Appropriate Serologic Testing to Evaluate Rheumatic Complaints

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Objectives

- Describe lab tests most useful in the evaluation of common rheumatic diseases
- Recognize the serologic associations of rheumatic diseases
- Apply sensitivity, specificity, likelihood ratio (LR) and positive predictive value to laboratory testing in clinical practice
Case study #1

- 28 y-o female with 6 months of HAs, fatigue and arthralgias. She hurts all day, Advil, Tylenol provide no relief. Occasional oral ulcers around menses. Going through divorce and worried about her kids
- On exam muscle and joints, including hands and feet, are tender, she is weepy
Case study #1

- What do you suspect?
  - Lupus
  - RA
  - Fibromyalgia
  - Depression/anxiety

- What would you order?
  - ANA, RF, ESR, uric acid
  - Sleep study
  - Vitamin D, TSH, hepatitis panel, CK
Objective 1

- Describe lab tests most useful in the evaluation of common rheumatic diseases
Initial Approach When Faced with Diffuse Rheumatic Disease Presentation

- Is it arthritis (in the joints) or not (bursitis, fibromyalgia, etc)
  - Answer by H&P

- Is it inflammatory or not?
  - Answer by H&P
  - Labs: ESR, CRP, CBC

- If arthritis, is it one of the common inflammatory conditions?
  - Answer by H&P
  - Labs: RF, CCP, ANA panel
Diagnostic Laboratory Evaluation of Possible Inflammatory Arthritis

- **Inflammatory markers**
  - ESR and/or CRP

- **For diagnosis/prognosis:** RF and CCP

- **Consider ANA panel**
  - Patients may be seronegative early in disease, and even have normal ESR/CRP, but a +ANA may heighten suspicion
RF is an autoantibody directed against IgG
Rheumatoid Factor

- Present in 70-80% of RA patients vs about 5% of normal population
- Also present in other rheumatic diseases and chronic disease
- Prognostic value: high levels associated with more severe joint disease and extra-articular disease
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)**
<table>
<thead>
<tr>
<th>AGE</th>
<th>Frequency of +RF</th>
</tr>
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<tbody>
<tr>
<td>20-60 yrs</td>
<td>2-4%</td>
</tr>
<tr>
<td>60-70 yrs</td>
<td>5%</td>
</tr>
<tr>
<td>&gt;70 yrs</td>
<td>10-25%</td>
</tr>
</tbody>
</table>
RF as “screening”

- **RA**
  - Prevalence of RA ~1.2% in US
  - +RF 80%

- **HCV**
  - Prevalence ~1-2% in US
  - RF+ rate 40-70%

- Given positive RF in US population, risk of HCV about the same as RA

- Consider HCV arthritis in RF+ patient with non-erosive disease or arthralgias
Cyclic Citrullinated Peptide antibody

- Also called ACPAs
- Citrullination is a post-translational modification of arginine
- Peptides after citrullination have increased affinity for MHCII binding groove of HLA DRB1 0401 allele
- Anti-CCP antibodies locally produced by plasma cells in synovium
Cyclic Citrullinated Peptide antibody

- Similar sensitivity as RF, **greater specificity**
  - Less common with Sjogrens or SLE
  - Not seen in HCV or other chronic infections or PMR
- Often present *early*, and predictive of severe, erosive disease
- Can be discordant with RF
## RF and CCP

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>Anti-CCP</td>
<td>77%</td>
<td>97%</td>
</tr>
<tr>
<td>RF</td>
<td>74%</td>
<td>78%</td>
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</table>
2010 Classification Criteria

Table 1. ACR/EULAR Revised RA Classification Criteria

<table>
<thead>
<tr>
<th>Domain</th>
<th>Score Range, points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number and site of involved joints</td>
<td>0-5</td>
</tr>
<tr>
<td>Serological abnormality</td>
<td>0-3</td>
</tr>
<tr>
<td>Elevated acute-phase response</td>
<td>0-1</td>
</tr>
<tr>
<td>Symptom duration (two levels)</td>
<td>0-1</td>
</tr>
</tbody>
</table>

Out of a possible 10 points, a score of ≥6 is one determining factor of definite RA

More emphasis on clinical presentation, shift away from older criteria like nodules and radiographic damage
## 2010 ACR/EULAR Classification Criteria for RA

