Dr.Imad Aboukhamis
Ph-D France

- Rheumatic Diseases
- الأمراض الروماتيزمية

Rheumatic Disease

الأمراض الروماتيزمية

- **Organ specific النوعية لجهاز**
  - Hashimoto‘s Thyroiditis
    التهاب الغدة الدرقية هاشيموتو
  - Celiac disease الزلاقي
    مرض الاضطرابات الهضمية
  - Pernicious anemia
    فقر الدم الخبيث
  - Goodpasture‘s syndrome متلازمة
  - AI Liver Diseases أمراض الكبد

- **Systemic الجهازية**
  - **Rheumatoid arthritis**
  - التهاب المفاصل الروماتويدي
  - **Systemic Lupus erythematodes (SLE)**
  - الذئبة الحمامية الجهازية
  - Antiphospholipid syndrome (APS) متلازمة الفوسفوليبيد
  - Wegeners‘s granulomatosis
  - الورم الحبيبي فيجنر

- „Rheuma“ is derived from the Greek and describes a flowing pain

الروماتيزم "مشتق من اليونانية ويصف الألم المتدفق

- A non-specific term for medical problems affecting the heart, bones, joints, kidney, skin and lung *no injury or tumor*

مصطلح غير محدد للمشاكل الطبية التي تؤثر على القلب والعظام والمفاصل والكلى والجلد والرئة دون إصابة أو ورم

- Rheumatism, about 400 diseases, that often differ significantly

الروماتيزم ، حوالي 400 مرض ، والتي غالبا ما تختلف اختلافا كبيرا

- in cause في سبب
- Symptoms الأعراض
- disease progression, therapy تطور المرض ، العلاج
- health consequences عواقب صحية

Overview of rheumatic diseases

نظرة عامة على الأمراض الروماتيزمية

1. Rheumatoid Arthritis التهاب المفاصل الروماتويدي
2. Systemic Lupus Erythematosus (Lupus)
3. Sjogren‘s syndrome متلازمة سجوغرن
4. Scleroderma تصلب الجلد
5. Poly&Dermatomyositis التهاب الجلد والعضلات
6. Mixed connective tissue disease, Sharp

مرض النسيج الضام المختلط

1. Reactive Arthritis (Reiter's Syndrome)

التهاب المفاصل التفاعلي (متلازمة رايتر)

مفتاح الحقائقKey facts

– Rheumatoid arthritis (RA) is:

- a chronic, progressive مزمن ، متطور
- disabling autoimmune disease

مرض مناعة ذاتية معطل

– RA causes:

- stiffness, pain, loss of mobility تصلب ، ألم ، فقدان الحركة
  inflammation&erosion in the joints التهاب التآكل في المفاصل
- RA affects 1 % of the population يؤثر على 1 ٪ من السكان

– over 40 % of RA patients are disabled within 3 years

– يتم تعطيل أكثر من 40 ٪ من مرضى التهاب المفاصل الروماتويدي في غضون 3 سنوات

What happens ماذا يحدث?

- Swelling of the synovial lining انتفاخ البطانة الزليليّة

  causing pain, stiffness تسبب الألم والتصلب

  redness swelling around the joint احمرار تورم حول المفصل

- Rapid division and growth of cells الانقسام السريع ونمو الخلايا
- which causes the synovium to thicken مما يسبب زيادة الغشاء الزليلي
- Inflamed cells release enzymes that damage, bone & cartilage

  الخلايا الملتهبة تطلق إنزيمات تتلف العظام والغضاريف

- The involved joint looses its shape and alignment

  المفصل المعني يفقد شكله ومحاذاة

- Pain and loss of movement الألم وفقدان الحركة

Diagnosis Rheumatoid Arthritis

تشخيص التهاب المفاصل الروماتويدي

Anamnesis and Clinical picture

سوابق وصورة سريرية

Morning stiffness of joints
Symmetrical joint inflammatio
Rheumatoid nodules
Fever
Myalgia

