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Antinuclear Antibody Testing

Draft for External Review
Questionnaire available at: https://surveymoh.health.gov.bc.ca/public/survey/gpac-ana-guideline

Effective Date: XX

Scope

This guideline describes the appropriate use of antinuclear antibody (ANA) testing in the diagnosis of Connective Tissue Diseases (CTDs)* 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 is only indicated if the diagnosis of a CTD (i.e., systemic lupus erythematosus, scleroderma, Sjögren'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.
  - to confirm a diagnosis of rheumatoid arthritis or osteoarthritis.
  - to monitor lupus flares.
- ANA testing need only be ordered once. Repeat ANA testing is not indicated following previous positive results. Serial monitoring of ANA is not indicated, as changes in ANA titres do not correlate with disease activity.
- Repeat ANA testing may be indicated after a negative result only when the clinical presentation changes.

Background

CTDs are a group of clinically uncommon inflammatory conditions associated with autoimmune dysregulation, that can lead to disability, organ failure and premature mortality.[1] CTDs include systemic lupus erythematosus (SLE), systemic sclerosis, inflammatory myositis (i.e. polymyositis and dermatomyositis), and Sjögren's syndrome.

* Systemic Autoimmune Rheumatic Diseases (SARDs) is the emerging term for related autoimmune disease states that encompass the Connective Tissue Diseases (CTDs). However, for the purposes of this document, we will continue to use the term CTDs.

As of 2021/2022, only 0.56% of the B.C. population was diagnosed with CTD; the estimated incidence per million is 56 for SLE, 19 for scleroderma, and <10 for dermatomyositis and polymyositis. Although the incidence of CTDs is low, ANA testing is frequently ordered. In 2022/23 over 114,000 ANA tests were performed in B.C., at a total cost of $2.2 million. **The number of tests ordered greatly exceeds the small number of new cases of CTDs expected per annum**. This volume of testing suggests that ANA tests are being ordered for patients with little probability of having ANA-associated CTD. Moreover, 31% of positive ANA tests were from repeat testing with the previous ANA test being positive.[†]

Definitions

ANA: Class of self-directed antibodies that bind to any cellular component of the nucleus, including proteins, DNA, RNA, and nucleic acid-protein complexes. ANAs are involved in disease pathogenesis, and the ANA test has been the foundation of diagnosis for autoimmune connective tissue diseases, including SLE, Sjögren's syndrome, and polymyositis/dermatomyositis.[2,3]

ENA: Extractable Nuclear Antigens (ENA) are a subset of ANAs. ENA testing is performed to clinically subclassify patients known to have a positive ANA screening test.

ENA testing is a multicomponent panel test used to diagnostically distinguish the different CTDs. In BC, the ENA panel is minimally comprised of dsDNA, anti-Ro (also called anti-SSA), anti-La (also called anti-SSB), anti-Sm (anti-Smith antibody), anti-RNP (anti-ribonucleoprotein), anti-Jo-1, and anti-Scl70. Discussion of the disease correlates of these tests is beyond the scope of this document but the interested reader is directed to pertinent reviews.

Testing

ANA testing is only indicated after clinical assessment reveals signs or symptoms suggestive of SLE, scleroderma, Sjögren's syndrome or polymyositis/ dermatomyositis.[4]
Indications to order an ANA test requires the presence of at least two of the following clinical findings unexplained by other causes (See **Table 1: Clinical Features of CTDs**).

Table 1: Clinical Features of CTDs[5]

☐ Lupus rash	☐ Hemolytic anemia, thrombocytopenia, neutropenia, or lymphopenia
☐ Inflammatory arthritis	☐ Seizures
☐ Myositis	☐ Psychosis*
☐ Oral ulcers	☐ Raynaud's phenomenon
☐ Pleurisy or pericarditis	☐ Scleroderma skin changes
☐ Proteinuria or active urinary sediments	☐ Scarring alopecia
☐ Sicca (dry mouth/ dry eyes)	

*In the context of a clinical presentation compatible with lupus.[6]

In the absence of two or more of the clinical signs and symptoms listed above, a positive ANA test only confounds the diagnostic process, and causes unnecessary anxiety for patients. ANAs are found in up to 16% of the normal population, higher in females and increasing with age.[7,8] Positive ANA tests may also be seen in a wide range of diseases, other than CTD, where they have no diagnostic or

