

Spondyloarthritis, including Psoriatic Arthritis

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- Clinical and research focus:
spondyloarthritis (animal models and translational research)

Disclosures

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Objectives

- Recognize clinical features of spondyloarthritis incl. axial SpA and PsA
- Discuss current treatment approach for axial SpA and PsA
- Identify reasons for diagnostic delay in axial SpA

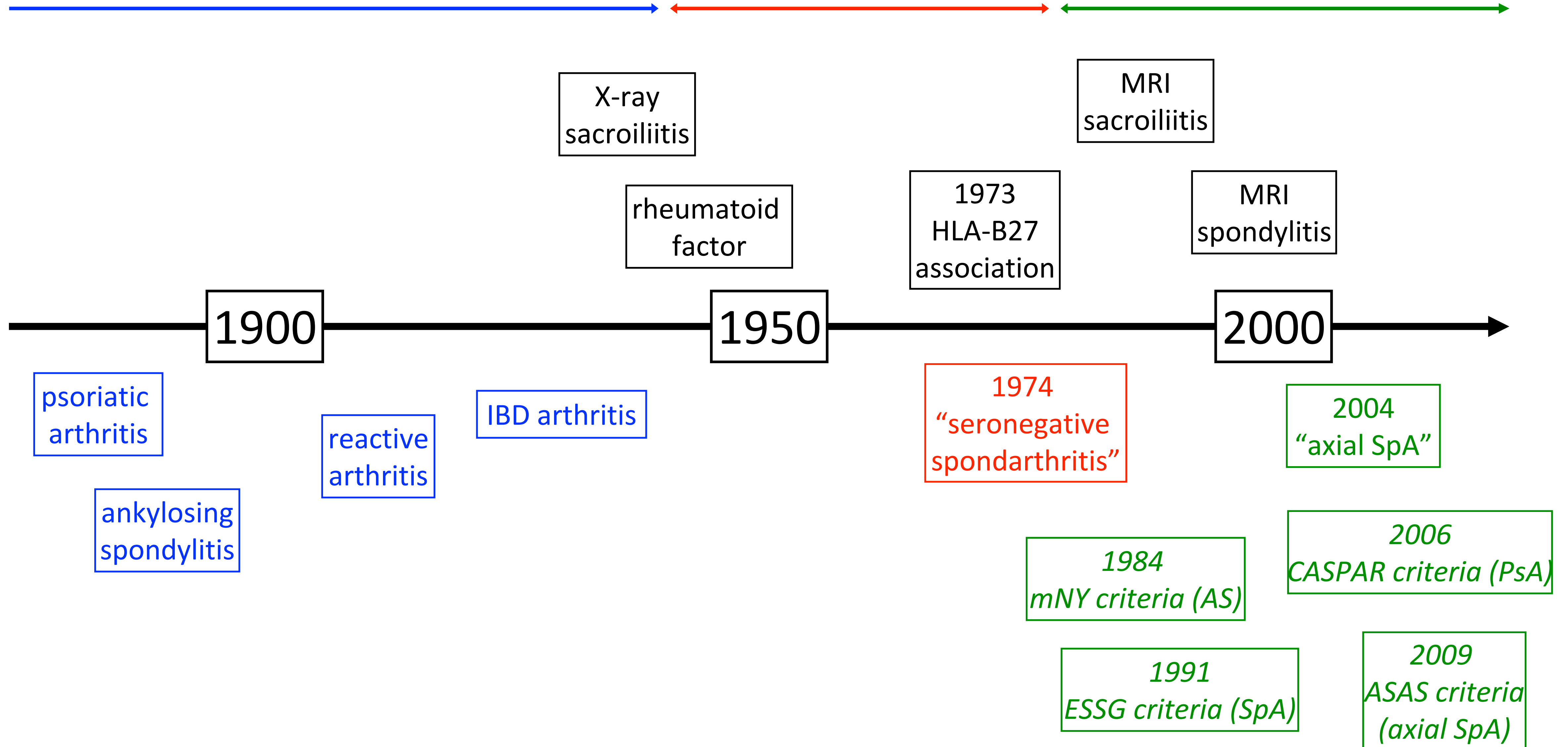
Spondyloarthritis (SpA)

- family of inflammatory rheumatic diseases with variable involvement of the axial and peripheral skeleton
- spondyloarthritis = spondylitis + arthritis
 - spondylos = vertebra (Greek)
 - arthros = joint (Greek)
 - spondyloarthritis preferred over spondyloarthropathy
- spondyloarthritis concept has evolved over the last 100 years

Description of the
individual disease entities

Recognition as a family
distinct from RA

Refinement and
development of criteria



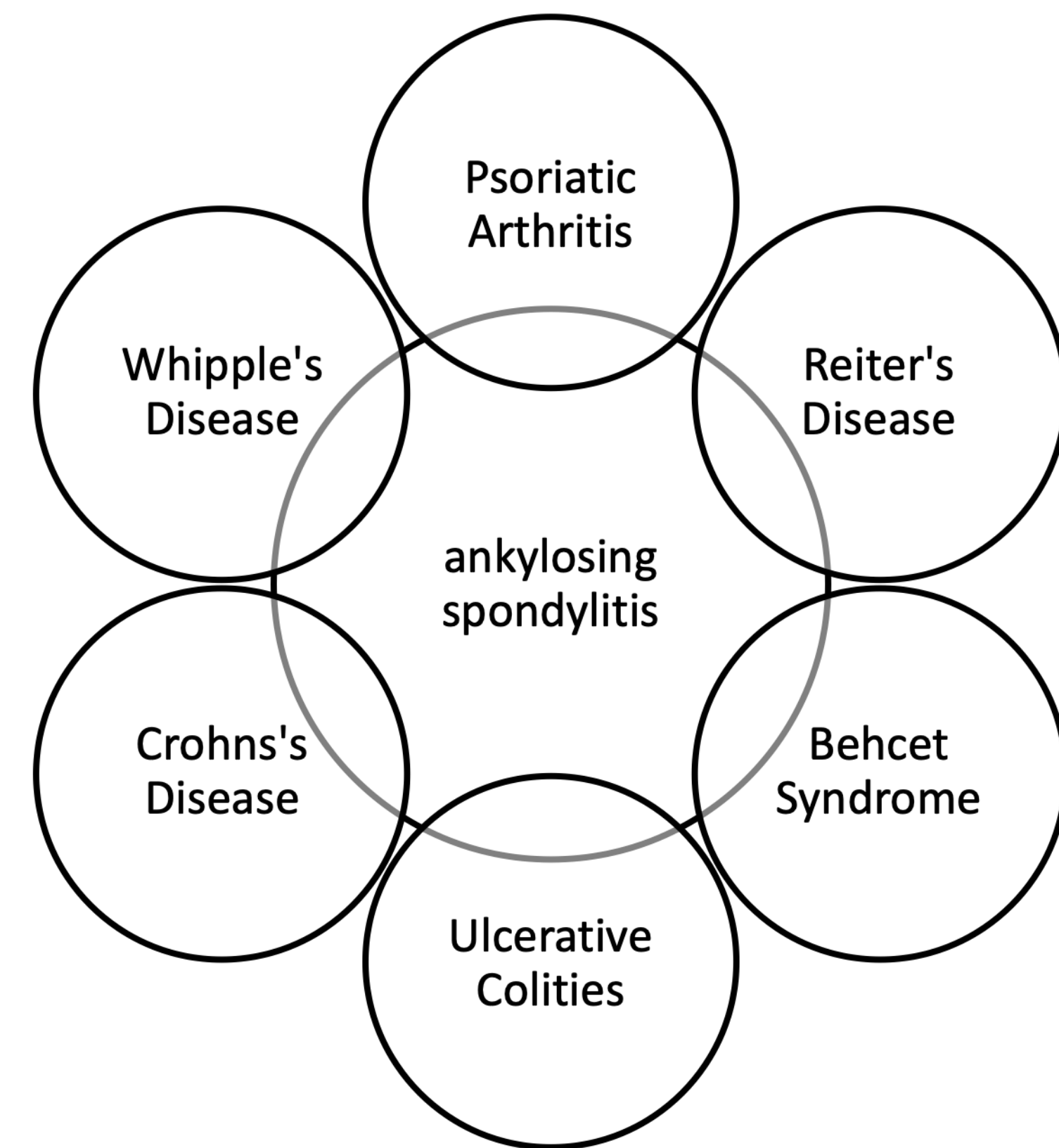
Spondyloarthritis concept 1974 (Moll and Wright)

MEDICINE
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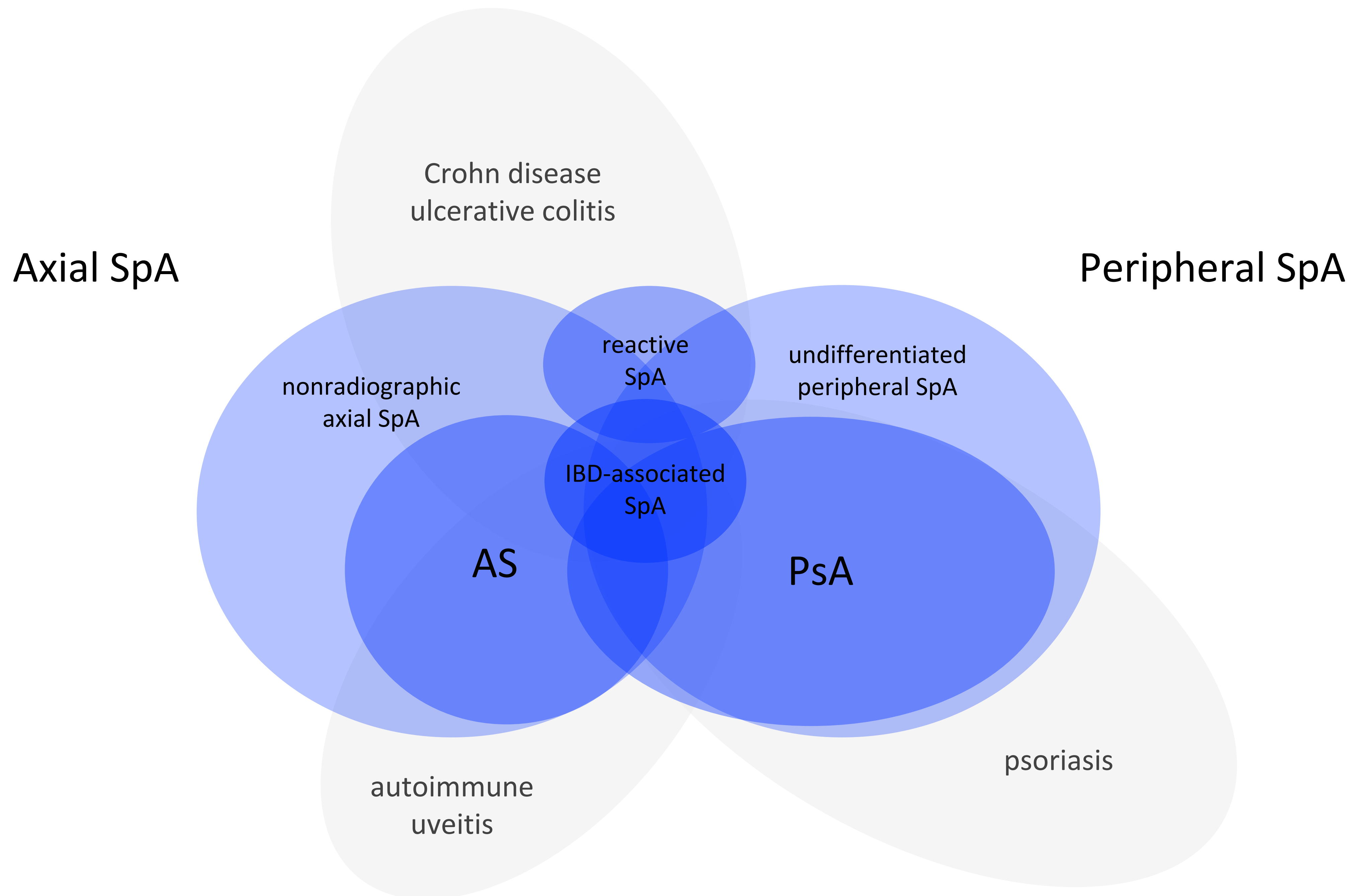
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ASSOCIATIONS BETWEEN ANKYLOSING SPONDYLITIS, PSORIATIC ARTHRITIS, REITER'S DISEASE, THE INTESTINAL ARTHROPATHIES, AND BEHCET'S SYNDROME

