# ACR

# UPDATE IN SPA


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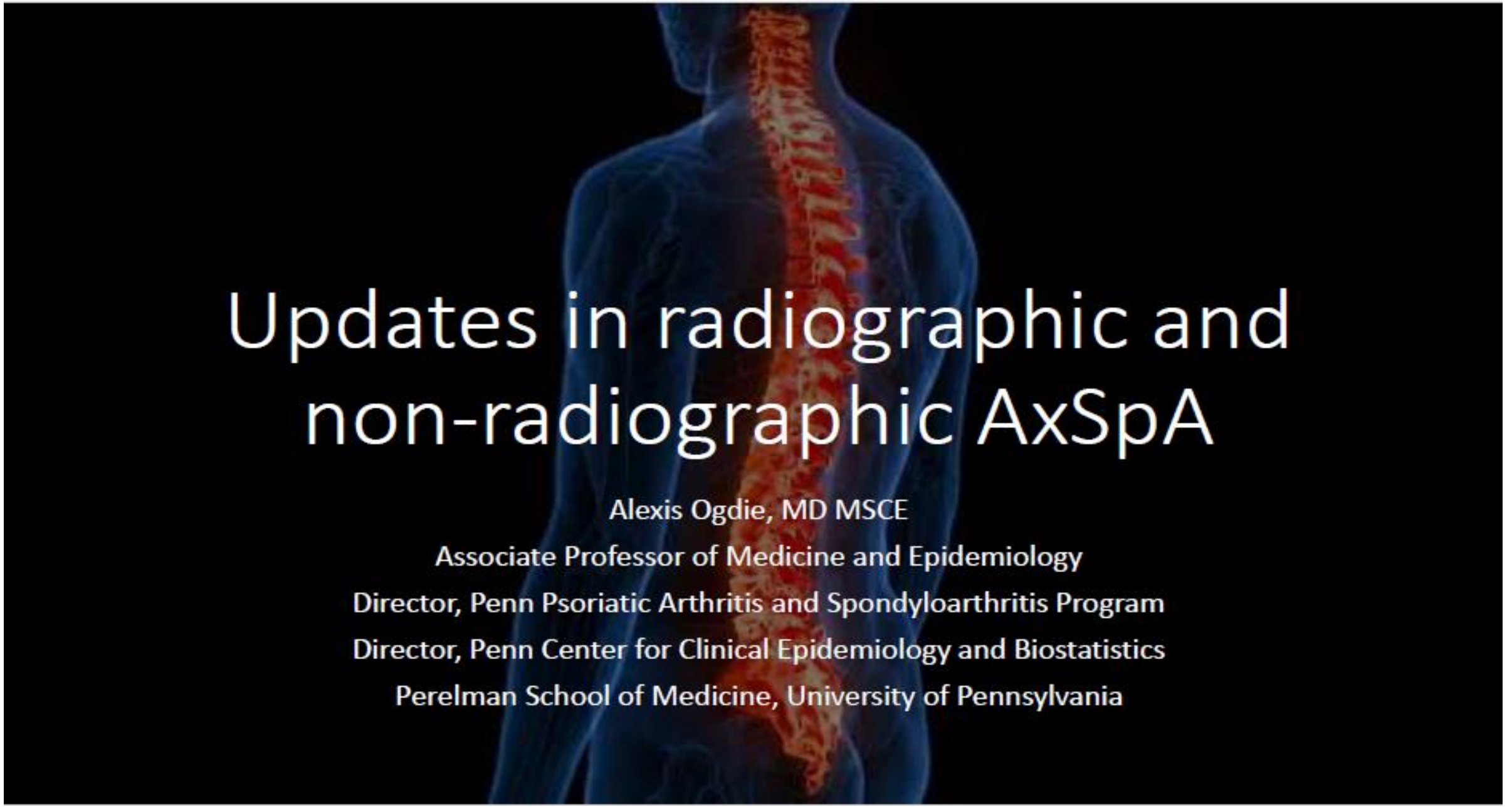

# Updates in radiographic and non-radiographic AxSpA

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Director, Penn Center for Clinical Epidemiology and Biostatistics
Perelman School of Medicine, University of Pennsylvania

ACR Convergence
Where Rheumatology Meets
#ACR23

# Diagnostic Approach to Non-Radiographic Axial Spondyloarthritis

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UTHealth Houston

# Outline

Diagnosis of AxSpA and subgroups of r- and nr-AxSpA

Prognosis and the risk for progression

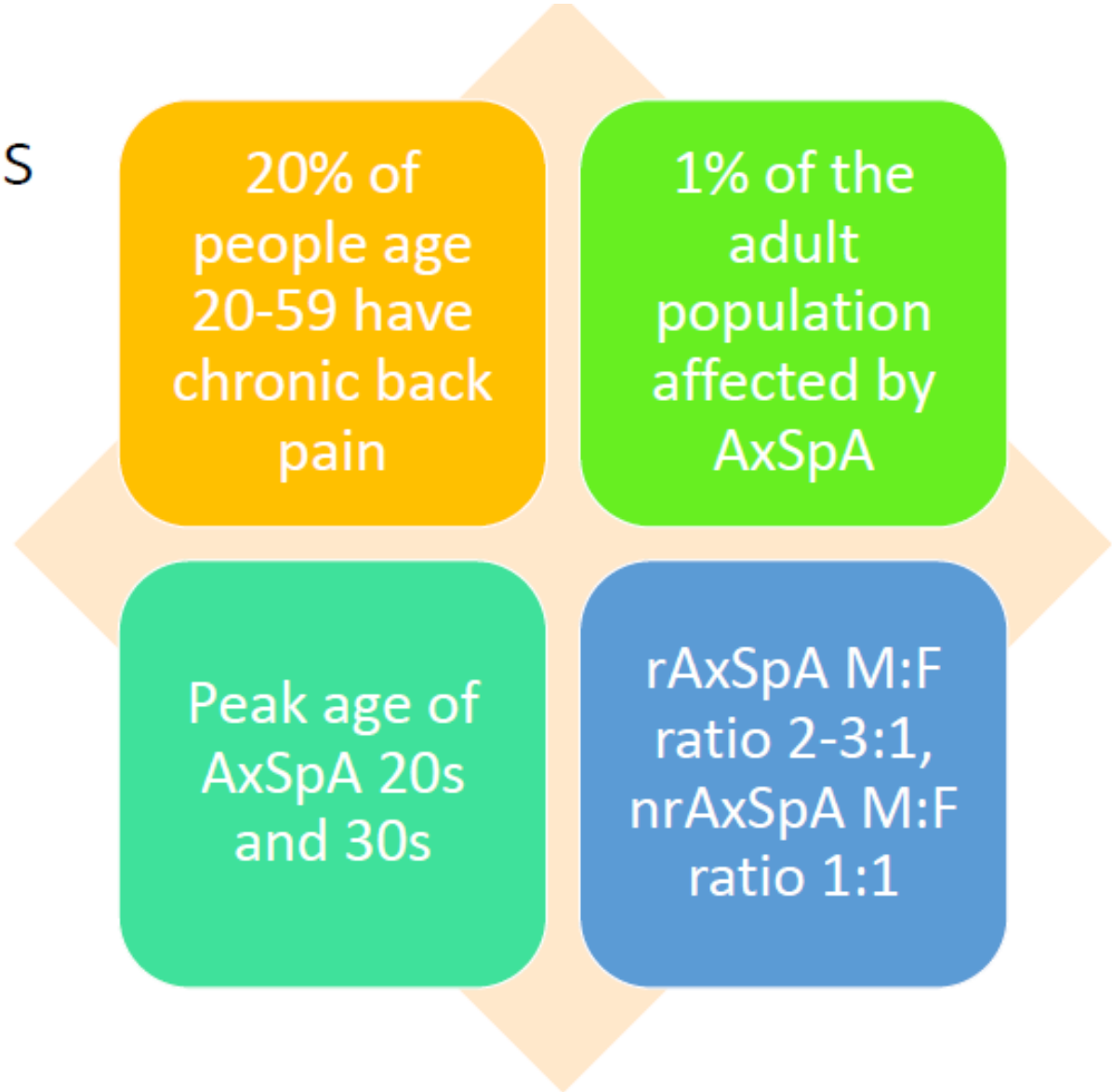
Treatment of AxSpA

# Objectives

- History of Spondyoarthritis (Hx of AxSpA)
  - Anyklosing Spondylitis -> Unified Concept of SpA
- Review clinical features of SpA (SpA Features)
  - Articular and Extra-Articular
- Diagnostic Decision Making for non-radiographic AxSpA (nr-AxSpA DDm)
  - Bayesian
  - Bordage


"My back hurts"
But does this patient have AxSpA?

# The basics


20% of people age 20-59 have chronic back pain
1% of the adult population affected by AxSpA
Peak age of AxSpA 20s and 30s
rAxSpA M:F ratio 2-3:1, nrAxSpA M:F ratio 1:1

# SpA Features: IBP vs. Mechanical Back Pain

## Inflammatory

- Onset prior to age 40
- Insidious onset
- Improvement w/ exercise
- No improvement w/ rest
- Pain at night (middle)
- Prolonged morning stiffness

## Mechanical

- More common with **advancing age**
- Insidious **or acute onset**
- Worse during/after activity (end of the day)
- Improved with rest or supine position

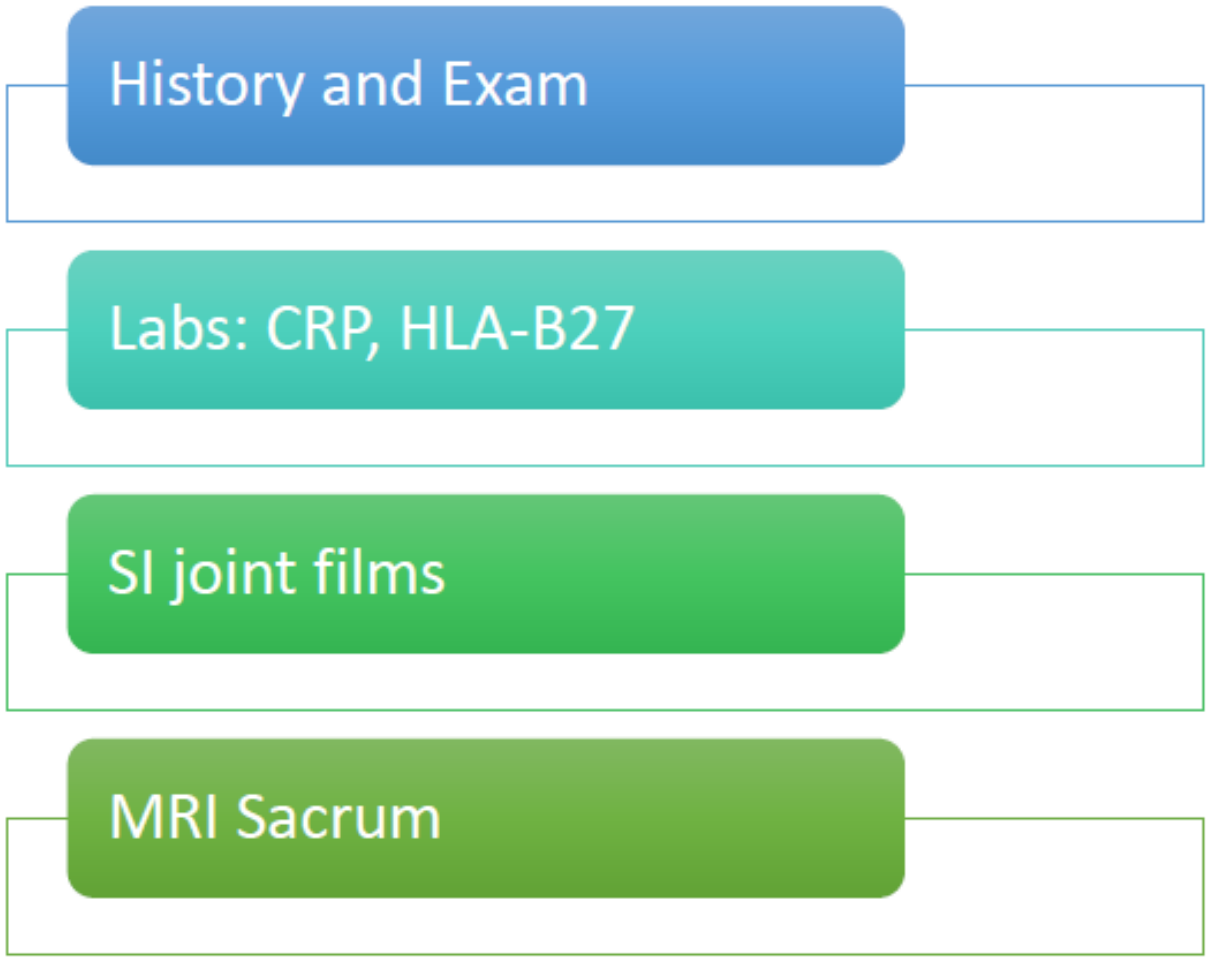
Calin et al JAMA 1977
Rudwaleit et al A&R 2006
Sieper et al ARD 2009

# Spa Features: Inflammatory Back Pain (IBP)

| Calin (1977)[4] | European Spondyloarthropathy Study Group (1991) [12] | Berlin (2006) [13] | ASAS (2009)[14] |
|---|---|---|---|
| • 1. Age at onset <40 years<br>• 2. Duration of back pain > 3 months<br>• 3. Insidious onset<br>• 4. AM stiffness<br>• 5. Improvement with exercise<br>• **IBP if 4 of 5 present** | • History or present symptoms of spinal pain in back, dorsal, or cervical region, with at least 4 of the following:<br>• 1. Onset before age 45<br>• 2. Insidious onset<br>• 3. Improved by exercise<br>• 4. Associated with morning stiffness<br>• 5.At least 3 months duration<br>• **IBP if 4 of 5 present** | • In patients < 50 years of age<br>• 1. AM stiffness of > 30 minutes duration<br>• 2. Improvement in back pain wih exercise but *not* with rest<br>• 3. Awakening beause of back pain during the second half of the night only<br>• 4. Alternating buttock pain<br>• **IBP if 2 of 4 present** | • 1. Age onset <40 years<br>• 2. Insidious onset<br>• 3. Improvement with exercise<br>• 4. No improvement with rest<br>• 5. Pain at night with improvement on getting up<br>• **IBP if 4 of 5 present** |

