Role of Serologic Testing in Rheumatic Diseases

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Disclosure

None
Objectives

- Discuss commonly available serologic testing useful in daily clinical practice
- Recognize the serologic associations of rheumatic diseases
- Recognize their diagnostic utilities and limitations
Diagnostic Accuracy for Lupus and other autoimmune diseases in the community setting

- 476 patients were evaluated at Autoimmunity Center of University of Florida, Gainesville for 13 months which were by from primary care physicians

- SLE was over diagnosed on many patients on the basis of + ANA

- 39 patients are taking prednisone 60 mg/day who have no autoimmune disease but only have + ANA

- Inappropriate diagnosis leads to inappropriate therapy, emotional and financial consequences

- The authors suggested continuing education in screening for autoimmune disease and identify patients who may benefit from early referral.
## Antinuclear Antibody (ANA) Testing for Connective Tissue Disease

### British Columbia Population:
Population: 4.631 million. More than 94,000 ANA tests were performed in B.C. in fiscal year 2011/12 at a cost of $2.24 million annually.

### Incidence and Estimated New Cases in B.C. for Selected CTDs

<table>
<thead>
<tr>
<th>Connective Tissue Disease</th>
<th>Disease incidence per million population</th>
<th>Estimated new BC cases/year *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
<td>56</td>
<td>259</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>19</td>
<td>88</td>
</tr>
<tr>
<td>Dermatomyositis &amp; polymyositis</td>
<td>&lt; 10</td>
<td>&lt; 46</td>
</tr>
</tbody>
</table>

Eighteen percent of first-time tested outpatients underwent unnecessary repeat testing in 2010/2011. In 57.2% of the repeat testing, both the initial and the repeat ANA tests were ordered by a GP. In 24.8% the initial test was ordered by a GP and the repeat test was ordered by a specialist, and in 10.2% both the initial and the repeat test were ordered by the same specialist.
ANA Testing for Connective Tissue Diseases

- The sensitivity and specificity of ANA has been reported as 40% and 66% (PPV = 29%, NPV = 77%) in a study looking at the diagnosis of any CTD as requested by primary care.

- More selective ordering of ANA tests would not only improve the predictive value of the test, but also reduce the volume of tests performed, unnecessary referrals, misdiagnosis, and inappropriate therapy.
Prevalence and Sociodemographic Correlates of Antinuclear Antibodies in the United States

- Serum samples from the US National Health and Nutrition Examination Survey (NHANES) from 1999 to 2004
- ~32 Million Americans (13.8%) have +ANA
- The most common specific autoantibodies were anti-Ro (3.9%) and anti-Su (2.4%).
- Prevalence is higher among females, older individuals, African Americans, and those with a normal body weight.
- No significant associations of ANA with education, family income, alcohol use, smoking history, serum levels of cotinine, or C-reactive protein were observed.

*Arthritis & rheumatism; 2012; 64 (7), 2319–2327*
Antinuclear Antibody (ANA) Test Results in a Hypothetical Population.
ANA⁺, No Rheumatic DX-Possibilities

- Autoimmune Rheumatic Disease, not yet diagnoses
- Other autoimmune disease with + ANA
  - Autoimmune thyroid, liver
- Transient, e.g., post-viral infection
- Positive end of bell-shaped normal distribution (low titer)
- Lab factors
  - Pre-or post-analytical: wrong specimen or report
  - Analytical: lab method
- ANA autoAb not associated with rheumatic disease
Many years ago there was a television commercial for a popular light beer in which two groups of football players shouted out what they liked about the product. “Tastes great!” one team yelled. “Less filling!” the other said. What was so wondrous, the advertisement implied, was that one beer could satisfy both groups.

Does it apply to ANA testing?
Representative ANA IFA quantification: US Lab proficiency test result 2015
How Often is a ‘Positive ANA’ Reported as Negative?

- Recent U.S. survey: usual, expected result 1:160
  - Range: negative to 1:5,120
- Negative result reported by 2.6% of labs
- EIA as ANA screen: 6.5% called negative
- IFA ANA screen: 1.5% called negative
- Multiplex bead assays: 2.0% called negative

2015 data
What Are the Current Methods for ANA Screening?

- Immunofluorescence microscopy
- ELISA
- Multiplex assays
  - Bead assays / addressable laser bead assays (‘Flow bead-ometer’)
Microscope-based ANA-Immunofluorescence Assay (IFA): ‘Gold Standard’

Cultured HEp-2 cells are the substrate for antibody binding.