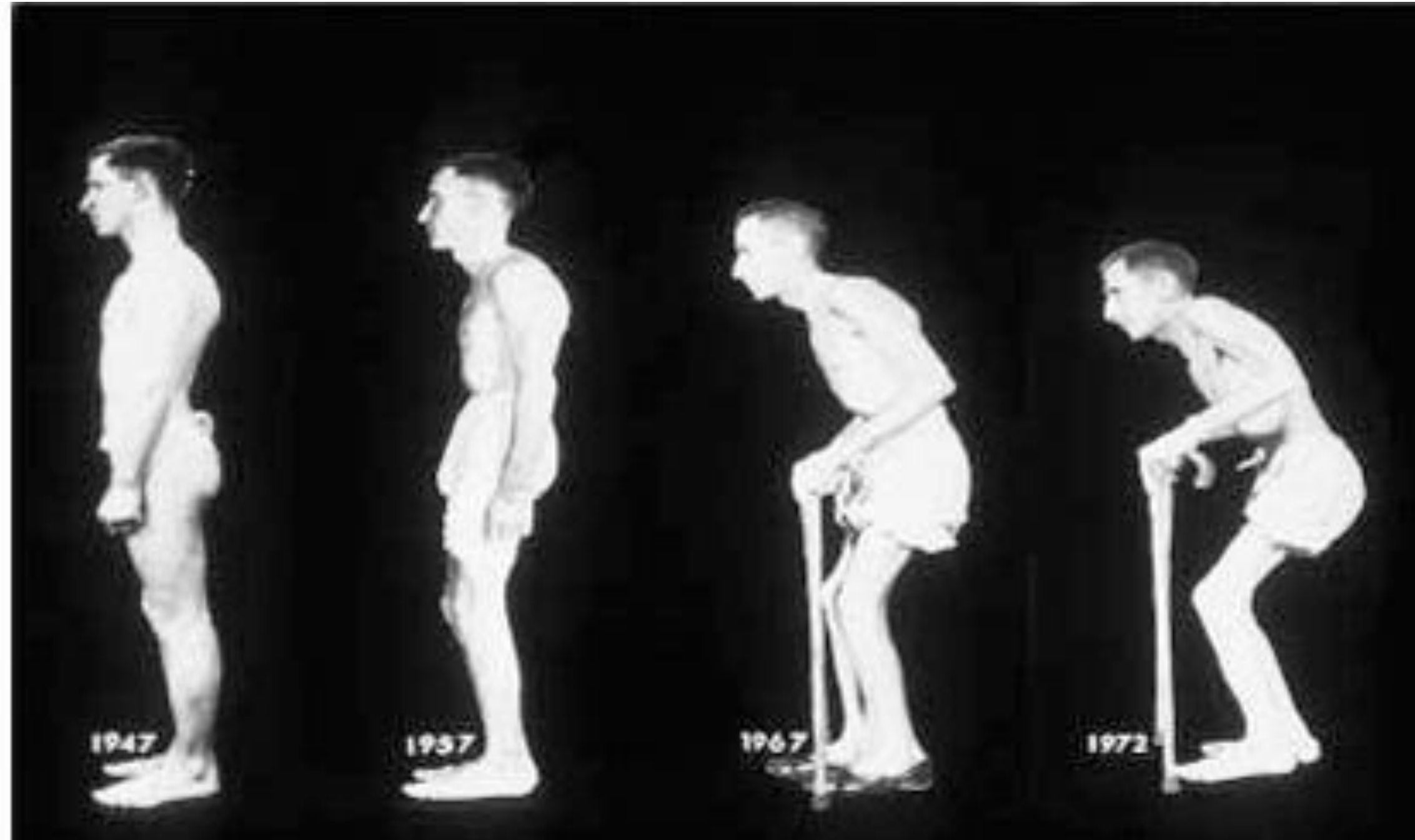
J. M. H. MOLL, B.Sc., D.M., M.R.C.P.,¹ IAN HASLOCK, M.D.,² I. F. MACRAE, M. B., B.S.³ AND V. WRIGHT, M.D., F.R.C.P.⁴



“The Leeds Idea” - seronegative spondarthritides



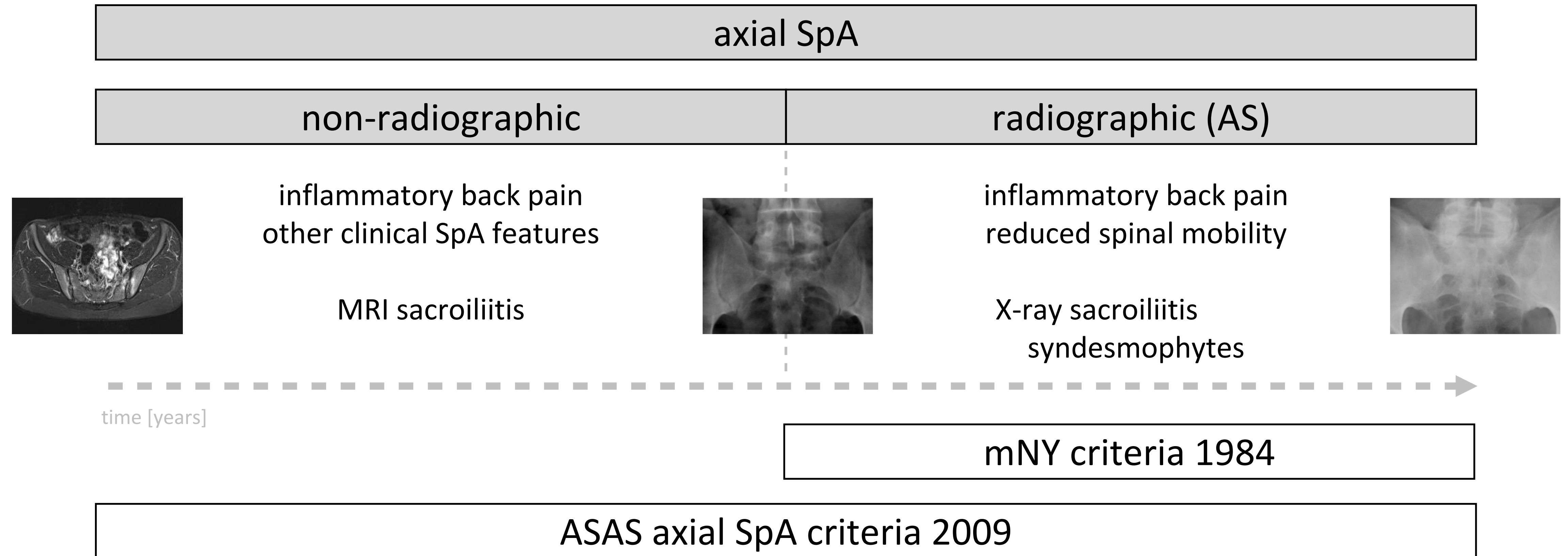
Ankylosing spondylitis (AS) = radiographic axial SpA



Little Am J Med 1976; 60:279-85

- young male (M:F = 2-3:1)
> 90% HLA-B27+ in Caucasians
- chronic back pain and stiffness
→ reduced mobility and deformity
- sacroiliitis, pathological bone formation, syndesmophytes
→ spinal ankylosis
- large joint arthritis, enthesitis, extra-articular disease (uveitis, aortic root, lung apex)

Axial spondyloarthritis



The term 'non-radiographic axial spondyloarthritis' is much more important to classify than to diagnose patients with axial spondyloarthritis

Atul Deodhar,¹ Vibeke Strand,² Jonathan Kay,³ Juergen Braun⁴

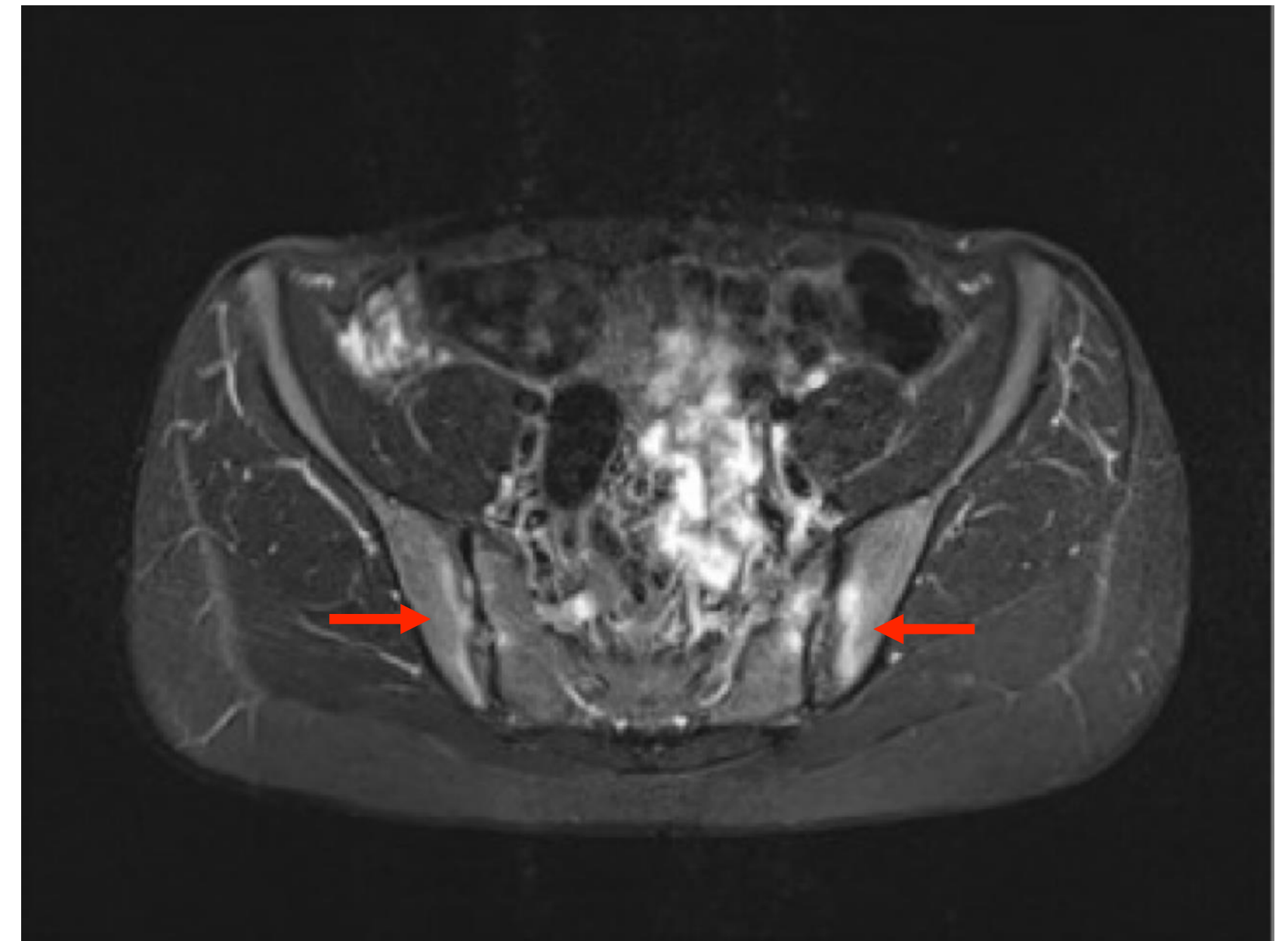
Goodbye to the term 'ankylosing spondylitis', hello 'axial spondyloarthritis': time to embrace the ASAS-defined nomenclature

Désirée van der Heijde ,¹ Anna Molto ,^{2,3} Sofia Ramiro ,^{1,4} Jürgen Braun ,⁵
Maxime Dougados ,⁶ Floris A van Gaalen ,¹ Lianne S Gensler ,⁷

Axial SpA

- symptom onset typically in 20s/30s
M:F = 1:1
- nr-axSpA → AS progression
20-40% over 10 years
risk factors: male sex, smoking,
high inflammatory activity, baseline damage
- symptoms similar in nr-axSpA and AS
 - inflammatory back pain
 - oligoarthritis, enthesitis
 - uveitis, psoriasis, IBD(functional limitations)

SIJ bone marrow edema



MRI STIR

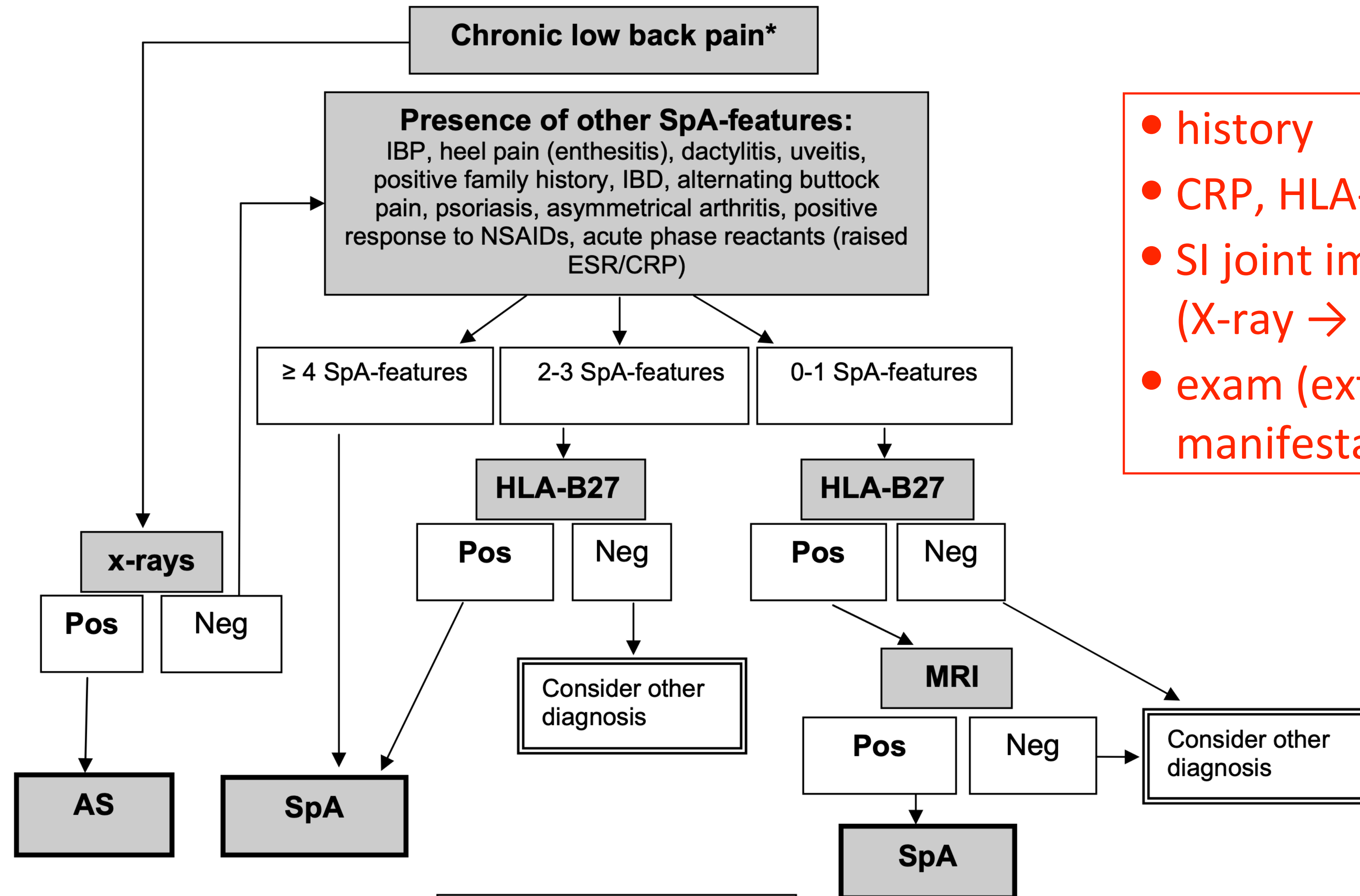
Inflammatory Back Pain (IBP)