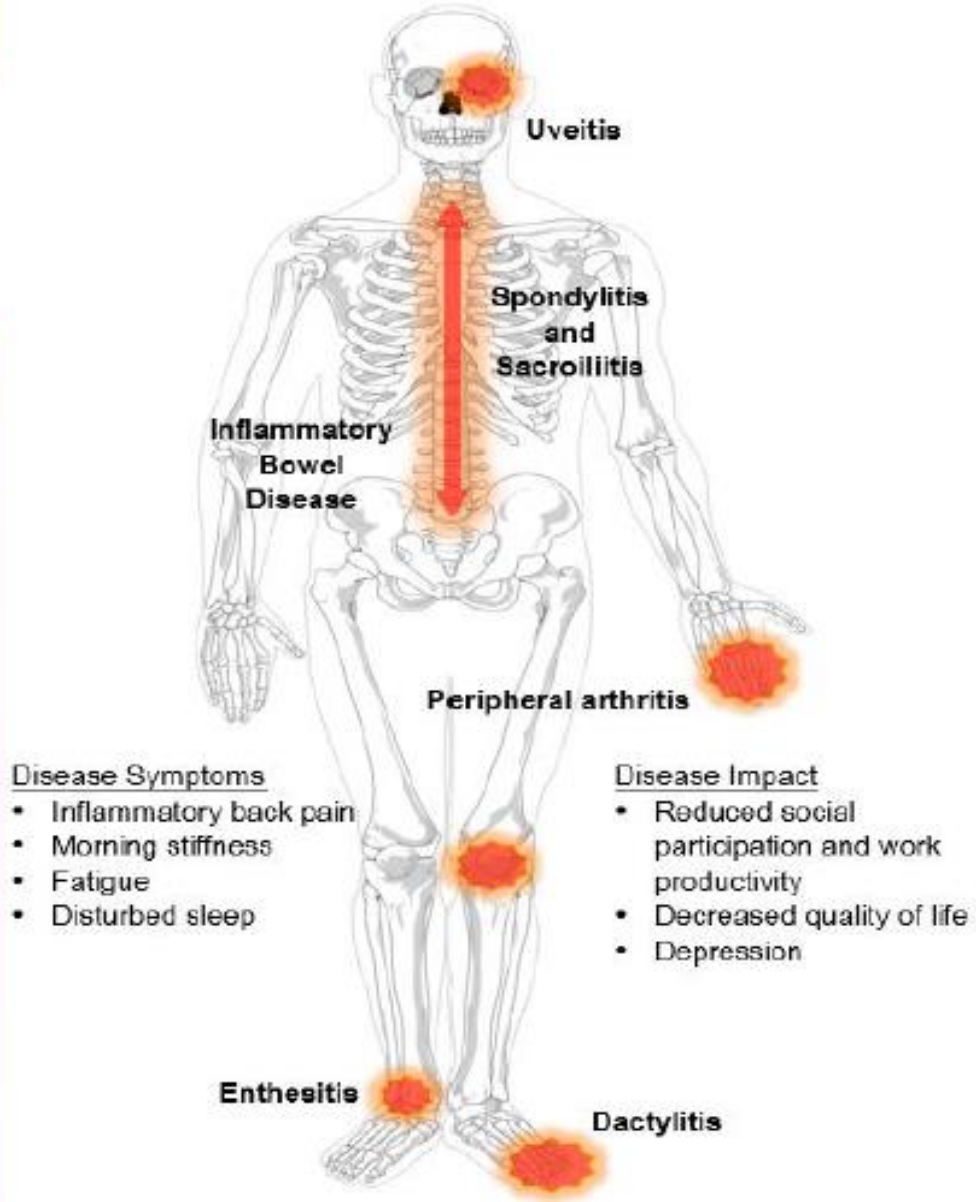
Reveille et al . Am J Med Sci. 2013

# Work up



# Introduction

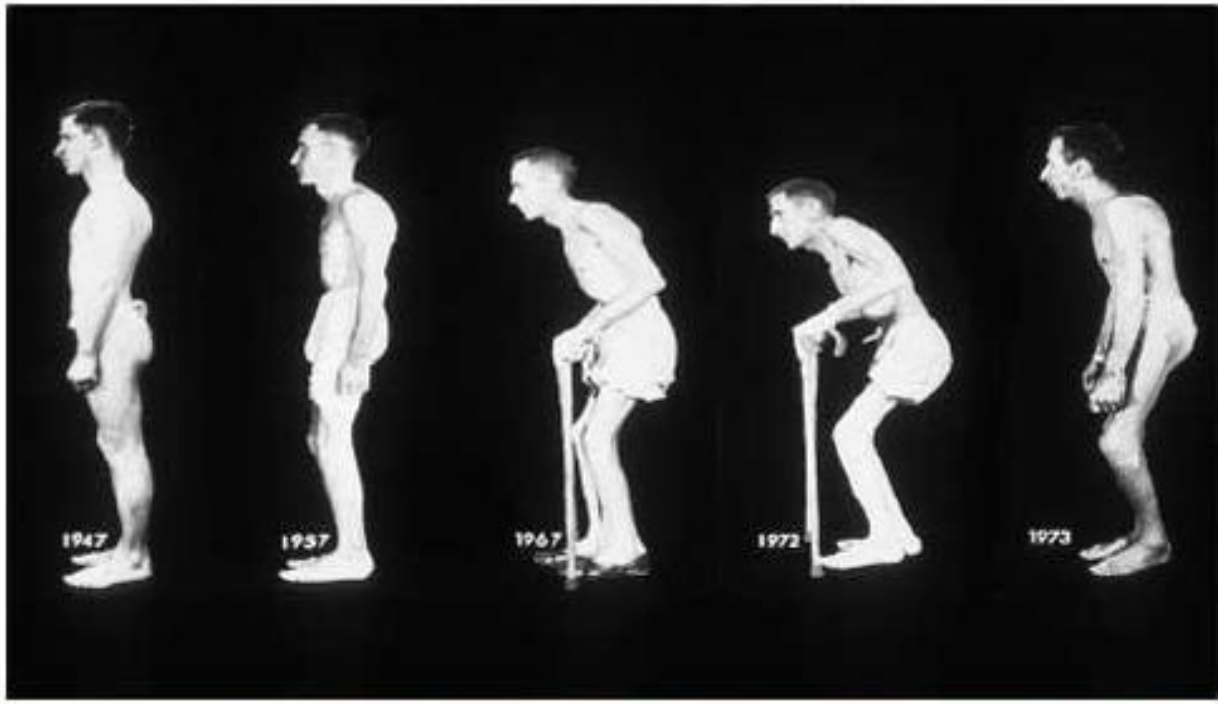
- **Spondyloarthritis (SpA)**
  - **Heterogeneous entities with common features**
    - **Clinical**
    - **Laboratory**
    - **Imaging**



# Hx of SpA: Ankylosing Spondylitis

- Ankylosing Spondylitis (AS)
  - formally characterized- 19th century
  - Well-established Mid-20th century
  - HLA-B27 association 50th year!
  - Modified New York Criteria for Ankylosing Spondylitis (mNY Criteria) 1984
    - Classification ≠ Diagnosis

## Progressive deformity due to AS over a period of 36 years




Little H, Swinson DR, Cruickshank B. *Am J Med*. 1976;60:279-285.
Reproduced with the permission of Cahner's Publishing Co.

*Taurog JD, et al. NEJM. 2016;374(26):2563-74.

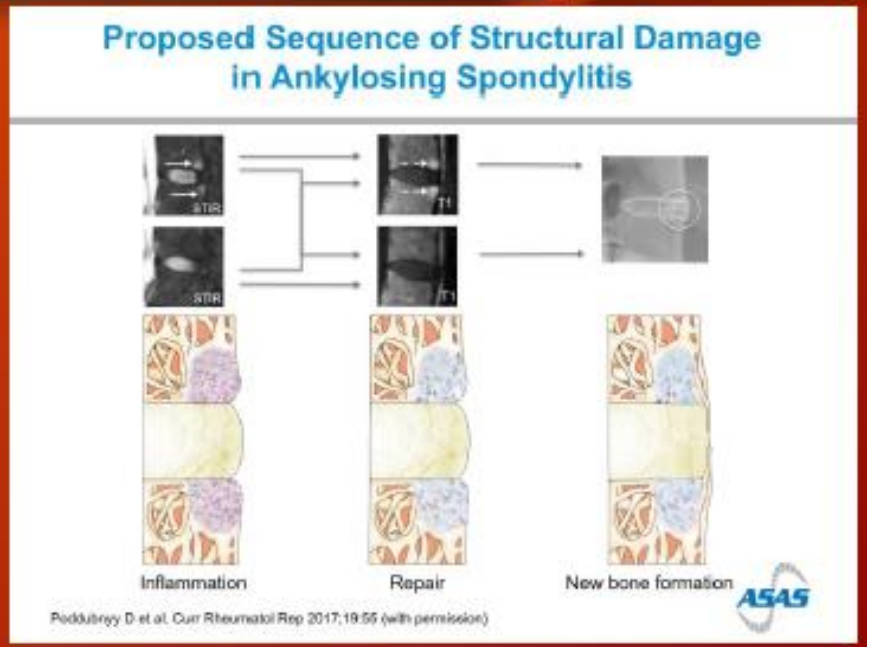
# SpA Features: Overview

| Axial | Peripheral | Extra-articular |
|---|---|---|
| Inflammatory Back Pain | Peripheral Arthritis | Uveitis |
| Chest Pain | Enthesitis | Skin manifestations |
| Restricted Spinal Mobility | Dactylitis | Gi Involvement |
| Structural Changes/Imaging | Hip Disease | |

# SpA Features: Other Axial Features

Chest Wall Pain

Restricted Spinal Mobility




Structural Changes

Weber U. AR&T 2013; 14:R3 *ASAS Slide library*

# SpA Features: Peripheral Skeletal

Peripheral Arthritis[1]

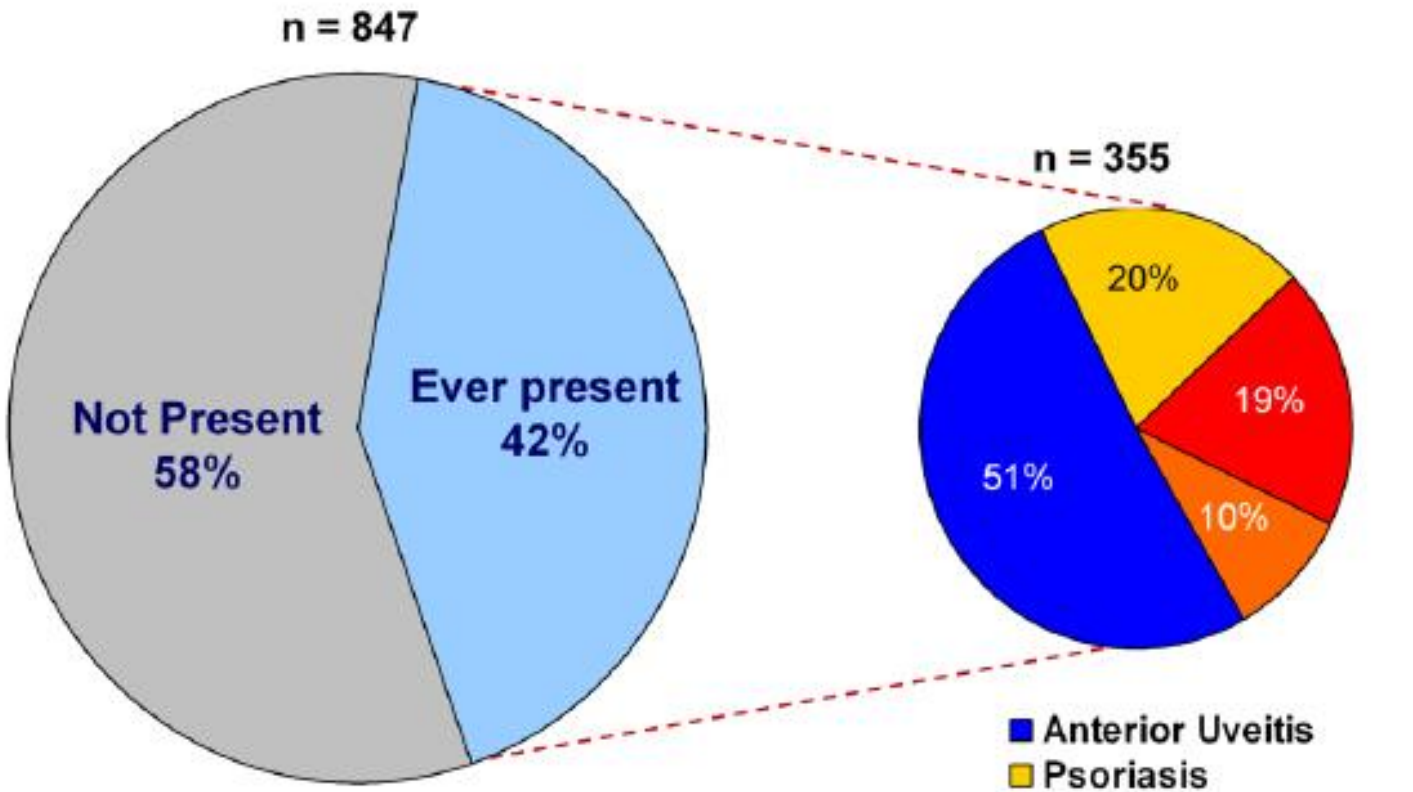
Enthesitis[2]

Dactylitis[3]

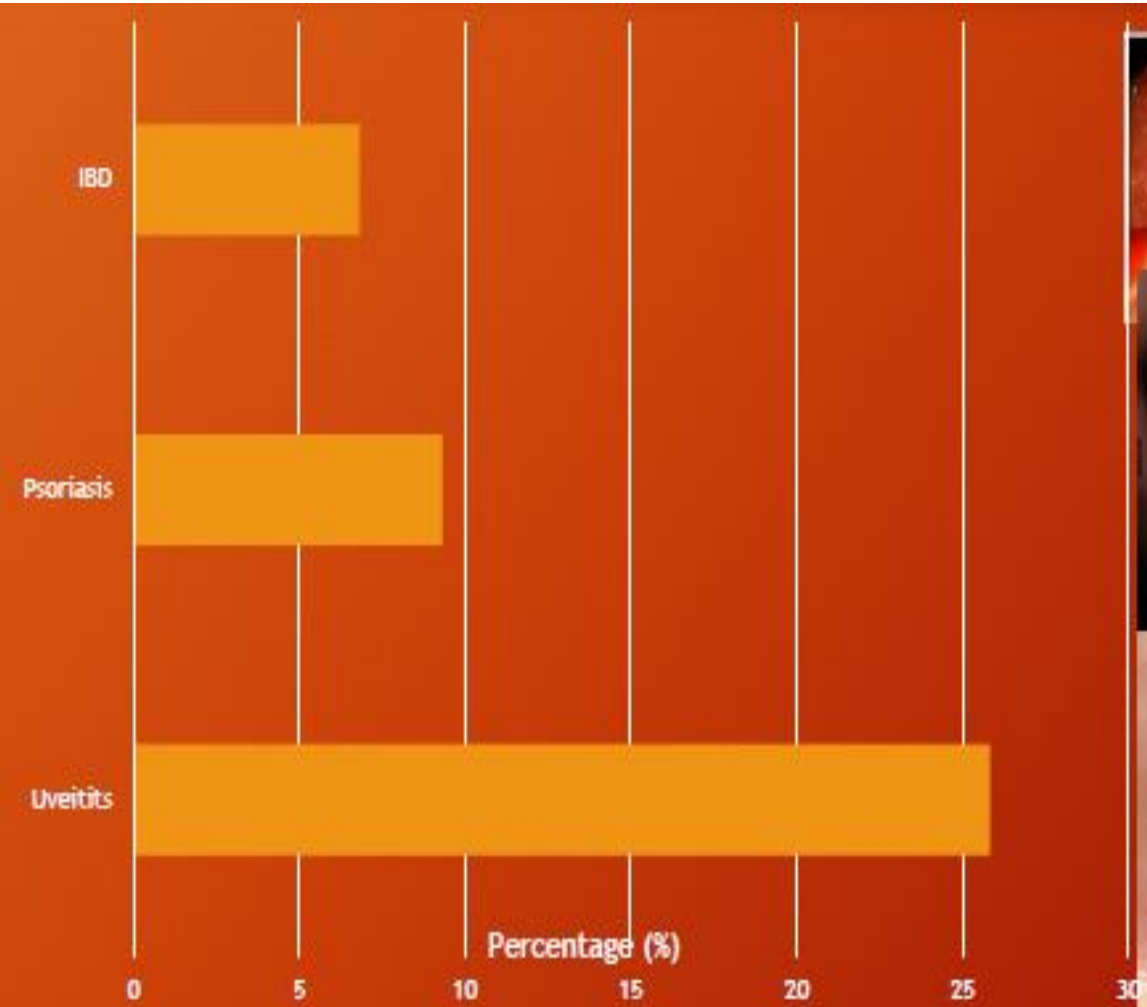
Hip Disease[4]

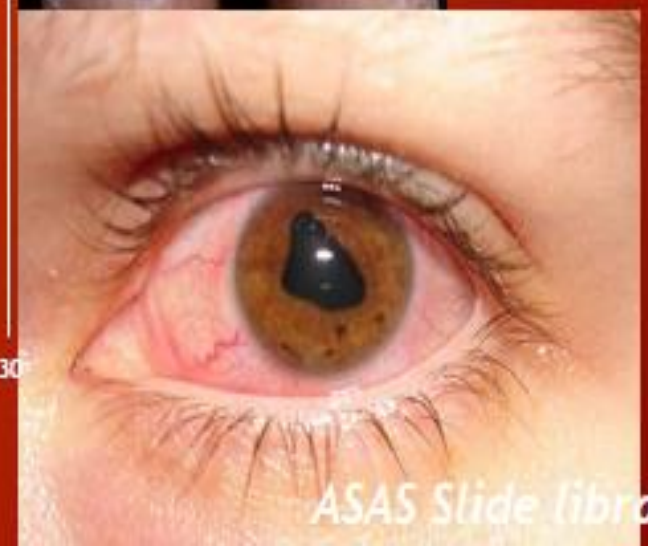

1. Coates et al. *Arthritis Rheumatol*. 2016;68(5):1060-1071.
2. 3. American College of Rheumatology. http://images.rheumatology.org
4. Han et al. Front Immunol. 2021 Mar 24;12:668969.

