A positive ANA test?
What next?

Lorenzo Dagna, MD

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Università Vita-Salute San Raffaele School of Medicine
San Raffaele Scientific Institute, Milan - Italy
Why the hell has an ANA test been ordered for this patient?
A positive ANA test - What next?

• Three clinical cases

• What is an ANA test

• When should an ANA test be ordered?

• Frequently asked questions about ANA
A positive ANA test - What next?

• Three clinical cases

• Brief history of ANA testing

• When should an ANA test be ordered?

• Frequently asked questions about ANA
Mrs. Smith, 72 y.o.

2-year history of pain in DIPs, PIPs, and knees.

Morning stiffness 30-40 min
Mrs. Smith, 72 y.o.

**Physical:** normal

**Lab:** normal (including ESR, CRP, RA test, WR)

**ANA pos. 1:320**
homogeneous pattern
Martha, 31 y.o.

2 weeks:
- fever (37.8°C/100.0°F)
- arthralgias
- erythematosus skin rash

Mrs. Smith, 72 y.o.

Physical: normal

Lab: normal (including ESR, CRP, RA test, WR)

ANA pos. 1:320 homogeneous pattern
Mrs. Smith, 72 y.o.

Physical: normal

Lab: normal (including ESR, CRP, RA test, WR)

ANA pos. 1:320 homogeneous pattern

Martha, 31 y.o.

Physical:

HR 92r, BP 110/70, RR 22

Chest: muffling of a respiratory sound in the pulmonary bases

Heart: muffled heart sounds

Otherwise normal
Mrs. Smith, 72 y.o.

**Physical:** normal

Lab: normal (including ESR, CRP, RA test, WR)

ANA pos. 1:320 homogeneous pattern

---

Martha, 31 y.o.

**Lab:**

- Hb 10.3 g/dL
- WBC 3200/mm³
- Plt 198,000/mm³
- crea 1.4 mg/dL
- ESR 36 mm/hr
- CRP 12.0 mg/L
- RA test/WR: neg

ANA pos. 1:160 homogeneous pattern
Mrs. Smith, 72 y.o.

Physical: normal

Lab: normal (including ESR, CRP, RA test, WR)

ANA pos. 1:320 homogeneous pattern

Martha, 31 y.o.

Lab:

Hb 11.8 g/dL
WBC 3200/mm³
Plt 198,000/mm³
crea 1.4 mg/dL

ESR 36 mm/hr
CRP 12.0 mg/L

RA test/WR: neg
ANA pos. 1:160 homogeneous pattern

Louise, 28 y.o.

Four-month history of weakness, fatigue, arthromyalgias
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<tr>
<td>WBC</td>
<td>3200/mm³</td>
<td>WBC 4600/mm³ (diff OK)</td>
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<tr>
<td>PLt</td>
<td>198,000/mm³</td>
<td>PLt 212,000/mm³</td>
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<tr>
<td>crea</td>
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<tr>
<td>CRP</td>
<td>12.0 mg/L</td>
<td>CRP 9.0 mg/L</td>
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<tr>
<td>RA test/WR</td>
<td>neg</td>
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<td>ANA</td>
<td>pos. 1:320 homogeneous pattern</td>
<td>ANA pos. 1:640 homogeneous pattern</td>
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Mrs. Smith, 72 y.o.

2-year history of pain in DIPs, PIPs, and knees, morning stiffness 30-40 min

ANA pos. 1:320
homogeneous pattern

Martha, 31 y.o.

Recent travel to Egypt
Fever, arthralgias, erythematous skin rash after sun exposure

ANA pos. 1:160
homogeneous pattern

Louise, 28 y.o.

Four-month history of weakness, fatigue, arthromyalgias

ANA pos. 1:640
homogeneous pattern
A positive ANA test - What next?

• Three clinical cases

• What is an ANA test

• When should an ANA test be ordered?