Inflammatory back pain	Other back pain ^[SEP] (mechanical, pathological)
<ul style="list-style-type: none">● age at onset < 40-45 years● chronic (duration > 3 months)● insidious onset● pain at night, may cause awakening in the second half of the night● morning stiffness > 30 minutes● improvement with exercise but not with rest● alternating buttock pain● good response to NSAIDs	<ul style="list-style-type: none">● age at onset > 40-45 years● acute● sudden onset● worse with standing, walking, exercise● Improvement with rest● association with fever, night sweats, weight loss● neurological symptoms and signs

Inflammatory Back Pain (IBP)

Calin	Berlin	ASAS Experts
<ul style="list-style-type: none"> • age at onset < 40 years • insidious onset • improvement with exercise • associated with morning stiffness • duration > 3 months 	<ul style="list-style-type: none"> • morning stiffness > 30 min • improvement with exercise but not with rest • awakening at second half of the night because of back pain • alternating buttock pain 	<ul style="list-style-type: none"> • age at onset < 40 years • insidious onset • improvement with exercise • no improvement with rest • pain at night (with improvement upon getting up)
<p>≥ 4 criteria^[SEP]sensitivity 89.9%^[SEP]specificity 52.5%</p>	<p>≥ 2 criteria sensitivity 70% specificity 81.4%</p>	<p>≥ 4 criteria sensitivity 79.6% specificity 72.4%</p>

Diagnosing axial SpA

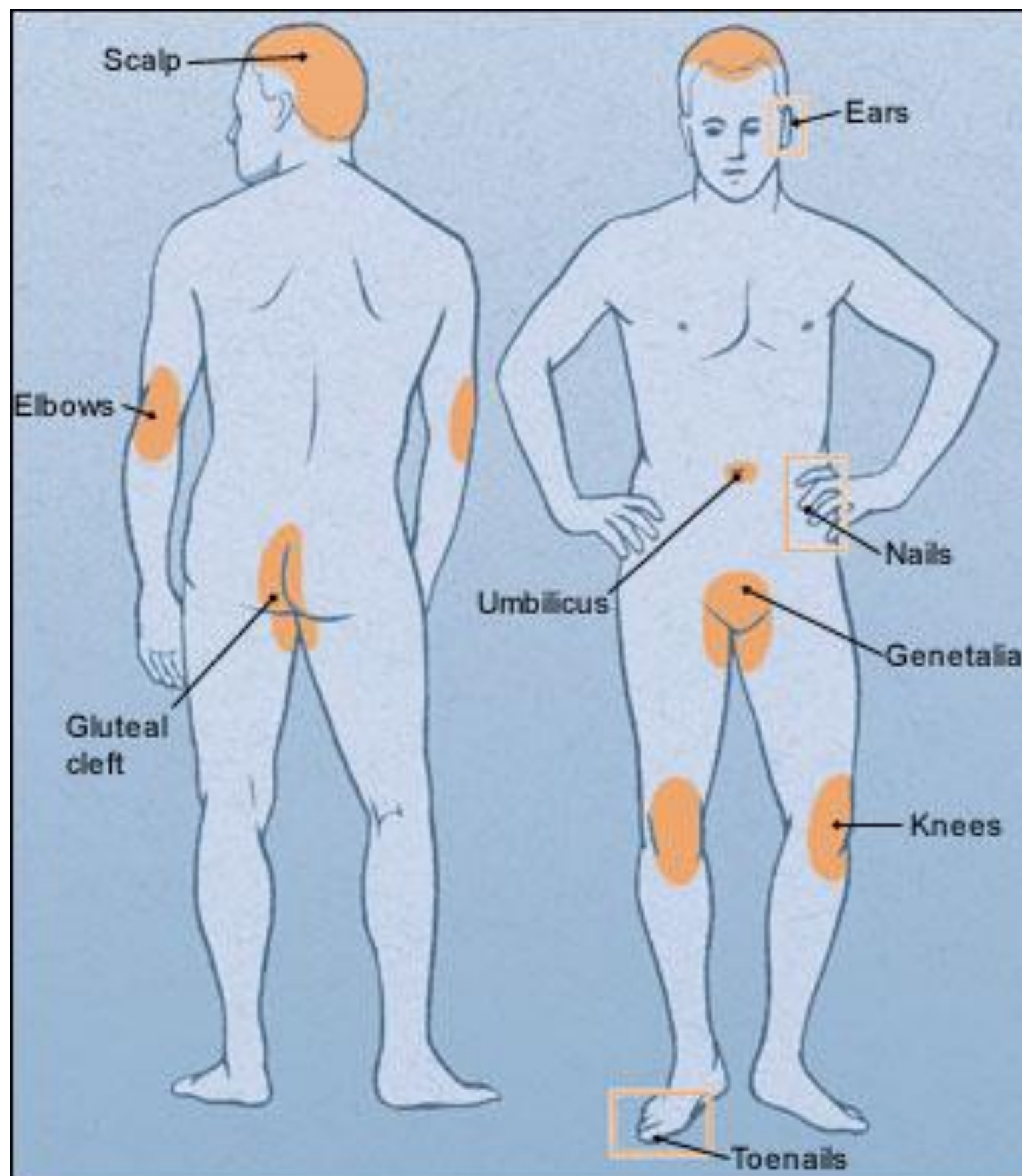


- history
- CRP, HLA-B27
- SI joint imaging (X-ray → MRI)
- exam (extraspinal manifestations?)

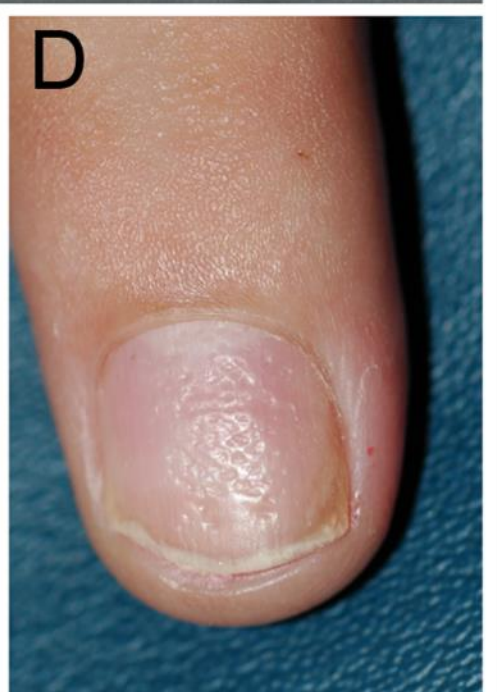
* >3 months, onset <45

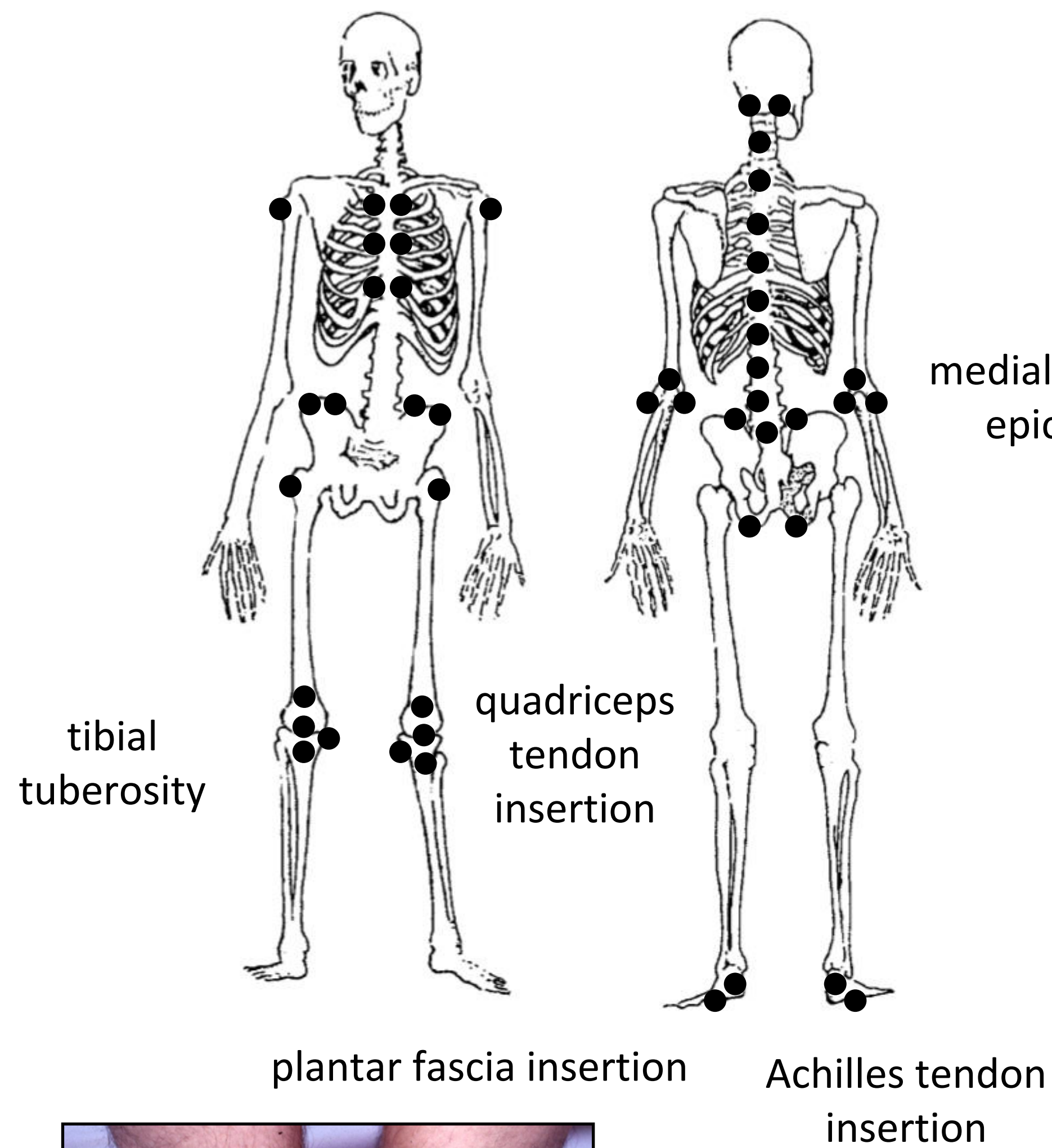
Psoriatic arthritis (PsA)

- 1-3% of caucasian populations have psoriasis
(less frequent in African Americans)
- 10-30% of psoriasis patients develop inflammatory arthropathy,
peak onset age 35-45, M = F
- skin disease typically precedes skeletal disease or begins at the same time
- several clinical subsets:
symmetric polyarthritits, asymmetric oligoarthritis, DIP arthritis,
arthritis mutilans, axial disease
- enthesitis, dactylitis, uveitis are common