# Extra-Musculoskeletal Manifestations




Vander Cruyssen B et al. Ann Rheum Dis 2007;66:1072-7




Stolwijk C. ARD 2015;74:65-73.

# ASAS Classification Criteria for AxSpA

At least 3 months back pain and age of onset <45

**Sacroiliitis on imaging plus at least 1 SpA feature**

**HLA-B27 plus at least 2 SpA features**

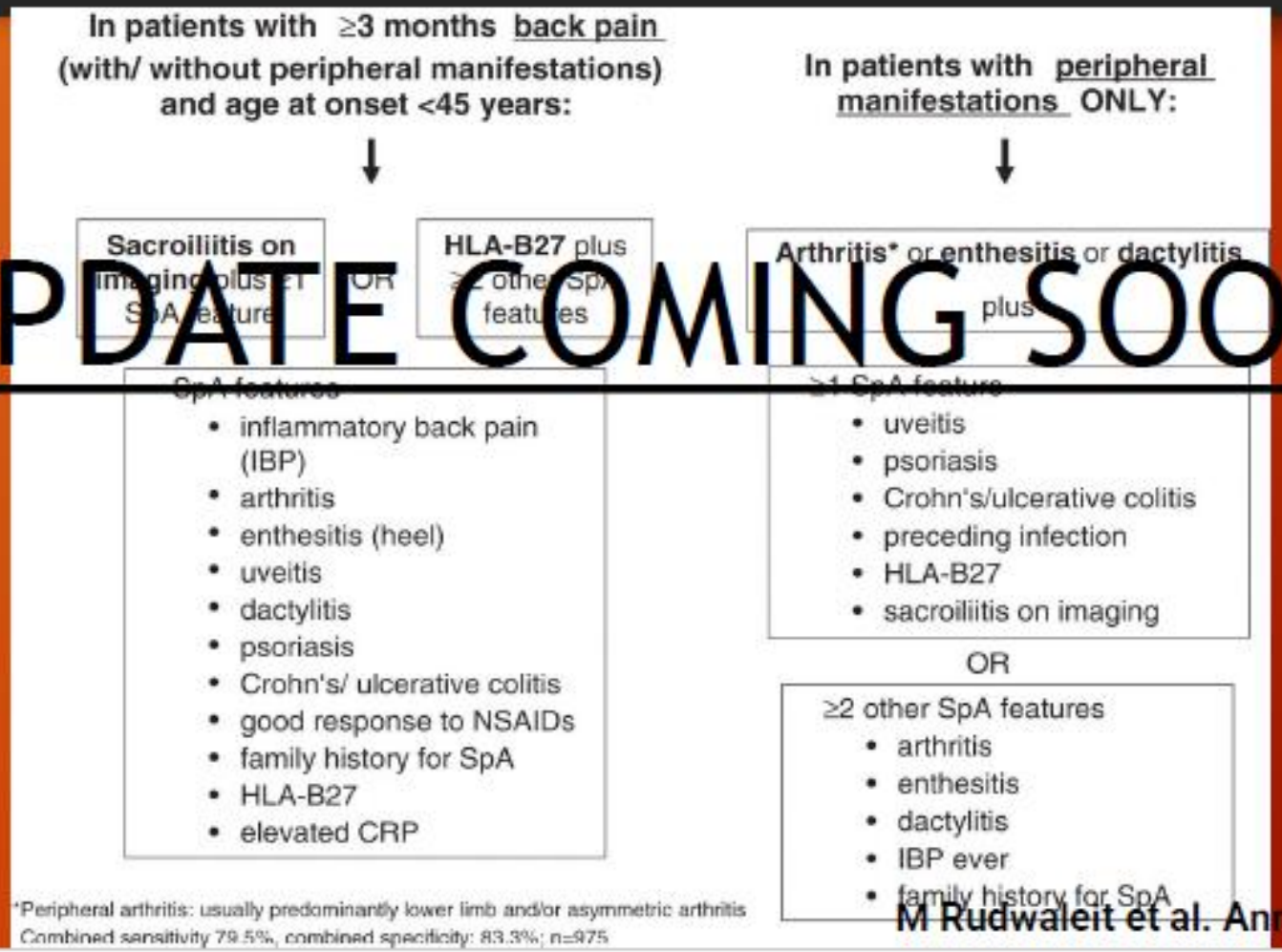
SpA Features

Inflammatory back pain
Arthritis
Enthesitis (i.e. heel)
Uveitis
Dactylitis
Psoriasis
Crohn's colitis
Good response to NSAIDs

HLA-B27
Elevated CRP
MRI sacroiliitis
NY Modified criteria xray sacroiliitis

Rudwaleit, Ann Rheum Dis 2009; 68:777

# Hx of SpA: Current Classification Schema



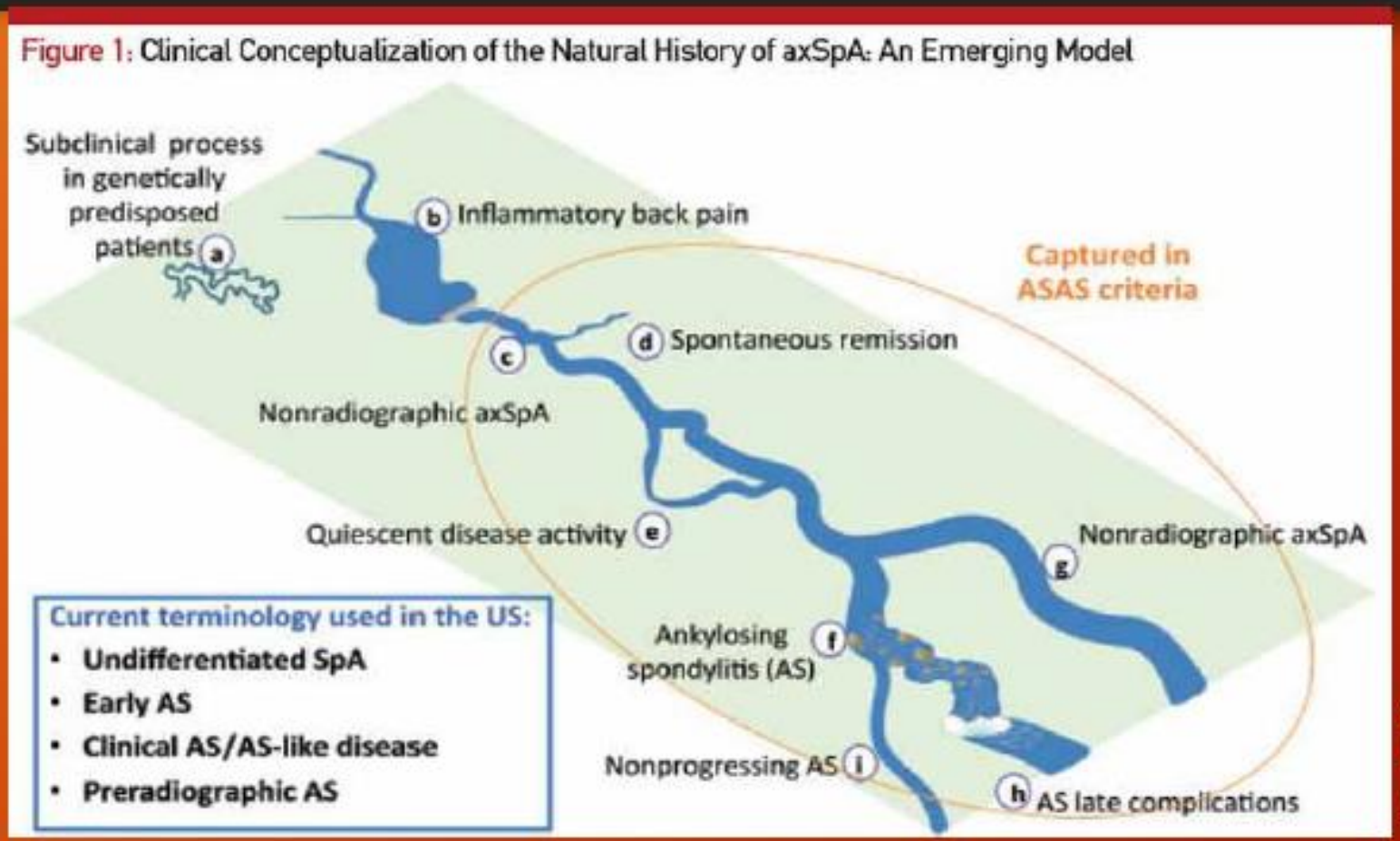

UPDATE COMING SOON!!!

Axial SpA

Peripheral SpA

M Rudwaleit et al. Ann Rheum Dis 2011;70:25-31

# Hx of SpA: Spectrum of AxSpA

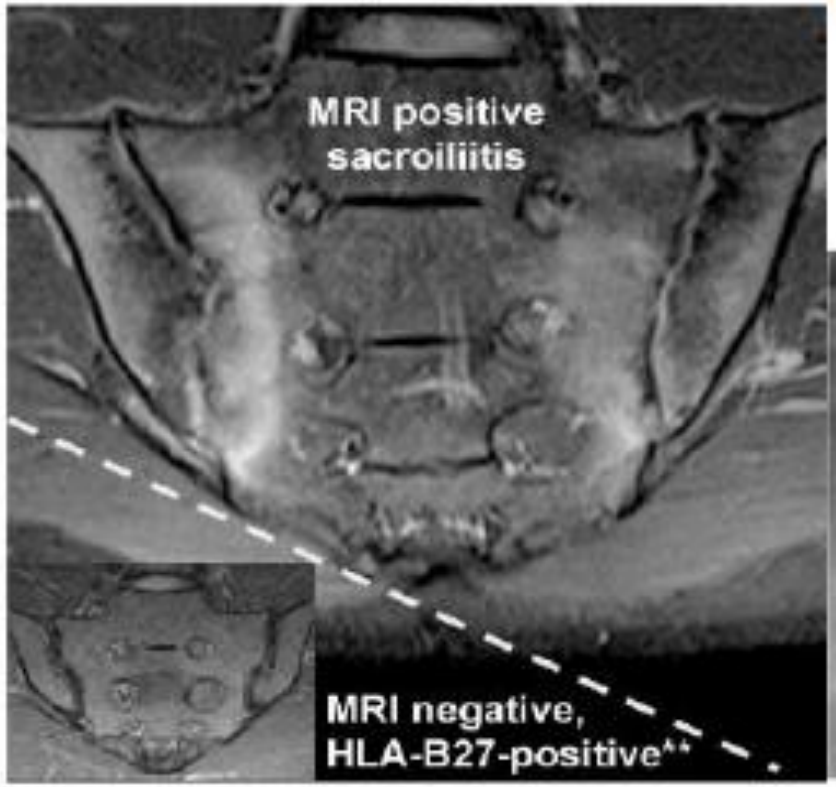



*Adapted from van Vollenhoven RF.* Nat Rev Rheumatol. *2011 Apr;7(4):205–215.*

## Patients with chronic back pain ≥3 months and aged <45 years

### Axial SpA (ASAS criteria)

**Non-radiographic stage**
X-ray-negative




### Ankylosing Spondylitis (modified New York criteria)

**Radiographic stage**
X-ray-positive sacroiliitis

**Radiographic stage**
X-ray-positive sacroiliitis and/or spinal changes***

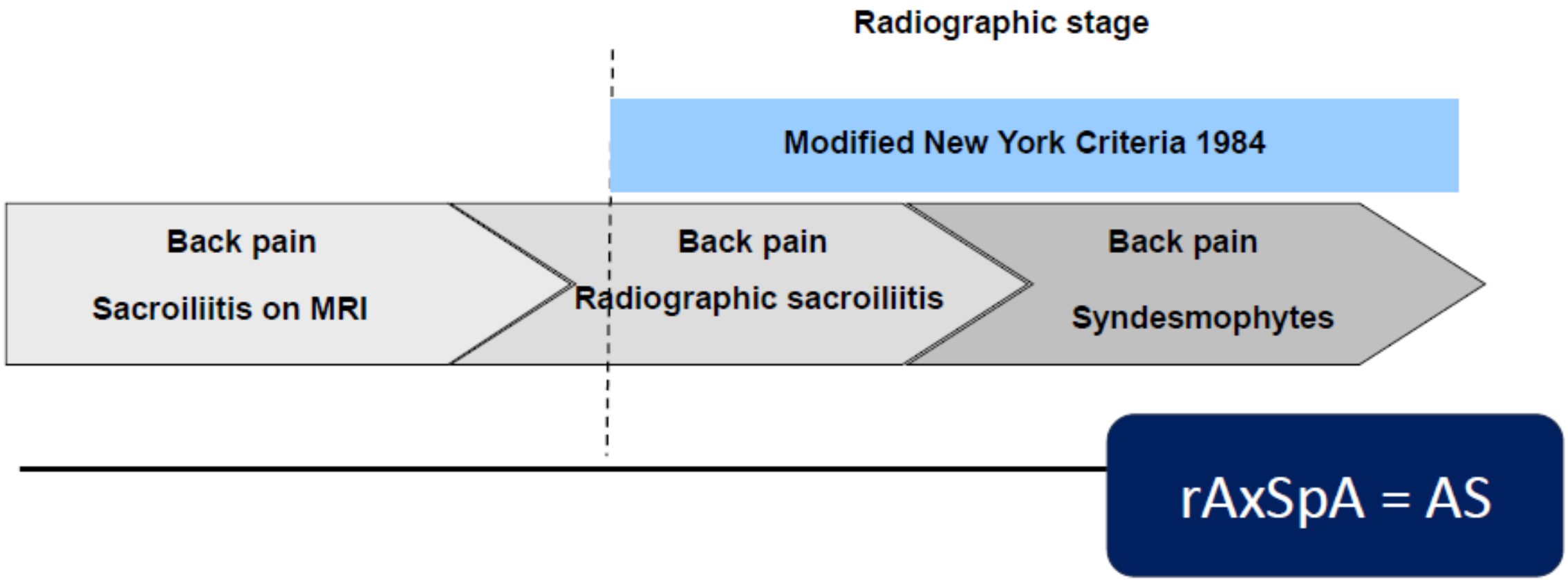
Estimated proportion of affected individuals*

Time

* Heights reflect an estimate of the proportion of patients in each group
** Clinical arm if non-radiographic axial SpA
*** Radiographic evidence of inflammatory spinal changes including i.e., syndesmophytes, fusion or posterior element involvement