### JOINT DISTRIBUTION (0-5)

<table>
<thead>
<tr>
<th>Joint Distribution</th>
<th>Score</th>
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<tbody>
<tr>
<td>1 large joint</td>
<td>0</td>
</tr>
<tr>
<td>2-10 large joints</td>
<td>1</td>
</tr>
<tr>
<td>1-3 small joints (large joints not counted)</td>
<td>2</td>
</tr>
<tr>
<td>4-10 small joints (large joints not counted)</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 small joints (at least one small joint)</td>
<td>5</td>
</tr>
</tbody>
</table>

### SEROLOGY (0-3)

- **Negative RF AND negative ACPA**: 0
- **Low positive RF OR low positive ACPA**: 2
- **High positive RF OR high positive ACPA**: 3

### SYMPTOM DURATION (0-1)

- **<6 weeks**: 0
- **≥6 weeks**: 1

### ACUTE PHASE REACTANTS (0-1)

- **Normal CRP AND normal ESR**: 0
- **Abnormal CRP OR abnormal ESR**: 1

≥6 = definite RA

What if the score is <6?

Patient might fulfill the criteria…

- **Prospectively** over time (cumulatively)
- **Retrospectively** if data on all four domains have been adequately recorded in the past
Acute Phase Proteins

- Proteins whose plasma concentrations change by at least 25% during inflammatory states
- Those that increase are called positive phase reactants, e.g. CRP, haptoglobin, ferritin
- Negative reactants decrease with inflammation, e.g. albumin, transferrin
Acute Phase Reactants

- Lack specificity, but can be useful in reflecting the presence and intensity of inflammatory process

- Most commonly used ESR and CRP
Case # 2

- 76 yo female awoke with stiffness in her neck and shoulders, trouble climbing out of bed; persisted for weeks
- Fatigue, anorexia, pain awakens her at night, feels weak, no swollen joints or vision changes
- One exam, normal temporal arteries, no scalp tenderness. She moves slowly, temp 100.1, give-way weakness of proximal muscles due to pain
- ESR 92 = PMR
ESR

- A measure of the distance in millimeters that RBCs fall in a tube over an hour
- An *indirect* measurement of alterations in acute-phase reactants
- Results can be affected by anemia
- Changes slowly with change in condition
- Normal values higher for women
ESR

- Markedly elevated (>100mm/hr)
  - Infection
  - Malignancy
  - Vasculitis (CTD-related, GCA)

- Markedly low
  - Afibrinogenemia
  - Agammaglobulinemia
  - Extreme polycythemia (Hct>65%)
  - Increased plasma viscosity
ESR

- It has been suggested that patients with PMR presenting with lower ESR may require lower doses of steroids and shorter duration of treatment.

- Patients with GCA and lower ESR are at higher risk for visual complications.
CRP

- Acute-phase reactant produced in response to IL-6 and other cytokines
- Elevation occurs within 4 hours of injury and peaks in 24-72 hours
- Able to activate the classic complement cascade
ESR vs CRP

- **CRP**
  - Better correlates with RA and seronegative spondyloarthritis disease activity

- **ESR**
  - Better correlates with SLE activity

- **Discrepancies found with some frequency**
  - Probably due to differences in production of specific cytokines or their modulators in different diseases
ESR and CRP

- Measurement of any acute phase reactant must take into account how the results will affect management
  - H&P generally more reliable reflection of disease activity

- Knowing which acute phase reactant historically correlates with the patient’s disease helps chose which to follow over time
Case # 3

- 57 y o with acute onset of toe and ankle pain
- HTN, DM II
- No trauma
- Low grade fever
- What do you order?
Mono/pauciarthrthritis

- The Eye of the Needle
  - Rule out infection, trauma, hemarthrosis
  - Confirm crystals
    - MSU – gout
    - CPPD – pseudogout
    - Apatite – pseudogout, crystals not birefringent, not seen on polarizing microscope

- Labs
  - Uric acid
  - Inflammatory markers
  - Coagulation panel
Serum uric acid

- Males post-puberty mean urate 5.2
  - ULN ~ 7mg/dl
  - Men with sUA>9.0, 22% develop gout after 5 years

- Pre-menopausal women mean 4.0
  - Estrogens have a uricosuric effect

- Post-menopausal mean 4.7
  - ULN ~ 6mg/dl
Uric acid

- Do not treat asymptomatic hyperuricemia
  - 43 million have hyperuricemia, 8 million with gout
- During gout flare, urate can be high, normal or low
  - Best time to check baseline is 2 weeks after flare has resolved
- 90% gout patients are underexcretors
  - 24 hour urine for urate and Cr excretion on regular purine diet
  - Urate >800mg, overproducer; <800mg is underexcretor
  - Spot urine urate not nearly as accurate
What if crystal exam is negative?