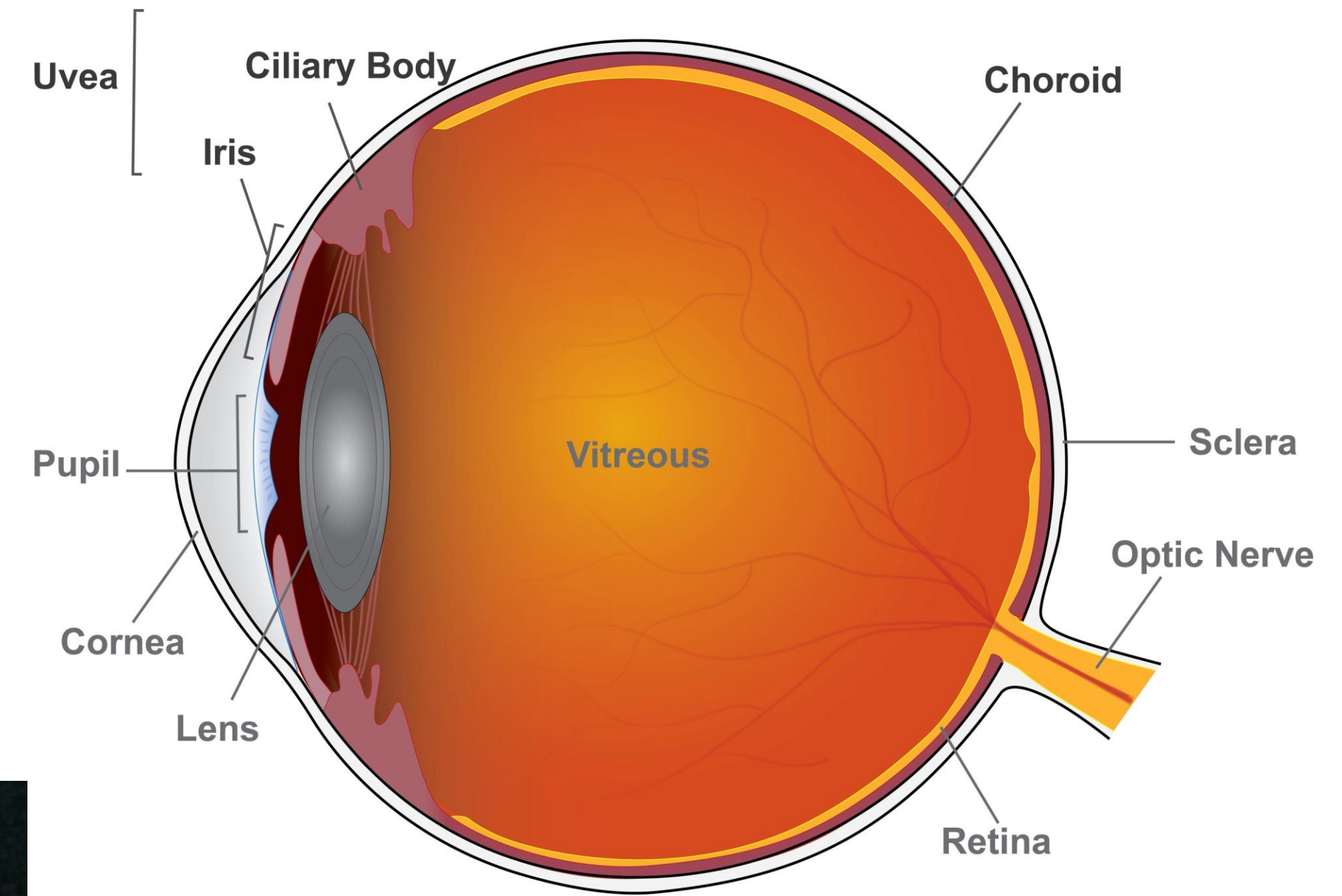
Psoriatic skin and nail disease



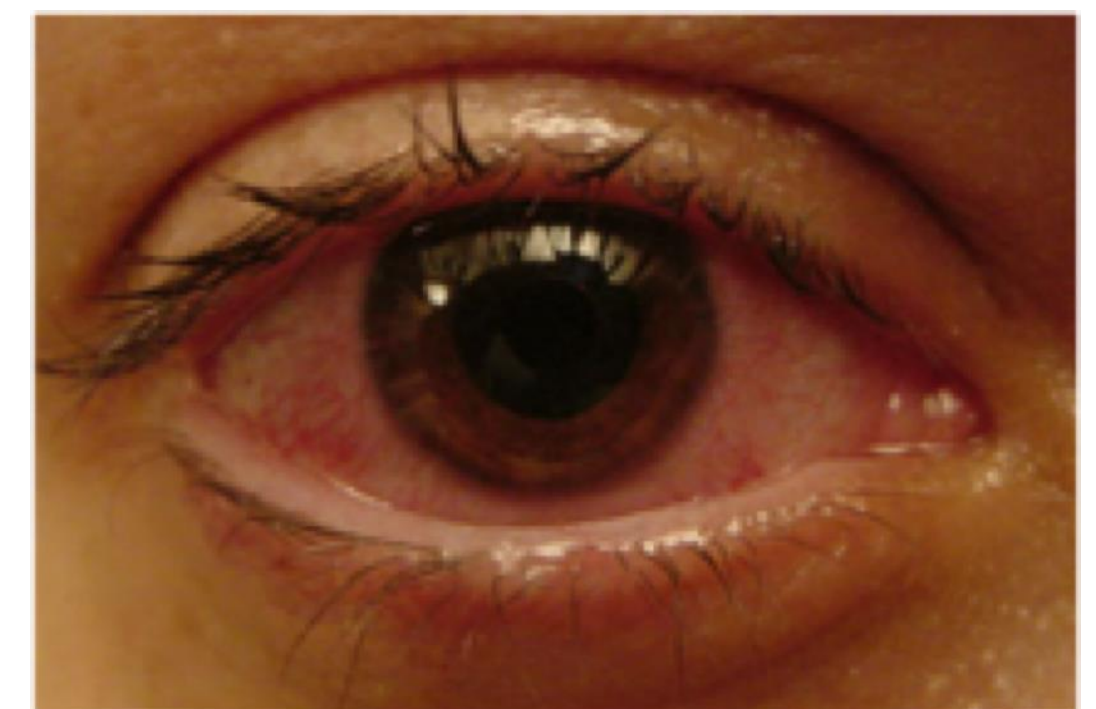


Enthesitis

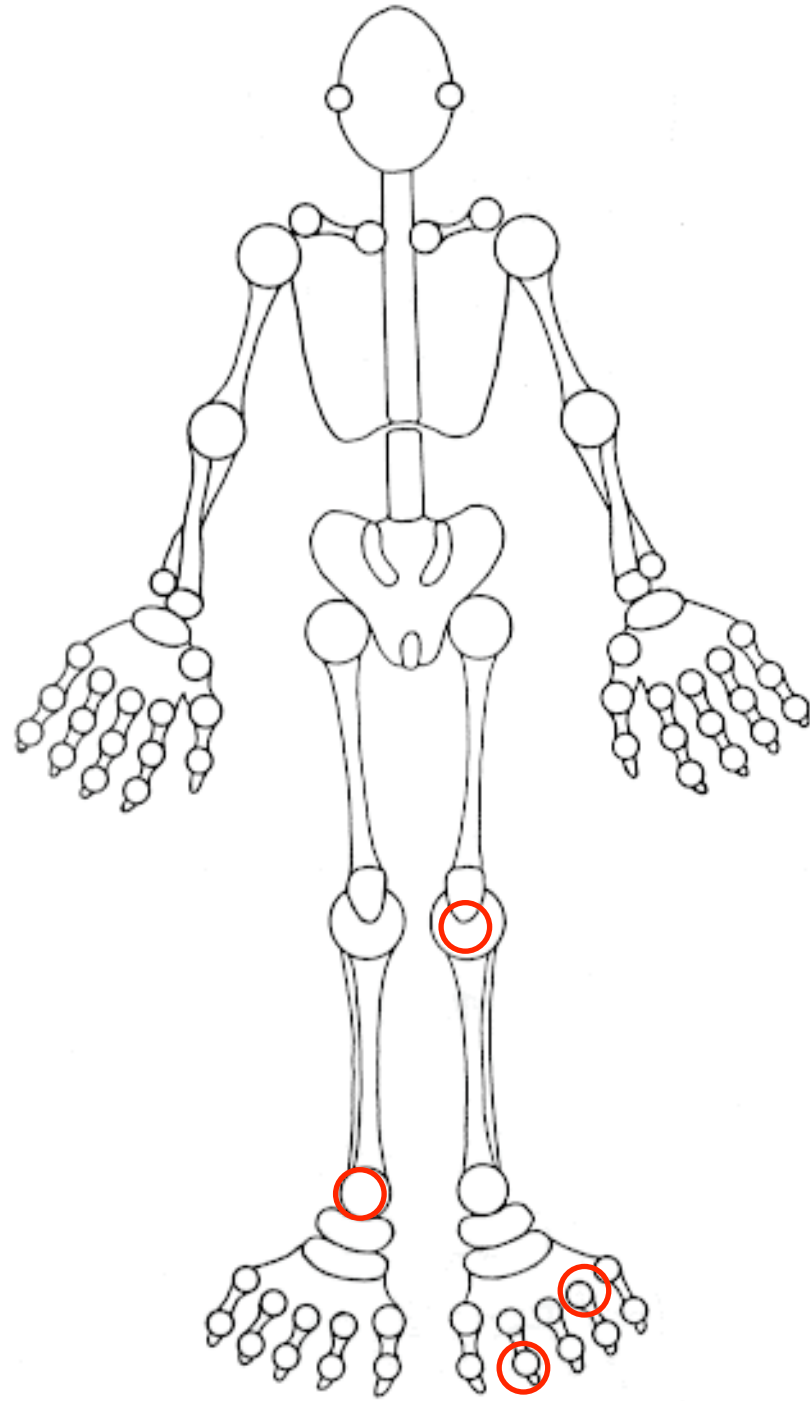
Dactylitis



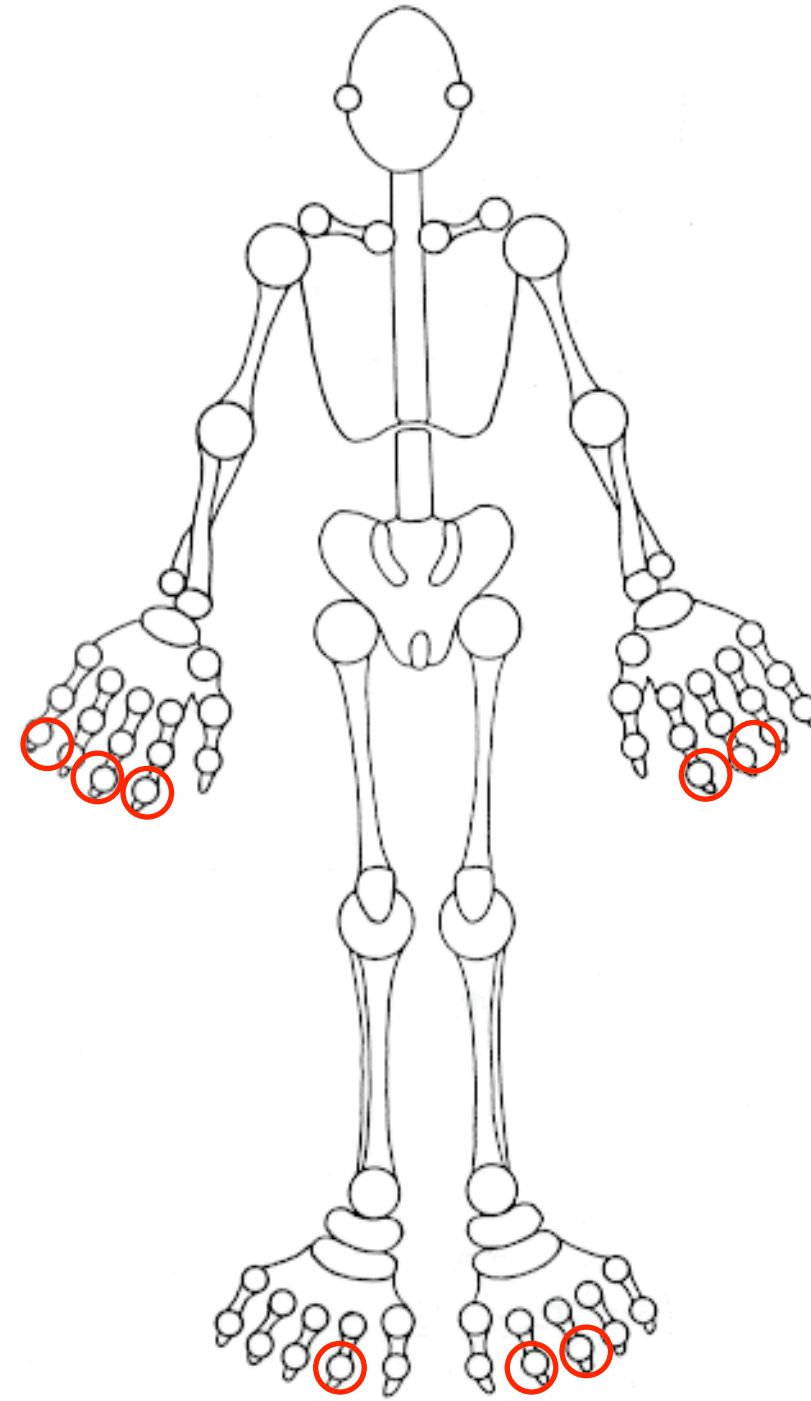
Uveitis



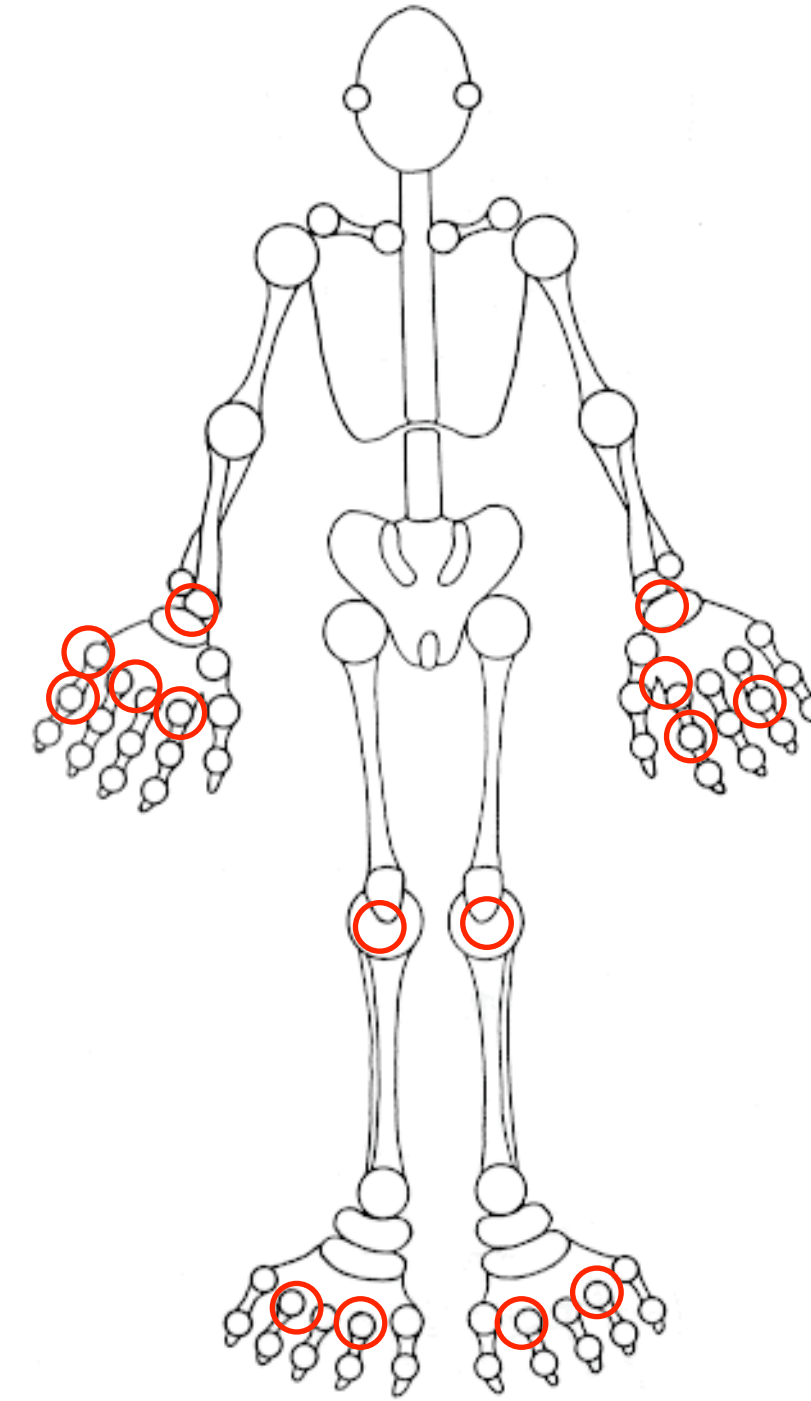
PsA joint involvement patterns



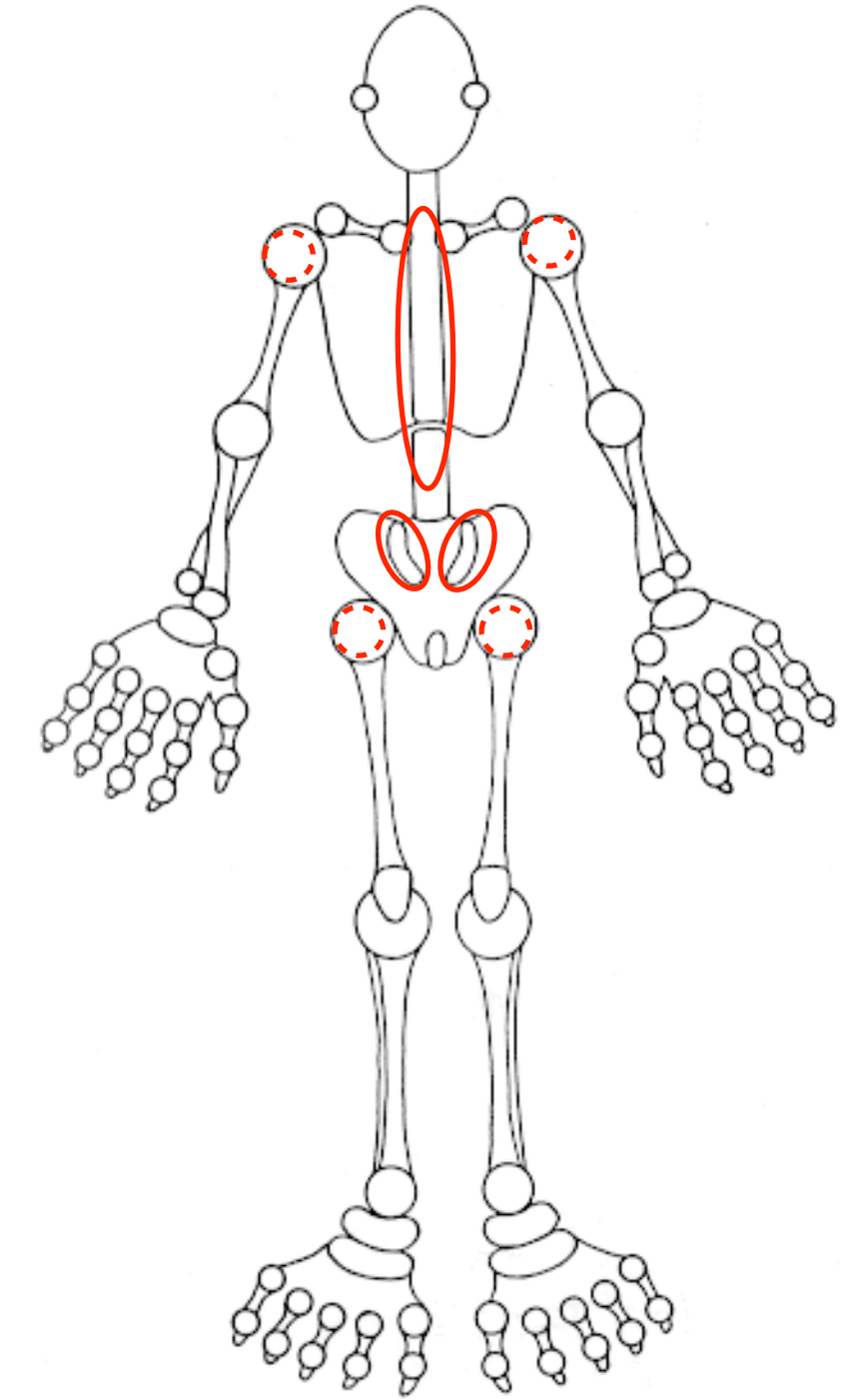
asymmetric
oligoarthritis



DIP arthritis



symmetric
polyarthritis



axial

Axial SpA vs. axial PsA

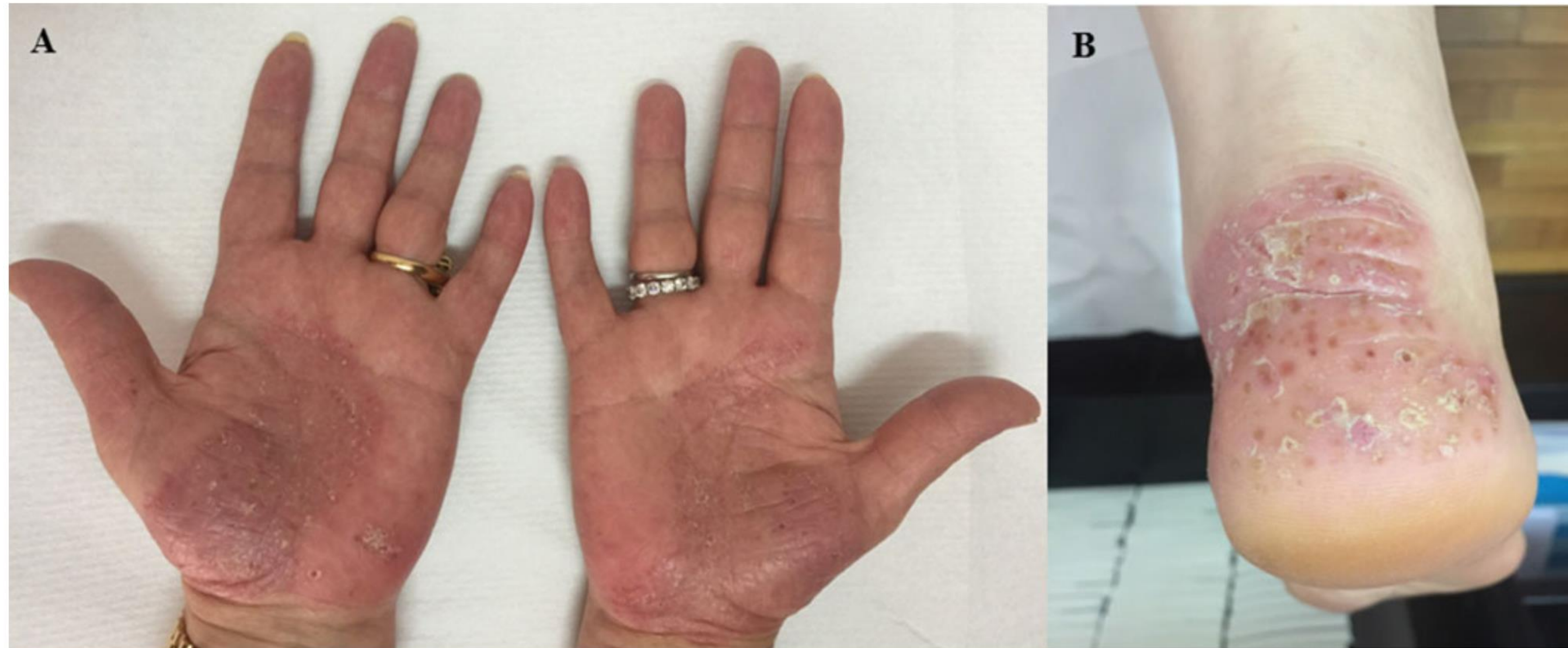
AxSpA		Axial PsA	
Demographic	<ul style="list-style-type: none"> • More frequently male • Younger age at onset 		<ul style="list-style-type: none"> • Similar frequency in males and females • Older age at onset
Clinical	<ul style="list-style-type: none"> • Back pain has inflammatory character in the majority of patients • Peripheral involvement in approximately 15%-30% of patients 		<ul style="list-style-type: none"> • Inflammatory back pain is less frequent than in axSpA • Peripheral involvement in most patients • Can be asymptomatic
Imaging	<ul style="list-style-type: none"> • Symmetrical sacroiliitis • Classical symmetrical and marginal syndesmophytes • More frequent fusion of lumbar facet joints 		<ul style="list-style-type: none"> • More frequent involvement of cervical spine • More frequent fusion of facet joints in cervical spine • Less severe sacroiliitis and frequently asymmetrical • Non-marginal syndesmophytes and paravertebral ossifications • Less syndesmophyte symmetry