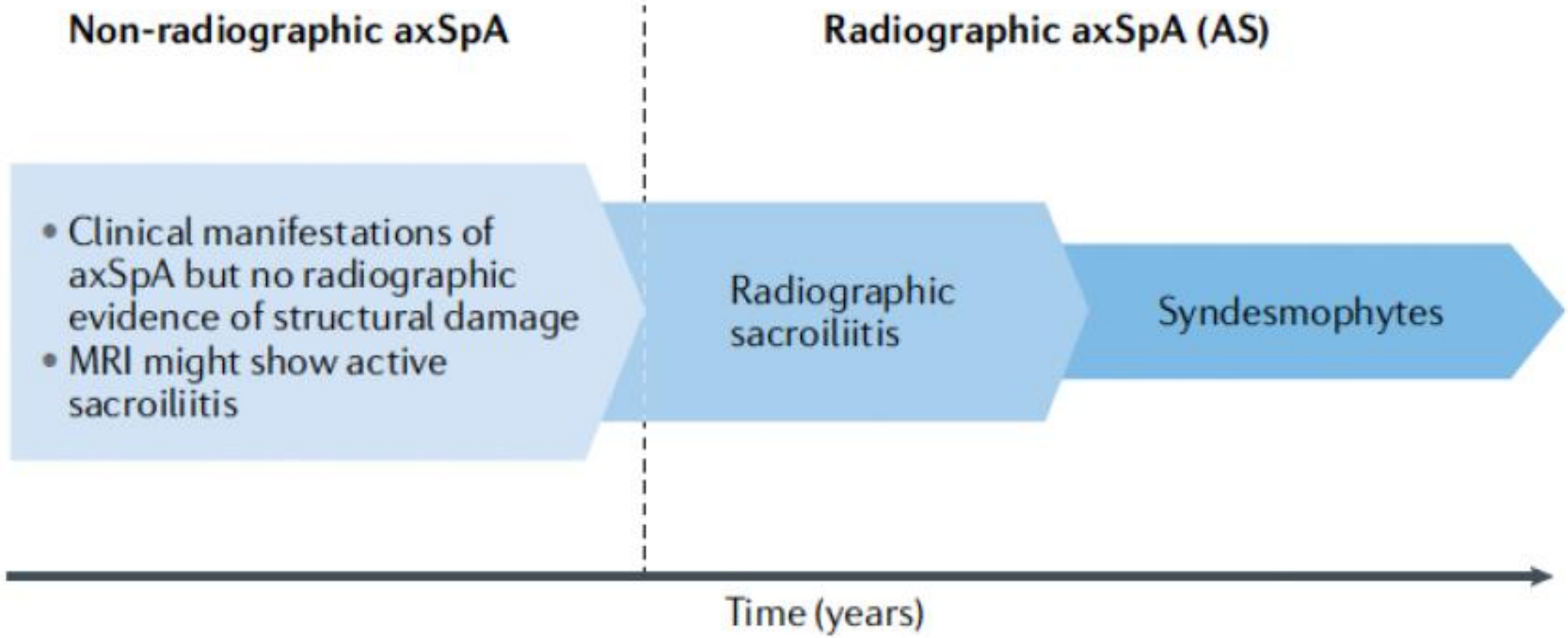
ASAS
ASAS Sli

# Non-radiographic Axial Spondyloarthritis



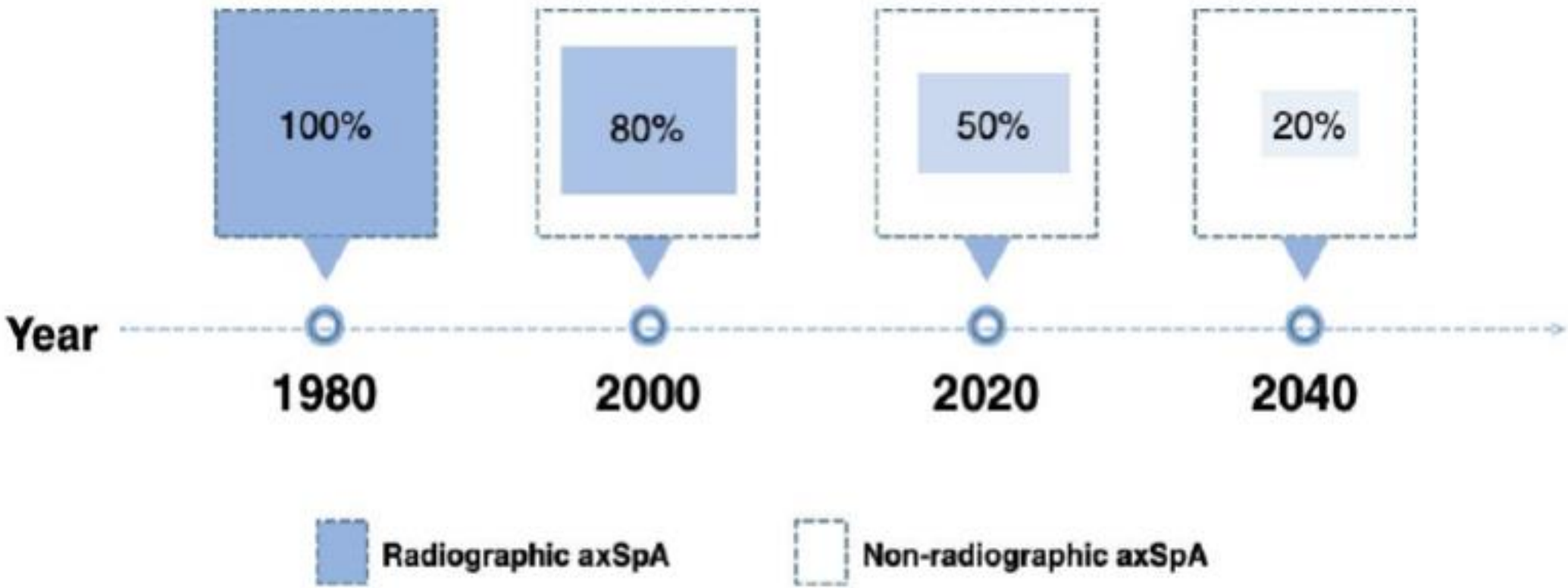

Rudwaleit M et al. Arthritis Rheum. 2005;52:1000-8.

# Evolution of the concept of nr- and r-AxSpA



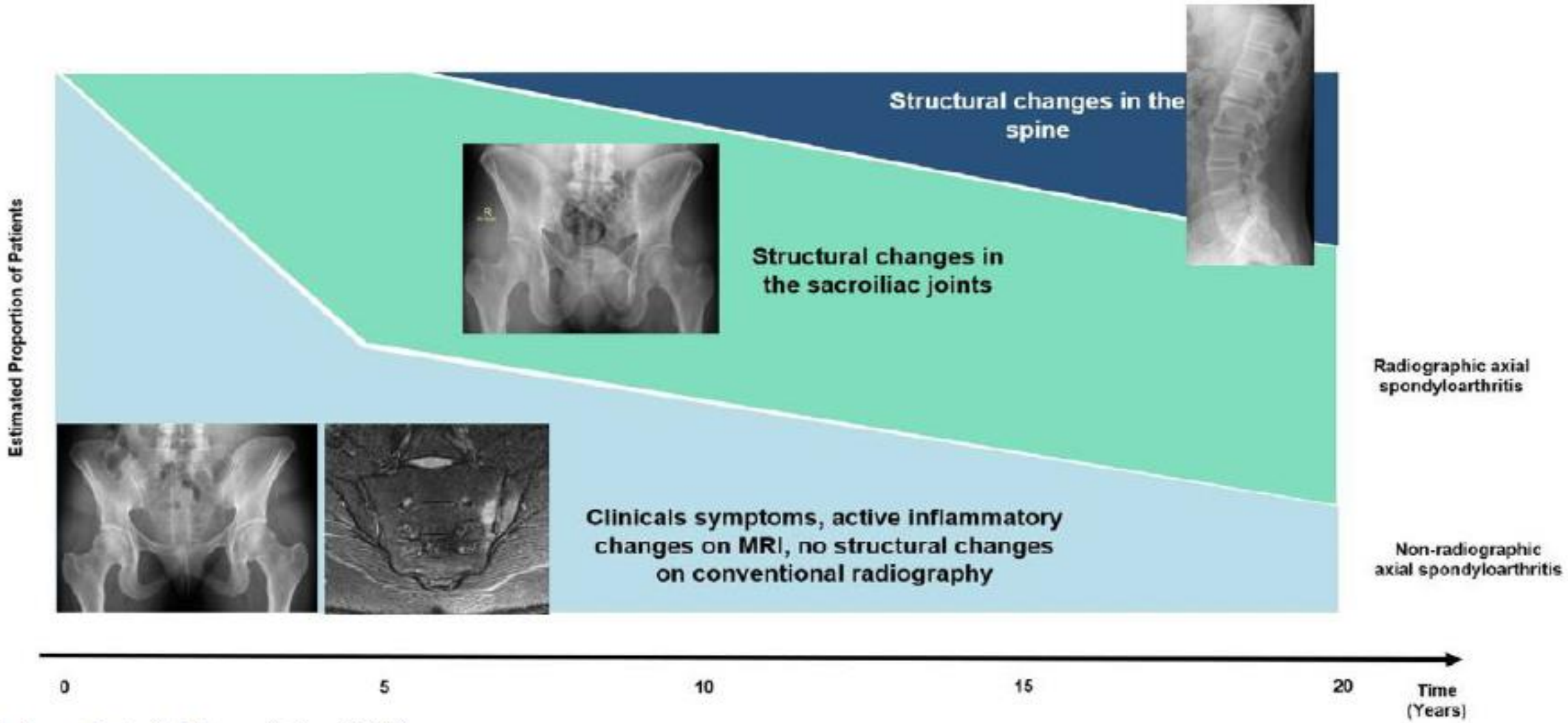

Robinson et al. Nat Rev Rheum 2021

# Distribution of r- and nr-axSpA



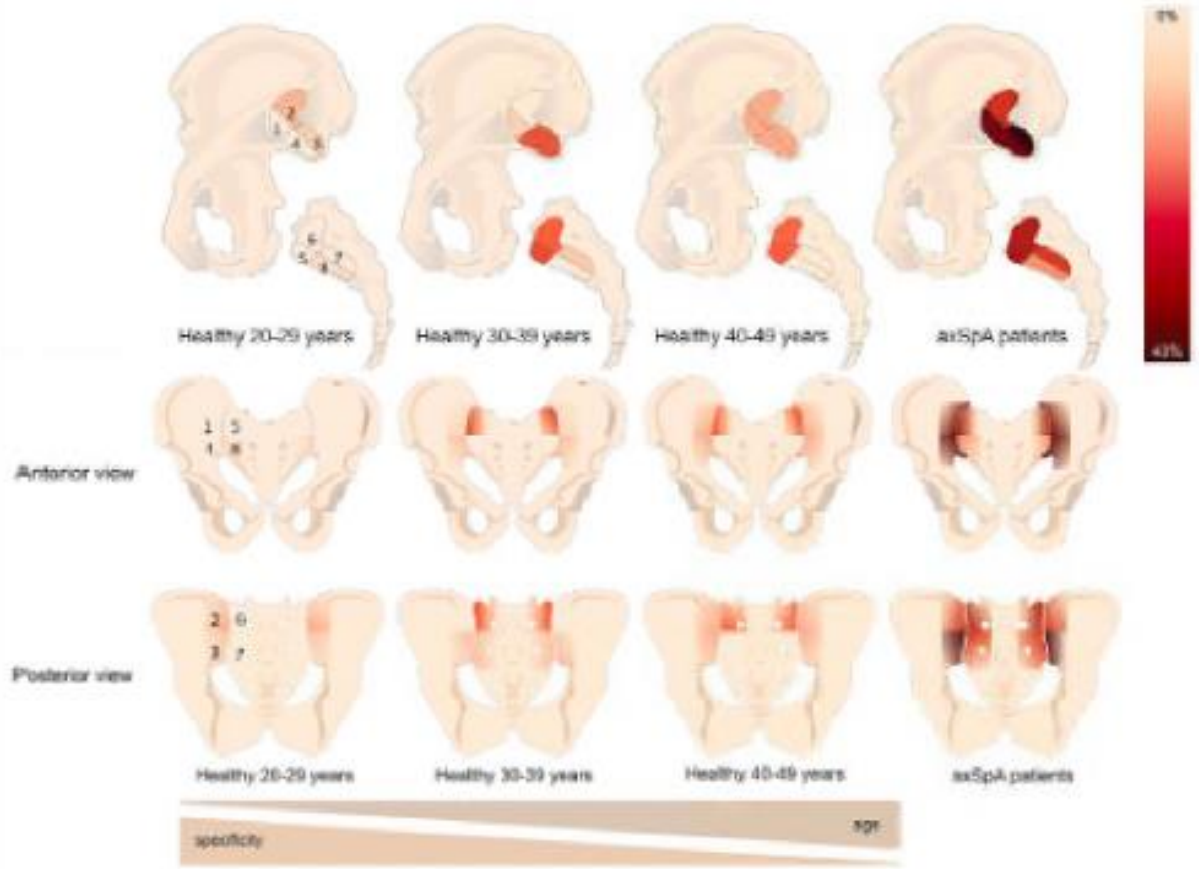

Navarro-Compan Ann Rheum Dis 2021

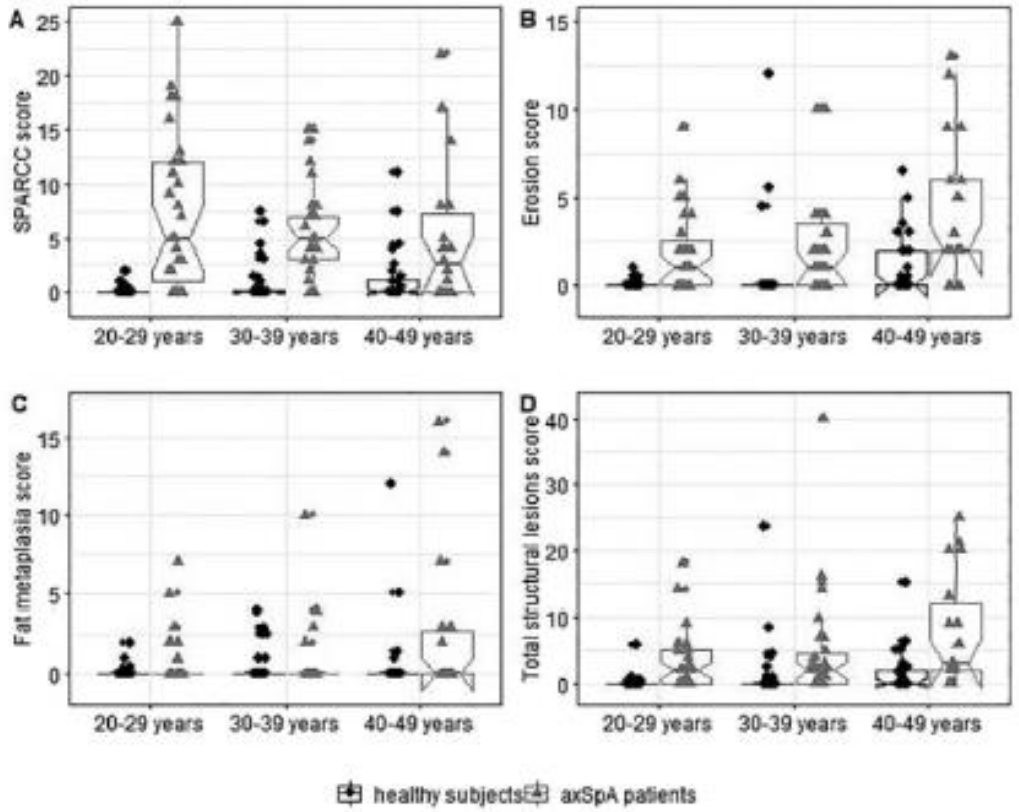
# The challenge of nrAxSpA




Poddubnyy D. Joint Bone Spine 2022

# Is MRI a good diagnostic test?




Renson et al. Arthritis Rheumatol 2022

# False positive MRI: subgroups and proportions

Table 2 | **Studies reporting positive MRI scans in populations with and without axSpA**