- Repeat synovial fluid analysis improves sensitivity
- EULAR does allow for presumptive diagnosis
Case # 4

- 52 y o female complains of fatigue, trouble climbing stairs, getting dressed but no pain
- Rash noted on exam, strength 4/5 proximal muscles
Idiopathic Inflammatory Myopathies
Polymyositis/Dermatomyositis

- Nonspecific abnormalities
  - CK, aldolase, AST, ALT, ESR, LDH
  - Elevations of CK can be due to macro-CK

- Myositis-associated and myositis-specific autoantibodies

- Mimics/DDx
  - TSH, serum and urine myoglobin, Vit D, drug screen, HIV
  - In myositis vs rhabdomyolysis, CK rarely above 50 x ULN
Myositis-associated abs

- ANA (50-80%)
- Anti-RNP ab (MCTD/OCTD)
- Anti-PM-Scl ab (PM-scleroderma)
- Anti-Ku ab (PM-scleroderma)
## Myositis-specific abs

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Prevalence DM/PM</th>
<th>Clinical Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antisynthetase e.g. anti-Jo-1</td>
<td>20-50%</td>
<td>Antisynthetase Syndrome</td>
</tr>
<tr>
<td>Anti-SRP</td>
<td>&lt;5%</td>
<td>Severe Resistant PM</td>
</tr>
<tr>
<td>Anti-Mi-2</td>
<td>5-10%</td>
<td>Classic DM</td>
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</table>
Objective #2

- Recognize the serologic associations of rheumatic diseases
Case # 5

- 34 y-o presents with rash after cruise to Caribbean
- Achey joints, low grade fevers, fatigue, weight loss
- What do you order?
ANA

- ANA panel
- ANA 95-100% sensitive in SLE, but far less specific
- Autoantibodies are hallmark of SLE: some diagnostic criteria, some useful for prognosis/markers of disease activity
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 it is not indicated to follow serially*
- Titers that disappear are less clinically significant.

Low titers common in general population and in first-degree relatives of patients with ANA-associated rheumatic disease.
Sensitivity of ANA in Rheumatic Diseases

- SLE (95-100%)
- Scleroderma (60-80%)
- MCTD (100%)
- RA (50%)
- Sjogren’s (40-70%)
- Discoid lupus (15%)
- Drug-induced lupus (100%)
Non-rheumatic diseases associated with +ANA

- Hashimoto’s thyroiditis (46% sensitivity)
- Graves’ disease (50%)
- Autoimmune hepatitis (100%)
- Primary autoimmune cholangitis (100%)
- Primary pulmonary hypertension (40%)
SLE and Autoantibody Subsets

ENA 1

- Smith
  - A diagnostic criteria and highly specific
  - Sensitivity 20-30%

- RNP
  - Defining feature of MCTD
Autoantibody Subsets

ENA 2

- **Ro/SSA**
  - Part of diagnostic criteria for Sjogren’s
    - High titer associated with extraglandular features
  - ANA-negative SLE
  - *Neonatal lupus and CHB*
    - *Mother anti-Ro+, risk of fetus with CHB 2-5%*
  - Subacute cutaneous lupus, cutaneous vasculitis, ILD and photosensitive dermatitis (normal population)

- **La/SSB**
  - Part of diagnostic criteria for Sjogren’s
  - 15% of SLE patients but rare in other systemic rheumatic diseases
  - Isolated SSB seen in some patients with PBC and AIH
SLE and Autoantibody Subsets

- dsDNA
  - A diagnostic criteria
  - Highly specific ~95%
    - Sensitivity ~80%
  - Marker of disease activity (renal)
    especially with low complement;
elevations often precede flares
Autoantibodies in Systemic Lupus

- **Department of Defense Serum Repository;** evaluated 130 controls prior to SLE diagnosis
- **115/130 (88%)** present before diagnosis (up to 9.4 years, mean 3.3)

- **ANA 78%**
- **dsDNA 55%**

- **Progression of development:**
  - ANA, Ro/La, APL abs
  - Later dsDNA then Sm/RNP