ANA Test Result: Patterns, Titers
Hep2 cells showing different ANA patterns

A, homogeneous; B, centromere; C, nucleolar; and D, speckled
Conventional methods of testing ANA

Tentative Diagnosis → ANA screening by IIF → Staining pattern, titer → ANA to specific antigens → ELISA for ENA

dsDNA, Sm, Sm/RNP, Jo-1, Scl-70, SS-A, SS-B
Multiplexing: Flow cytometric immunoassay based on multiplexed fluorescent microspheres (beads)

Multiple antibodies can be detected in 1 reaction using multiple antigen beads.

Patient’s SSA antibody = Y

Detection antibody = Y
Multiplex Testing Dominant in Large Labs

- Automated
- Multiple results from one sample
- Different manufacturers have similar design, but not identical
- Used to report individual autoAb results, and also by some labs to replace the IFA-ANA
Perspective of the American College Rheumatology
ACR position statement on ANA testing, February 2009

www.rheumatology.org/publications/position/ana_position

• **IFA-ANA test** should remain the gold standard for ANA testing.
How to Handle Variability of Lab Tests for ANAs

- Labs differ. “Know your lab”

- Worth repeating tests that do not support your clinical impression

- Feedback to lab director if questions or problems

- Professional interaction between ACR and the College of American Pathologists (CAP) to improve and coordinate
ANA testing: (Most) Clinical Lab Directors’ Perspective

1. There is no ANA gold standard.
2. ANA testing is one of the least standardized areas of lab testing. Modest standardization remains a goal.
Antinuclear Antibody Testing: A Study of Clinical Utility

The sensitivity of the ANA test for SLE was high, but overall the positive predictive value was low for SLE or other rheumatic diseases. Sensitivity was low for ANA testing among patients with non—SLE rheumatic disease. More selective test ordering might improve the clinical utility of this test. Clinicians ordering the ANA test should be aware of the test's low-positive predictive value in settings with a low prevalence of rheumatic disease, particularly among older patients.

Arch Intern Med. 1996;156:1421-1425
Receiver operating characteristic curve displaying results of the antinuclear antibody testing across a range of cutoff points for systemic lupus erythematosus (SLE), other rheumatic disease (ORD), and any rheumatic disease (ARD). Titer of positive antinuclear antibody test results decrease (to 1:40) from left to right.
Presence of a high titer (>1:640) increases suspicion of an autoimmune disease, but is not diagnostic

- Titers can fluctuate
  - *This is not reflective of disease activity, and is not indicated to follow serially*

  - Titers that disappear are less clinically significant

- For diagnosis of SLE, sensitivity of ~95% and specificity of 57%

+ Primary utility diagnostically is the NPV for SLE if ANA is negative
Positive ANA

High probability of autoimmune rheumatic disease

- Identify specific antigen
- Search for evidence of other disease or organ involvement
- Ancillary tests e.g. Complement, Coombs
Positive ANA

Low probability of autoimmune rheumatic disease

- Low titer or transient titer: Reassure patient
- High titer or persistent titer: Search for alternative dx
- High titer or persistent titer: Follow patient
Algorithm for the use of anti-nuclear antibodies (ANAs) in the diagnosis of connective tissue disorders

Kelley and Firestein's Textbook of Rheumatology, 10th ed. 2017
## Specific auto-antibodies in SLE

<table>
<thead>
<tr>
<th>Autoantibodies</th>
<th>Prevalence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-ds-DNA</td>
<td>70%</td>
<td>activity of SLE and lupus nephritis. Level monitored in lupus nephritis</td>
</tr>
<tr>
<td>Anti-Sm</td>
<td>25%</td>
<td>specific for SLE, correlation with disease activity and any particular lupus features is uncertain, also seen along with RNP antibody, common in blacks and Asians than whites</td>
</tr>
<tr>
<td>Anti-RNP</td>
<td>40%</td>
<td>Defining autoantibody in mixed connective-tissue disease, not specific for SLE, Common in blacks than whites</td>
</tr>
<tr>
<td>Anti-Ro (SS-A)</td>
<td>30%</td>
<td>Sjögrens syndrome, neonatal lupus, Congenital heart block, photosensitive rash, subacute cutaneous lupus erythematosus, decreased risk of nephritis</td>
</tr>
<tr>
<td>Anti-La (SS-B)</td>
<td>10%</td>
<td>associated with reduced risk of nephritis, Sjögrens syndrome, neonatal lupus</td>
</tr>
<tr>
<td>Anti Histone antibody</td>
<td>70%</td>
<td>SLE, Drug induced SLE</td>
</tr>
<tr>
<td>Anti erythrocyte antibody</td>
<td>60</td>
<td>Measured as direct Coombs test, Hemolysis</td>
</tr>
<tr>
<td>Anti Ribosomal antibody</td>
<td>20%</td>
<td>Depression and Psychosis</td>
</tr>
</tbody>
</table>
Don’t test ANA sub-serologies without a positive ANA and clinical suspicion of immune-mediated disease.