Imaging Technologie

تقنيات التصوير

X-Ray
Ultrasound
MRT

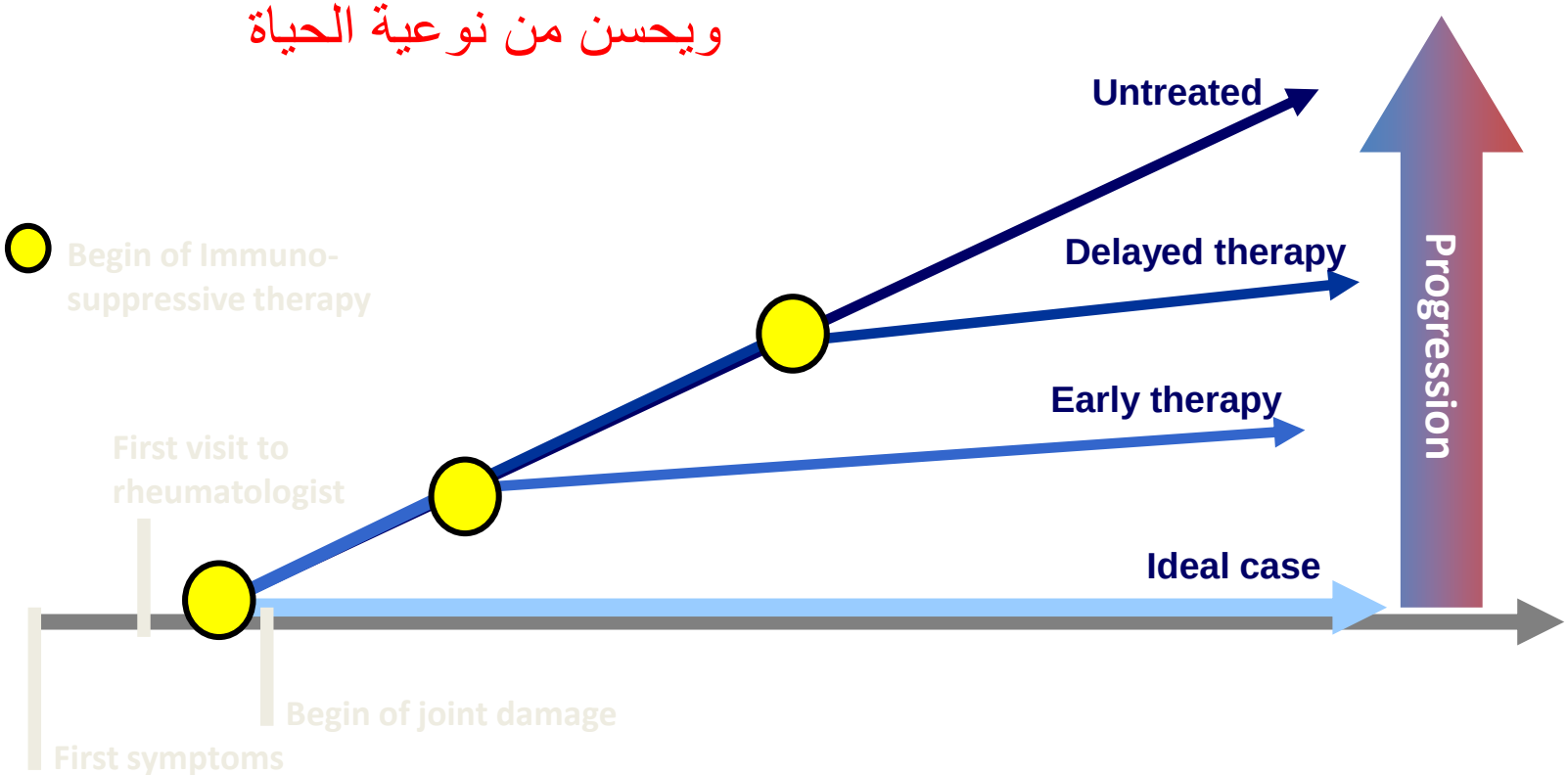
Laboratory Tests

اختبارات المخبرية

ESR
CRP
Rheumatoid Factors
Anti-CCP

Early treatment prevents progressive joint damage and increases quality of life

العلاج المبكر يمنع تلف المفاصل التدريجي
ويحسن من نوعية الحياة

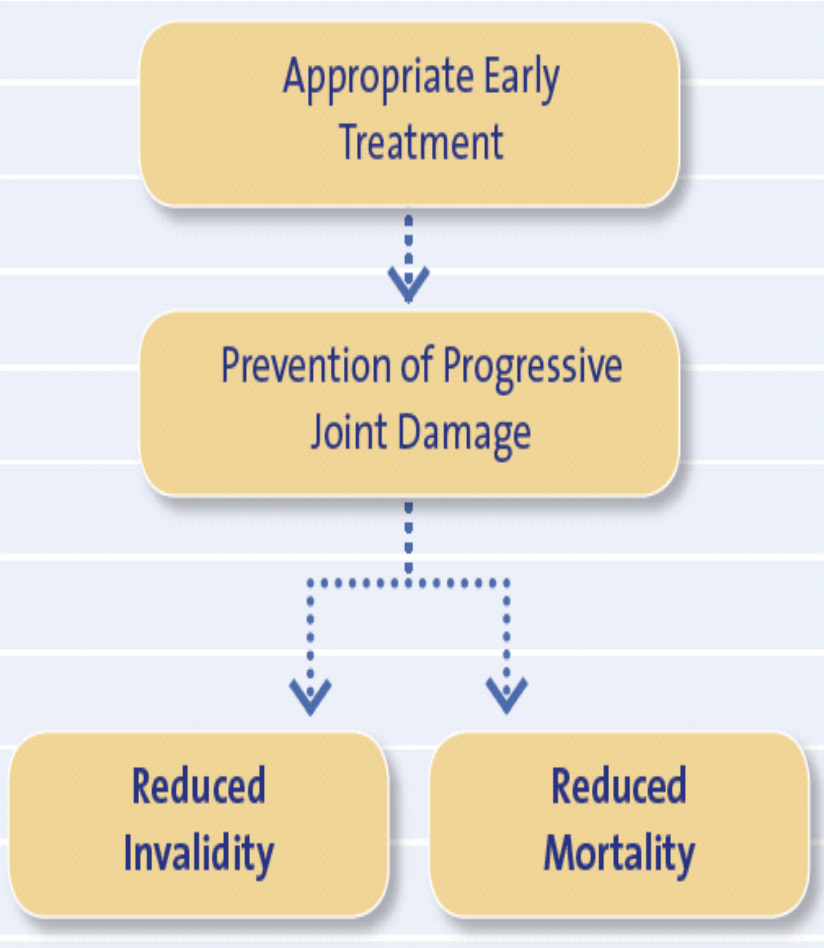


Defining markers of a bad prognosis early on in RA facilitates therapeutic decision-making

إن تحديد علامات التشخيص السيئ في وقت مبكر من التهاب المفاصل الروماتويدي يسهل عملية اتخاذ القرار العلاجي.

New emphasison more aggressive therapy early on in disease course decreases joint morbidity

التركيز الجديد أكثر عدوانية العلاج في وقت مبكر في مسار المرض يقلل من اعتلال المفاصل



Diagnostic Criteria for RA

معايير التشخيص

ACR Criteria (American College of Rheumatology)

For the classification of different rheumatologic diseases. The ACR criteria are often thought to be diagnostic criteria, in effect are an aid for the differentiation of rheumatic diseases

هي معايير تشخيصية ، فهي ACR غالبًا ما يُعتقد أن معايير في الواقع أداة مساعدة للتمييز بين الأمراض الروماتيزمية

DAS-28 (Disease Activity Score)

For the determination of the disease activity and monitoring of rheumatoid arthritis

لتحديد نشاط المرض ومراقبة التهاب المفاصل الروماتويدي

Serologic Markers for RA
علامات مصلية

1. Rheumatoid Factors IgM - IgG, IgA
2. Filaggrin- associated Ab
    1. Anti-CCP
    2. Antiperinuclear Factor (APF)
    3. Anti-Keratin-Ab (AKA)
    4. Anti-Filaggrin-Ab (AFA)
3. Anti-RA 33
4. Anti-Sa (Vimentin)

Rheumatoid Factors
العوامل الروماتويدية

1. Antibodies directed against human γ-globulin Fc (mainly IgM, less IgG or IgA)
2. IgM RF calibrated against WHO reference
3. Sensitivity 80% in patients with RA
4. Specificity ranges from 80-90%

– **High titer predicts outcome**: تتوقع النتيجة بارتفاع عيار

1. erosive arthritis التهاب المفاصل التآكل
2. vasculitis التهاب الأوعية الدموي

Methods Rheumatoid Factor Detection

طرق اكتشاف عامل الروماتويد

1. Laser nephelometry
2. ELISA
3. Agglutination IgG coated latex/RBC
4. Indirect immunofluorescence
5. Radioimmuno assay

Why testing RF on ELISA ?

1. Fully automatable
2. Detection of all relevant Ig-classes

   الكشف عن جميع الفئات ذات الصلة

3. **The simultaneous detection of IgA and IgM class RF is nearly 100 % specific for RA**
4. High sensitivity
5. Standardized method

Domer et al., Curr Opin Rheumatol 2004;16:246–253.

Anti-CCP

A Specific Marker for Rheumatoid Arthritis

واسم نوعي لالتهاب المفاصل الروماتويدي

- Ab to cyclic citrullinated peptide (derived from filaggrin)

- Sensitivity 60 - 80 %
- Specificity > 95 %
- Prognostic markerpositive up to 9 years before clinical manifestations

يعطي انذار قبل 9 سنوات من المظاهر السريرية

- approx. 30 % of CCP^+ are RF IgM^-

RA33-Antibodies

1. Anti-RA33 associated with mild disease
   heterogeneous nuclear ribonucleoprotein A2البروتين النووي الريبي الغير متجانس

المرتبطة بأمراض خفيفة

2. Single Early RA-Marker in 13 % of RA Patients

الوحيد موجب في وقت مبكر في 13 ٪ التهاب المفاصل الروماتويدي

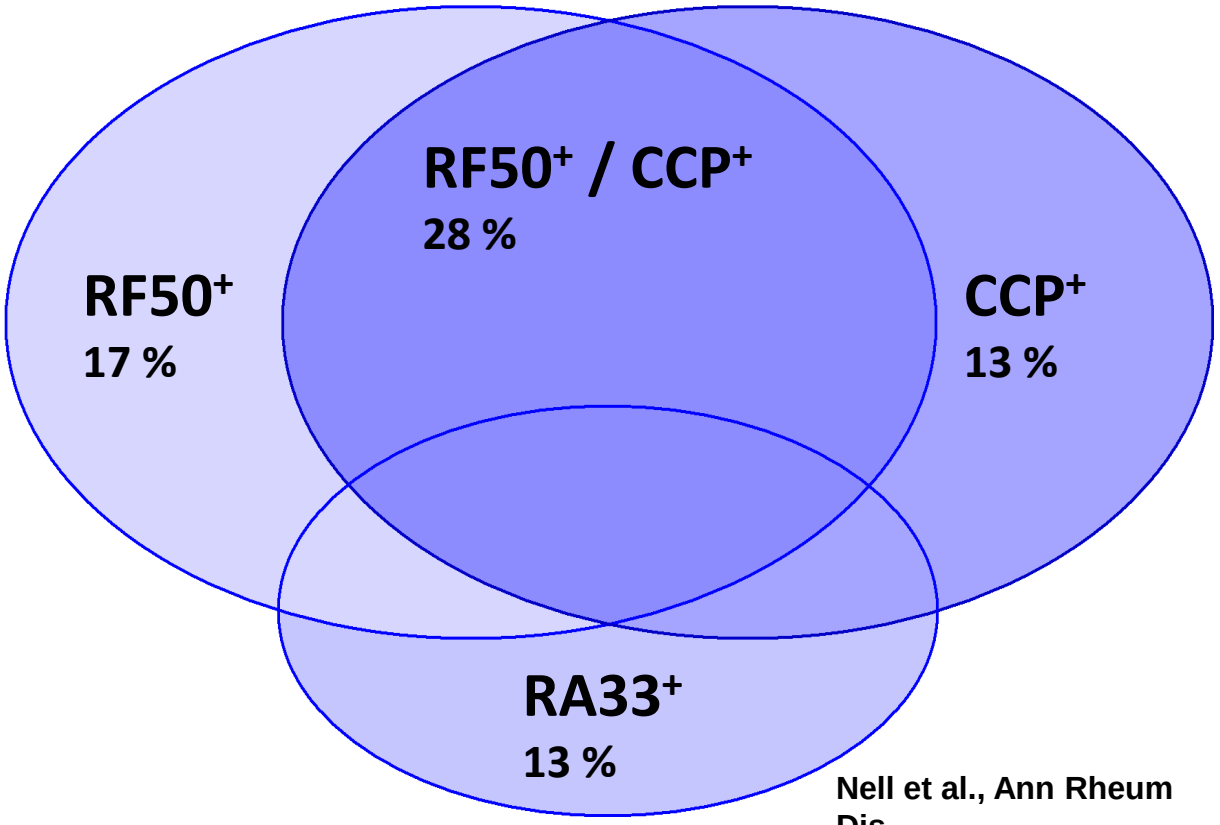
3. Specificity of 90 ٪ 90 نوعية%
4. increasing to 96 % if negative for Anti-U1-snRNP