Genetic	<ul style="list-style-type: none"> • Higher proportion of HLA-B27–positive patients (90%) 		<ul style="list-style-type: none"> • Only 14% to 44% of patients are HLA-B27 positive • More frequently associated with HLA-B08 and HLA-B38
Treatment Response	<ul style="list-style-type: none"> • NSAIDs, TNFis, and IL-17 inhibitors are effective treatment options; lack of efficacy of IL-23 inhibitors 		<ul style="list-style-type: none"> • Positive data from one randomized controlled trial with an IL-17 inhibitor (secukinumab) • Data from post hoc analyses of IL-23 inhibitor (guselkumab) and IL-12/23 inhibitor (ustekinumab) • Efficacy of NSAIDs and TNFis is assumed based on axSpA data



Reactive arthritis

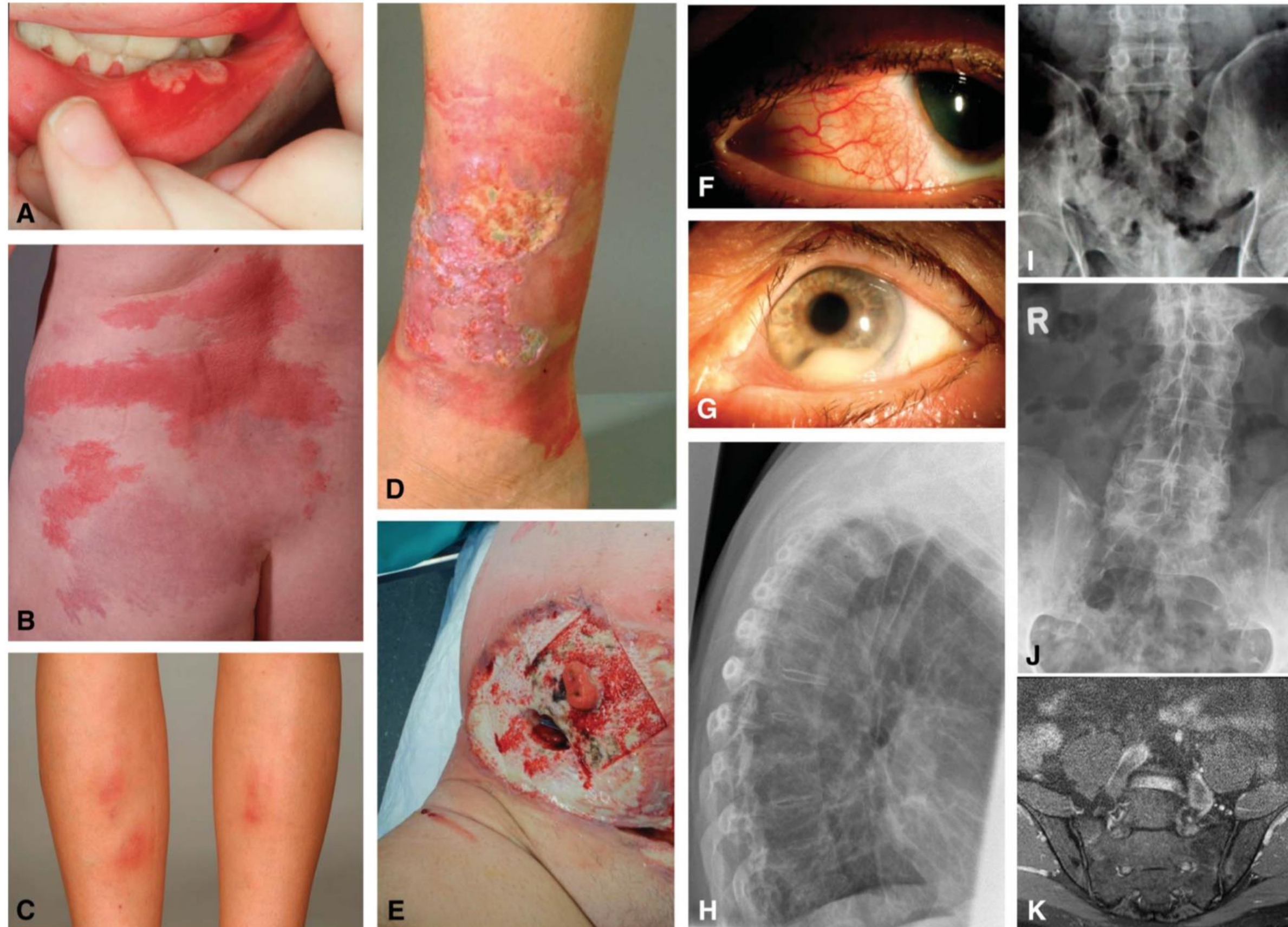
- “reactive arthritis” term introduced in 1969, preferred term “Reiter’s syndrome” commonly used in USA until early 2000s
- SpA within 4 weeks after UTI or infectious diarrheal illness: chlamydia, salmonella, shigella, yersinia, campylobacter
- preceding infection often not apparent (urine PCR for chlamydia, serum antibodies for enteric pathogens)
- no culture of microorganisms from synovial fluid
- acute presentation → 50% monophasic, 50% chronic
 - asymmetric oligoarthritis
 - enthesitis, dactylitis
 - sacroiliitis
 - keratoderma blennorrhagica, circinate balanitis