Tests for anti-nuclear antibody (ANA) sub-serologies (including antibodies to double-stranded DNA, Smith, RNP, SSA, SSB, Scl-70, centromere) are usually negative if the ANA is negative. Exceptions include anti-Jo1, which can be positive in some forms of myositis, or occasionally, anti-SSA, in the setting of lupus or Sjögren’s syndrome. Broad testing of autoantibodies should be avoided; instead the choice of autoantibodies should be guided by the specific disease under consideration.
Antiphospholipid Antibody Syndrome

Diagnosis:

- Lupus anticoagulant (LAC) - antibodies that prolong phospholipid-dependent coagulation reactions e.g., APTT and/or DRVVT are prolonged and do not correct after equal mix with normal plasma.

- Anti-cardiolipin antibodies (aCL) - detected by ELISA (IgG or IgM or IgA)

- Anti-β2-glycoprotein I antibody (Ig G, IgM, IgA)
Antiphospholipid Antibody Syndrome

- Both LAC, ACL, AND Anti-β₂-glycoprotein I antibody should be checked
  - Both LA & aCL + in 60-70%
  - LA +, aCL neg 15-20%
  - aCL +, LA neg 15-20%

- The strongest clinical associations have been seen with IgG aCL. IgM or IgA antibodies may be associated with the syndrome.

- A positive aPL test should be confirmed by repeating in 6 to 8 weeks
Measurement of Complement

- Disease associated with hypocomplementemia or deficiency of complement component
- Monitor disease activity such as SLE
- Measured by CH50, C3, C4
  - CH 50: Functional assay, checks classical pathway, can be false positive
  - C3 & C4: More accurate, measured by nephelometry
- Synthesized in liver, can be low in liver diseases
- Acute phase reactants, can be high in inflammatory states
Hypocomplementemia

- Systemic lupus erythematosus
- Vasculitis
  - Hypocomplementemic urticarial vasculitis
  - Polyarteritis nodosa (especially hepatitis B-associated)
- Glomerulonephritis
  - Poststreptococcal
  - Membranoproliferative
- Cryoglobulinemia (types II and III)
- Subacute bacterial endocarditis
- Serum sickness
- Inherited deficiency states
Clinical Syndromes Associated with Deficiencies of Components

<table>
<thead>
<tr>
<th>Component</th>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathway components</strong></td>
<td></td>
</tr>
<tr>
<td>C1q, C4, C2</td>
<td>Lupus-like syndromes</td>
</tr>
<tr>
<td>C3</td>
<td>Recurrent pyogenic infections</td>
</tr>
<tr>
<td>C5, C6, C7, C8</td>
<td>Recurrent Neisserial infection</td>
</tr>
<tr>
<td><strong>Regulatory proteins</strong></td>
<td></td>
</tr>
<tr>
<td>C1 inhibitor</td>
<td>Angioedema</td>
</tr>
</tbody>
</table>
Classification of scleroderma and clinical subsets

Type I: LIMITED
Type II: DIFFUSE
Type III:
# Autoantibodies in Systemic Sclerosis

<table>
<thead>
<tr>
<th>Common Autoantibodies Seen in SSc</th>
<th>Disease Manifestation Associations</th>
<th>North American Caucasian Frequency of Autoantibody Presence in SSc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti–Scl-70/Anti-topoisomerase I</td>
<td>dcSSc and severe pulmonary fibrosis</td>
<td>20%</td>
</tr>
<tr>
<td>Anticentromere</td>
<td>lcSSc and PAH</td>
<td>21%</td>
</tr>
<tr>
<td>Anti–RNA polymerase III*</td>
<td>dcSSc and SRC</td>
<td>24%</td>
</tr>
<tr>
<td>Anti–PM-Scl</td>
<td>SSc and inflammatory myopathy overlap</td>
<td>2%</td>
</tr>
<tr>
<td>Anti-U1 RNP</td>
<td>Mixed connective tissue disease/overlap syndrome</td>
<td>14%</td>
</tr>
<tr>
<td>Anti-U3-RNP*</td>
<td>ILD and PAH</td>
<td>4%</td>
</tr>
<tr>
<td>Anti-Th/To*</td>
<td>lcSSc, severe pulmonary fibrosis, and PAH</td>
<td>5%</td>
</tr>
</tbody>
</table>
Myositis antibodies: Why I need to order it

- About 50% of patients with polymyositis or dermatomyositis have myositis-specific antibodies.