زيادة إلى 96 ٪ إذا كانت سلبية ل

for Anti-U1-snRNP

Diagnosis of Early Rheumatoid Arthritis

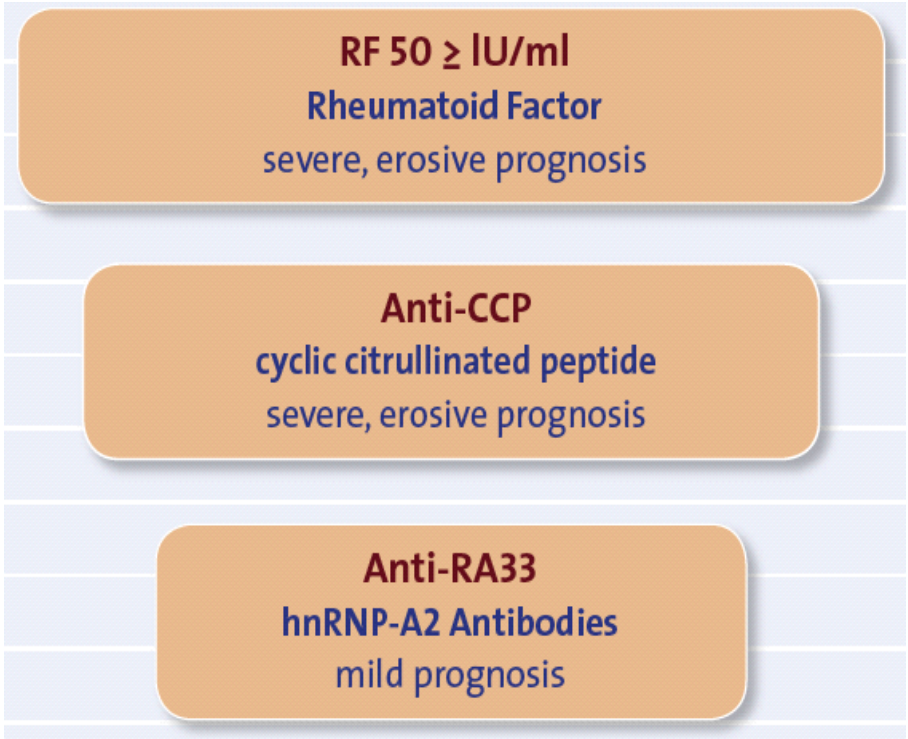
التشخيص المبكر لالتهاب المفاصل الروماتويدي



Nell et al., Ann Rheum Dis 2005;64:1731–1736.

Rheumatoid Arthritis

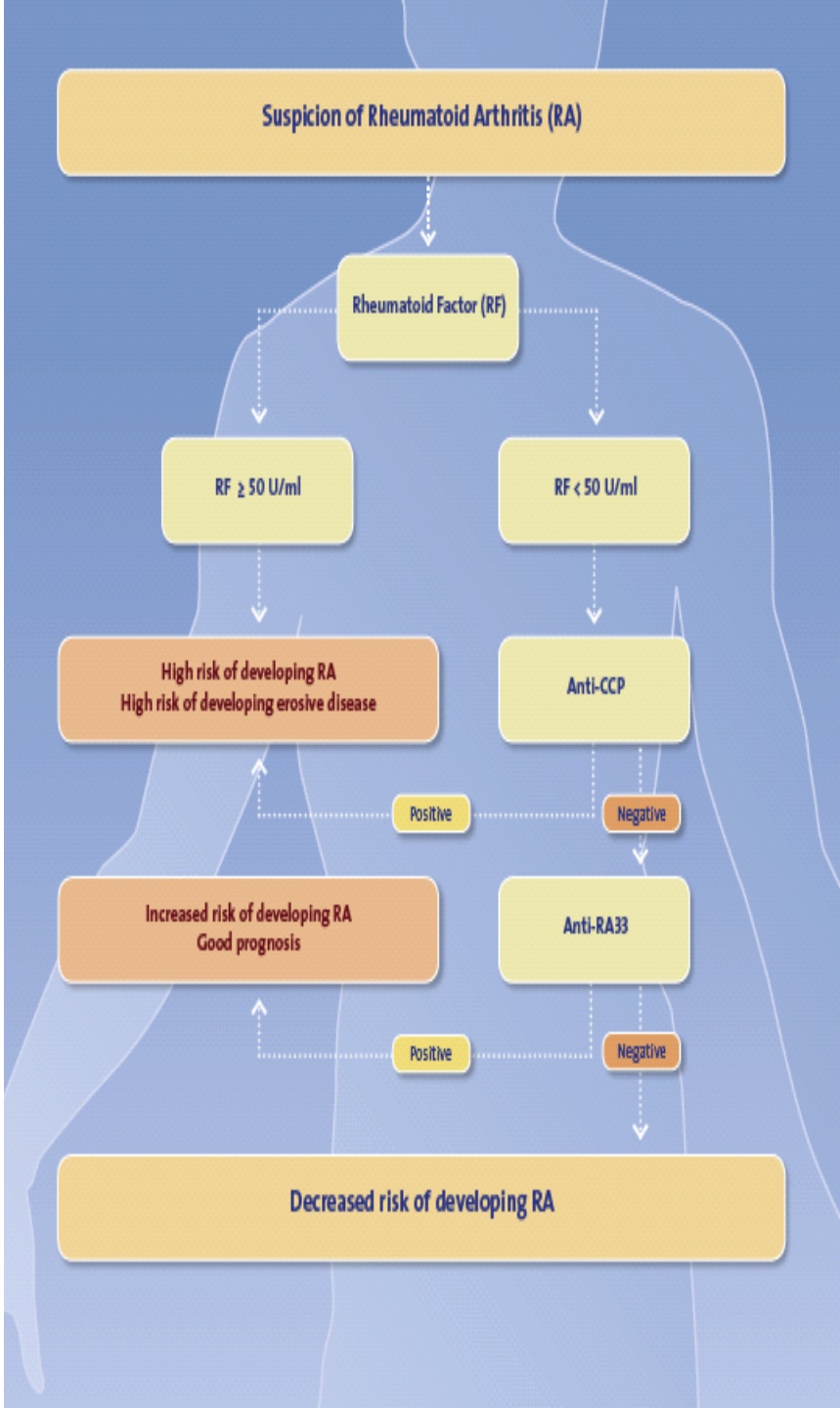
- Staged Multimarker Concept مفهوم متعدد العلامات



Multimarker Concept

- Cost-efficient Screening for High-Titer RF
- High Specificity for Early RA Diagnosis by Detection of Anti-CCP
- Increased Sensitivity by Sequential Testing with RF, CCP and RA33
- Prognosis of Disease Outcome Allows Individually Tailored Therapies

تشخيص يسمح بالعلاجات الفردية



Clinical Evaluation of Anti-Mutated Citrullinated Vimentin by ELISA in Rheumatoid Arthritis

LILLA SOÓS, ZOLTÁN SZEKANECZ, ZOLTÁN SZABÓ, ANDREA FEKETE, MARGIT ZEHER, ILDIKÓ F. HORVÁTH, KATALIN DANKÓ, ANIKÓ KAPITÁNY, ANIKÓ VÉGVÁRI, SANDOR SIPKA, GYULA SZEGEDI, and GABRIELLA LAKOS

Table 2. Diagnostic sensitivity and specificity, and positive and negative predictive values of IgM RF, anti-CCP2, and anti-MCV tests in RA at manufacturer recommended cutoff levels.

