved from https://pubmed.ncbi.nlm.nih.gov/24557776/
18. Franco, J. S., Amaya-Amaya, J., & Anaya, J. M. (Eds.). (2018). Thyroid disease and autoimmune diseases. In Autoimmunity: From Bench to Bedside (Chapter 30). Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK459466/#
19. Soy, M., Guldiken, S., Arikan, E., Altun, B. U., & Tugrul, A. (2007). Frequency of rheumatic diseases in patients with autoimmune thyroid disease. Rheumatology International, 27, 575-577.
20. Uramoto, K. M. (1999). Trends in the incidence and mortality of systemic lupus erythematosus. 1950-1992. Arthritis & Rheumatism, 42(1), 46-50.
21. Mayes, M. D. (1996). Scleroderma epidemiology. Rheumatic Disease Clinics of North America, 22(4), 751-764.
22. Kovacs, S. O., & Kovacs, S. C. (1998). Dermatomyositis. Journal of the American Academy of Dermatology, 39(6), 899-920.
23. Suarez-Almazor, M., Gonzalez-Lopez, L., Gamez-Nava, I., et al. (1998). Utilization and predictive value of laboratory tests in patients referred to rheumatologists by primary care physicians. The Journal of Rheumatology, 25(10), 1980-1985.
24. Man, A., Shojania, K., Phoon, C., et al. (2013). An evaluation of autoimmune antibody testing patterns in a Canadian health region and an evaluation of a laboratory algorithm aimed at reducing unnecessary testing. Clinical Rheumatology, 32(5), 601-608.

This guideline is based on scientific evidence current as of the Effective Date. This guideline was developed by the SASK Guidelines Committee. The principles of the SASK Guidelines Committee are to:

- To encourage appropriate responses to common medical situations.
- To recommend actions that are sufficient and efficient, neither excessive nor deficient.
- To permit exceptions when justified by clinical circumstances.

Contact Information: SASK Guidelines Committee, Webpage:
https://www.ehealthsask.ca/services/Referral-and-Consult-Tools/Pages/SASKGuidelines.aspx

Email: SKconsultationtools@health.gov.sk.ca