• Frequently asked questions about ANA
ANAs

- A family of antibodies to nuclear constituents
- Best studied with immuno-fluorescence-based tests based on HEP-2
  --> homogeneous/diffuse, rim/peripheral, nucleolar, centromeric
Homogeneous speckled
Nucleolar
Centromeric
Other ANA tests

- **EIA/ELISA testing**
  - \(\rightarrow\) *greater ease of performance*
  - \(\rightarrow\) *lower cost of the test*

For generic ANA:
- *not subject to widespread population testing*
- *lower sensibility*
- *no possibility to establish the ANA pattern*

\(\rightarrow\) *Useful for specific autoAbs to nuclear Ags* (SSA, SSB, dsDNA)
A positive ANA test - What next?

• Three clinical cases
• What is an ANA test
• When should an ANA test be ordered?
• Frequently asked questions about ANA
“No test for ANA and for specific autoantibodies to nuclear antigens should be performed without a clinical evaluation that leads to a presumptive diagnosis”

When should an ANA test be ordered?
When is an ANA test useful?

- To help establishing a diagnosis in a patient with clinical features suggestive of an autoimmune or connective tissue disorder
- To exclude such disorders in patients with few or uncertain clinical findings
- To subclassify a patient with an established diagnosis of an autoimmune or connective tissue disease
- To monitor disease activity
Conditions associated with positive IF-ANA test results

- **Diseases for which an ANA test is very useful for diagnosis**
  - SLE: 95-100%
  - Systemic sclerosis (scleroderma): 60-90%

- **Diseases for which an ANA test is somewhat useful for diagnosis**
  - Sjögren syndrome: 40-70%
  - Idiopathic inflammatory myositis (dermato/polymyositis): 30-80%

- **Diseases for which an ANA test is useful for monitoring/prognosis**
  - Juvenile chronic oligoarticular arthritis with uveitis: 20-50%
  - Raynaud phenomenon: 20-60%

- **Diseases for which a positive ANA test is an intrinsic part of diagnostic criteria**
  - Drug-induced SLE: ≈ 100%
  - MCTD: ≈ 100%
## Conditions associated with positive IF-ANA test results

### Diseases for which an ANA test is not useful in diagnosis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Frequency</th>
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</thead>
<tbody>
<tr>
<td>rheumatoid arthritis</td>
<td>30-50%</td>
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<tr>
<td>multiple sclerosis</td>
<td>≈ 25%</td>
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### Normal young persons*

<table>
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<tr>
<th>ANA cut-off</th>
<th>Frequency</th>
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<tr>
<td>≥ 1 : 40</td>
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<td>≥ 1 : 80</td>
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</tr>
<tr>
<td>≥ 1 : 160</td>
<td>≈ 5%</td>
</tr>
<tr>
<td>≥ 1 : 320</td>
<td>≈ 3%</td>
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* Frequency increases with female sex and increasing age
Conditions associated with positive IF-ANA test results

- Infections classically associated with a positive ANA test
  - infectious mononucleosis
  - HCV infection
  - subacute bacterial endocarditis
  - tuberculosis
  - HIV infection

- Drugs
  - procainamide
  - hydralazine
  - minocycline
  - diltiazem
  - penicillamine
  - isoniazid
  - TNF-α blockers
  - IFN-α
  - anticonvulsants (phenytoin)
  - quinidine
  - anti-thyroid drugs
  - rifampin
  - beta blockers
  - lithium
“No test for ANA and for specific autoantibodies to nuclear antigens should be performed without a clinical evaluation that leads to a presumptive diagnosis”

Conditions associated with positive IF-ANA test results

- **Diseases for which an ANA test is very useful for diagnosis**
  - SLE 95-100%
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- **Diseases for which an ANA test is somewhat useful for diagnosis**
  - Sjögren syndrome 40-70%
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- **Diseases for which an ANA test is useful for monitoring/prognosis**
  - Juvenile chronic oligoarticular arthritis with uveitis 20-50%
  - Raynaud phenomenon 20-60%

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Conditions associated with positive IF-ANA test results

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  - *drug-induced SLE* ≈ 100%
  - MCTD ≈ 100%
Systemic lupus erythematosus