Clinical Images: Keratoderma blennorrhagica



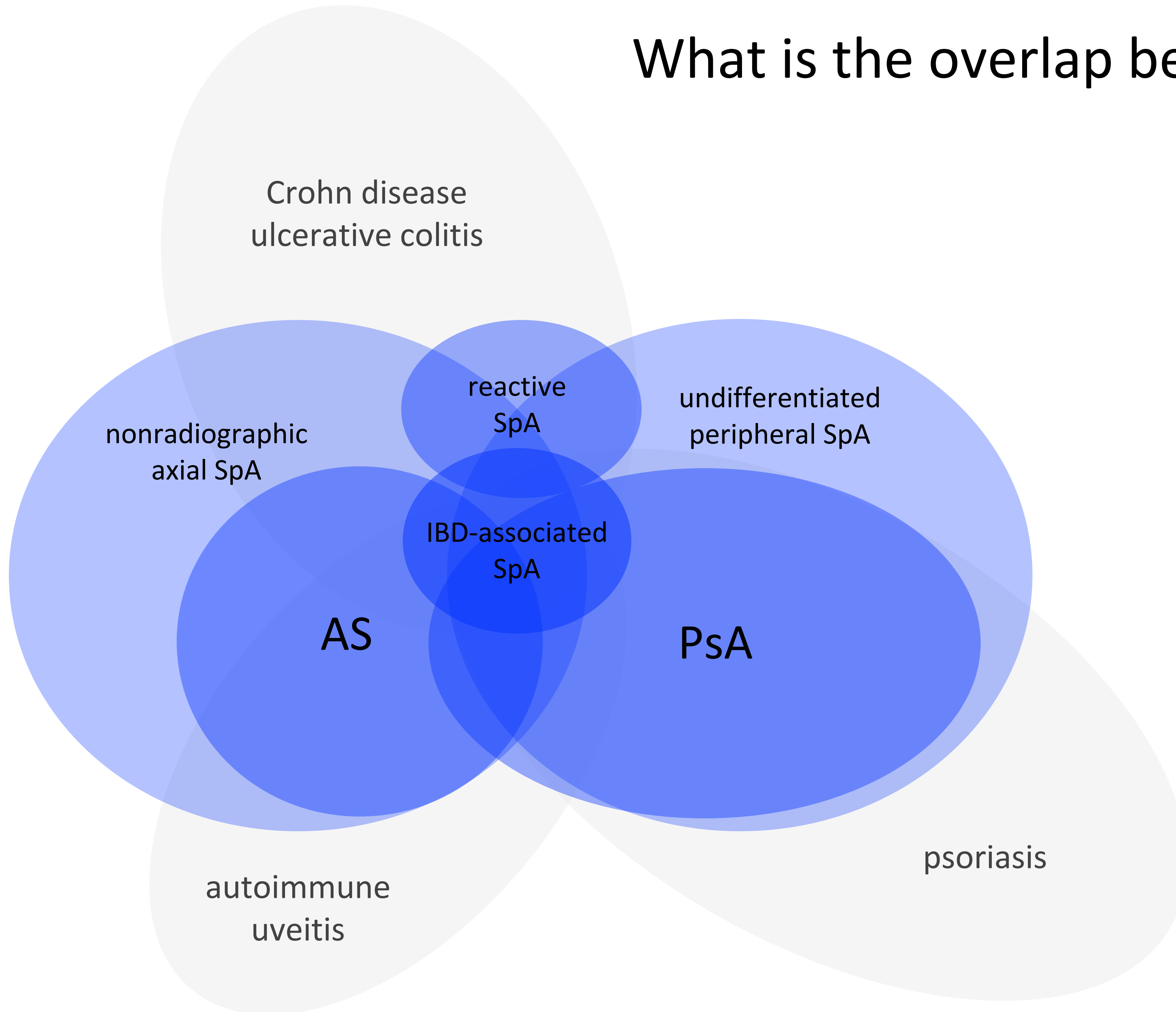
The patient, a 46-year-old woman, was referred for possible psoriatic arthritis. She had a 4-week history of psoriasiform lesions of the palms of the hands and soles of the feet as well as knee pain and a 2-month history of dysuria. Physical examination revealed mild arthritis of the left knee and brown, waxy vesiculopustular lesions of the palms of the hands (A) and soles and heels of the feet (B), which fused together into crusted plaques on an erythematous base. Physical examination revealed no further abnormalities, and family history was unremarkable. Laboratory tests showed mild leukocytosis, elevated C-reactive protein level (35 mg/liter [normal <5]), negative VDRL and positive HLA-B27, while a cervical swab sample was positive for *Chlamydia trachomatis*. Palmoplantar skin lesions were attributed to keratoderma blennorrhagica secondary to reactive arthritis (ReA). For her *C trachomatis*, the patient was

SpA is the most common extra-intestinal manifestation of IBD

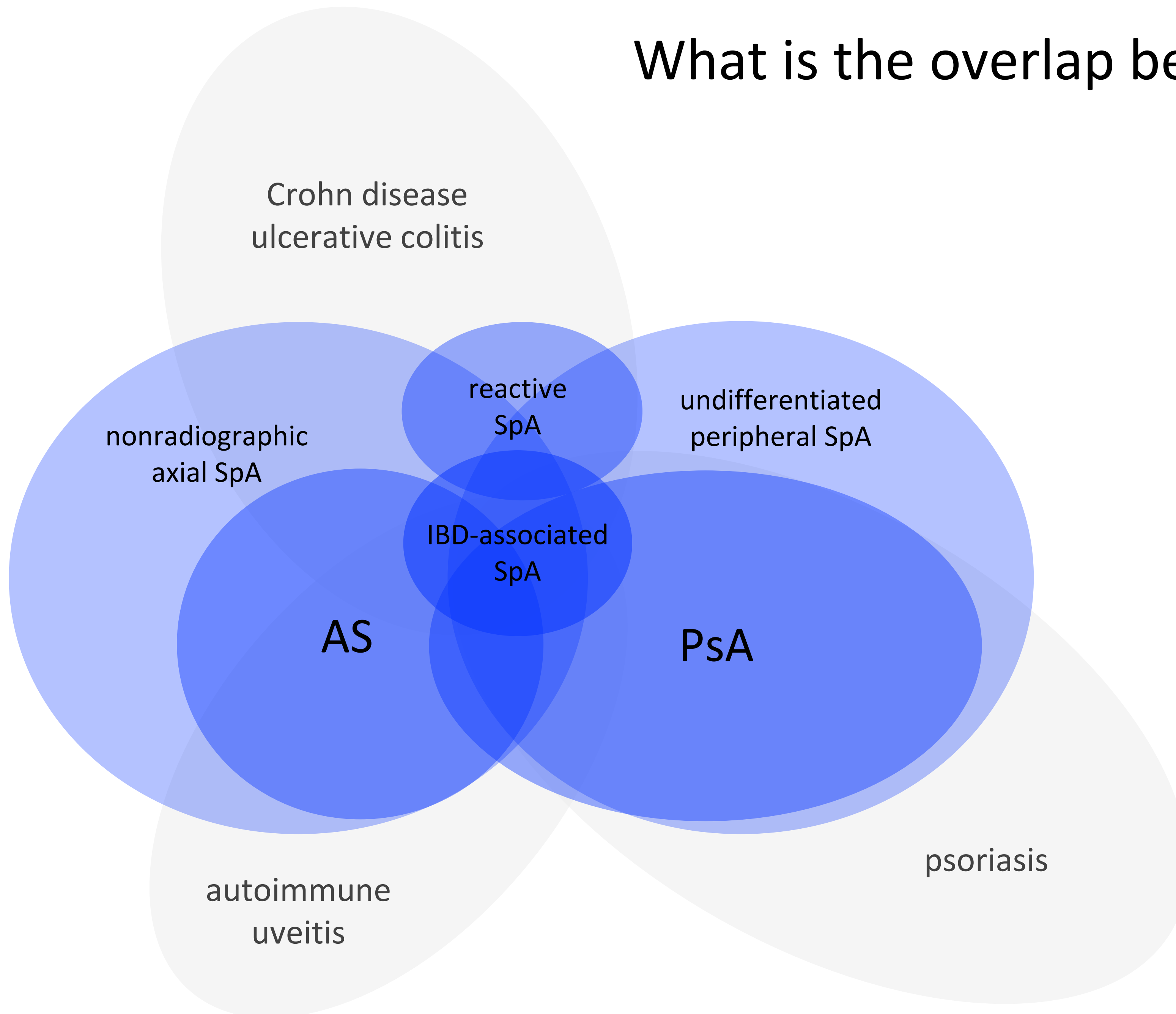


- musculoskeletal (up to 20%)
 - peripheral arthritis (5-10% UC, 10-20% CD)
 - axial SpA (3-5%)
 - radiographic sacroiliitis (up to 25%)
- skin (up to 15%)
 - E. nodosum
 - pyoderma gangrenosum
 - oral lesions
- ocular (2-5%)
 - scleritis, episcleritis
 - uveitis
- hepatobiliary
 - primary biliary cirrhosis (UC)

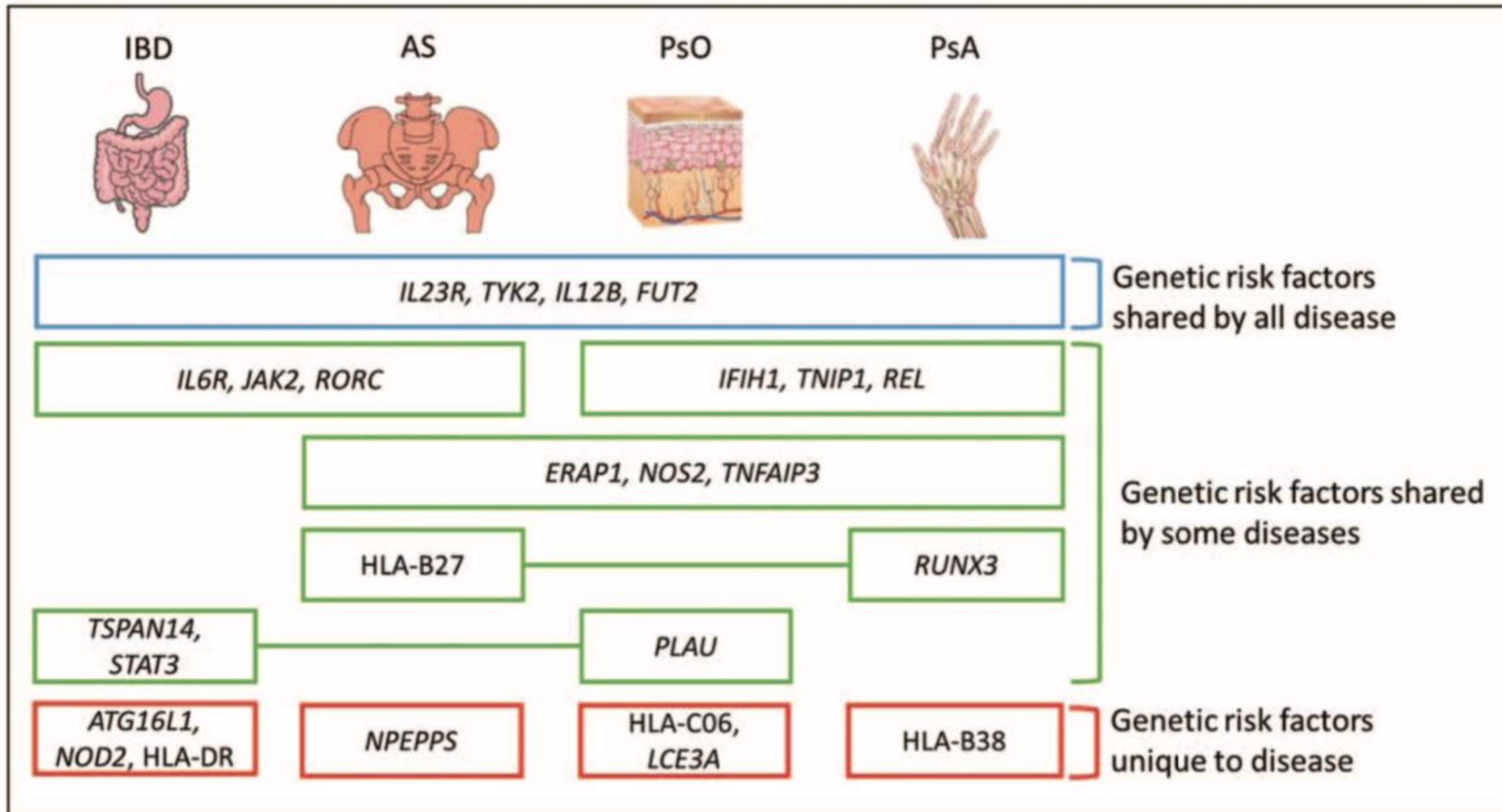
What is the overlap between the SpA variants?



What is the overlap between the SpA variants?



- clinical manifestations are shared between diseases
- individual patients may have more than one disease
- positive family history for one variant increases risk for other SpA variants
- overlap of genetic risk variants and treatment responses



HLA-B27 association with AS and SpA in [SEP]populations of Northwestern European extraction

- ankylosing spondylitis ~90%
- reactive arthritis 30-70%
- IBD-associated SpA 30-70%
- psoriatic SpA 40-50%
- undifferentiated SpA ~70%
- acute anterior uveitis ~50%
- general population ~8%

HLA-B27 is strongly associated with Ankylosing spondylitis

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April 28, 1973

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HIGH ASSOCIATION OF AN HL-A ANTIGEN, W27, WITH ANKYLOSING SPONDYLITIS

LEE SCHLOSSTEIN, M.D., PAUL I. TERASAKI, PH.D., RODNEY BLUESTONE, M.D., AND CARL M. PEARSON, M.D.

Abstract The frequencies of 24 HL-A antigens were examined in 40 patients with ankylosing spondylitis, 119 with rheumatoid arthritis, and 66 with gout. No significant deviation from control frequencies of HL-A specificities was noted in patients with gout and rheumatoid arthritis. Specificity W27 was noted in 35 of 40 patients with ankylosing spondylitis, or 88 per cent, as compared to 8 per cent of the 906 normal controls (p < 0.0001). There was concomitant reduction in HL-A7 of

the second segregant series associated with the increased frequency of occurrence of W27, but this decrease was of borderline significance (p < 0.05). This association between W27 and ankylosing spondylitis is so marked that it is possible to assume either very close genetic linkage of a specific immune responsiveness gene to the disease or perhaps a strong immunologic cross-reaction between W27 and the etiologic agent involved.

ALTHOUGH the possible association of HL-A with disease susceptibility has been investigated for many diseases, it has only been in the past year that three convincing examples have been obtained. One is the high incidence of HL-A1, approximately 2½ times normal frequency, and HL-A8, approximately three times normal frequency, in patients with celiac disease as shown by Stokes et al.¹ and independently by Falchuk and his co-workers.² The second is the high incidence of W17 and HL-A13, each approximately three times normal frequency in psoriatic patients with evidence of inheritance from family studies.^{3,4} The third is the increased incidence of HL-A1 and HL-A8, again approximately three times normal frequency, in patients with chronic active hepatitis as reported by Mackay and Morris.⁵ All other possible associations with HL-A previously described do not approach the high statistical significance found in these three diseases. We report here a fourth disease, ankylosing spondylitis, in which a strikingly high association was found. This disease, in common with psoriasis and celiac disease, has a strongly identifiable genetic component,⁶ although basic similarities in etiology are probably remote. For comparison, patients with rheumatoid arthritis and gout were also studied.

MATERIALS AND METHODS

Patients

Caucasian patients attending the Wadsworth Veterans Administration Hospital Arthritis and Gout clinics, the UCLA Arthritis Clinic, and patients referred by the clinical staff of the 2 hospitals were interviewed and examined. Forty patients with ankylosing spondylitis, 119 with definite rheumatoid arthritis and 66 with typical primary gout were studied.