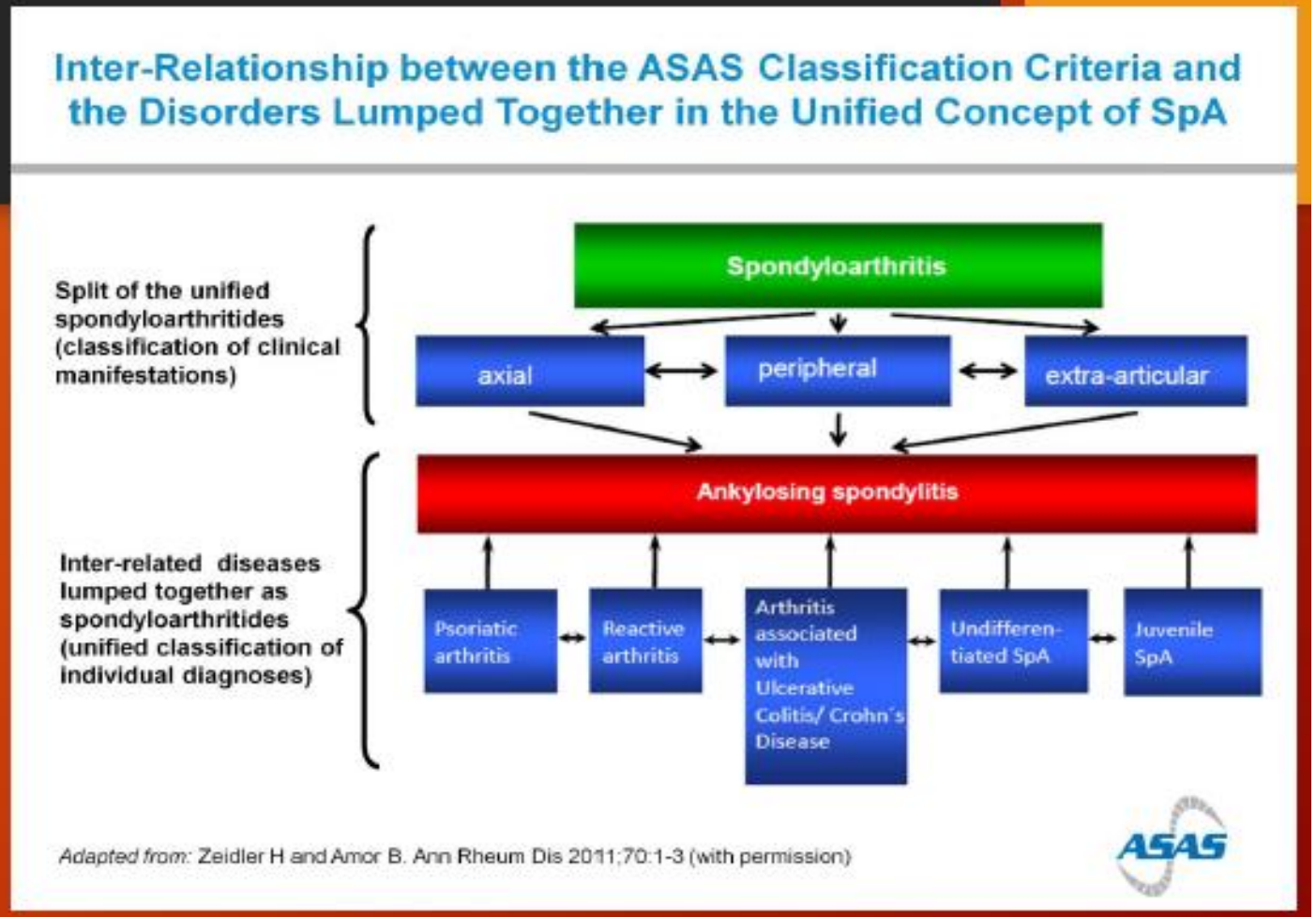
| Study population | n | Sex | Back pain | Proportion with a positive MRI scan[a] | Study | Ref. |
|---|---|---|---|---|---|---|
| Healthy men | 29 | Male | No | 0% | Seven et al. (2019) | 33 |
| Hospital cleaning staff | 26 | Female | No | 4% | Seven et al. (2019) | 33 |
| Long-distance runners | 23 | Male and female | No | 4% | Seven et al. (2019) | 33 |
| Individuals with chronic back pain | 47 | Male and female | Yes | 6% | De Winter et al. (2018) | 34 |
| Individuals with lumbar disc herniation | 25 | Male and female | Yes | 8% | Seven et al. (2019) | 33 |
| Runners | 24 | Male and female | No | 13% | De Winter et al. (2019) | 34 |
| Participants in a community health study | 793 | Male and female | 57%[b] | 17% | Baraliakos et al. (2019) | 35 |
| Women without post-partum buttock and/or pelvic pain | 14 | Female | No | 21% | Seven et al. (2019) | 33 |
| Individuals with chronic back pain | 1,020 | Male and female | Yes | 21% | Arnbak et al. (2016) | 89 |
| Healthy individuals | 47 | Male and female | No | 23% | De Winter et al. (2018) | 34 |
| Runners (post-running) | 20 | Male and female | NS | 30% | Weber et al. (2018) | 37 |
| Runners (pre-running) | 20 | Male and female | NS | 35% | Weber et al. (2018) | 37 |
| Military recruits (at baseline) | 11 | Male and female | No | 41% | Varkas et al. (2018) | 36 |
| Women with post-partum buttock and/or pelvic pain | 46 | Female | Yes | 41% | Seven et al. (2019) | 33 |
| Elite ice hockey players | 22 | Male | NS | 41% | Weber et al. (2018) | 37 |
| Military recruits after 6 weeks' training | 11 | Male and female | No | 50% | Varkas et al. (2018) | 36 |
| Individuals with axSpA | 41 | Male and female | Yes | 56% | Seven et al. (2019) | 33 |
| Women with post-partum back pain | 7 | Female | Yes | 57% | De Winter et al. (2018) | 34 |
| Post-partum women within 10 days of vaginal delivery | 25 | Female | 31% | 64% | Renson et al. (2020) | 88 |
| Individuals with axSpA | 47 | Male and | Yes | 92% | De Winter et al. (2018) | 34 |

Robinson et al. Nat Rev Rheum 2021

# Hx of SpA: Unified Concept of SpA

## Lumping vs. Splitting

- Diagnoses
- Classification



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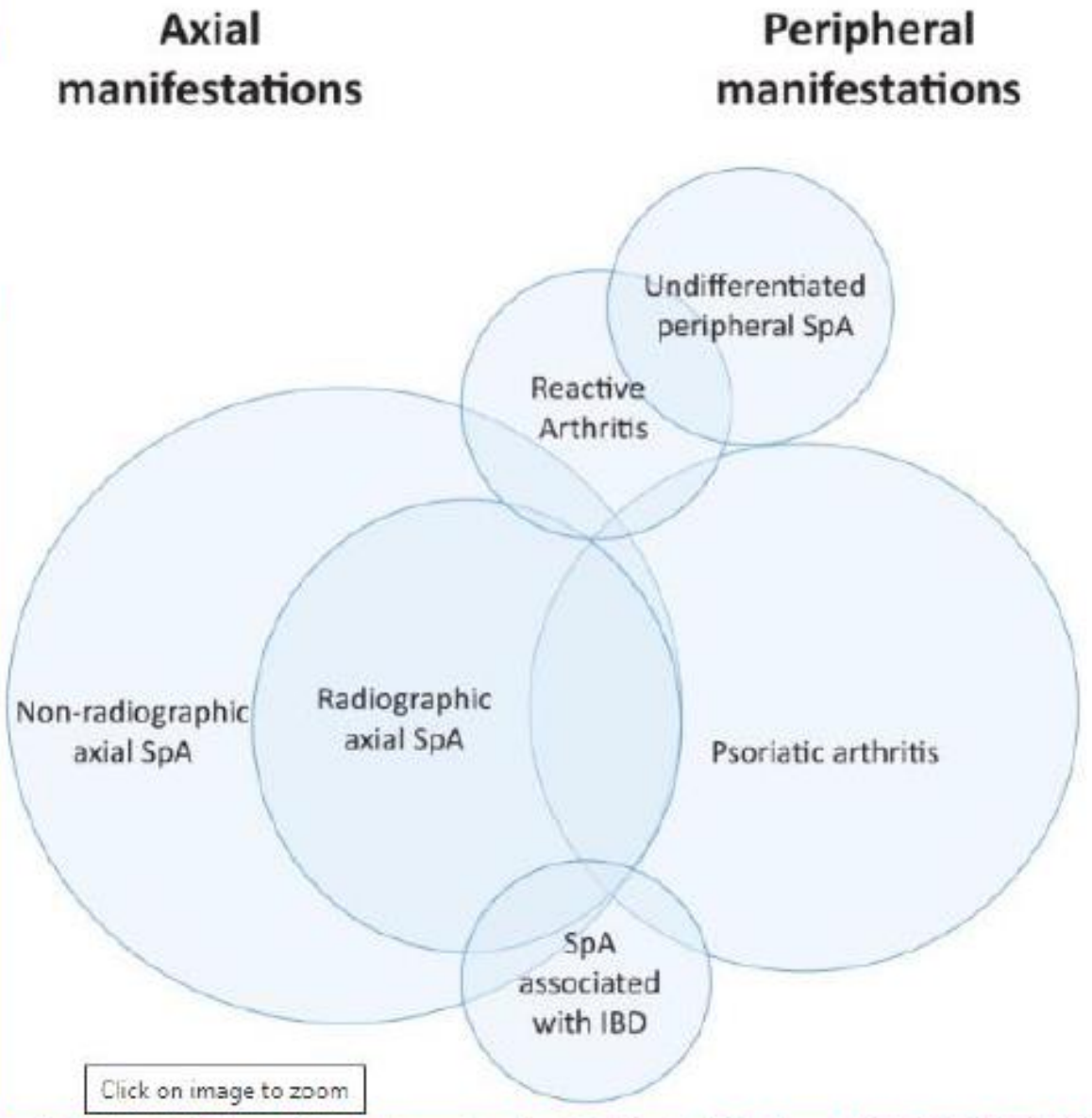


Proft F et al. Ther Adv Musculoskelet Dis. 2018 Jun;10(5-6):129-139

# Hx of SpA: Unified Concept of SpA

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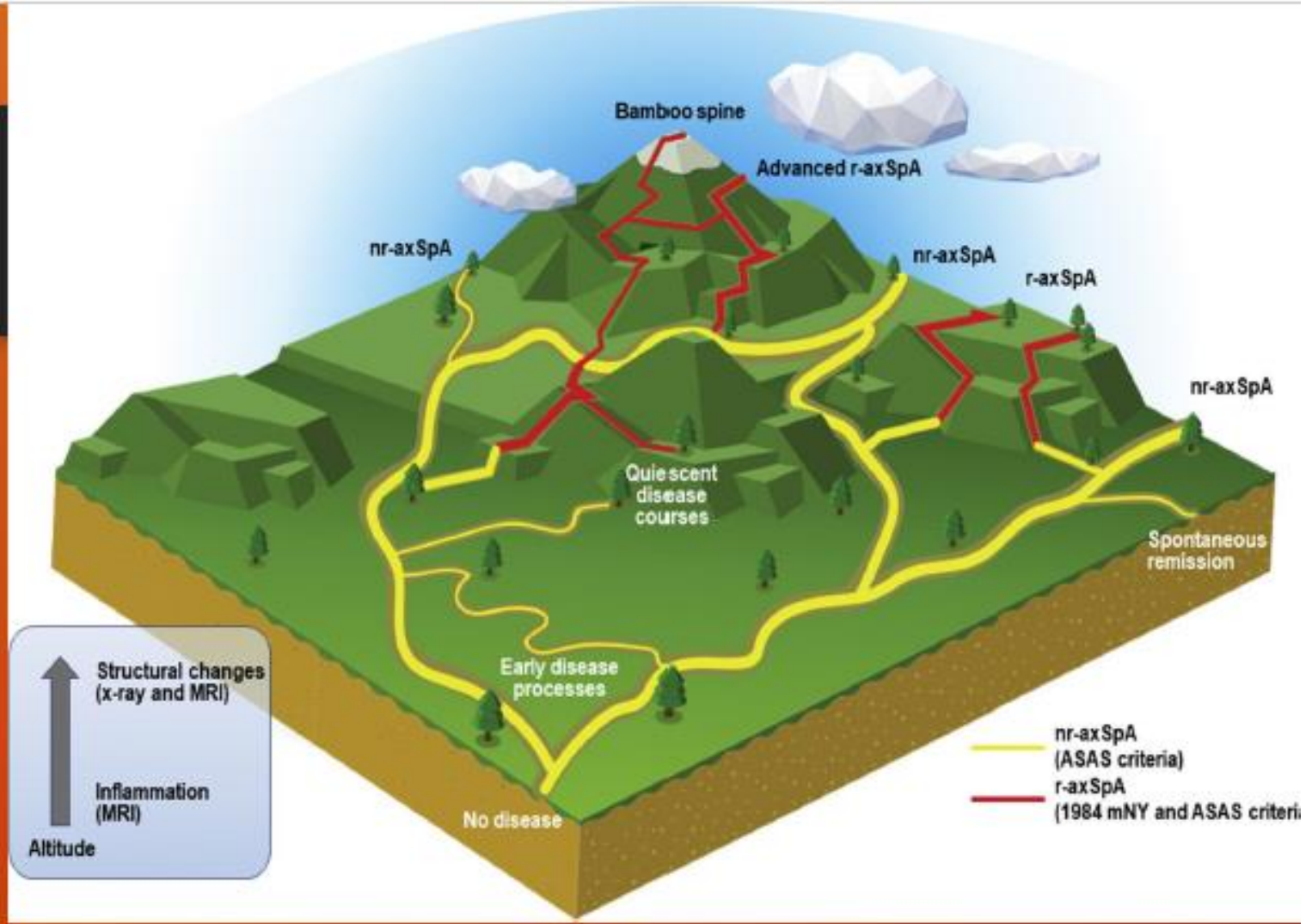
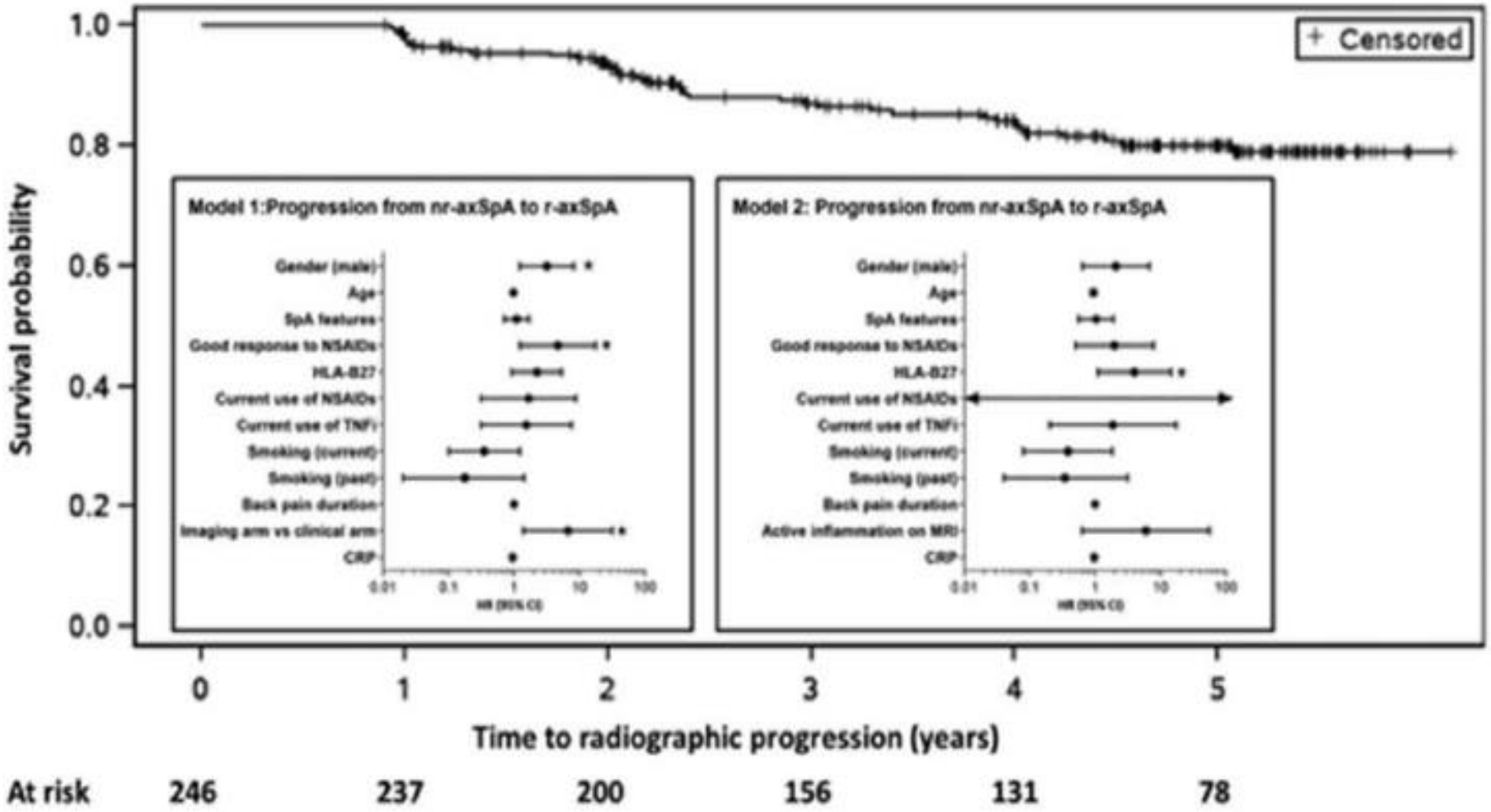
- Diagnoses
- Classification