Test, %	RF IgM	RF IgA	RF IgG	Anti-CCP2	Anti-MCV
Sensitivity	71.4	36.9	37.8	66.4	75.6
Specificity* (RA/healthy subjects)	97.7	97.7	100	100	95.5
Specificity* (RA/all controls)	82.2	88.9	87.3	98.3	91.5
Positive predictive value	80.2	77.2	75.0	97.6	90.0
Negative predictive value	74.0	58.3	58.2	74.4	78.8

* Specificity was calculated for RA versus healthy controls only (RA/healthy subjects), and for RA versus healthy + disease controls (RA/all controls). RF: rheunatoid factor; CCP: cyclic citrullinated peptide; MCV: mutated citrullinated vimemtin; RA: rheumatoid arthritis.

Systemic Lupus erythematosus
الذئبة الحمامية الجهازية

- Systemic Lupus erythematosus (SLE) is a systemic immune complex disease
- Common complaints:الشكاوى الشائعة
  1. Fever
  2. Malaiseتوعك
  3. joint painالم المفاصل
  4. myalgias and fatigueألم عضلي والتعب
- **Autoantibodies** the mainstay of serologic tests

Classification Criteria for SLE معايير التصنيف

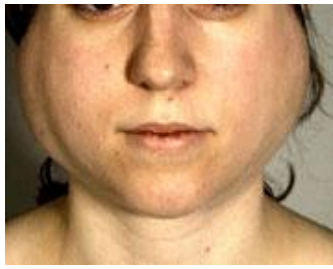
1. Malar rash طفح جلدي
2. Discoid rash طفح الديسكو
3. Photosensitivity حساسية للضوء
4. Oral or nasopharyngeal ulcers قروح الفم أو البلعوم
5. Nonerosive arthritis التهاب المفاصل الاتآكلي
6. Pleuritis or pericarditis التهاب الجنب أو التامور
7. Nephritis التهاب الكلية
8. Neurologic disorders اضطرابات عصبية
9. Antinuclear antibodies الاضداد المضادة للنواة
10. Anti-Phospholipid antibodies أضدادة للفوسفوليبيد

Sjogren‘s Syndromeمتلازمة سجوغرن

1. Chronic-inflammatory Autoimmune Disease of exocrin glandsالغدد خارجية الإفراز
2. Isolated form (primary),اولي او ثانوي secondary form is associated with other diseases (RA, SLE, Scleroderma, PBC)
3. Prevalence1-2 %, Women 9x more often affected
4. Hallmarkسمة مميزة

– are autoantibodies against SS-A/Ro und SS-B/La

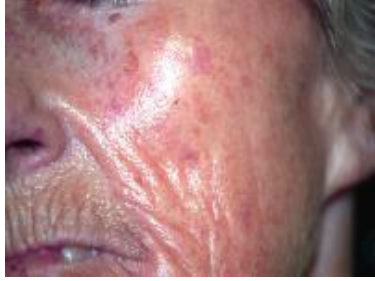
Classification criteriaمعايير التصنيف



1. Ocular symptoms (Anamnesisسوابق المريض) Dry eyesعيون جافة
2. Oral Symptom (Anamnesis) Dry mouthفم جاف
3. Ocular signs (Schirmer-I-Test, Bengalrosa-Score)
4. Histopatholoy (Lip biopsy) (Fokus-Score)(خزعة الشفة)
5. Salivary gland signsعلامات الغدد اللعابية
6. Autoantibodies against SS-A/Ro and SS-B/La

(adaptiert nach Vitali et al., 1996)

Systemic Sclerosis تصلب لويحي



Sclerodermaتصلب الجلد

- rare multi-organ disease with inflammation and fibrosis of skinتليف الجلد, blood vessels, often lungأحيانا الرئة, gutالقناة الهضمية, kidney or heart
- Diffuse Sclerodermaانتشار تصلب الجلد
- Morpheaالمورفيا/linear sclerodermaتصلب خطي
- **R**aynaud‘s syndromeمتلازمة رينود
- **E**sophageal dysmotility خلل المريء
- **S**clerodactylyتصلب الأصابع
- **T**elangiectasiaتوسع الشعريات

Classification criteria for Scleroderma

معايير التصنيف

Main criteria المعايير الرئيسية

Scleroderma of in proximity to finger joints

تصلب الجلد بالقرب من مفاصل الأصابع

Secondary criteria

1. Sclerodactyly تصلب الأصابع
2. Digital pitting scars or loss of substance from the finger pad

ندوب أو فقدان مادة من لوحة الأصابع

3. Pulmonary fibrosis التليف الرئوي

adapted from MASI et al., 1980

Mixed Connective Tissue Disease أمراض النسيج الضام المختلط

(MCTD; Sharp‘s Syndrome)Combination of symptoms:

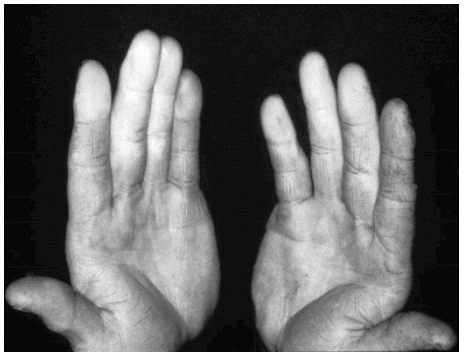
1. SLE الذئبة الحمامية الجهازية
2. Scleroderma تصلب الجلد
3. Dermatomyositis التهاب الجلد والعضلات
4. Raynaud‘s Syndrome متلازمة رينود
5. Swelling of hands and fingers تورم اليدين والأصابع
6. Myalgia ألم عضلي
7. Muscle weakness ضعف العضلات

Classification criteria for Mixed Connective Tissue Disease

معايير تصنيف أمراض النسيج الضام المختلط

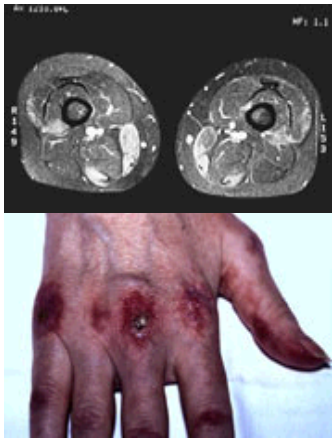
1. U1snRNP-Antibodies
2. At least two systemic diseases (SLE, Scleroderma,Myositis or RA)
3. At least three of the following symptoms:

A. Raynaud‘s Syndrome
B. Swollen Hands
C. Synovitis
D. Scleroderma
E. Proximal Muscle weakness



Poly-/Dermatomyositis

بولي / التهاب الجلد



1. Systemic inflammatory Disease of skeletal muscles
2. In Dermatomyositis further more skin involvement
3. Incidence 1:100.000

معايير التصنيف لالتهاب الجلد المتعدد

Classification criteria forPoly-/Dermatomyositis

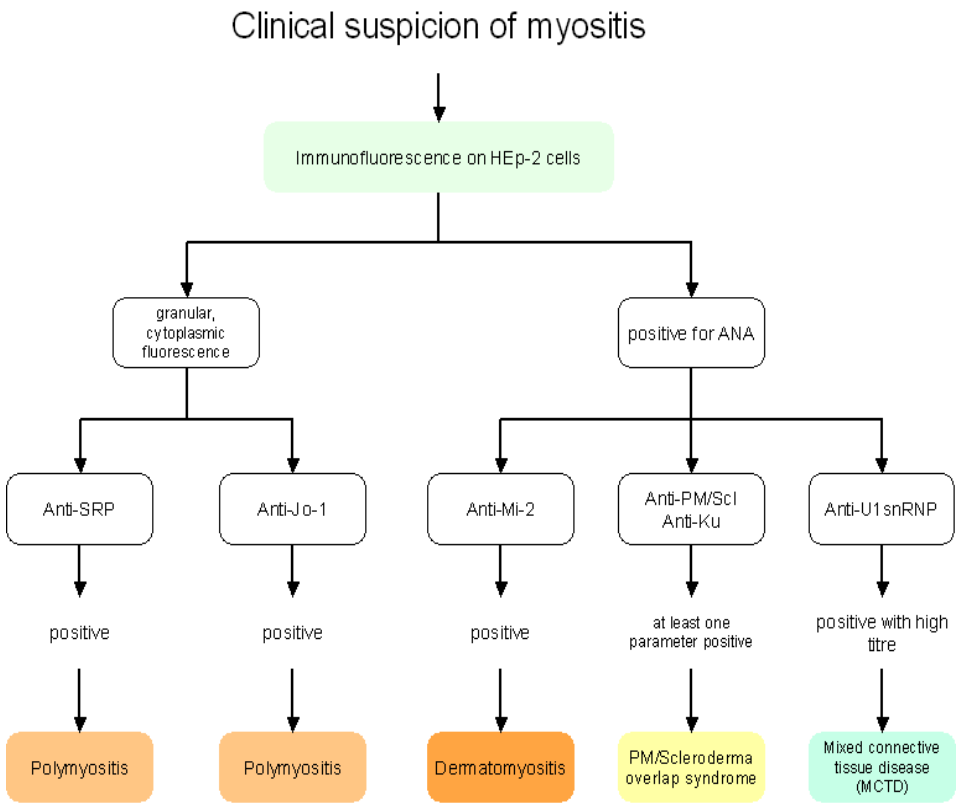
1. Proximal muscle weaknessضعف العضلات القريب
2. Histologically determined necrosis of Typ I- und Typ-II-Muscle fibres