- Presence of these antibodies can be strong supporting evidence for the diagnosis.

- Presence of myositis specific antibodies can confirm the diagnosis, biopsy can be avoided in certain situations.

- Myositis-specific antibodies have also improved our understanding of myositis by leading to the identification of certain clinical patterns.

- Identification of antibodies is associated with prognosis of certain subtypes of myositis.

- Again presence of antibodies without appropriate clinical symptoms would not confirm the diagnosis.
## Myositis Autoantibodies

<table>
<thead>
<tr>
<th>Myositis-Specific Antibodies</th>
<th>Myositis-Associated Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Jo-1</td>
<td>Anti-PM/Scl</td>
</tr>
<tr>
<td>Anti-PL-12</td>
<td>Anti-Ku</td>
</tr>
<tr>
<td>Anti-PL-7</td>
<td>Anti-SS-A (Ro) 52 kD, IgG</td>
</tr>
<tr>
<td>Anti-OJ</td>
<td>Anti-U1 RNP</td>
</tr>
<tr>
<td>Anti-EJ</td>
<td>Anti-U2 snRNP</td>
</tr>
<tr>
<td>Anti-SRP</td>
<td>Anti-Fibrillarin U3 RNP</td>
</tr>
<tr>
<td>Anti-Mi-2</td>
<td></td>
</tr>
<tr>
<td>Anti-TIF-1γ/TIF-1α (formerly P155/140 kD)</td>
<td></td>
</tr>
<tr>
<td>Anti-MDA5 (formerly part of P140 kD)</td>
<td></td>
</tr>
<tr>
<td>Anti-NXP-2 (MJ) (formerly part of P140 kD)</td>
<td></td>
</tr>
</tbody>
</table>
Myositis Autoantibody Phenotypes Differ in Clinical Presentation, Genetics and Prognosis

Anti-aminoacyl-tRNA synthetases
- Interstitial lung disease, Arthritis, Fevers, Mechanic’s hands; DR3
  - 75% 5-year survival

Anti-Signal Recognition Particle
- Acute-onset PM, Severe weakness, Myalgias, Myocarditis; DQA1*0104
  - 25% 5-year survival

Anti-Mi-2: chromodomain helicase DNA binding protein 4
- Classic Dermatomyositis, V-sign & shawl rashes, Cuticular overgrowth; DR7
  - 90% 5-year survival
MSA/MAAs and clinical associations in adult myositis

SEVERE MYOPATHY
- SRP
- DYSPHAGIA

NECROTISING MYOPATHY
- HMGCR
- STATINS

LUNG DISEASE
- Ha
- Jo-1
- Zo
- EJ
- PL7
- OJ
- PL12
- KS
- CTD OVERLAP
- Ku
- SnRNP
- Ro
- PmScI
- La

SKIN DISEASE
- MDA5
- Mi-2
- SAE

CALCINOSIS
- NXP2
- TIF1

MALIGNANCY
Case # 3

30 year old male patient admitted to the Regional One Hospital with renal failure and necrotizing skin lesions.

Urine drug screen is + for cocaine

Bx of the kidney: Pauci-immune GN

The question is do I need to order serology and how it can be helpful??
Frequency of PR3- and MPO-ANCA specificity by clinical phenotypes

Probability of relapse-free survival by ANCA specificity

ANCA-type and Treatment Response
Achievement of Complete Remission by 6 Months in RAVE

- **MPO-ANCA**
  - Rituximab: 60.6%
  - Cyclophosphamide: 63.6%
  - P = 0.80

- **PR3-ANCA**
  - Rituximab: 65.2%
  - Cyclophosphamide: 47.7%
  - P = 0.04

n=66 for MPO-ANCA
n=131 for PR3-ANCA
**ANCA: Types, Frequency, Target and Disease associations**