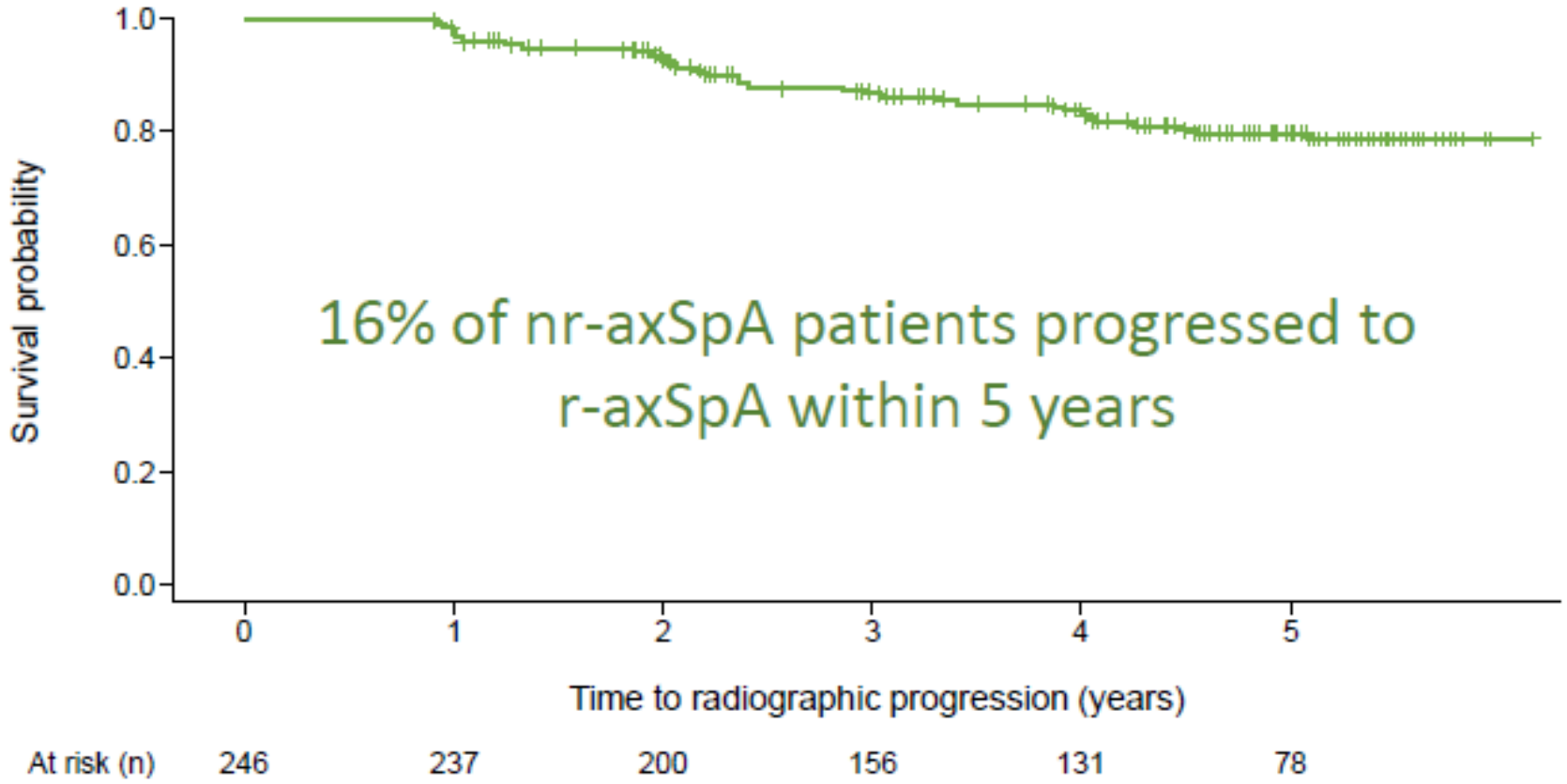

*Schwartzman et al Mayo Clinic Proceedings* 2022 97134-145

# Will my patient progress?

# In general, less than 20% of patients progress over 5 years

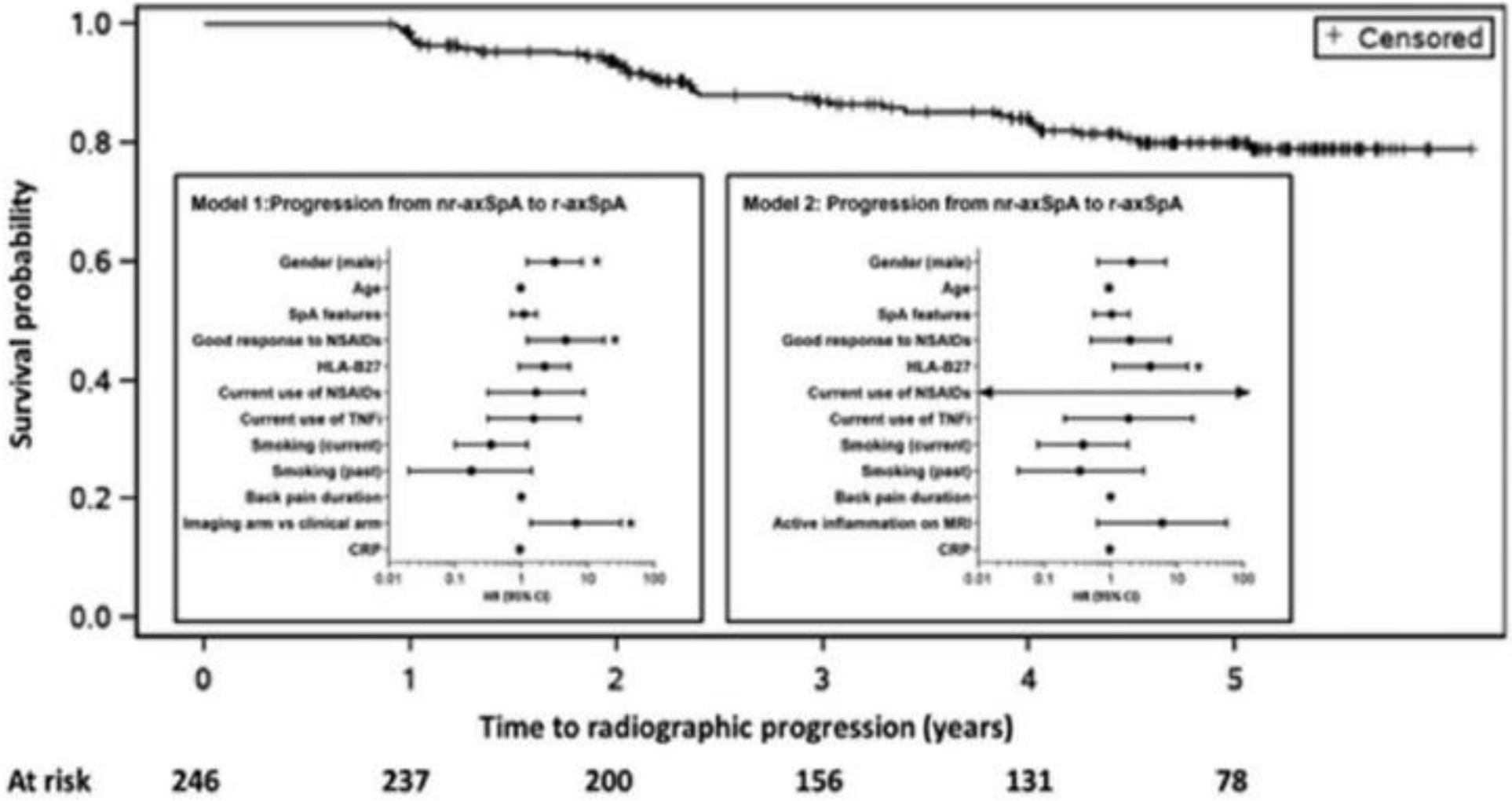


# Progression from nr- to r-AxSpA: the PROOF study




Poddubnyy D, et al. EULAR 2022 Abstract OP0149

# In general, less than 20% of patients progress over 5 years

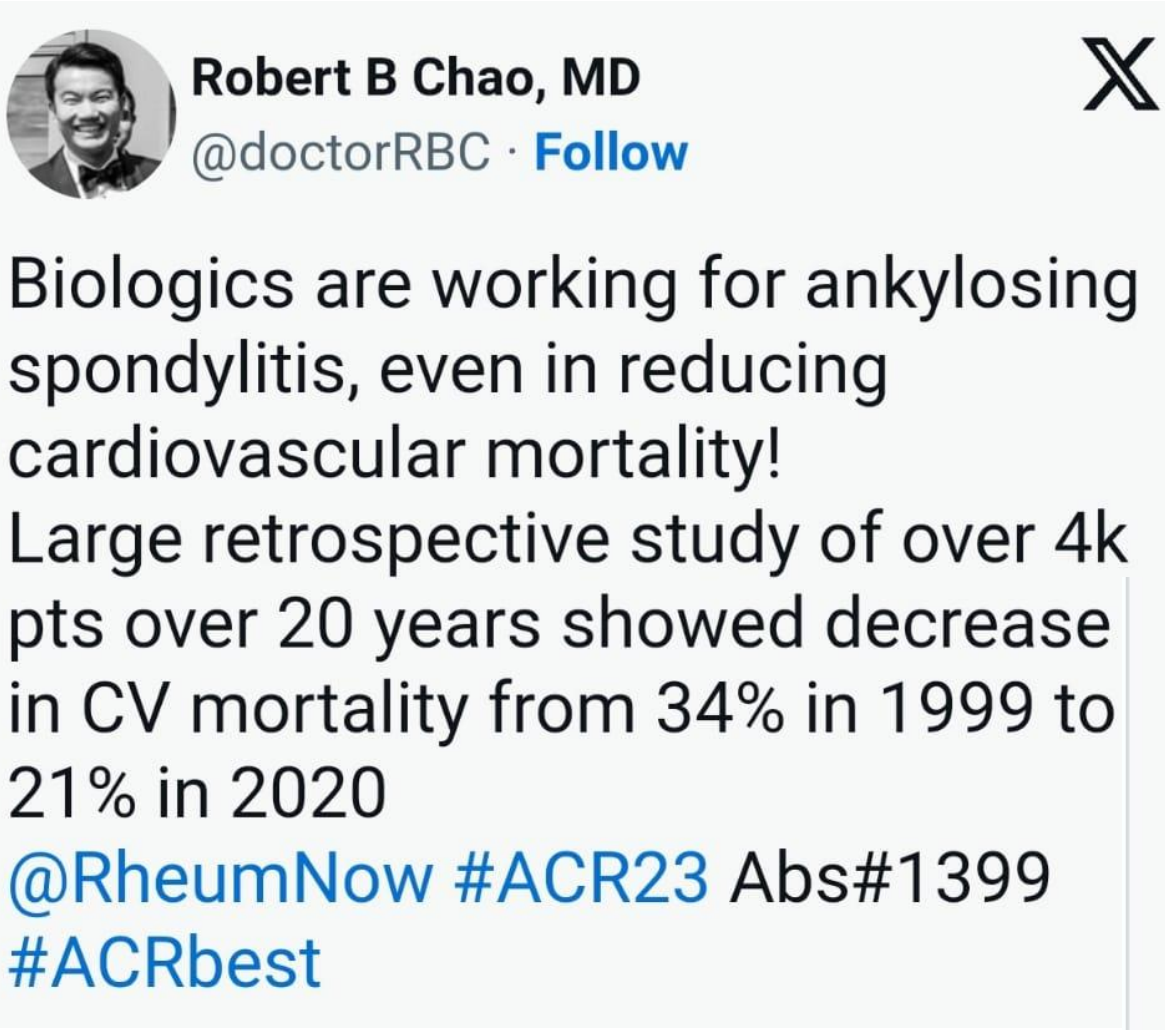


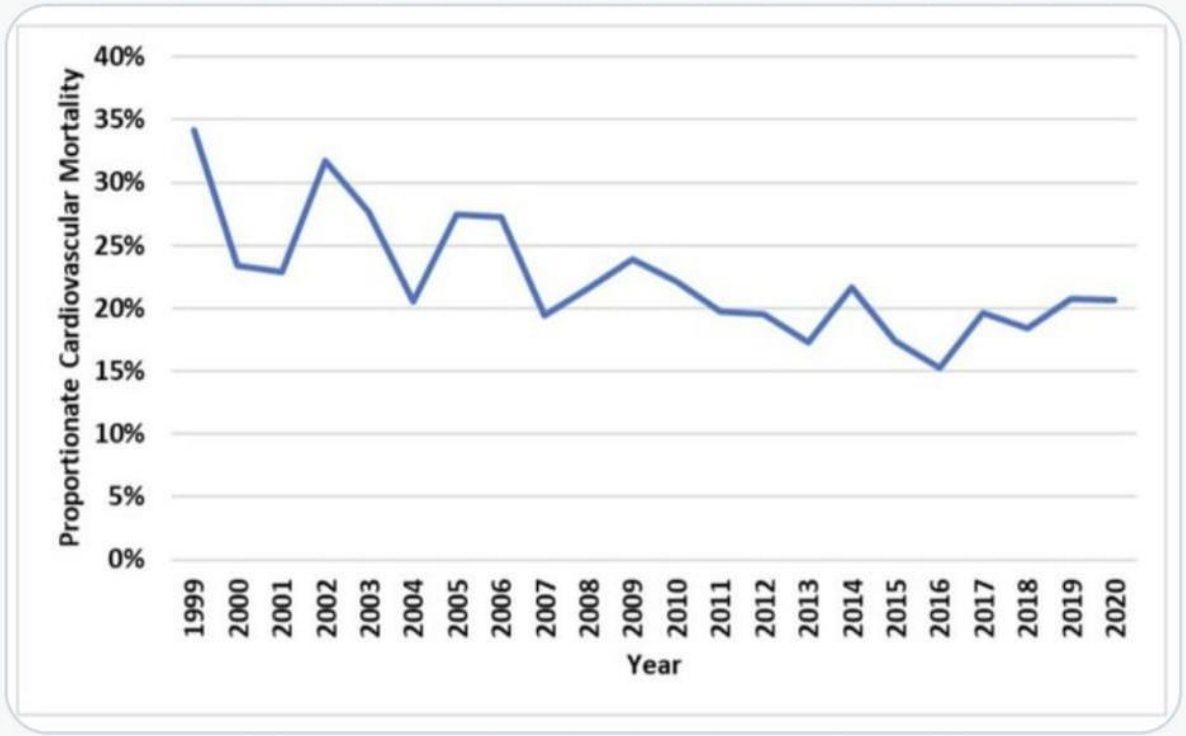
# Risk factors for progression

- HLA-B27 positive
- Elevated CRP
- Imaging findings
  - Low grade radiographic changes
  - Structural changes on MRI at baseline
  - Active sacroiliitis on MRI (+/-)
- Smoking status
- Previous uveitis

