Systemic Sclerosis Antibodies

Indications for Ordering

Comprehensive evaluation of systemic sclerosis (SSc)

Test Description

Panel includes
- Scleroderma (Scl-70) (ENA) Antibody, IgG (antitopoisomerase)
  - Semiquantitative multiplex bead assay
- RNP (U1) (Ribonucleic Protein) (ENA) Antibody, IgG
  - Semiquantitative multiplex bead assay
- Antinuclear Antibody (ANA) with HEp-2 Substrate, IgG by IFA
  - Semiquantitative indirect fluorescent antibody (IFA)
  - Reports centromere pattern
- Fibrillarin (U3 RNP) Antibody, IgG
  - Qualitative immunoblot
- PM/Scl-100 Antibody, IgG by Immunoblot
  - Qualitative immunoblot
- RNA Polymerase III Antibody, IgG
  - Semiquantitative enzyme-linked immunosorbent assay (ELISA)

Tests to Consider

Typical testing strategy

Initial testing
- CBC with platelet count and automated differential
- Nuclear antibody (ANA) by IFA, IgG
  - Confirmatory or secondary testing based on one or more of the following
    - ANA IFA patterns with three main patterns observed (centromere, nucleolar, and speckled patterns)
    - Clinical presentation
    - Ethnicity

Primary tests

Comprehensive Systemic Sclerosis Panel 3000480
- Indicated when suspicion for SSc is high and patient presents with features of overlap syndrome
- Individual tests in panel (may also be ordered separately)
  - Scleroderma (Scl-70) (ENA) Antibody, IgG 0050599
  - RNP (U1) (Ribonucleic Protein) (ENA) Antibody, IgG 0050470
  - Antinuclear Antibody (ANA) with HEp-2 Substrate, IgG by IFA 3000082
  - Fibrillarin (U3 RNP) Antibody, IgG 2012173
  - PM/Scl-100 Antibody, IgG by Immunoblot 2003040
  - RNA Polymerase III Antibody, IgG 2001601

Criteria Systemic Sclerosis Panel 3000479
- Indicated for patients with distinct features of SSc
- If ANA IFA is positive and SSc-specific markers are negative, testing for other markers associated with SSc or connective tissue disease based on observed ANA IFA pattern(s) is performed
- Negative results do not rule out SSc
  - If negative and suspicion for SSc is strong, consider testing for U3 RNP (fibrillarin), PM/Scl-100, U1RNP, Th/Tho, or other connective tissue disease autoantibodies based on patient's clinical presentation
- Individual tests in panel (may also be ordered separately)
  - Antinuclear Antibody (ANA) with HEp-2 Substrate, IgG by IFA 3000082
  - Scleroderma (Scl-70) (ENA) Antibody, IgG 0050599
  - RNA Polymerase III Antibody, IgG 2001601

Related tests

- Antinuclear Antibody (ANA) with HEp-2 Substrate, IgG by IFA with Reflex by Pattern 3000601
- Myositis Extended Panel 2013961
- Connective Tissue Diseases Profile 0051668
- Centromere Antibody, IgG 0050714
  - Test suggested if low titer (≤1:160) or questionable centromere pattern from Nuclear Antibody (ANA) by IFA, IgG

Disease Overview

Incidence – 3-20/million

Age of onset – peak onset 20-30 years

Sex – M<F, 1:3-8

Ethnicity – overall slight increase in prevalence for African Americans compared to Caucasians
- 10-fold increase in Choctaw Indians

Symptoms

- Dermatologic
  - Digital ulcers
  - Hair loss
  - Sclerodactyly
  - Abnormal nailfold capillaries
  - Raynaud phenomenon
  - Skin thickening
  - Telangiectasia
- Gastrointestinal
  - Gastroparesis/constipation
  - Esophageal dysmotility
  - Gastroesophageal reflux disease
  - Malabsorption
- Pulmonary
  - Pulmonary hypertension leading to interstitial fibrosis
- Musculoskeletal
  - Arthralgias/myalgias
  - Arthritis
  - Myopathy (usually proximal)
- Cardiovascular
  - Conduction abnormalities (eg, arrhythmias)
  - Myocardial fibrosis
  - Pericarditis
  - Valvular abnormalities
- Otorhinolaryngologic
  - Sicca syndrome
- Renal
  - Glomerulonephritis
  - Scleroderma renal crisis

Diagnostic issues

- Autoimmune connective tissue diseases may present with similar features, particularly early in disease, making diagnosis difficult
- ANA IFA patterns may help define diagnostic pathways
  - Most patients with SSc will have one of the following antibodies, and ordering tests for only these three antibodies is adequate for initial evaluation (van den Hoogen, 2013)
    - Centromere
    - Scl-70
    - RNA polymerase III
- The presence of SSc-specific antibodies may help predict disease phenotype
  - **C**alcinosis, **R**aynaud phenomenon, **e**sophageal dysmotility, **s**clerodactyly, and **t**elangiectasia (CREST) syndrome
    - Antibodies against centromere are most common
  - Diffuse cutaneous SSc
    - Antibodies against Scl-70 and RNA polymerase III are most common
- Antibody patterns may differ by ethnicity
  - Testing for less commonly associated SSc antibodies (eg, U3-RNP, PM/Scl, and Th/To) may be appropriate when results for antibodies commonly associated with SSc are negative.
    - Antibodies against U3-RNP are most common in African Americans
    - Th/To and PM/Scl are more common in Caucasians with limited SSc

Test Interpretation

Clinical sensitivity

- Sensitivity for ANA by IFA for SSc ranges from 90-95%
- Sensitivity for individual SSc-specific marker is dependent on ethnicity

Results

Reports ANA patterns (including centromere)

- If positive, pattern and titers are reported

Limitations

- Negative antibody test result does not exclude SSc
  - 5-10% of SSc patients are ANA IFA negative
- Panel does not include Th/To

Reference

- van den Hoogen, et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. Ann Rheum Dis. 2013;72:1747-1755
- Salazar, et al. Antinuclear antibody-negative systemic sclerosis. Semin Arthritis Rheum. 2015;44(6):680-686