Diagnostic Criteria for Ankylosing Spondylitis — Rome Criteria⁷

These criteria were low-back pain and stiffness of over 3 months' duration not relieved by rest, pain and stiffness in the thoracic re-

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ANKYLOSING SPONDYLITIS AND HL-A 27

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Summary

Using a standard microcytotoxicity technique of tissue typing, the HL-A 27 antigen was identified in 72 out of 75 patients with classical ankylosing spondylitis and in 3 out of 75 controls. The same antigen was found in 31 out of 60 first-degree relatives.

Introduction

SINCE Aird and his colleagues studied the relationship between gastric carcinoma and blood-group A,¹ several similar associations have been established between diseases and blood-groups, and, in a few, pedigree studies have indicated autosomal linkages. Of interest to rheumatologists is the uncommon nail-patello-femoral syndrome, which is thought to be closely linked to the ABO blood-group locus.² Ankylosing spondylitis is not associated with a particular blood-group.³

Studies of skin-grafts and tissue rejection led to the discovery of the leucocyte system of isoantigens, including the HL-A system, and the identification of the HL-A antigens is an essential part of tissue typing. In Caucasians it is now usually possible to identify four HL-A antigens, and these are believed to be genetically determined, probably transmitted by two related loci on each of a pair of chromosomes. Relationships between diseases and particular HL-A antigens are now being studied extensively. Associations have been reported in lymphoma (HL-A 5 and W 18),⁴⁻⁶ multiple myeloma (W 18),⁸ adult celiac disease (HL-A 1 and 8),⁹ systemic lupus erythematosus (HL-A 13 and W 17),¹⁰⁻¹² lymphoblastic leukaemia (HL-A 27),¹³ and psoriasis (HL-A 13 and W 17).¹⁴ No definite association has been established with rheumatoid disease.¹⁵⁻¹⁷

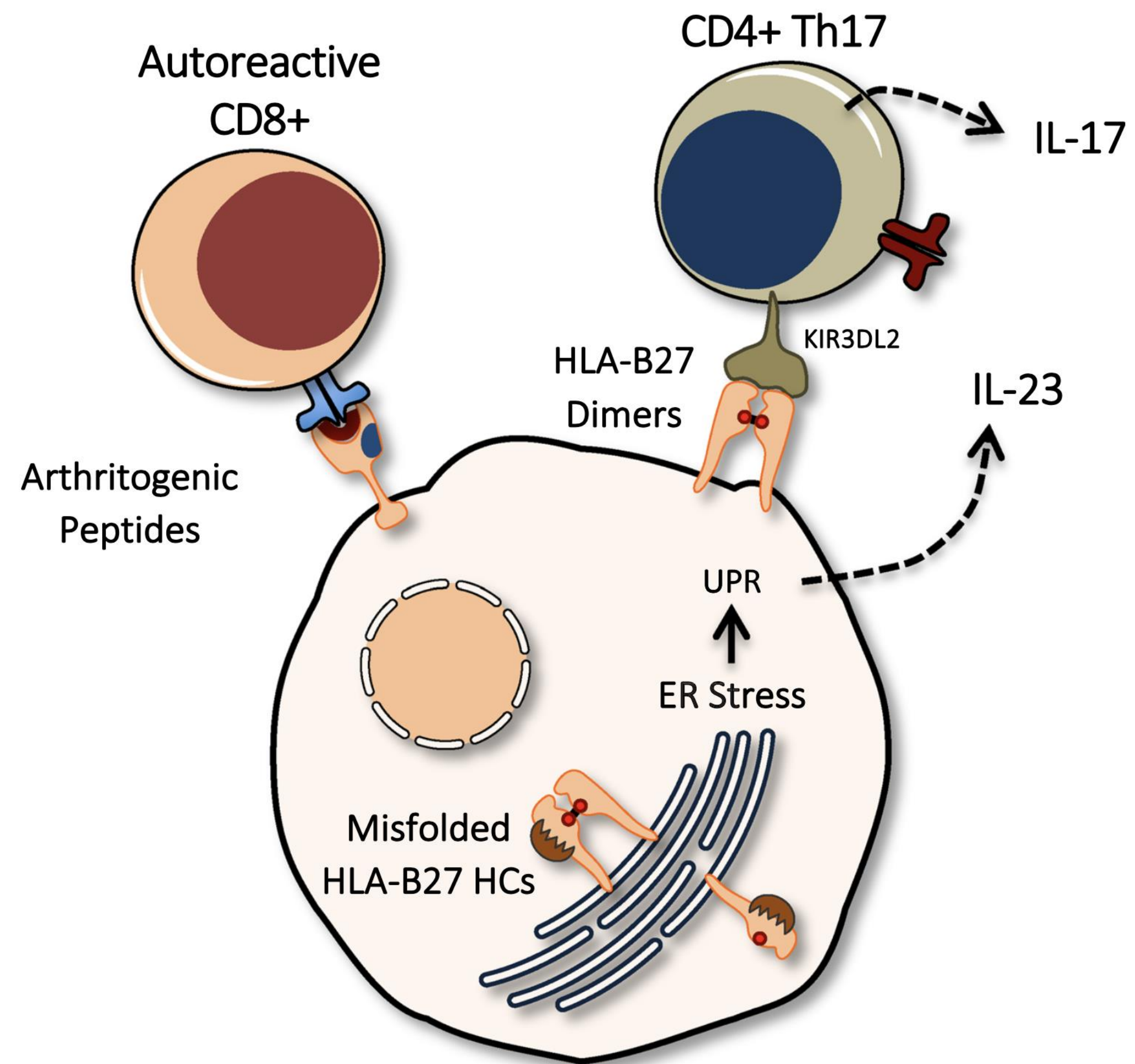
There are several reports of ankylosing spondylitis in 2 or more patients in the same family,¹⁸⁻²³ with a few instances of the disease in pairs of identical twins.²³ Hersh, Stecher, and their colleagues^{19,19} suggested that the inheritance was as an autosomal dominant, with 70% penetrance in men and 10% in women. They also reviewed the evidence that when there is a woman with the disease the penetrance is approximately 100% in first-degree relatives, with half of the males and females affected. Bremner and her colleagues²² studied 250 first-degree relatives and found clinical ankylosing spondylitis in 4%, compared to an estimated prevalence of 0.1-0.2% in the population.²⁴ In the same relatives radiographic bilateral sacroiliitis was found in 16%: 4 out of 24 fathers (17%); 0 out of 30 mothers; 13 out of 82 brothers (16%); 5 out of 30 sisters (17%); and 8 out of 22 sons (36%). Daughters were not investigated because no radiographs were taken of women under forty-five. In discussing this study Emery and

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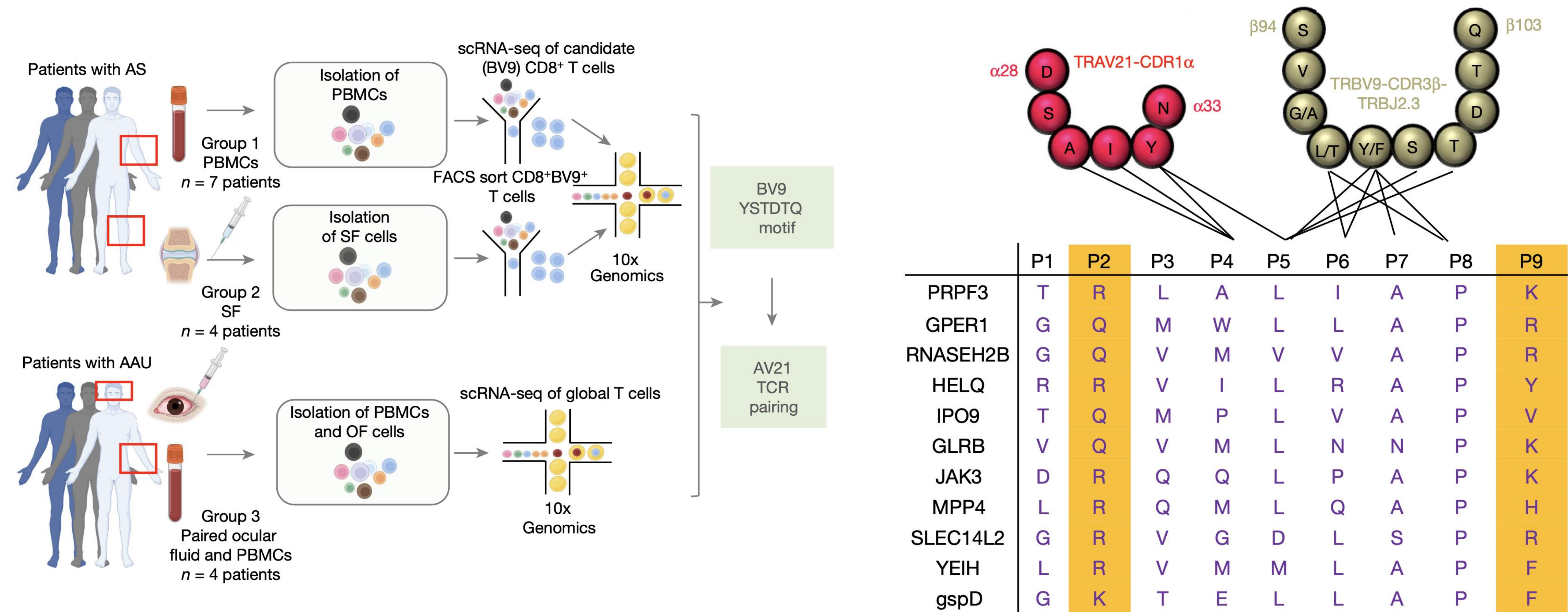
“Psychiatrists do not diagnose their patients like other doctors do. They discard four of their senses and literally play it by ear. It is the no-touch technique adapted to new purpose. Physical examination and laboratory investigation, which transformed medicine from guess-work and theory to fact and science, are spurned or positively discouraged. It is alleged that they deflect attention from study in depth of the patient's mind, and impede rapport. Presenting symptoms are elevated to the status of a disease like varieties of fever were in the eighteenth century. The pharmaceutical industry provides corresponding antidotes and reinforces the illusion.”—Dr RICHARD HUNTER, *Proc. R. Soc. Med.* 1973, **66**, 359.

Hypotheses for HLA-B27 association with SpA



1. arthritogenic peptide hypothesis
2. misfolding hypothesis
3. KIR hypothesis
4. dysbiosis hypothesis

Identification of CD8+ T cells with conserved TCR motif in HLA-B27+ AS and AAU - finally an explanation?



Which of the following is a feature of inflammatory back pain?

- A. morning stiffness lasting less than 30 minutes
- B. sudden onset within 1 month after a urinary tract infection
- C. no benefit from oral NSAIDs
- D. improvement with exercise but not rest

Which of the following is a feature of inflammatory back pain?

- A. morning stiffness lasting less than 30 minutes
- B. sudden onset within 1 month after a urinary tract infection
- C. no benefit from oral NSAIDs
- D. improvement with exercise but not rest

In a 30 yo male with inflammatory back pain and normal radiograph of the SI joints, what is the most appropriate next diagnostic step?

- A. HLA-B27, ANA, rheumatoid factor, anti-CCP (Rheum panel)
- B. MRI of the SI joints
- C. X-ray of cervical, thoracic and lumbar spine
- D. PET-CT

In a 30 yo male with inflammatory back pain and normal radiograph of the SI joints, what is the most appropriate next diagnostic step?

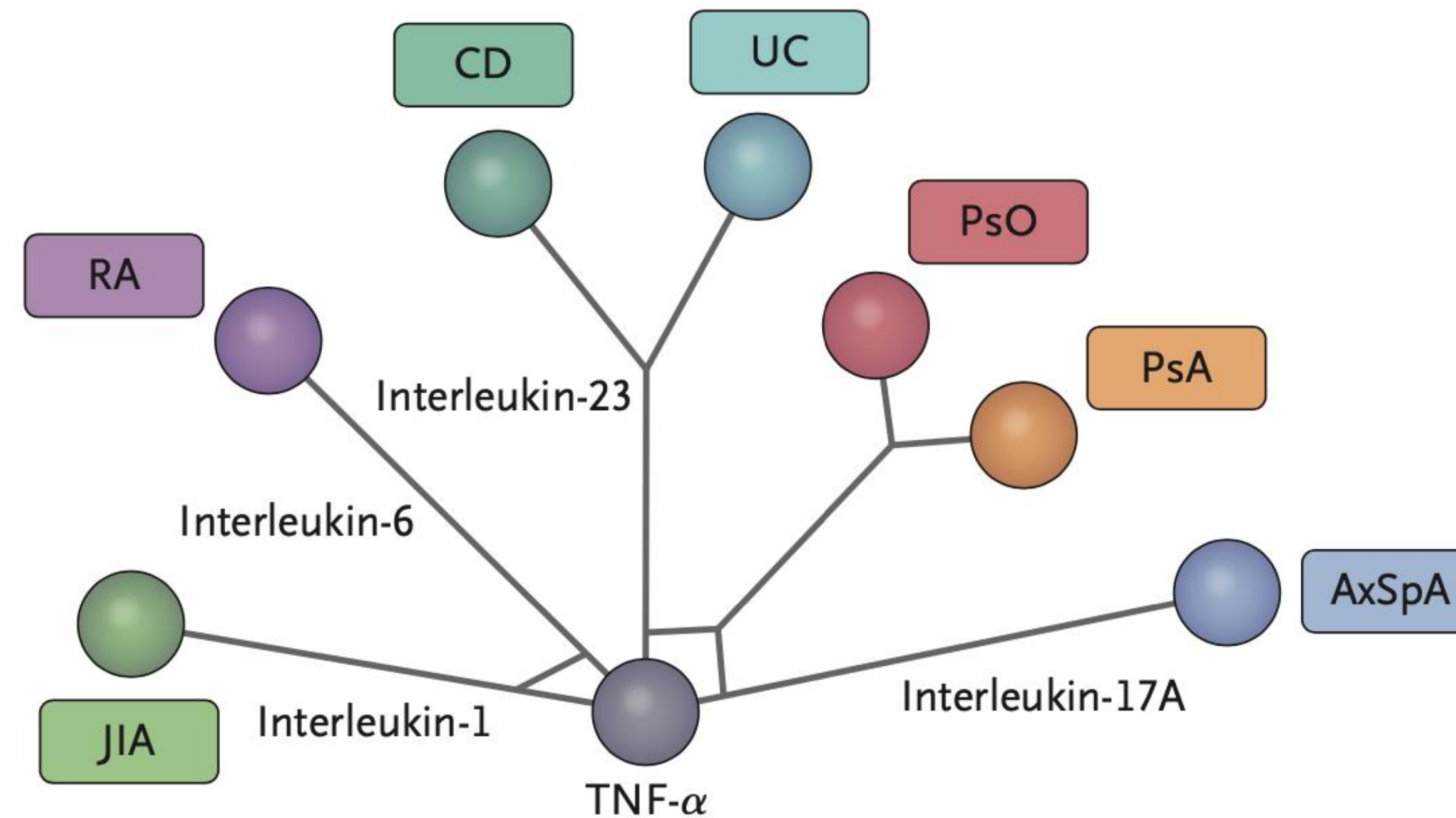
- A. HLA-B27, ANA, rheumatoid factor, anti-CCP (Rheum panel)
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SpA treatment recommendations

axial SpA/AS	PsA
ACR/SAA/SPARTAN <i>Ward Arthritis Rheumatol 2016; 68:282-98</i> <i>Ward Arthritis Rheumatol 2019; 71:1599-1613</i>	ACR/NPF <i>Singh Arthritis Rheumatol 2019; 71:5-32</i>
ASAS/EULAR <i>van der Heijde Ann Rheum Dis 2017; 76:978-91</i> <i>Ramiro Ann Rheum Dis 2023; 82:19-34</i>	EULAR <i>Gossec Ann Rheum Dis 2020; 79:700-12</i> <i>Gossec Ann Rheum Dis 2024; 83:706-19</i>
PANLAR <i>Bautista-Molano Nat Rev Rheumatol 2023;19: 724-37</i>	GRAPPA <i>Coates Nat Rev Rheumatol 2022; 18:465-79</i>