Protopopov M and Poddubnyy D. Expert Review of Clin Immunology 2018

# Role of biological therapy in SPA



# Diagnostic Decision Making for non-radiographic AxSpA

## Some potential analytical frameworks

Bayesian Method
Bordage's Method

# Bordage's Method: Intro

- Structured approach by medical education research*†
- Four Key Steps
  - Data Gathering
  - Problem Representation
  - Illness Script Retrieval
  - Hypothesis testing

*Bordage G et al. Med Educ. 1990 Sep;24(5):413-25.
†Kumar B et al Cureus. 2021 Nov 18;13(11):e19722

# Bordage's Method: Data Gathering

- Collect relevant data!
  - Patient interview
    - Quality/characteristics of their MSK problems
  - Medical history
    - Family Hx of disease?
  - Symptom assessment
    - Joint Exam (At least 44)
    - Spinal mobility
    - Extra-articular ds symptoms

# Bordage's Method: Problem Representation

Patient with chronic lower back pain

Some suspicion of SpA

# Ankylosing Spondylitis / Axial Spondyloarthritis
# Typical Manifestations

## Bayesian

- Use clinical features and literature-based weighting

| | Sensitivity | Specificity | LR+ | LR- |
|---|---|---|---|---|
| • inflammatory back pain | 71-75 % | 75-80 % | 3.1 | 0.33 |
| • enthesitis (heel pain) | 16-37 % | 89-94 % | 3.4 | 0.71† |
| • peripheral arthritis | 40-62 % | 90-98 % | 4.0 | 0.67† |
| • dactylitis | 12-24 % | 96-98 % | 4.5 | 0.85† |
| • anterior uveitis | 10-22 % | 97-99 % | 7.3 | 0.80† |
| • psoriasis | 10-20 % | 95-97 % | 2.5 | 0.94† |
| • inflammatory bowel disease | 5-8 % | 97-99 % | 4.0 | 0.97† |
| • positive family history for SpA | 7-36 % | 93-99 % | 6.4 | 0.72 |
| • good response to NSAIDs | 61-77 % | 80-85 % | 5.1 | 0.27 |
| • elevated acute phase reactants | 38-69 % | 67-80 % | 2.5 | 0.63 |
| • HLA-B27 (axial involvement) | 83-96 % | 90-96 % | 9.0 | 0.11 |
| • sacroiliitis on MRI | 60-85 % | 90-97 % | 20.0* | 0.41 |
| • sacroiliitis (≥ grade 3) on x-rays | 40 % | 98 % | 20.0* | 0.61 |

* best estimate

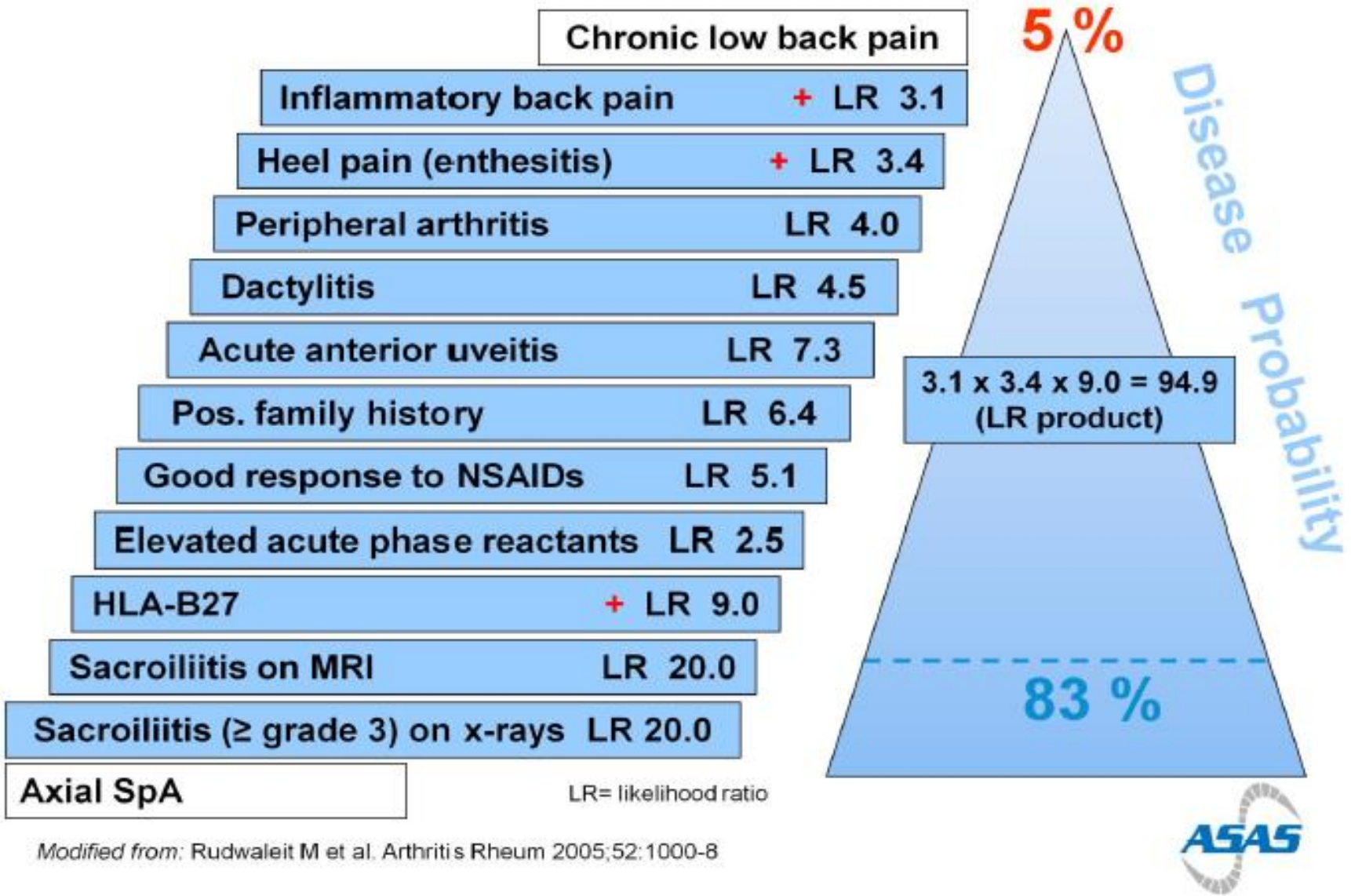
Positive likelihood ratio (LR+) = sensitivity / (100 – specificity)
Negative likelihood ratio (LR-) = (100 – sensitivity) / specificity

† It is recommended to ignore a negative test result of these tests in an early state of possible axial SpA

*Modified from:* Rudwaleit M et al. Ann Rheum Dis 2006;65:1251-2

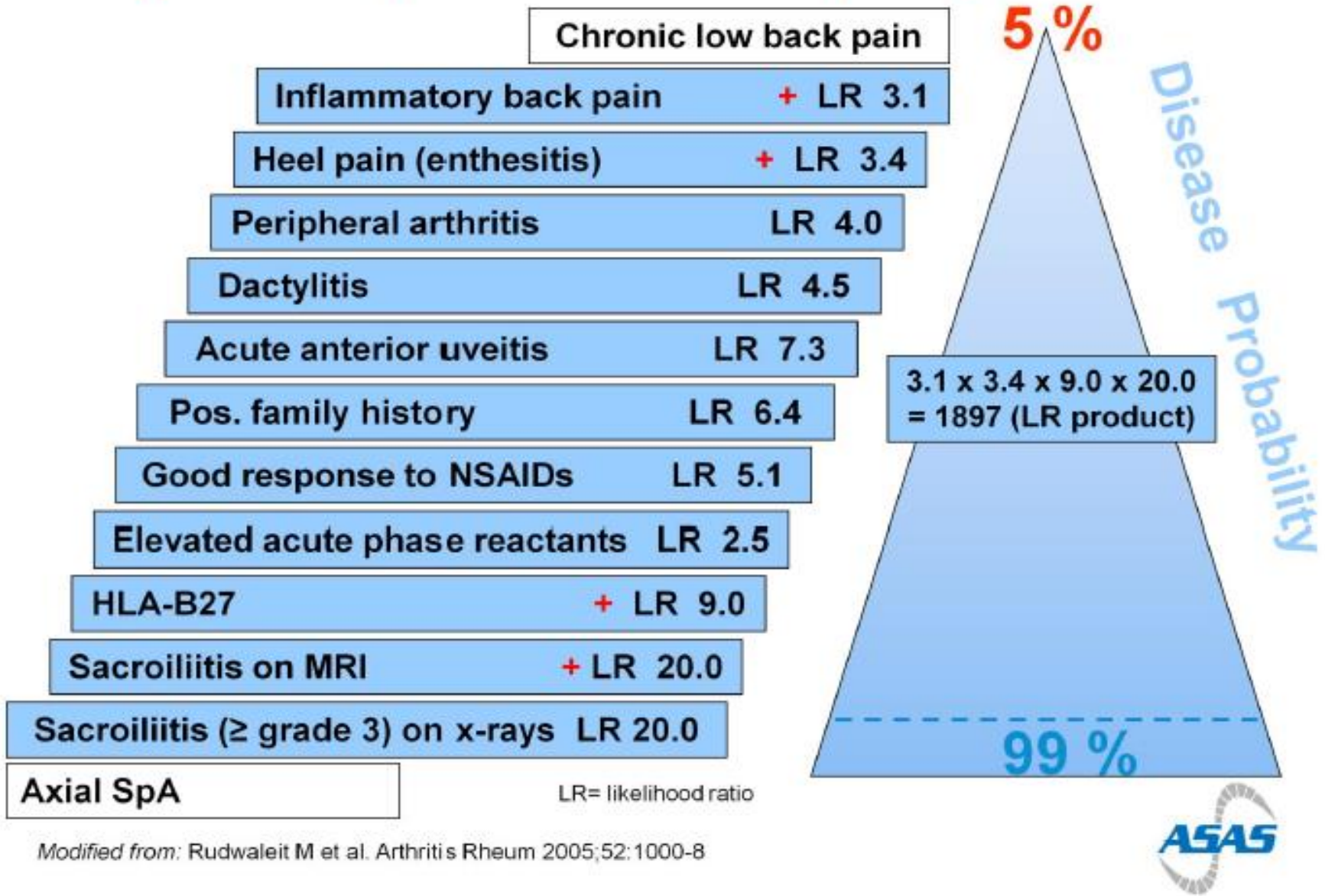
# Bayesian

- Positive and negative likelihood ratios of SpA need to be considered!



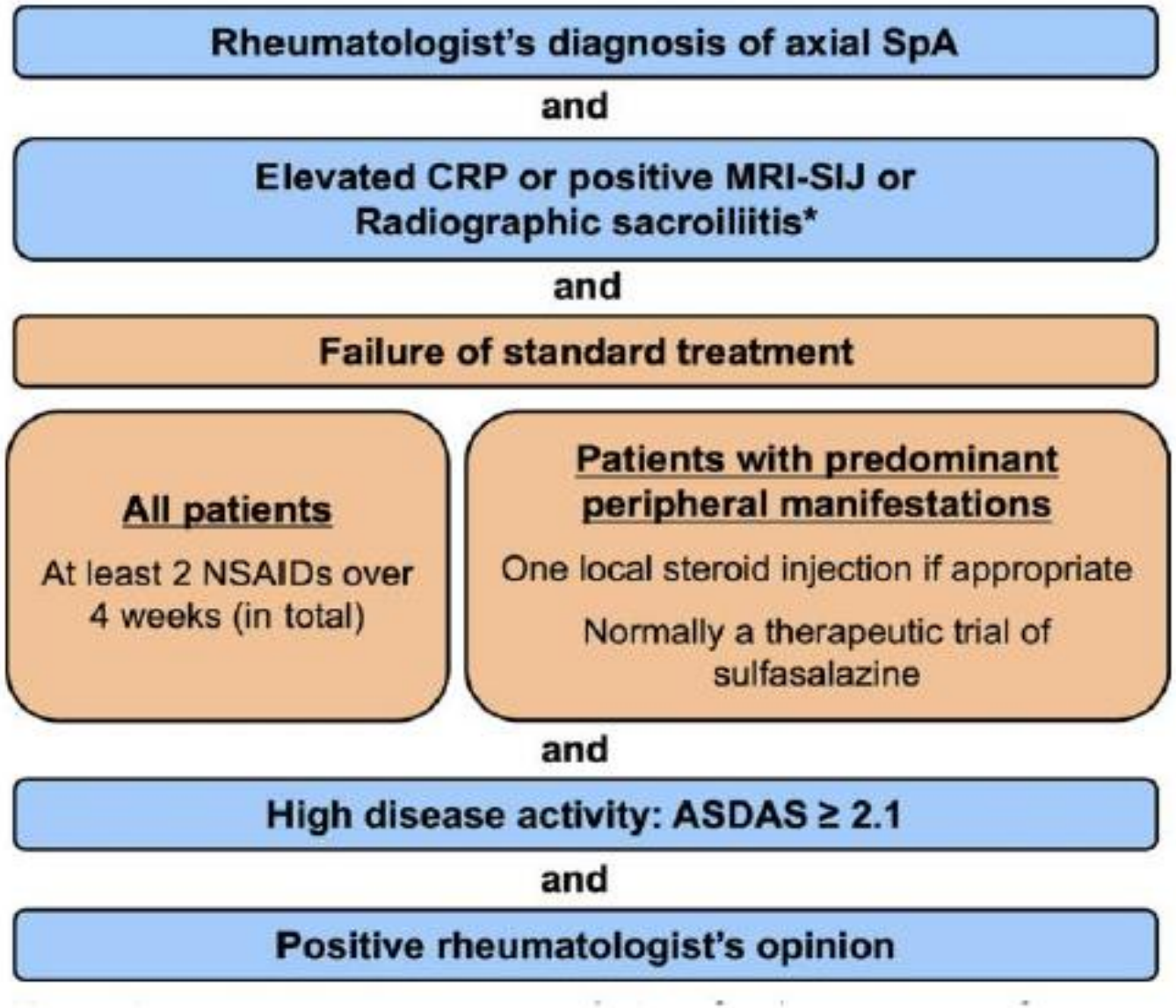
# Bayesian

- Posterior probability based on:
  - pre-test probability and features



# How do I discuss this risk with the patient?

# Treatment of AxSpA




Ramiro S et al. Ann Rheum Dis 2023

# Treatment toolbox

NSAIDs

Physical therapy

Patient education

TNFi

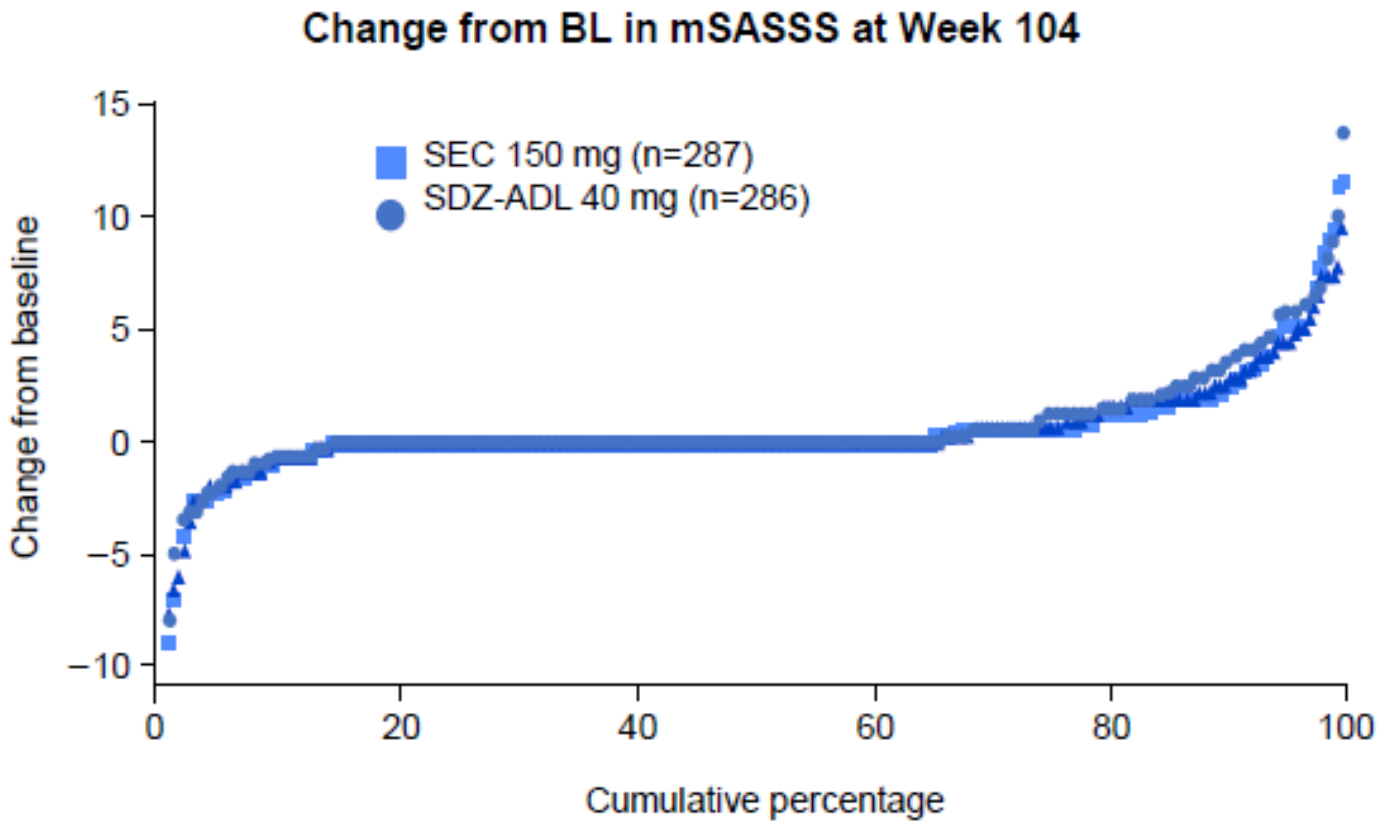
IL17i

JAKi

Navarro-Compán Ann Rheum Dis 2021

# TNFi vs IL17i for rAxSpA? The SURPASS trial

*Proportion of patients with no radiographic progression*:
SEC 150 mg **66.1%**, SEC 300 mg **66.9%**, and biosimilar ADA (SDZ-ADL) **65.6%** (P=NS)