   نخر محدد تشريحيا من ألياف النمط الأول من نوع العضلات
3. Elevated serum CRP level ارتفاع مستوى المصلCRP
4. Electromyographic findingsالنتائج الكهربائي
5. Skin changes (Erythema or Oedema)حمامي أو ذمة

•(adapted from Bohan und Peter, 1975)

Myositis

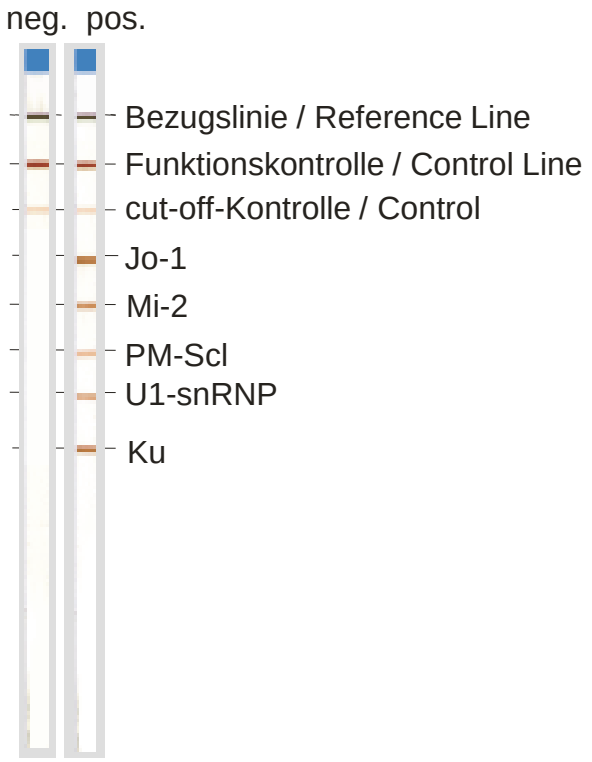
1. Jo-1 [histidyl-tRNA-synthetase]
2. Anti-Mi2 [Helicase]
3. Anti-PM/Scl [complex / >11 proteins]
4. Anti-Ku (p70/p80)
5. Anti-U1-snRNP
6. Anti-SRP [Signal Recognition Particle]



Adapted from
Conrad et al., Autoantibodies in Systemic Autoimmune Diseases. 2002. Pabst Sci. Publ. Lengerich. ISBN3-936142-87-4

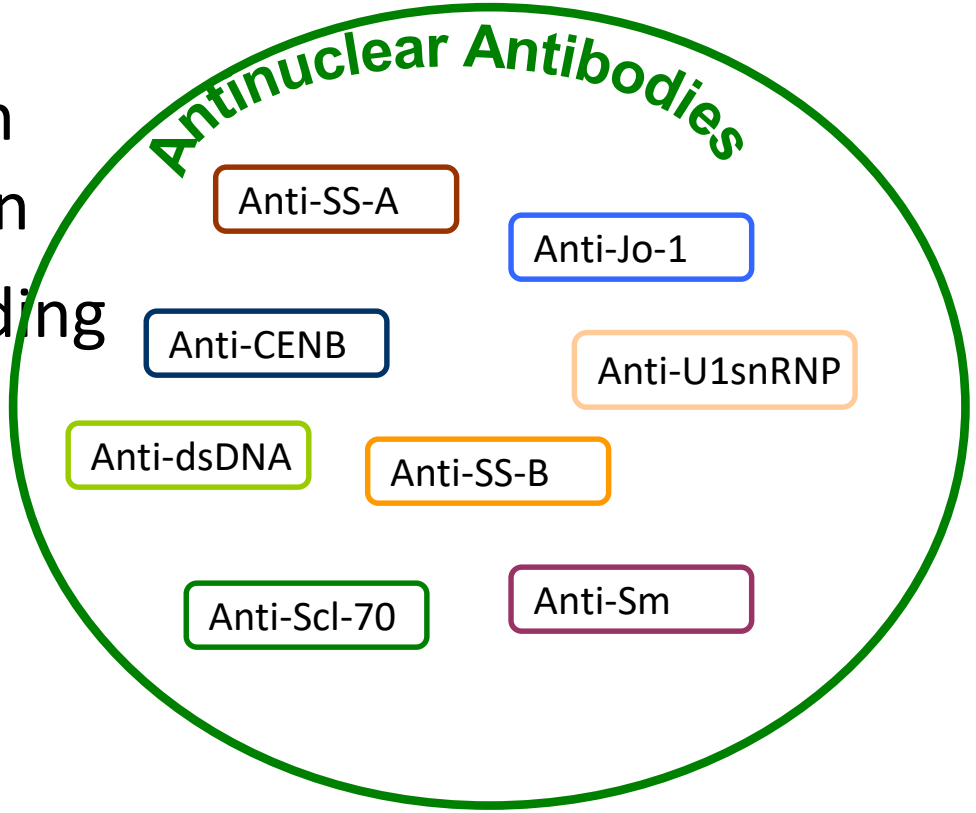
Myositis-LIA

1. comfortable and reliable differential diagnosis if myositis is suspected
2. presentation of a Ku70/Ku80 heterodimer, conformational epitopes on Ku70/80 are detectable, therefore superior to denatured proteins on blots
3. human recombinant Mi-2 antigen ensures highest sensitivity and specificity