Sensitivity: 95-100%
PPV general population: 11-13%

Acceptable specificity and positive predictive value

ONLY IF

there is a reasonable pre test clinical suspicion of SLE

→ should not be used for screening for SLE

Kavanaugh A et al., 2000
Systemic sclerosis (scleroderma)

Sensitivity: 60-90%

- A positive ANA test supports the diagnosis in the presence of clinical signs and symptoms
- A negative ANA test should lead the physician to consider other fibrosing illnesses (linear/local scleroderma, eosinophilic fasciitis, scleredema)
## Conditions associated with positive IF-ANA test results

<table>
<thead>
<tr>
<th>Classification</th>
<th>Diseases</th>
<th>Utility</th>
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<tr>
<td>Very useful for diagnosis</td>
<td>SLE</td>
<td>95-100%</td>
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<td>systemic sclerosis (scleroderma)</td>
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<tr>
<td>Somewhat useful for diagnosis</td>
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Sjögren syndrome
Idiopathic inflammatory myopathies

Sensitivity: 40-70% (SS) / 30-80% (IIM)

• A positive ANA test supports the diagnosis in the presence of the specific clinical signs and symptoms

• A negative ANA test does not rule out the diagnosis

Fossaluzza A et al., 1992; Love M, 1991
Raynaud phenomenon (RP)

- **primary RP (81%)**: patients who will never develop a systemic rheumatic disease
- **secondary RP (19%)**: patients who will develop a rheumatic disease (SLE, RA, SScl, …)

An ANA test in patients with RP

*If positive*, increases the likelihood of a secondary RP (19% → 30%)

*If negative*, reduces the likelihood of a secondary RP (19% → 7%)

Spencer-Green G, 1998
A positive ANA test - What next?

• Three clinical cases

• What is an ANA test

• When should an ANA test be ordered?

• Frequently asked questions about ANA
Q: If the ANA result is negative, should be the test repeated or should other tests be done (ENA) ?

A: No, if errors in testing are not suspected
Q: What other testing should be done following a positive ANA test result?

A: Different tests, according to the suspected diagnosis.
## ANA Positive – What next?

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Test</th>
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<tr>
<td>SLE</td>
<td>dsDNA, Sm, Ro/SSA, La/SSB, aCL, anti-beta2-gpl, LLAC</td>
</tr>
<tr>
<td>Sjogren</td>
<td>Ro/SSA, La/SSB, RF, Waaler-Rose</td>
</tr>
<tr>
<td>PM/DM</td>
<td>Jo1 (<em>anti-synthetase syndrome</em>)</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>Centromere (CREST), Scl70 (diffuse)</td>
</tr>
<tr>
<td>Drug induced-SLE</td>
<td>Histones H2A/H2B</td>
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</table>
Q: What tests should be performed in young women with symmetric arthralgias?

A: 1) arthralgias (not arthritis) ≤ 6 wks: nothing
   - Viruses frequently: HBV, HCV, rubella (also vaccine), parvo
     occasionally: EBV, HIV, mumps, HAV, coxsackie, echo, adeno, VZV, HSV, CMV

2) arthralgias ≥ 6 wks or arthritis:
   ➔ further investigation warranted
Q: What tests should be performed in young women with symmetric arthralgias ≥ 6 wk or arthritis?

A: RF & ANA

- if RF positive, consider RA also in the presence of a positive ANA
- a positive ANA with negative RF does not rule out RA (7.5% of pts with RA are RF-/ANA+ [typically anti-histones])

- If ANA strongly pos & RF neg/low titer:
  anti-ds-DNA, anti-Sm, anti-RNP, anti-centromere, anti-Scl-70, anti-Ro/SSA, La-SSB

- consider autoimmune hepatitis, Hashimoto’s thyroiditis, Lyme disease
Q: My patient has anti-phospholipid syndrome (APS). Should an ANA test be performed?

A: - ANA test is not useful for diagnosing APS
- 40-50% of patients with APS have ANA

A positive ANA test in patients with APS increases the likelihood that APS is secondary to SLE

Petri M, 1994
Q: What other testing should be after in an ANA positive asymptomatic patient?

A: ??????
Why the hell has an ANA test been ordered for this patient?