Baraliakos X, et al. EULAR 2023, Milan, OP0059

# EULAR treatment recommendations

**"Treatment should be guided according to a predefined treatment target."**

Ramiro S. Ann Rheum Dis 2022

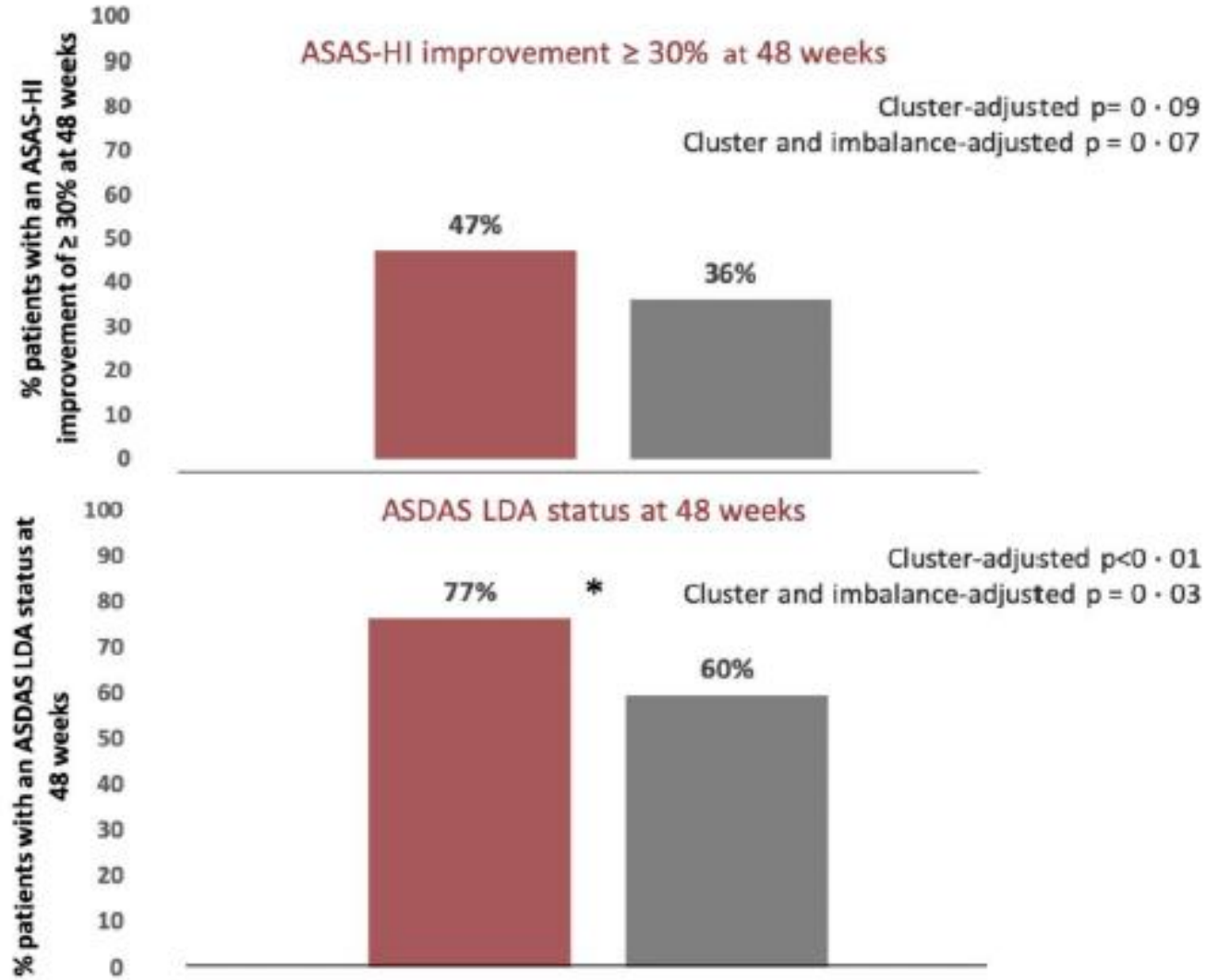
**Table 1** ASAS-EULAR recommendations for the management of axSpA, 2022 update

| | | | LoA (0–10) | |
|---|---|---|---|---|
| | **Overarching principles** | | **Mean (SD)** | **% with score ≥8** |
| A | axSpA is a potentially severe disease with diverse manifestations, usually requiring multidisciplinary management coordinated by the rheumatologist. | | 9.8 (0.4) | 100 |
| B | The primary goal of treating the patient with axSpA is to maximise health-related quality of life through control of symptoms and inflammation, prevention of progressive structural damage, and preservation/normalisation of function and social participation. | | 9.8 (0.5) | 100 |
| C | The optimal management of patients with axSpA requires a combination of non-pharmacological and pharmacological treatment modalities. | | 9.8 (0.5) | 100 |
| D | Treatment of axSpA should aim at the best care and must be based on a shared decision between the patient and the rheumatologist. | | 9.5 (1.8) | 97 |
| E | axSpA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist. | | 9.5 (0.9) | 94 |
| | **Recommendations** | **Level of evidence/grade of recommendation*** | | |
| 1 | The treatment of patients with axSpA should be individualised according to the current signs and symptoms of the disease (axial, peripheral, extramusculoskeletal manifestations) and the patient characteristics including comorbidities and psychosocial factors. | 5/D | 9.6 (0.8) | 97 |
| 2 | Disease monitoring of patients with axSpA should include patient-reported outcomes, clinical findings, laboratory tests and imaging, all with the appropriate instruments and relevant to the clinical presentation. The frequency of monitoring should be decided on an individual basis depending on symptoms, severity and treatment. | 5/D | 9.5 (1.1) | 97 |
| 3 | Treatment should be guided according to a predefined treatment target. | 5/D | 9.0 (1.2) | 85 |
| | smoking; physiotherapy should be considered. | 5/D (stop smoking)<br>1a /A (physiotherapy) | | |
| 5 | Patients suffering from pain and stiffness should use an NSAID as first-line drug treatment up to the maximum dose, taking risks and benefits into account. For patients who respond well to NSAIDs, continuous use is preferred if needed to control symptoms. | 1a/A | 9.5 (0.8) | 97 |
| 6 | Analgesics, such as paracetamol and opioid-(like) drugs, might be considered for residual pain after previously recommended treatments have failed, are contraindicated, and/or poorly tolerated. | 5/D | 8.9 (1.4) | 79 |
| 7 | Glucocorticoid injections directed to the local site of musculoskeletal inflammation may be considered. Patients with axial disease should not receive long-term treatment with systemic glucocorticoids. | 2/B (injections)<br>5/D (long-term systemic GCs) | 9.6 (0.8) | 100 |
| 8 | Patients with purely axial disease should normally not be treated with csDMARDs; sulfasalazine may be considered in patients with peripheral arthritis. | 1a/A (sulfasalazine, methotrexate)<br>1b/A (leflunomide)<br>4/A (other csDMARDs)<br>1a/A (sulfasalazine peripheral disease) | 9.6 (0.9) | 94 |
| 9 | TNFi, IL-17i† or JAKi‡ should be considered in patients with persistently high disease activity despite conventional treatments (figure 1); current practice is to start a TNFi or IL-17i†. | 1a/A | 9.2 (1.2) | 94 |
| 10 | If there is a history of recurrent uveitis or active IBD§, preference should be given to a monoclonal antibody against TNF¶ In patients with significant psoriasis, an IL-17i† may be preferred. | 2b/B (uveitis, IBD)<br>1a/B (psoriasis) | 9.1 (1.8) | 97 |

In September of this year the American College of Rheumatology released the first ever recommendations for physicians in the US for the treatment of ankylosing spondylitis and non-radiographic axial spondyloarthritis.

- “Key ACR recommendations;
- In adults with active AS, strongly recommend treatment with NSAIDs over no treatment with NSAIDs
- In adults with active AS, despite treatment with NSAIDs, strongly recommend treatment with TNFi over no TNFi
- In adults with active AS, no recommendation for a preferred TNFi, unless the patient has concomitant inflammatory bowel disease or recurrent iritis
- In adults with inflammatory bowel disease, strongly recommend treatment with TNFi monoclonal antibodies over treatment with etanercept
- In adults with active AS, strongly recommend against treatment with systemic glucocorticoids
- In adults with active AS, strongly recommend physical therapy over no physical therapy
- In adults with AS and advanced hip arthritis, strongly recommend total hip arthroplasty over no surgery
- In adults with active non-radiographic axial SpA despite treatment with NSAIDs, conditionally recommend treatment with TNFi over no treatment with TNFi

# Treat-to-target in AxSpA?

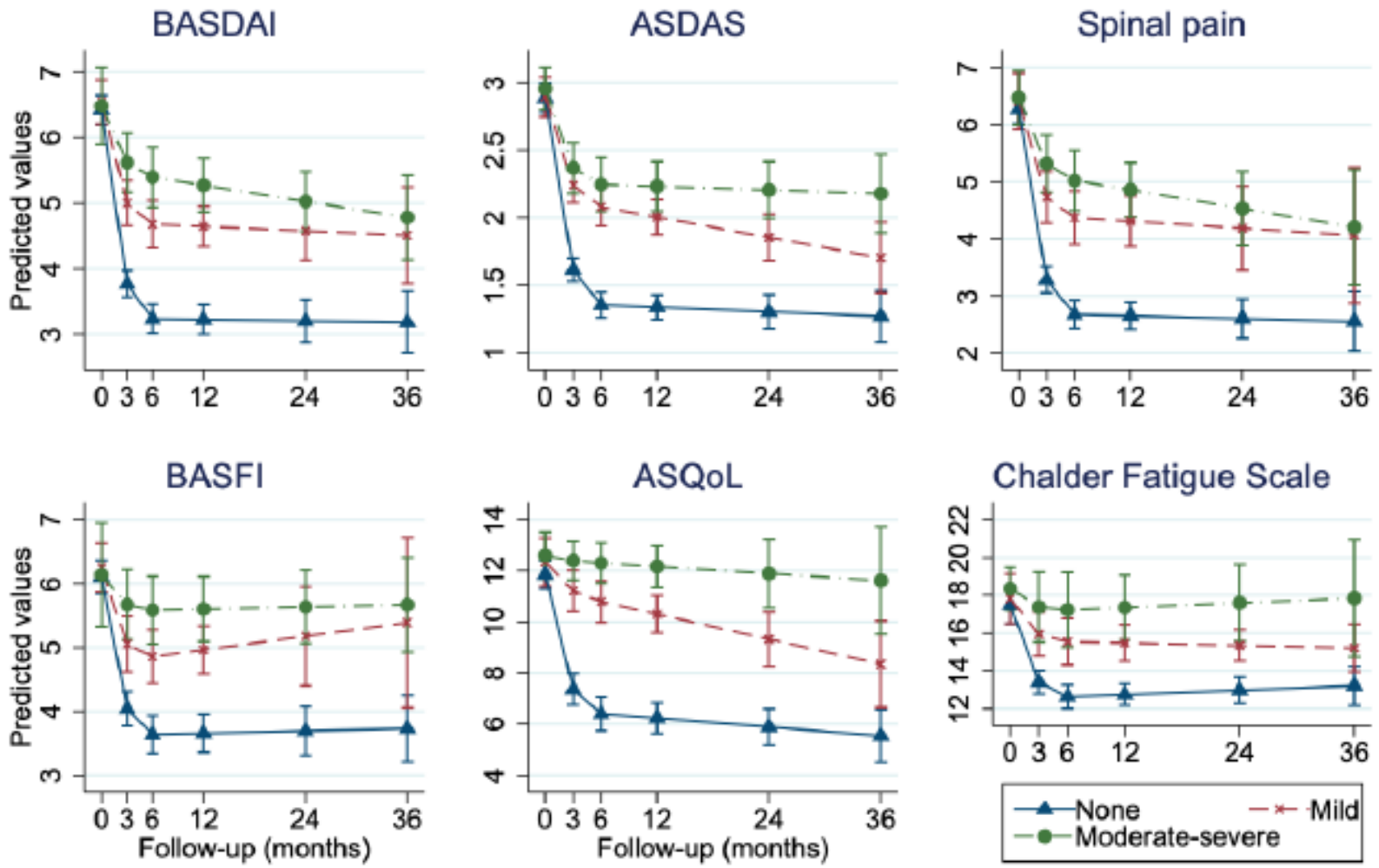



Molto A et al. Ann Rheum Dis 2021

# Pain in AxSpA is complicated

- Approximately 30% have centralized pain or fibromyalgia
- Separating the central pain from the AxSpA activity is challenging
- Imaging can be helpful but has short comings
- Opiates are still commonly used (not good!)
- Insufficient pain control results in miserable patients, poor performance of outcome measures and therapies, and therapy cycling

# Depression Impacts Response to Therapy




Zhao SS, et al. *Rheum Oxford*. 2021

# Treatment toolbox

| | | | | |
|---|---|---|---|---|
| NSAIDs | Physical therapy | Patient education | Biologics | PM&R |
| Non-opiate pain meds | Talk Therapy | Sleep mgmt | Exercise | Health Coach |
| Comorbidity Mgmt | Smoking Cessation | Diet | Acupuncture | |

The patient never responds well: Does this patient really have AxSpA?

# Summary

- AxSpA is a spectrum of disease
  - nr-AxSpA = non-AS/r-Axial SpA patients
- Clinical features, Labs, Imaging
  - Weighting towards Imaging
- Constant, iterative process to diagnosing nr-AxSpA
  - Rule out alternative diagnoses & staying up-to-date on available tools
- Understanding of nr-AxSpA continues to be refined

# Can Rheumatologists Accurately Diagnose axSpA in Patients with Chronic Back Pain?

# Key References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Thank you!