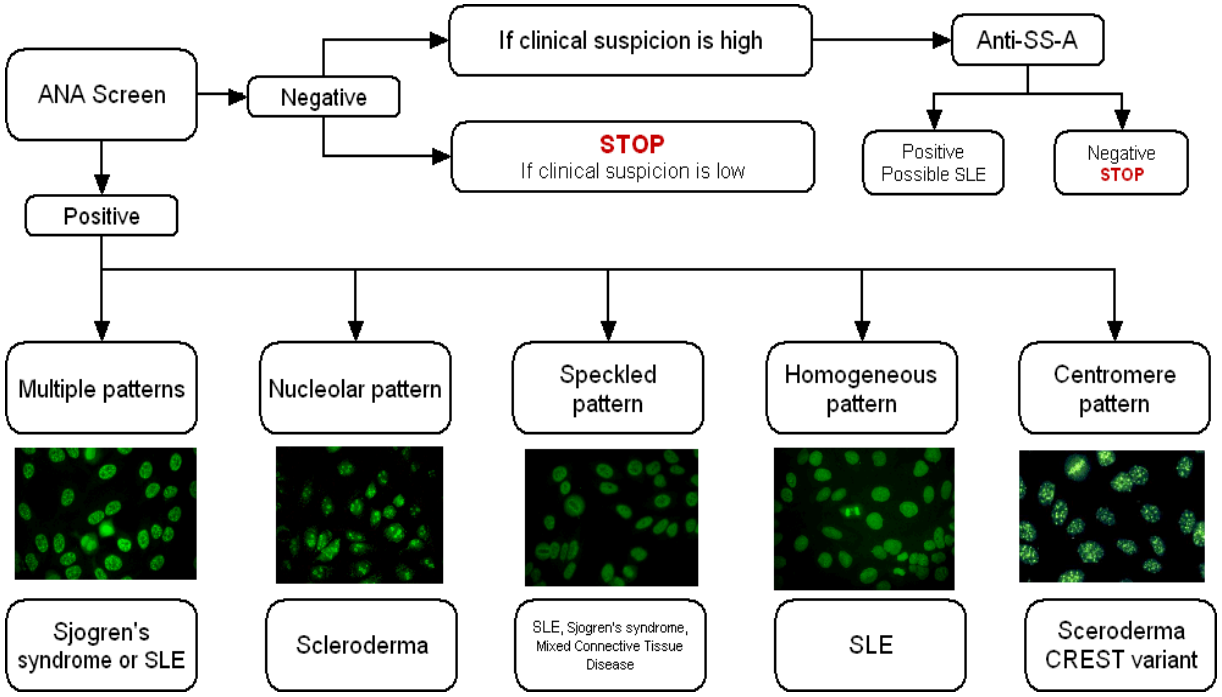


SLE Diagnosis includes a screening for antinuclear antibodies

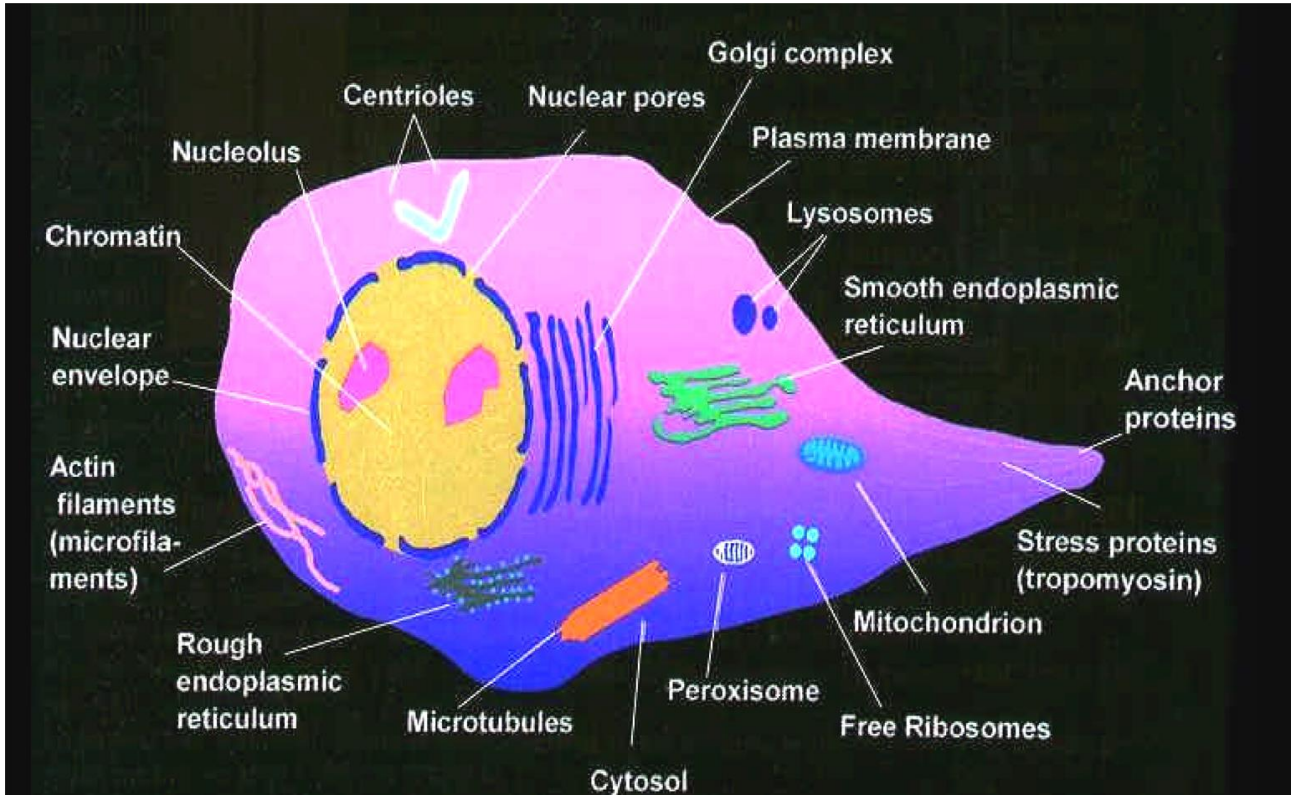
1. Immunofluorescence on Hep-2 cells
2. Line Immuno Assay with one line for each antigen
3. ANA Screen ELISA including all antigens in one well