<table>
<thead>
<tr>
<th>Disease</th>
<th>IIF-ANCA</th>
<th>Antigen targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wegener granulomatosis</td>
<td>c-ANCA (75 - 80)</td>
<td>PR3</td>
</tr>
<tr>
<td></td>
<td>p-ANCA (10 - 15)</td>
<td>MPO</td>
</tr>
<tr>
<td>Microscopic polyangiitis</td>
<td>c-ANCA (25 - 35)</td>
<td>PR3</td>
</tr>
<tr>
<td></td>
<td>p-ANCA (50 - 60)</td>
<td>MPO</td>
</tr>
<tr>
<td>Churg-Strauss syndrome</td>
<td>c-ANCA (25 - 30)</td>
<td>PR3</td>
</tr>
<tr>
<td></td>
<td>p-ANCA (25 - 30)</td>
<td>MPO</td>
</tr>
</tbody>
</table>
ANCA in Non Vasculitis Diseases

- Drugs: Cocaine, Levamisole, PTU, Minocycline
- SLE, Felty’s syndrome, Rheumatoid Arthritis
- IBD, Sclerosing cholangitis, autoimmune hepatitis
- Infections: suppurative lung infections, endocarditis etc
Indirect Immunofluorescence (IIF) testing for ANCA

Formalin Fixation

- Strong cationic proteins (e.g., MPO)
- Weakly cationic or neutral proteins (e.g., PR3)

Ethanol Fixation

- c-ANCA
- Antibodies to strong cations

- p-ANCA
- Antibodies to neutral proteins of weak cations (e.g., PR3)

Abelson A. Cleveland Clinic Journal of Medicine 2010
ANCA testing algorithm

IFT on ethanol-fixed and formalin-fixed neutrophils

- Cytoplasmic staining on both ethanol-fixed and formalin-fixed cells
  - C-ANCA pattern
    - PR3-ANCA ELISA
      - MPO-ANCA ELISA
        - Other ANCA ELISA
          - C-ANCA (PR3-ANCA)

- Perinuclear/nuclear staining on ethanol-fixed cells
  - P-ANCA pattern
    - MPO-ANCA ELISA
      - MPO-ANCA ELISA
        - Other ANCA ELISA
          - P-ANCA (MPO-ANCA)

- Nuclear staining on formalin-fixed cells
  - IFT on HEP2
    - ANA
      - A-ANCA

- Mixed cytoplasmic and perinuclear/nuclear staining on ethanol-fixed cells
  - Cytoplasmic staining on formalin-fixed cells
    - A-ANCA pattern
      - MPO-ANCA ELISA
        - MPO-ANCA ELISA
          - PR3-ANCA ELISA
            - Other ANCA ELISA
              - A-ANCA
Diagnostic Performance of Antineutrophil Cytoplasmic Antibody Tests for Idiopathic Vasculitides

J Rheumatol 2001;28;1584-1590
Lab testing in RA
Normal labs do not r/o RA

Observational study of 2370 patients

- Median ESR at presentation: 30
- ESR normal in 45%
- CRP normal in 33%
- All RF tests negative in 37%
- 37% of patients had ESR < 28, normal CRP, or all negative RF tests

Sokka T, Pincus T. J Rheumatol 2009;36:1387
Rheumatoid Factor

RF is an immunoglobulin that binds the Fc portion of another immunoglobulin
Cyclic Citrullinated Peptide Antibody (CCP Ab, ACPA Ab)

Post translational modification of proteins
RF and CCP

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-CCP</td>
<td>77%</td>
<td>97%</td>
</tr>
<tr>
<td>RF</td>
<td>74%</td>
<td>78%</td>
</tr>
</tbody>
</table>
Clinical Significance of Combined Anti-Cyclic Citrullinated Peptide Antibody and Rheumatoid Factor Assays in Rheumatoid Arthritis Diagnosis

70 RA patients (13 males, 57 females; mean age 49.2±12.1 years; range 35 to 61 years) and 112 non-RA patients (35 males, 77 females; mean age 42.5±7.1 years; range 35 to 49 years) were retrospectively and statistically analyzed.

<table>
<thead>
<tr>
<th>Detection indicator</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Total consistent rate</th>
<th>Diagnosis index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-cyclic citrullinated peptide</td>
<td>70.0</td>
<td>97.3</td>
<td>86.8</td>
<td>67.3</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td>77.1</td>
<td>95.5</td>
<td>88.5</td>
<td>72.6</td>
</tr>
<tr>
<td>Anti-cyclic citrullinated peptide + rheumatoid factor</td>
<td>93.1</td>
<td>94.6</td>
<td>91.8</td>
<td>81.7</td>
</tr>
</tbody>
</table>
Predictive Value of the CCP Antibody for RA Across a Range of Pretest Probabilities