Dagna L. et al., unpublished
You may have “a rheumatic disorder”....
Murphy’s law on doctors

Lyall’s Principle

Just because doctors have a name for your condition doesn’t mean they know what it is.
“No test for ANA and for specific autoantibodies to nuclear antigens should be performed without a clinical evaluation that leads to a presumptive diagnosis”

Q: What other testing should be after in an ANA positive asymptomatic patient?

A: Nothing more.....

but......
Development of Autoantibodies before the Clinical Onset of Systemic Lupus Erythematosus

Melissa R. Arbuckle, M.D., Ph.D., Micah T. McClain, Ph.D., Mark V. Rubertone, M.D., R. Hal Scofield, M.D., Gregory J. Dennis, M.D., Judith A. James, M.D., Ph.D. and John B. Harley, M.D., Ph.D.

N Engl J Med
Volume 349;16:1526-1533
October 16, 2003
Autoantibodies appear years before the onset of autoimmune diseases

- **Systemic lupus erythematosus** (*dsDNA, SSA/SSB, Sm*)
- **Scleroderma** (*centromere, Scl-70*)
- **Sjögren syndrome** (*Ro/SSA, La/SSB*)
- **Rheumatoid arthritis** (*CCP*)
- **Autoimmune myositis** (*tRNA synthetases*)
- **Primary biliary cirrhosis** (*mitochondria E2*)
- **T1DM, autoimmune thyroiditides, celiac disease, pemphigus, multiple sclerosis, vitiligo, …**

René Magritte, L’èchelle du feu, 1934
## Conditions associated with positive IF-ANA test results

### Diseases for which an ANA test is not useful in diagnosis

- rheumatoid arthritis 30-50%
- multiple sclerosis ≈ 25%
- idiopathic thrombocytopenic purpura 10-30%
- thyroid disease 30-50%
- discoid lupus 5-25%
- infectious diseases wide variations
- malignancies wide variations
- patients with silicone breast implants 15-25%
- fibromyalgia 15-25%
- healthy relatives of pts with SLE o scleroderma 5-25%

### Normal young persons*

- ANA ≥ 1 : 40 20-30%
- ANA ≥ 1 : 80 10-12%
- ANA ≥ 1 : 160 ≈ 5%
- ANA ≥ 1 : 320 ≈ 3%

* Frequency increases with female sex and increasing age
Frequency of ANA positivity increases with female sex and increasing age.
So... what to do?
Always consider history, physical and simple lab tests
Patient with a significantly positive ANA test

evaluate

Skin ± joint involvement
- dsDNA, RNP, Sm, SSA/SSB, aPL
  - SLE

Drug exposure
- histones
  - SSc
  - MCTD
  - DM/PM
  - drug induced LE

Raynaud, sclerodactyly, myositis, teleangectasis esophageal & lung involvement
- Scl-70, PM/Sc, centromere, RNP, Jo-1

Sicca symptoms
- SSA/SSB

Sjogren
# Conditions associated with positive IF-ANA test results

## Diseases for which an ANA test is not useful in diagnosis

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* Frequency increases with female sex and increasing age
A positive ANA test - What next?

- Three clinical cases
- What is an ANA test
- When should an ANA test be ordered?
- Frequently asked questions about ANA
Mrs. Smith, 72 y.o.
2-year history of pain in DIPs, PIPs, and knees, morning stiffness 30-40 min

Maria, 31 y.o.
Recent travel to Egypt
Fever, arthralgias, erythematous skin rash after sun exposure

Louise, 28 y.o.
Four-month history of weakness, fatigue, arthromyalgias

ANA pos. 1:320 homogeneous pattern
ANA pos. 1:160 homogeneous pattern
ANA pos. 1:640 homogeneous pattern
Mrs. Smith, 72 y.o.

2-year history of pain in DIPs, PIPs, and knees, morning stiffness 30-40 min

ANA pos. 1:320
homogeneous pattern
Mrs. Smith, 72 y.o.