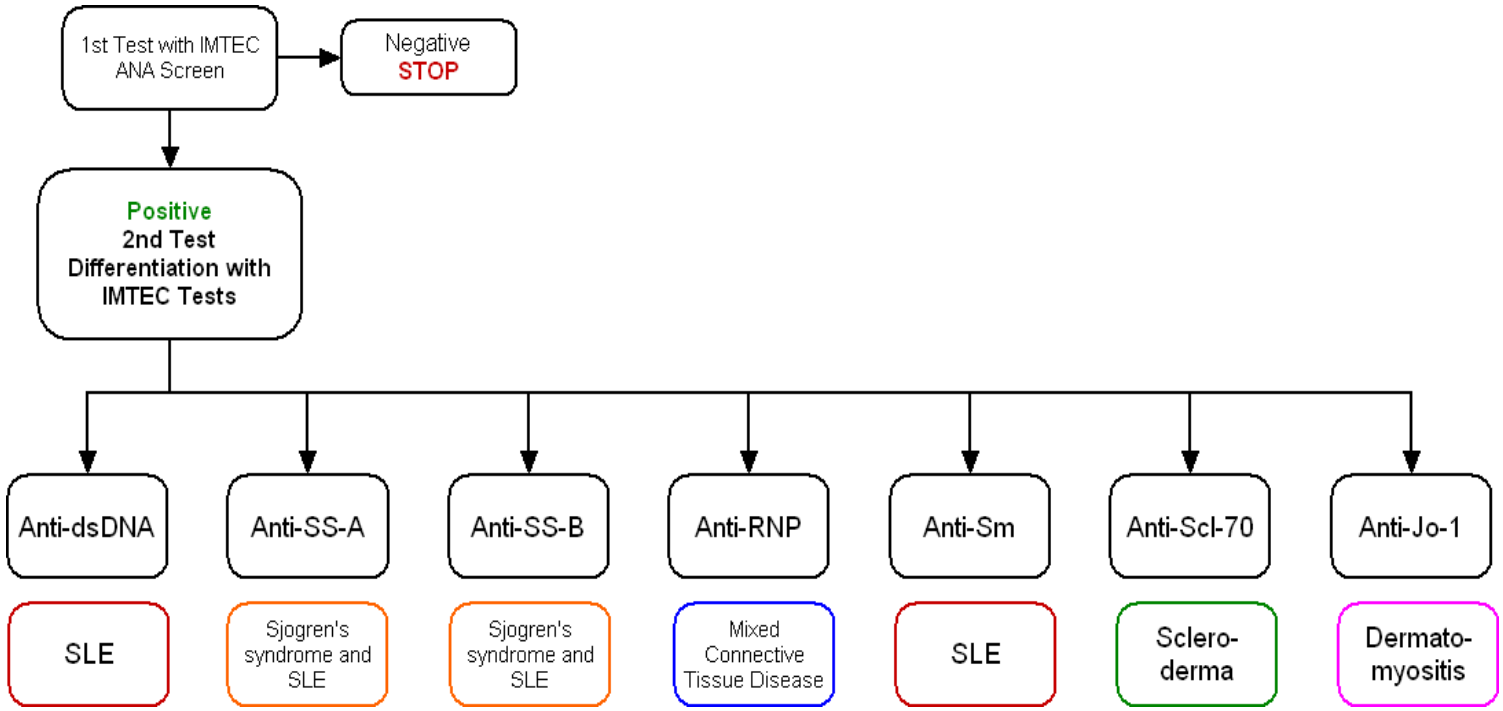
ANA Screening by Immunofluorescence



The Hep-2 cell



Screening by ELISA

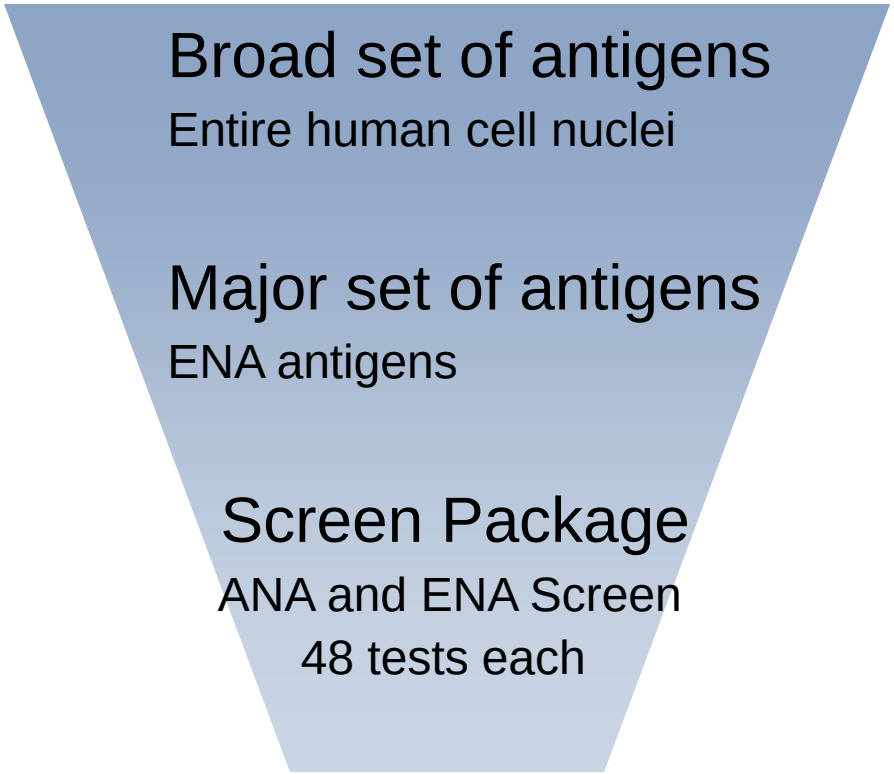


Prerequisites for modern ANA diagnostics

1. High Sensitivity and Specificity
2. Reduced Workload
    1. Automation for screening an
       differentiation
3. Cost and time efficient test portfolio
    1. reduced cost
    2. short turn-around time

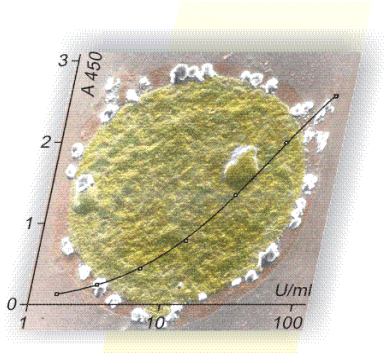
Rheumatic Diseases

- ELISA Screening Options
- ANA Screen
- ENAscreen
- ANA/ENA Combi Screen



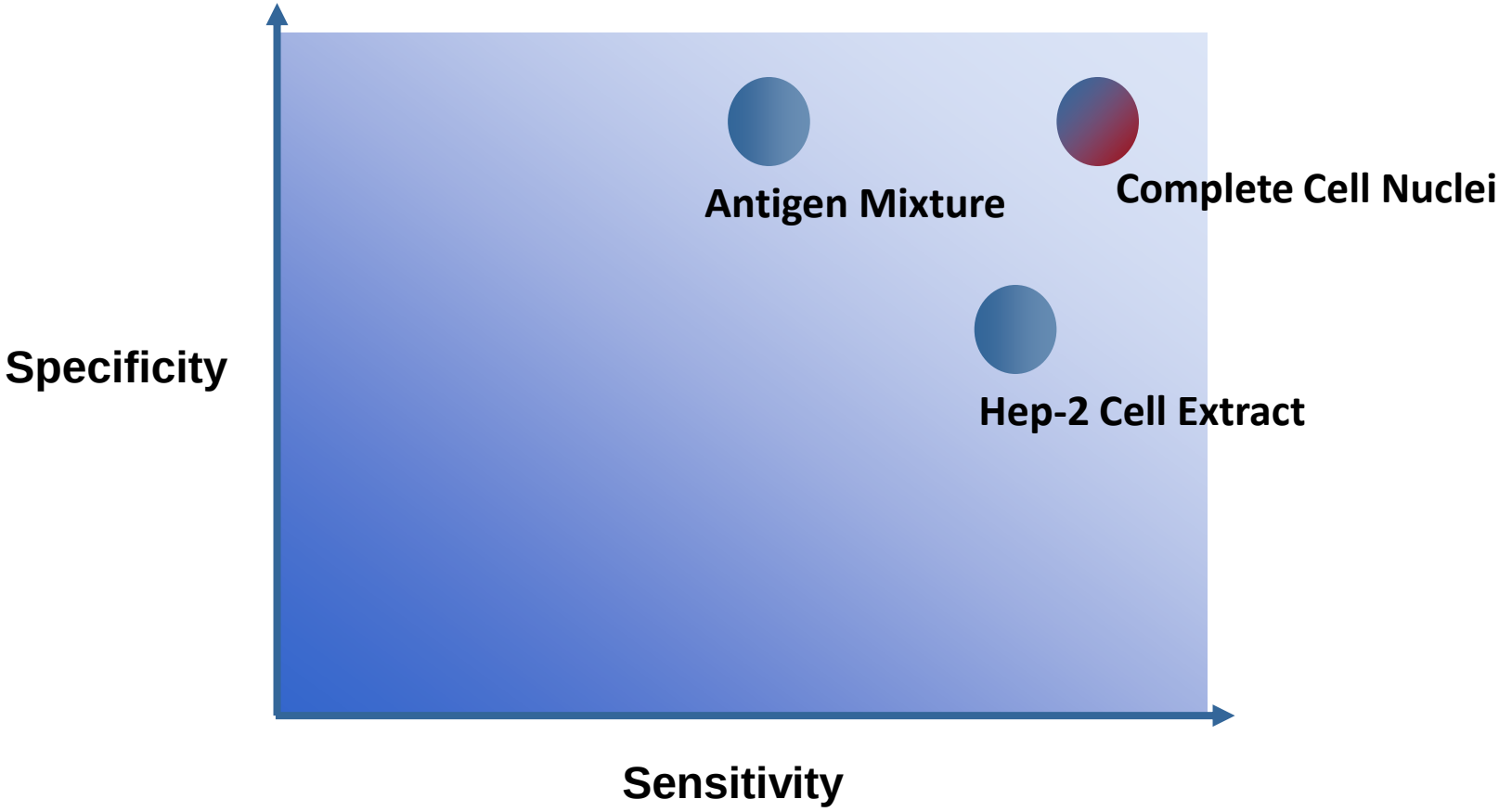
ANA Screen

•Quantitative determination of antinuclear antibodies

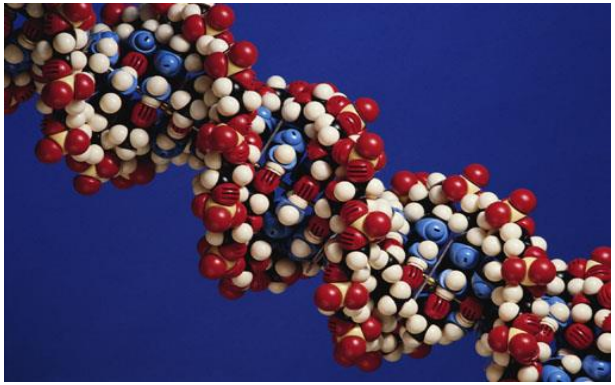


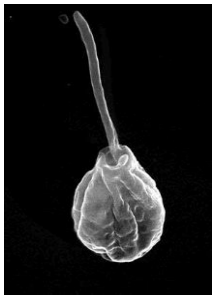
- Standardized and cost-efficient screening
- Entire human cell nuclei ensure highest sensitivity
- Qualitative or quantitative results
- Calibrated against international reference sera (CDC)

