# Test Definition: CMA

Centromere Antibodies, IgG, Serum

## Overview

### Useful For

Evaluating patients with features of systemic autoimmune rheumatic disease, particularly systemic sclerosis, Sjogren's syndrome, or overlap disease

Aiding in the phenotypic stratification of patients with systemic sclerosis (limited cutaneous vs diffuse cutaneous or risk for specific clinical manifestations)

### Testing Algorithm

For more information see Connective Tissue Disease Cascade.

### Special Instructions

- Connective Tissue Disease Cascade

### Method Name

Multiplex Flow Immunoassay

### NY State Available

No

## Specimen

### Specimen Type

Serum

### Specimen Required

**Supplies:** Sarstedt Aliquot Tube, 5 mL (T914)
**Collection Container/Tube:**
**Preferred:** Serum gel
**Acceptable:** Red top
**Submission Container/Tube:** Plastic vial
**Specimen Volume:** 0.5 mL
**Collection Instructions:** Centrifuge and aliquot serum into a plastic vial.

### Specimen Minimum Volume

0.35 mL

### Reject Due To

| | |
|---|---|
| Gross hemolysis | Reject |

| | |
|---|---|
| Gross lipemia | Reject |
| Gross icterus | OK |
| Heat-Treated | Reject |

### Specimen Stability Information

| Specimen Type | Temperature | Time | Special Container |
|---|---|---|---|
| Serum | Refrigerated (preferred) | 21 days | |
| | Frozen | 21 days | |

## Clinical & Interpretive

### Clinical Information

The presence of anti-centromere antibody (ACA) is associated with antinuclear antibody and demonstrates a characteristic discrete nuclear speckled staining pattern of both interphase nuclei and metaphase chromatin on HEp-2 substrate by indirect immunofluorescence assay (IFA).(1,2) ACA has a broad specificity for the centromere–kinetochore macro-complex.(2) Several putative epitopes associated with this autoantigenic complex have been described with CENP-A (18 kDa), CENP-B (80 kDa), CENP-C (140 kDa, and CBX as the main targets.(1-4) The CENP-B antigen is believed to be the primary autoantigen in systemic autoimmune diseases and is recognized by most, if not all, sera that contain centromere antibodies.(1-4) Together with anti-Scl 70 and anti-RNA polymerase III autoantibodies, ACA is recommended for the diagnostic classification systemic sclerosis (SSc) by the American College of rheumatology/European League Against Rheumatism collaborative initiative.(5)

Historically, ACA has been associated with SSc but also occur in varying frequencies in autoimmune diseases such as Sjögren's syndrome (SjS), primary biliary cholangitis (PBC), PBC overlap disease, or overlap connective tissue disease (CTD), and rheumatoid arthritis.(1-7) ACA is the most detected SSc-specific autoantibody and it is typically associated with the limited cutaneous SSc (lcSSc), previously referred to as CREST syndrome which is comprised of calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia.(1,3,6,8) In addition, ACA has a higher frequency in Caucasian than in African American or Asian cohorts.(1,7,8) The lcSSc is characterized by skin fibrosis of the fingers (sclerodactyly) and, in some cases, of the face and neck or the skin distal to the elbows and/or knees, sparring the upper arms, upper legs, or trunk.(1,7,8) Based on the autoantibody and cutaneous phenotypic characterization, ACA-positive patients with lcSSc generally have the highest 20-year survival, lowest incidence of clinically significant pulmonary fibrosis, scleroderma renal crisis, and lowest incidence of cardiac SSc.(2,5,7,8)

In addition to SSc, ACAs occur in patients with SjS, rheumatoid arthritis, PBC overlap, or overlap CTD.(1-7) Recent studies aimed at determining the fine specificities ACA in different CTD demonstrated comparative frequencies to CENP-B, the major ACA target.(2,4) In both studies, ACA recognize centromere “complex” rather than individual protein, and this feature is common among patients with Sjogren’s syndrome, SSc and PBC.

In routine clinical evaluation, ACA as well as ACA-specific for CENP-B and CENP-A, can be detected using a variety of methods.(1,9,10) The ACA detected using HEp-2 substrate by IFA, broadly defines a heterogeneous population of centromeric proteins (centromere-kinetochore macro-complex) while most solid-phase immunoassays for clinical evaluation are designed with mainly CENP-B antigen.(10)

## Reference Values

<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

## Interpretation

Anti-centromere antibodies are mainly associated with systemic sclerosis and may be useful in the risk stratification for cutaneous and organ involvement as well as survival outcomes. They may also be observed in other autoimmune diseases such as Sjogren's syndrome, rheumatoid arthritis, primary biliary cholangitis and overlap diseases.