### Sensitivity and specificity of different antinuclear antibodies

<table>
<thead>
<tr>
<th>Antibody</th>
<th>ds DNA</th>
<th>55 DNA</th>
<th>Histone</th>
<th>Nucleoprotein</th>
<th>Sm</th>
<th>RNP</th>
<th>Ro</th>
<th>La</th>
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<tbody>
<tr>
<td>SLE</td>
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<tr>
<td>Sen</td>
<td>70 percent</td>
<td>80</td>
<td>30-80</td>
<td>58</td>
<td>30</td>
<td>27</td>
<td>25-35</td>
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<td>82 percent</td>
<td>87-94</td>
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<tr>
<td>Drug LE</td>
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<td>80</td>
<td>95</td>
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<td>1 percent</td>
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<tr>
<td>Spec</td>
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<td>RA</td>
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<td>mod</td>
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<td>25</td>
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<td>47</td>
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<td>low</td>
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<tr>
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<tr>
<td>Scleroderma</td>
<td></td>
<td>&lt;1 percent</td>
<td>&lt;1 percent</td>
<td>&lt;1 percent</td>
<td>20</td>
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<td>Sen</td>
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<td>PM/DM</td>
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<td>&lt;1 percent</td>
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<td>low</td>
<td>mod</td>
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</tbody>
</table>

Sen: sensitivity; Spec: specificity. Other associations: RNP: Mixed connective tissue disease (MCTD); Ro: Subacute cutaneous lupus erythematosus, Primary biliary cirrhosis, Vasculitis, Congenital heart block.
Anti-Centromere antibody (ACA)

- Highly specific for scleroderma ~98%
- Found almost exclusively in limited systemic sclerosis (CREST) (57%)
  - Calcinosis
  - Raynauds
  - Esophageal dysmotility
  - Sclerodatryly
  - Telangiectasias
Anti-SCL-70 antibodies (topoisomerase-1)

- Highly specific for scleroderma ~95%
- Tightly affiliated with diffuse systemic sclerosis
  - Associated with high risk of ILD
Anti-histone antibodies

- Present in 95% of DIL (drug-induced lupus) patients
- Procainamide, Hydralazine, Isoniazid
- Also present in up to 80% of SLE pts
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
ANA

- A hallmark of rheumatic disease
- For diagnosis of SLE, sensitivity of ~95% and specificity of 57%
- Primary utility diagnostically is the NPV for SLE if ANA is negative
- May support the diagnosis of other rheumatic disease but does not rule in or out other specific diseases
Case # 6

- 60 yo male hospitalized with pneumonia, dehydration/nausea from oral antibiotics
- Cr 1.1  Hb 12  plt 120  WBC 12  cANCA 1:160
- Does this patient have Granulomatosis with Polyangiitis (Wegeners)?
Anti-Neutrophil Cytoplasmic Antibody (ANCA)

- **Two patterns:**
  - **c-ANCA** = diffuse granular staining throughout cytoplasm
    - Antigen recognized is usually a PMN granule constituent proteinase-3 (Pr-3)
    - Found primarily in Granulomatosis with Polyangiitis (Wegeners)
  - **p-ANCA** = perinuclear staining of cytoplasm
    - Many antigens (elastase, lysozyme, lactoferrin) **but most common and important is PMN granule constituent myeloperoxidase (MPO)**
    - Non-MPO pANCAs seen with non-rheumatic diseases (IBD, HIV, drug-induced ANCA e.g.); recognized as atypical ANCA
# Sensitivity of c-ANCA for Granulomatosis with Polyangiitis

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>Active Disease</th>
<th>Inactive (treated) Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic, multi-system WG</td>
<td>95%</td>
<td>65%</td>
</tr>
<tr>
<td>Limited WG</td>
<td>65%</td>
<td>35%</td>
</tr>
</tbody>
</table>
Case # 6

- No history renal dz, sinusitis, hemoptysis
- No prior med use, only Levaquin
- CXR RLL infiltrate, sinus films negative
- Patient is unlikely to have Granulomatosis with Polyangiitis because of low PPV of this test
ANCAs

- The predictive value depends upon clinical presentation
- Negative ANCA does not exclude the diagnosis of AAV
Objective 3

- Apply sensitivity, specificity, likelihood ratio and positive predictive value to laboratory testing in clinical practice
Sensitivity and Specificity

- **Sensitivity** = True Positives/Total with Disease
  - $\frac{TP}{TP+FN}$

- **Specificity** = True Negatives/Total without Disease
  - $\frac{TN}{TN+FP}$

### Table:

<table>
<thead>
<tr>
<th></th>
<th>Positive Test Result</th>
<th>Negative Test Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject With Dx</td>
<td>True Positive (TP)</td>
<td>False Neg. (FN)</td>
</tr>
<tr>
<td>Subject W/o Dx</td>
<td>False Positive (FP)</td>
<td>True Neg. (TN)</td>
</tr>
</tbody>
</table>
Prevalence of SLE in USA