[†] Antibody Testing Update on Test Utilization Fiscal Year 2022/23, provided by B.C. Provincial Laboratory Medical Services.

prognostic value. Positive ANA results may be seen in individuals with viral infections and conditions including malignancies, primary biliary cirrhosis, and other autoimmune disorders. Additionally, certain medications [e.g., statins, ß-blockers, Angiotensin-converting enzyme (ACE) inhibitors, Non-steroidal anti-inflammatory drugs (NSAIDs) and biologics] can induce lupus-like symptoms, accompanied by positive ANA results.[9,10]

More selective ordering of ANA tests would reduce the volume of tests performed, improve the predictive value of the test, reduce avoidable misdiagnoses, reduce unnecessary referrals, and inappropriate therapy.[11] However, atypical clinical presentations of CTD can occur and clinical judgment should guide ANA testing in these cases.

- **ANA testing is <u>not</u> indicated:**
  - unless a CTD is clinically suspected.
  - to confirm a diagnosis of rheumatoid arthritis or osteoarthritis.
  - to investigate chronic fatigue, back pain, or other musculoskeletal pain unless accompanied by two or more of the clinical findings listed above (See **Table 1: Clinical Features of CTDs**).
  - for serial monitoring, as changes in ANA titres do not correlate with disease activity (e.g., lupus flares).
  - as a screening test for disease in the general healthy population.

Repeat ANA testing is <u>rarely</u> indicated: Repeat testing after a prior negative test is only indicated when there is a change in the patient's condition that now suggests the emergence of a CTD. Although higher ANA values are more specific for CTD, serial monitoring of ANAs does not contribute to improved clinical outcomes.[12,13]

- **ENA testing**

ENA testing may help characterize nuclear antibodies associated with specific CTD diagnoses and may help to further distinguish CTD diagnoses. It is not a standalone test and will be performed by laboratories in BC only following a positive ANA. It may be ordered by practitioners in the presence of a positive ANA or performed at laboratory discretion to help further characterize high ANA titres. In either case, the primary care practitioner may receive a quantitative report of tests in the ENA battery. ENA interpretation is challenging. Prior to making a clinical decision based on ENA results, a call to the RACE line or a discussion with a rheumatologist, internist, or laboratory consultant is recommended.

Referral

If the patient has two clinical symptoms suggestive of CTD (See **Table 1: Clinical Features of CTDs**)) and a positive ANA/ENA, a referral or a call to the RACE line is recommended. Based on positive ANA/ENA results alone, without clinical correlates, only a minority of patients need referral.

Resources

Abbreviations

CTDs	Connective Tissue Diseases
ANA	Antinuclear Antibody
SLE	Systemic Lupus Erythematosus
ENA	Extractable Nuclear Antigens
dsDNA	Double stranded DNA
ACE	Angiotensin Converting Enzyme
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs

Practitioner Resources

- **RACE Line**: Rapid Access to Consultative Expertise Program: raceconnect.ca/. A phone consultation line for physicians, nurse practitioners and medical residents. If the relevant specialty area is available through your local RACE line, please contact them first.

- **PathwaysBC**: An online resource that allows GPs and nurse practitioners and their office staff to quickly access current and accurate referral information, including wait times and areas of expertise, for specialists and specialty clinics. See: pathwaysbc.ca/login

- **Health Data Coalition**: An online, physician-led data sharing platform that can assist you in assessing your own practice in areas such as chronic disease management or medication prescribing. HDC data can graphically represent patients in your practice with chronic diseases in a clear and simple fashion, allowing for reflection on practice and tracking improvements over time. See: Health Data Coalition – Better Information. Better Care. Better Patient Outcomes. (hdcbc.ca)

Patient, Family and Caregiver Resources

- **HealthLinkBC**: You may call HealthLinkBC at 8-1-1 toll-free in B.C., or for the deaf and the hard of hearing, call 7-1-1. You will be connected with an English-speaking health-service navigator, who can provide health and health-service information and connect you with a registered dietitian, exercise physiologist, nurse, or pharmacist. See: healthlinkbc.ca/
    - HealthLinkBC ANA testing

Billing Codes

90280
90281

Associated Documents

The following documents accompany this guideline:

- List of Contributors

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