**Physical:** normal

**Lab:** normal (including ESR, CRP, RA test, WR)

**ANA pos. 1:320**
homogeneous pattern
Mrs. Smith, 72 y.o.

**Hand XRay:**
narrowing of joint spaces, no erosions
Mrs. Smith, 72 y.o.

**D:** primary osteoarthritis

**ANA:** aspecific

**Rx:** Coxibs
Mrs. Smith, 72 y.o.

**Physical:** normal

Lab: normal (including ESR, CRP, RA test, WR)

ANA pos. 1:320 homogeneous pattern

Martha, 31 y.o.

**2 weeks:**

- fever (37.8° C/100.0° F)
- arthralgias
- erythematous skin rash
Mrs. Smith, 72 y.o.

**Physical:** normal

Lab: normal (including ESR, CRP, RA test, WR)

ANA pos. 1:320 homogeneous pattern

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Martha, 31 y.o.

**Physical:**

HR 92r, BP 110/70, RR 22

**Chest:** muffling of respiratory sound in the pulmonary bases

**Heart:** muffled heart sounds

Otherwise normal
Mrs. Smith, 72 y.o.

Physical: normal

Lab: normal (including ESR, CRP, RA test, WR)

ANA pos. 1:320 homogeneous pattern

Martha, 31 y.o.

Lab:

Hb 11.8 g/dL
WBC 3200/mm³
Plt 198.000/mm³
crea 1.4 mg/dL

ESR 36 mm/hr
CRP 12.0 mg/L

RA test/WR: neg

ANA pos. 1:160 homogeneous pattern
Martha, 31 y.o.

**Physical:** normal

**Chest Xray:** bilateral pleural effusion, cardiac shadow enlargement

Mrs. Smith, 72 y.o.

**Lab:** normal (including ESR, CRP, RA test, WR)

ANA pos. 1:320 homogeneous pattern
Mrs. Smith, 72 y.o.

Physical: normal

Lab: normal (including ESR, CRP, RA test, WR)

ANA pos. 1:320 homogeneous pattern

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Martha, 31 y.o.

Lab: anti-ds-DNA pos
    anti-Sm neg
    anti-SSA/SSB neg
    anti-β2-gpl neg

Urinalysis w/
proteinuria
    & micro: pending res.
<p>| | | |</p>
<table>
<thead>
<tr>
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<tr>
<td>1. Malar rash</td>
<td>Fixed erythema, flat or raised, over the malar eminences</td>
<td></td>
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<tr>
<td>2. Discoid rash</td>
<td>Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur</td>
<td></td>
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<tr>
<td>3. Photosensitivity</td>
<td>Exposure to <strong>UV</strong> light causes rash</td>
<td></td>
</tr>
<tr>
<td>4. Oral ulcers</td>
<td>Includes oral and nasopharyngeal, observed by physician</td>
<td></td>
</tr>
<tr>
<td>5. Arthritis</td>
<td>Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion</td>
<td></td>
</tr>
<tr>
<td>6. Serositis</td>
<td>Pleuritis or pericarditis documented by ECG or rub or evidence of pericardial effusion</td>
<td></td>
</tr>
<tr>
<td>7. Renal disorder</td>
<td>Proteinuria &gt; 0.5 g/d or &gt; 3+, or cellular casts</td>
<td></td>
</tr>
<tr>
<td>8. Neurologic disorder</td>
<td>Seizures without other cause or psychosis without other cause</td>
<td></td>
</tr>
<tr>
<td>9. Hematologic disorder</td>
<td>Hemolytic anemia or leukopenia (&lt; 4000/µL) or lymphopenia (&lt; 1500/µL) or thrombocytopenia (&lt; 100,000/µL) in the absence of offending drugs</td>
<td></td>
</tr>
<tr>
<td>10. Immunologic disorder</td>
<td>Anti-dsDNA, anti-Sm, and/or anti-phospholipid</td>
<td></td>
</tr>
<tr>
<td>11. Antinuclear antibodies</td>
<td>An abnormal titer of <strong>ANAs</strong> by immunofluorescence or an equivalent assay at any point in time in the absence of drugs known to induce ANAs</td>
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</tbody>
</table>

*If four of these criteria are present at any time during the course of disease, a diagnosis of systemic lupus can be made with 98% specificity and 97% sensitivity.*

Mrs. Smith, 72 y.o.