Detectable levels of anti-centromere antibodies may predate overt clinical features of systemic sclerosis or related diseases.

## Cautions

Absence of anti-centromere antibodies by any of the methods, especially solid-phase immunoassays, does not rule out a diagnosis of systemic sclerosis or associated diseases.

Low levels of anti-centromere antibodies detected using solid-phase immunoassays may have low predictive value for disease. Confirmation using HEp-2 substrate by immunofluorescence assay may be useful if clinical suspicion for systemic sclerosis is high.

Using HEp-2 substrate, the centromere pattern maybe positive and the CENP-B solid-phase negative due to differences in the expression of antigens between the two methods.

## Clinical Reference

1. Stochmal A, Czuwara J, Trojanowska M, et al. Antinuclear antibodies in systemic sclerosis: an update. Clin Rev Allergy Immunol 2020;58(1):40-51
2. Kajio N, Takeshita M, Suzuki K, et al. Anti-centromere antibodies target centromere-kinetochore macrocomplex: a comprehensive autoantigen profiling. Ann Rheum Dis. 2021;80(5):651-659
3. Earnshaw W, Bordwell B, Marino C, Rothfield N. Three human chromosomal autoantigens are recognized by sera from patients with anti-centromere antibodies. J Clin Invest. 1986;77(2):426-430
4. Takeshita M, Suzuki K, Kaneda Y, et al. Antigen-driven selection of antibodies against SSA, SSB and the centromere 'complex', including a novel antigen, MIS12 complex, in human salivary glands. Ann Rheum Dis. 2020;79(1):150-158
5. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of rheumatology/European League against rheumatism collaborative initiative. Ann Rheum Dis 2013;72(11):1747-1755
6. Kuramoto N, Ohmura K, Ikari K, et al. Anti-centromere antibody exhibits specific distribution levels among anti-nuclear antibodies and may characterize a distinct subset in rheumatoid arthritis. Sci Rep. 2017;7(1):6911
7. Cavazzana I, Vojinovic T, Airo P, et al. Systemic sclerosis-specific antibodies: novel and classical biomarkers. Clin Rev Allergy Immunol. 2023;64(3):412-430
8. Nihtyanova SI, Sari A, Harvey JC, et al. Using autoantibodies and cutaneous subset to develop outcome-based disease classification in systemic sclerosis. Arthritis Rheumatol. 2020;72(3):465-476
9. Fritzler MJ, Rattner JB, Luft LM, et al. Historical perspectives on the discovery and elucidation of autoantibodies to centromere proteins (CENP) and the emerging importance of antibodies to CENP-F. Autoimmun Rev. 2011;10(4):194-200
10. Bossuyt X, De Langhe E, Borghi MO, Meroni PL. Understanding and interpreting antinuclear antibody tests in systemic rheumatic diseases. Nat Rev Rheumatol. 2020;16(12):715-726

## Performance

### Method Description

Recombinant centromere protein B (CENP-B) antigen is coupled covalently to polystyrene microspheres, which are impregnated with fluorescent dyes to create a unique fluorescent signature. Centromere antibodies, if present in diluted serum, bind to the CENP-B antigen on the microspheres. The microspheres are washed to remove extraneous serum proteins. Phycoerythrin (PE)-conjugated antihuman IgG antibody is then added to detect IgG anti-CENP-B bound to the microspheres. The microspheres are washed to remove unbound conjugate, and bound conjugate is detected by laser photometry. A primary laser reveals the fluorescent signature of each microsphere to distinguish it from microspheres that are labeled with other antigens, and a secondary laser reveals the level of PE fluorescence associated with each microsphere. Results are calculated by comparing the median fluorescence response for CENP-B microspheres to a 4-point calibration curve.(Package insert:  BioPlex 2200 ANA Screen. Bio-Rad Laboratories; 02/2019)

### PDF Report

No

### Day(s) Performed

Monday through Friday, Sunday

### Report Available

Same day/1 to 3 days

### Specimen Retention Time

14 days

### Performing Laboratory Location

Mayo Clinic Jacksonville Clinical Lab

## Fees & Codes

### Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

### Test Classification

This test has been cleared, approved, or is exempt by the US Food and Drug Administration and is used per manufacturer's instructions. Performance characteristics were verified by Mayo Clinic in a manner consistent with CLIA requirements.

### CPT Code Information

83516

## LOINC® Information

| Test ID | Test Order Name | Order LOINC® Value |
|---|---|---|
| CMA | Centromere Ab, IgG, S | 31290-0 |

| Result ID | Test Result Name | Result LOINC® Value |
|---|---|---|
| CMA | Centromere Ab, IgG, S | 31290-0 |