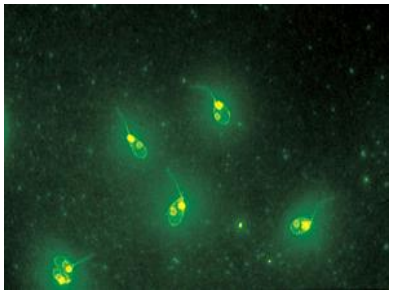
Performance of ANA Screen ELISA



Excursion - Detection of dsDNA Antibodies





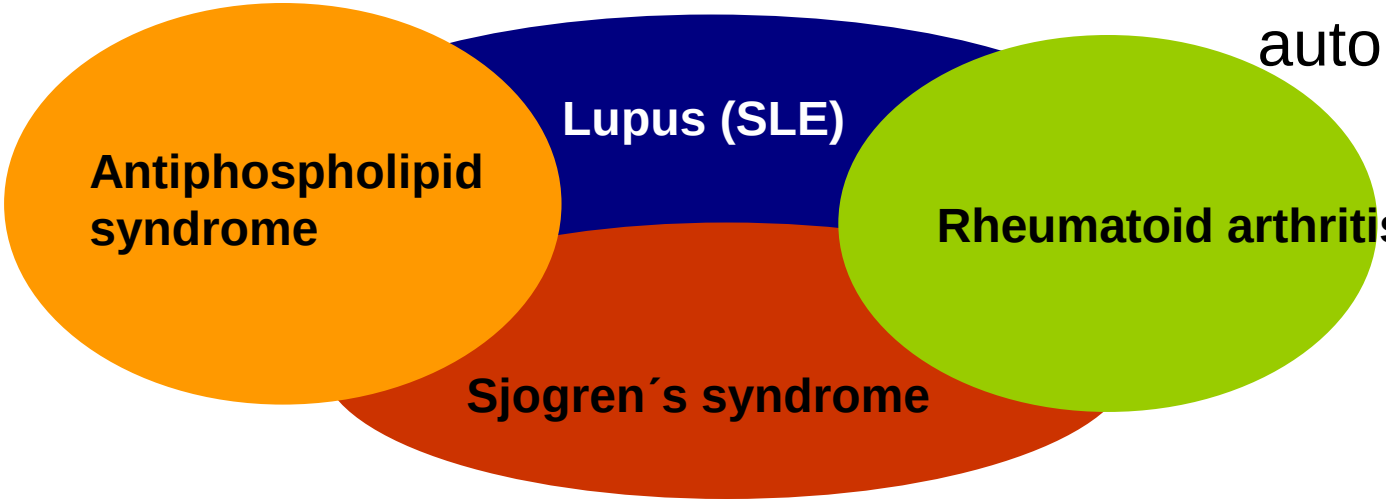


- Immunfluorescence on *Crithidia luciliae*
  kinetoplast, no histones
- ELISA
  Calibration with int. reference preparation Wo/80
- Radioimmunoassay (Farr)
  Calibration with int. reference preparation Wo/80; DNA strand breaks, interference with CIC and RFs, not automatable
- Line Immuno Assay

Overlap syndromes

التداخل بين المتلازمات

In some cases, a person may have more than one autoimmune disease



... this requires several tests to be performed.

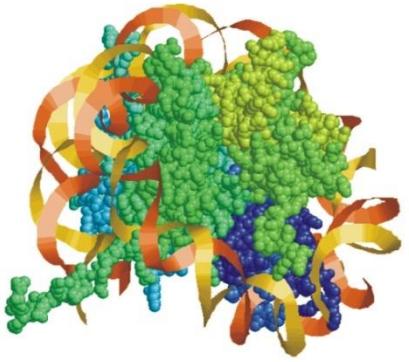
dsDNA antibodies

•Quantitative determination of IgG class antibodies against dsDNA

1. Important ACR criterion for the diagnosis of SLE
2. Disease activity marker and therapy control
3. Calibrated against WHO reference preparation for human Anti-dsDNA IgG Wo/80

Nucleosome antibodies

- Quantitative determination of IgG class
- against nucleosomes



  - Early and highly sensitive marker for SLE
  - High correlation to disease activity marker and nephritis

SS-A (Ro) antibodies

- Qualitative determination of IgG class SS-A (Ro)

1. Highly specific marker for primary and secondary Sjogren‘s syndrome
2. Recognises Ro52 and Ro60 antigen Ro52 E3-Ubiquitin-Ligase, Ro60 (hy-RNP-complex)

Indications for SS-A (Ro) Antibodies

1. Sjogren Syndrome 96 % pSS, 80 % sSS
2. SLE 25 - 60 %
3. Neonatal Lupus 90 %
4. Congenital heart block SS-A/Ro 52

SS-B (La) antibodies

- Qualitative determination of IgG class antibodies against SS-B (La)

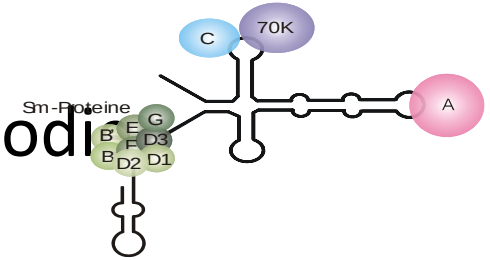
1. Sensitivity of 70 % for Sjogren‘s syndrome
2. Anti-SS-B often occur together with Anti-SS-A

SmD1 antibodies

- Quantitative determination of IgG class antibodies against SmD1

1. Highly specific marker for SLE (ACR criterion)
2. Increased sensitivity of $SmD1_{83\text{-}119}$ peptide antigen compared to entire protein
3. High correlation to disease activity marker and nephritis

U1-snRNP antibodies



- Qualitative determination of IgG class antibodi
- against U1-snRNP

1. Diagnostic marker for **M**ixed **C**onnective **T**issue **D**isease (MCTD) or Sharp‘s syndrome
2. Sensitivity of up to 100 % and specificity of 98 %
3. Recombinant RNP proteins A, C and 68 kD

Jo-1 antibodies

- Qualitative determination of IgG class antibodies against Jo-1

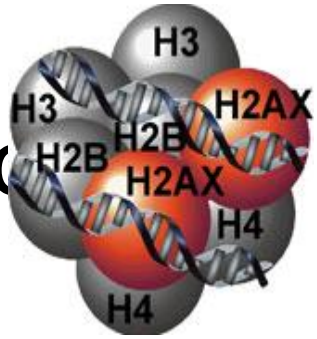
1. Jo-1 identified as histidyl-tRNA synthetase
2. Diagnostic marker for dermato- and polymyositis
3. Marker antibodies for for a subset of myositis with lung disease (diffuse fibrosing alveolitis)

Scl-70 antibodies

- Qualitative determination of IgG class antibodies against Scl-70

1. Scl-70 identified as DNA topoisomerase I
2. Diagnostic marker for systemic scleroderma
3. More severe clinical cause and a poorer diagnosis

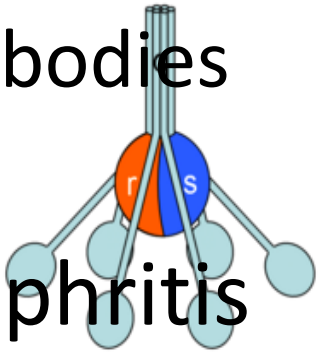
Histone antibodies



- Quantitative determination c
class antibodies against Histo

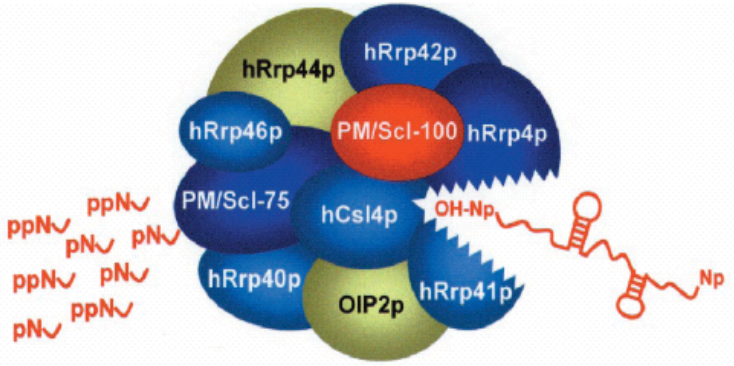
  - Diagnostic marker for drug induced lupus

C1q antibodies



- Quantitative determination of IgG class antibodies against C1q
  1. Highly specific marker for lupus nephritis
  2. C1q is a sucomponent of the complement cascade and itself binds to circulating immune complexes
  3. Special sample buffer ensures highest specificity

PM-Scl antibodies



Schematic representation of the human exosome complex. The associations between individual components of the human exosome are hypothetical, since no structural data have been presented to date. All human exosome components analyzed so far (PM/Scl-100, PM/Scl-75, hRrp4p, hRrp40p, hRrp41p, hRrp42p, hRrp46p, and hCsl4p) are recognized by autoantibodies present in IIM sera, although some (PM/Scl-100, PM/Scl-75, and hRrp4p) are preferentially recognized.

- Qualitative determination of IgG Class antibodies against PM-Scl

1. Nucleolar antibodies in immunofluorescence human exosome complex (PM-Scl-100)
2. Diagnostic marker for poly- and dermatomyositis
3. Marker for PM with scleroderma overlap syndrome