Physical: normal

Lab: normal (including ESR, CRP, RA test, WR)

ANA pos. 1:320 homogeneous pattern

Martha, 31 y.o.

D: idiopathic SLE

Rx: PDN 1 mg/kg
Mrs. Smith, 72 y.o.

**Physical:** normal

**Lab:** normal (including ESR, CRP, RA test, WR)

ANA pos. 1:320 homogeneous pattern

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Martha, 31 y.o.

**D:** idiopathic SLE

**Rx:** PDN 1 mg/kg

---

Louise, 28 y.o.

**Four-month history of weakness, fatigue, arthromyalgias**
Mrs. Smith, 72 y.o.

Physical: normal

Lab: normal (including ESR, CRP, RA test, WR)

ANA pos. 1:320 homogeneous pattern

Martha, 31 y.o.

D: idiopathic SLE

Rx: PDN 1 mg/kg

Louise, 28 y.o.

Physical: normal

Lab:

Hb 12.2 g/dL
WBC 4600/mm³ (diff OK)
Plt 212,000/mm³

ESR 31 mm/hr
CRP 9.0 mg/L

ANA pos. 1:640 homogeneous pattern
Louise, 28 y.o.

Lab: anti-ds-DNA neg
anti-Sm neg
anti-SSA/SSB neg

Mrs. Smith, 72 y.o.

Physical: normal

Lab: normal (including ESR, CRP, RA test, WR)

ANA pos. 1:320 homogeneous pattern

Martha, 31 y.o.

D: idiopathic SLE

Rx: PDN 1 mg/kg
Mrs. Smith, 72 y.o.

**Physical:** normal

Lab: normal (including ESR, CRP, RA test, WR)

ANA pos. 1:320
homogeneous pattern

---

Martha, 31 y.o.

**D:** idiopathic SLE

**Rx:** PDN 1 mg/kg

---

Louise, 28 y.o.

**Lab:**
- anti-TPO 1210 U/L
- anti-TG 890 U/L
- fT3 0.1 ng/dL
- fT4 0.65 ng/dL
- TSH 8.26 mU/L
Mrs. Smith, 72 y.o.

Physical: normal

Lab: normal (including ESR, CRP, RA test, WR)

ANA pos. 1:320 homogeneous pattern

Martha, 31 y.o.

D: idiopathic SLE

Rx: PDN 1 mg/kg

Louise, 28 y.o.

D: Hashimoto’s thyroiditis

Rx: levothyroxin 50 μg
Mrs. Smith, 72 y.o.

2-year history of pain in DIPs, PIPs, and knees, morning stiffness 30-40 min

ANA pos. 1:320 homogeneous pattern

D: primary osteoarthritis

Martha, 31 y.o.

Recent travel to Egypt

Fever, arthralgias, erythematous skin rash after sun exposure

ANA pos. 1:160 homogeneous pattern

D: idiopathic SLE

Louise, 28 y.o.

Four-month history of weakness, fatigue, arthromyalgias

ANA pos. 1:640 homogeneous pattern

D: Hashimoto’s thyroiditis
Take home messages

- No test for ANA should be performed without a clinical evaluation that leads to a presumptive diagnosis (SLE, SSc, Sjögren, PM/DM, JCOA, Raynaud, drug-induced SLE, autoimmune hepatic disease, MCTD)

- ANA testing have an extremely low specificity and PPV in the general population.

- ANA and ENA are different tests (ANA more sensitive, anti-ENA more specific)
Take home messages (2)

- Many diseases may cause ANA positivity; many healthy individuals have a positive ANA test.

- Some ANA patterns (nucleolar, centromeric) can be more specific than others (diffuse, homogeneous, speckled).

- Patient referred for a positive ANA should be evaluated considering for signs and symptoms of the above mentioned disease. If those are absent, no further investigations may be warranted.
Ceci n’est pas une pipe.
Ceci n’est pas une maladie auto-immune.