- 2008 reported to be 100 per 100,000 adult women
- Prevalence of 0.1%
- SLE in men 1/10th
- Does a +ANA = SLE?
Does +ANA = SLE? NO

Pretest probability in random population = prevalence = 0.1%
If ANA 95% sensitive and 95% specific

<table>
<thead>
<tr>
<th></th>
<th>SLE</th>
<th>SLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>ANA +</td>
<td>950</td>
<td>~50,000</td>
</tr>
<tr>
<td>ANA -</td>
<td>50</td>
<td>~949,000</td>
</tr>
</tbody>
</table>

+ANA post-test probability = 950/50,000 = 1/50 = 2%
What if ANA only 80% Specific?

Pretest probability in random population = prevalence = 0.1%

ANA 95% sensitive and **80% specific**

<table>
<thead>
<tr>
<th></th>
<th>SLE Yes</th>
<th>SLE No</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA +</td>
<td>950</td>
<td>~199,800</td>
<td>200,750</td>
</tr>
<tr>
<td>ANA -</td>
<td>50</td>
<td>~799,200</td>
<td>799,250</td>
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<tr>
<td><strong>Totals</strong></td>
<td><strong>1000</strong></td>
<td><strong>999,000</strong></td>
<td><strong>1,000,000</strong></td>
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</tbody>
</table>

+ANA post-test probability = $950/200,750 = 0.5\%$
Likelihood Ratio

- Positive LR
  - True positive rate/
    false positive rate
  - TP/FP

- Negative LR
  - False neg. rate/
    true neg. rate
  - FN/TN
Likelihood Ratio

- **Positive LR**
  - Higher is better
  - LR+>5 considered good test

- **Negative LR**
  - Lower is better
  - LR-<0.2 considered good test

- LR+ or LR- close to 1.0: test not predictive

- LR multiplied by pre-test odds = post-test odds
LR with Low Pre-test Probability

- ANA 1:40 threshold, 95% sensitivity and specificity for given lab
  - LR+ = 95%/5% = 19
  - LR- = 5%/95% = 0.053

- Patient with estimated pre-test probability of SLE of 1% (0.01)

- If ANA negative at 1:40, then post-test odds ~ $0.01 \times 0.05 = 0.0005$ (1:2000)

- If ANA positive at 1:40, then post-test odds ~ $0.01 \times 19 = 0.19$ (1:5) odds still strongly against having SLE
LR with High Pre-test Probability

- ANA 1:40 threshold, 95% sensitivity and specificity for given lab
  - LR+ = 95%/5% = 19
  - LR- = 5%/95% = 0.053

- Patient with estimated pre-test probability of SLE 50% (odds 1:1 or 1.0)
- If ANA is negative at 1:40, then post-test odds ~ 1.0 x 0.5 = 1:19
- If ANA is positive at 1:40, then post-test odds ~ 1 x 19 = 19 = 19:1 odds, strongly in favor of SLE
Positive Predictive Value

- How many of test positive patients truly have the disease
  \[ \frac{TP}{TP+FP} \]

- Dependent on the prevalence of the disease in the population being examined (pretest probability of disease)
Positive Predictive Value

\[
PPV = \frac{(sensitivity)(prevalence)}{(sensitivity)(prevalence) + (1-specificity)(1-prevalence)}
\]
Case # 6

- The PPV of c-ANCA is low because:
  - cANCA specificity is only 25%
  - cANCA sensitivity is only 40%
  - Low prevalence of disease
  - The negative likelihood ratio is high
Case # 6

- Does he have Granulomatosis with Polyangiitis?
- NO

- WHY?
  - Low prevalence of disease
  - 3 per 100,000 in US (0.00003%)
Conclusions

- Lab tests can be supportive of the diagnosis and useful to monitor disease activity, *but are rarely diagnostic*
- Lab test must be interpreted in the context of clinical presentation, and understanding of sensitivity, specificity, prevalence of disease
Case # 1

- 28 y-o female, tired, HAs, hurts all over
- ANA 1:160

- What does she have?
- FIBROMYALGIA
References

- ACR online Advanced Rheumatology Course
Clinical Pearls

- Upper limit of ESR for men age/2 but for women (age + 10)/2
- High RF and CCP+ is highly specific for RA and portends a worse prognosis
- High RF and negative CCP: think HepC
- The negative predictive value of an ANA is high, but the PPV is low
- Gout does not occur in premenopausal women
- Don’t order a lab test unless it will change your management plan