<table>
<thead>
<tr>
<th>Pretest Probability of RA, %</th>
<th>Posttest Probability: Positive for Anti-CCP Antibody (Positive Predictive Value), %</th>
<th>Posttest Probability: Negative for Anti-CCP Antibody (Negative Predictive Value), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>41</td>
<td>2</td>
</tr>
<tr>
<td>11&lt;sup&gt;b&lt;/sup&gt;</td>
<td>62</td>
<td>4</td>
</tr>
<tr>
<td>13&lt;sup&gt;c&lt;/sup&gt;</td>
<td>67</td>
<td>5</td>
</tr>
<tr>
<td>24&lt;sup&gt;d&lt;/sup&gt;</td>
<td>81</td>
<td>10</td>
</tr>
<tr>
<td>50</td>
<td>93</td>
<td>26</td>
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<tr>
<td>75</td>
<td>98</td>
<td>51</td>
</tr>
<tr>
<td>90</td>
<td>99</td>
<td>76</td>
</tr>
<tr>
<td>95</td>
<td>99.6</td>
<td>87</td>
</tr>
</tbody>
</table>

Abbreviations: Anti-CCP, anti–cyclic citrullinated peptide; RA, rheumatoid arthritis

<sup>a</sup>Estimated sensitivity of anti-CCP antibody testing, 0.67; estimated specificity of anti-CCP antibody testing, 0.95.<sup>8</sup>

<sup>b</sup>Estimated pretest probability of RA when rheumatoid factor is negative.<sup>33</sup>

<sup>c</sup>Estimated pretest probability of RA among patients for whom a rheumatoid factor test is ordered.<sup>33</sup>

<sup>d</sup>Estimated pretest probability of RA when rheumatoid factor is positive.<sup>33</sup>
Rheumatoid Factor

+ Assists in diagnosis
  - In a patient with suggestive findings (symmetric polyarthritis), presence increases the certainty of diagnosis, if other causes excluded

+ Assists in prognosis
  - High titer increases the progression to erosive arthritis

+ Assists in treatment decisions
  - Warrants early DMARD use
Clinical associations of RF

- Rheumatoid arthritis (75-80%)
- Other rheumatic disease
  - Sjogren’s syndrome (~90%)
  - SLE (15-20%)
  - Sarcoidosis (~15%)
  - Parvovirus arthropathy (~15%, transient)
  - Mixed cryoglobulinemia (95%)
- Chronic infections
  - Chronic Hep C
  - Osteomyelitis
  - Bacterial endocarditis
- Monoclonal IgM paraproteins
- Normal aging (present at low titer)
Specific Autoantibodies Precede the Symptoms of RA: A Study of Serial Measurements in Blood Donors

![Graph showing the percentage of positive patients over years before the start of symptoms for IgM or ACPA, ACPA, and IgM-RF.](image)
**Rheumatoid Factor (RF)**

- 50% of patients with RA become positive for RF in first 6 months
- 85% become positive over the first 2 years, repeat testing advised.
- Current detection methods cannot differentiate between naturally occurring, transiently induced, and RA-associated rheumatoid factor.
- The levels are generally higher in RA than in many non-RA disorders, but significant overlap occurs.
- 10% to 15% of RA patients remain seronegative for rheumatoid factor throughout the disease course.
- The level does not vary with the activity of RA. So serial testing is not advised.
- Seropositive (+ RF & CCP Ab), better response to Rituximab Therapy
ACPAs are present in nearly 20% of unaffected first-degree relatives and more than 10% of more distant relatives of RA patients.

ACPAs are also produced by synovial tissue B cells and can be detected in synovial fluid.

ACPAs are predictors of more aggressive disease marked by bone and cartilage destruction.

Accelerated atherosclerosis in RA, independent risk factor for ischemic heart disease.

In patients with early undifferentiated inflammatory arthritis, ACPAs are also predictive for individuals who will progress to RA.
14-3-3η Biomarker

- 14-3-3η protein is released into the blood during synovial inflammation
- More accurate diagnosis of early RA
- Increases sensitivity for identifying early RA
- Helps diagnose RA in seronegative (anti-CCP- and RF-) patients
- Monitoring clinical improvement in RA
- Predictive of erosive disease in Psoriatic Arthritis (PSA)
Musculoskeletal complaints are common in the general population

Prevalence of inflammatory rheumatic diseases are low

Serologic tests are not often highly diagnostic (not gold standard)

Positive predictive value of many rheumatologic tests is low when tests these are ordered indiscriminately