Treatment of SpA

- SpA treatment options differ from RA
 - methotrexate - anchor drug in RA, used in PsA, no benefit in axSpA
 - major differences in efficacy of biologic DMARDs



Treatment of SpA

- SpA treatment options differ from RA
 - methotrexate - anchor drug in RA, used in PsA, no benefit in axSpA
 - major differences in efficacy of biologic DMARDs
- important classes of drugs

axSpA	PsA
<ul style="list-style-type: none">● NSAIDs● TNF inhibitors● IL-17A inhibitors● JAK inhibitors	<ul style="list-style-type: none">● Methotrexate● TNF inhibitors● IL-17A inhibitors● IL-12/23 inhibitors● JAK inhibitors● PDE4 inhibitors

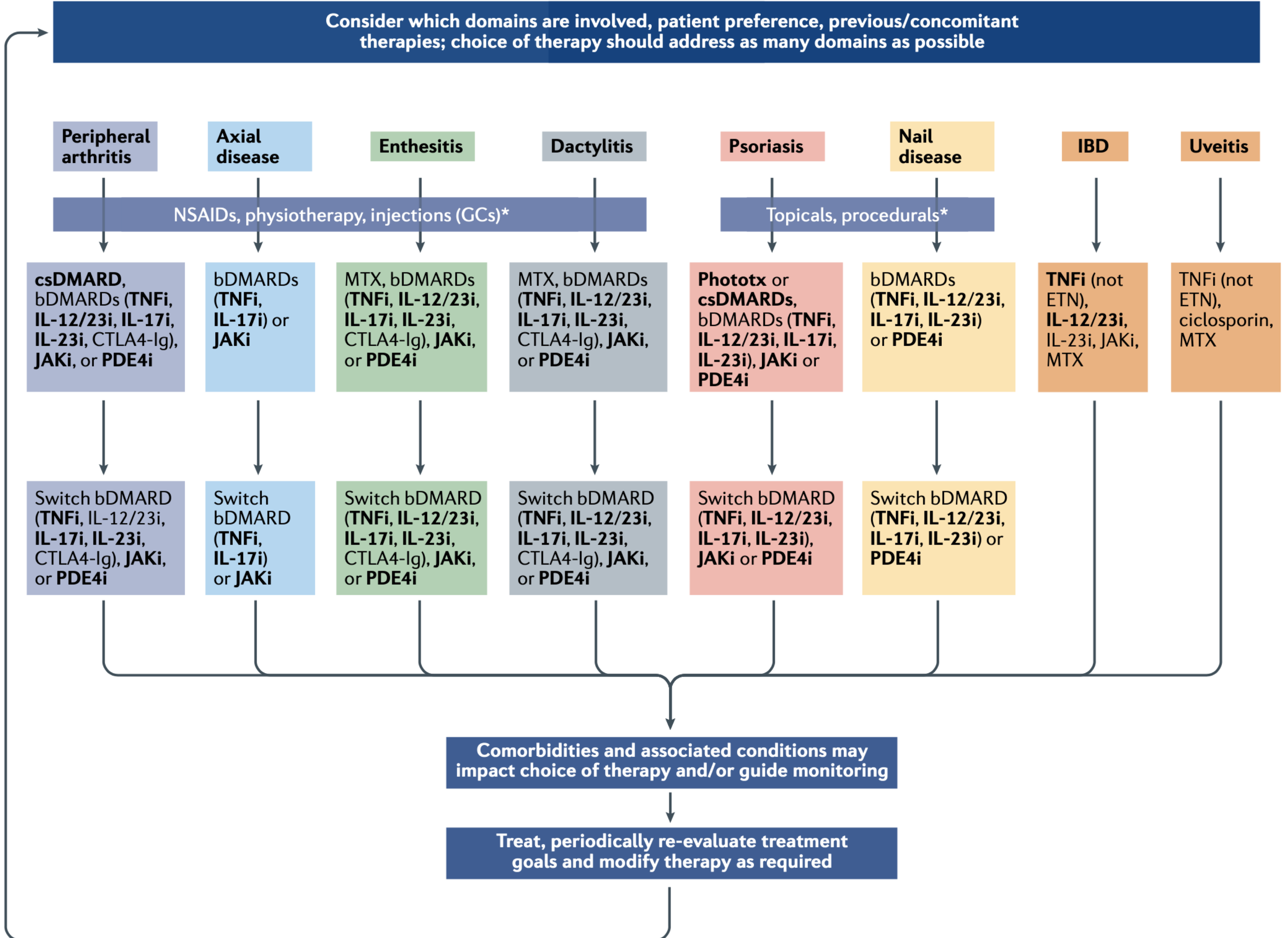
Treatment of SpA

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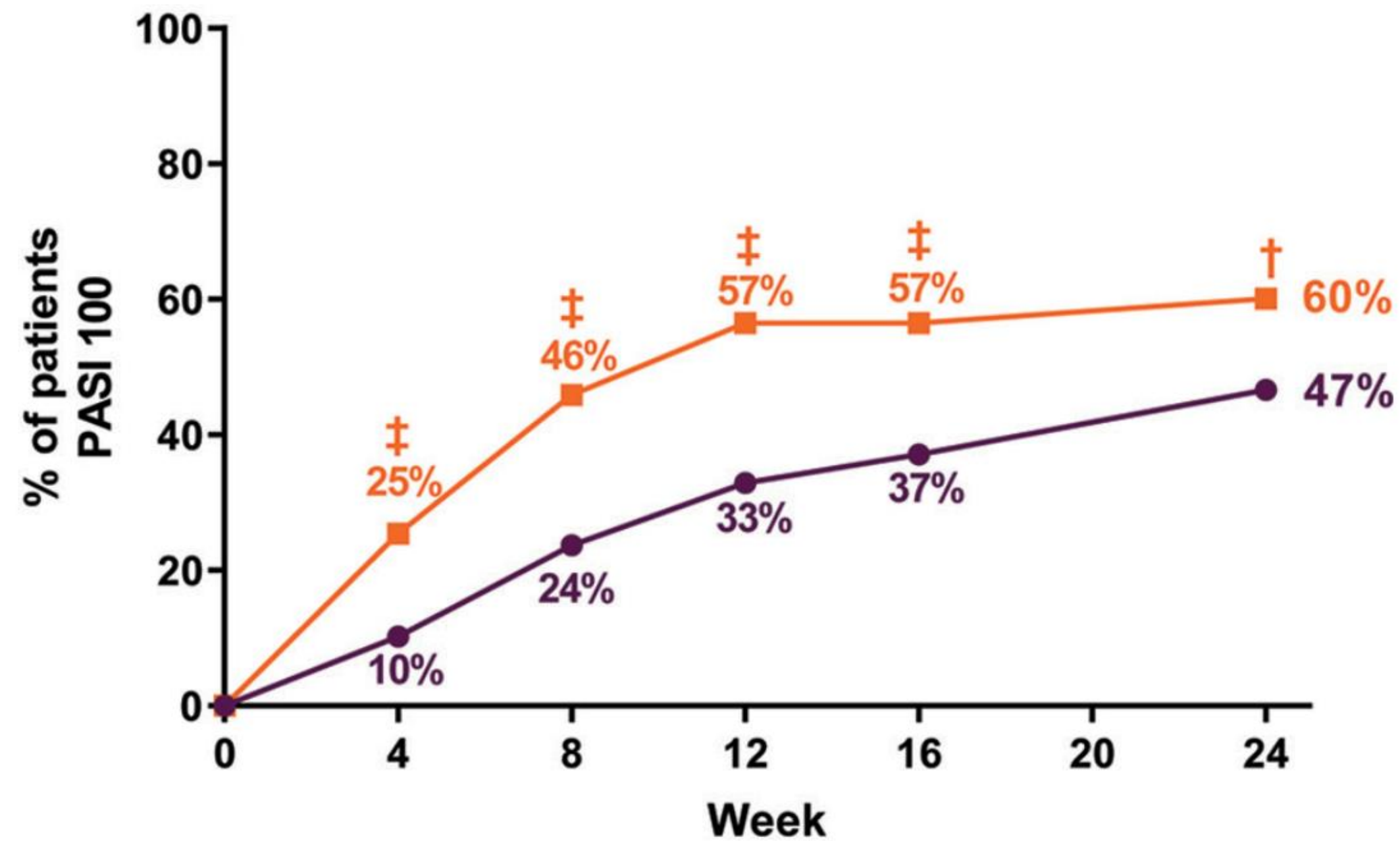
- treatment decisions can be complex → need to individualize
 - peripheral vs. axial disease
 - extra-skeletal disease manifestations (psoriasis, IBD, uveitis), co-morbidities

Disease phenotype is critical in managing patients with PsA

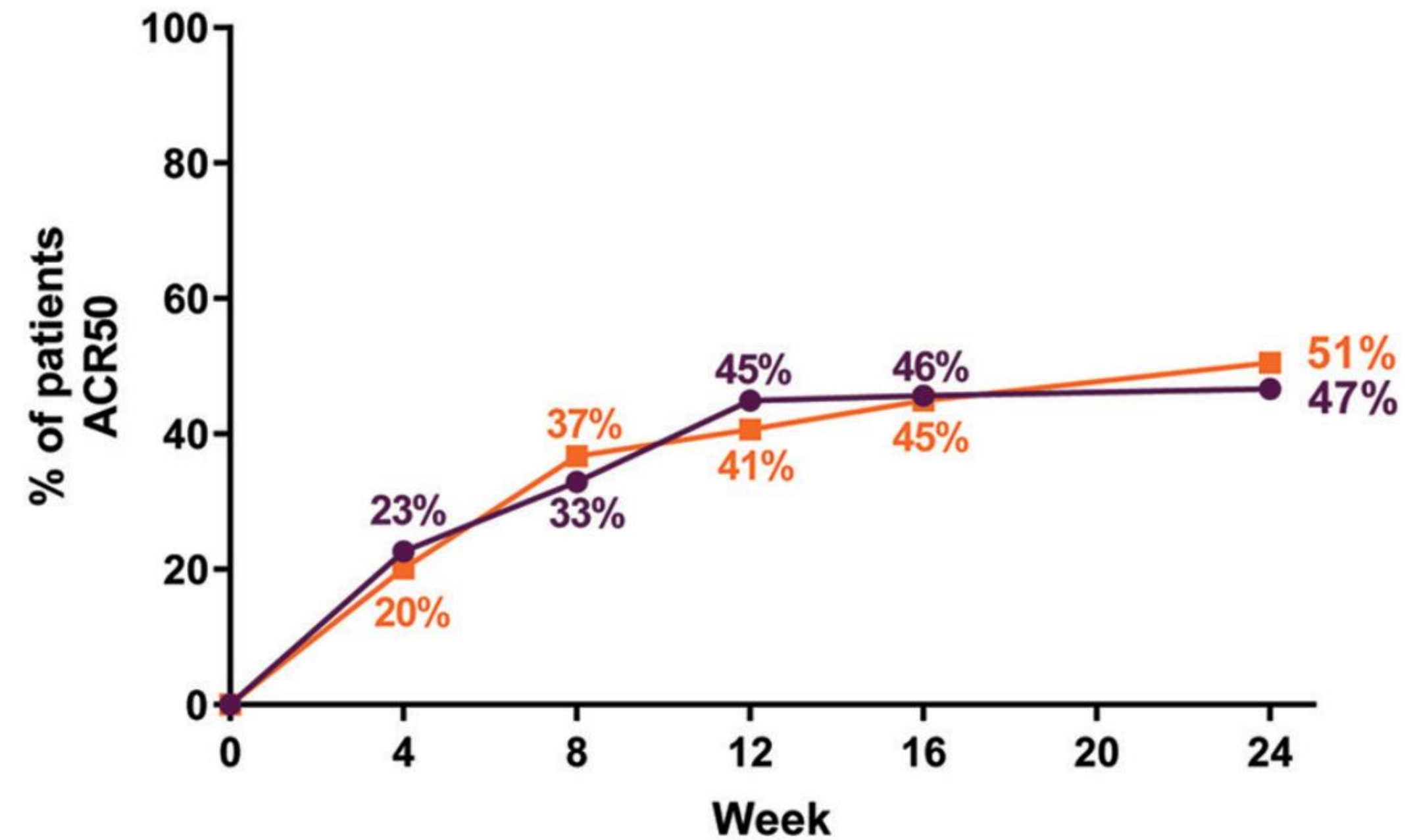


In PsA, IL-17A inhibitors are superior to TNF inhibitors in treating psoriasis, effects on arthritis are similar

psoriasis



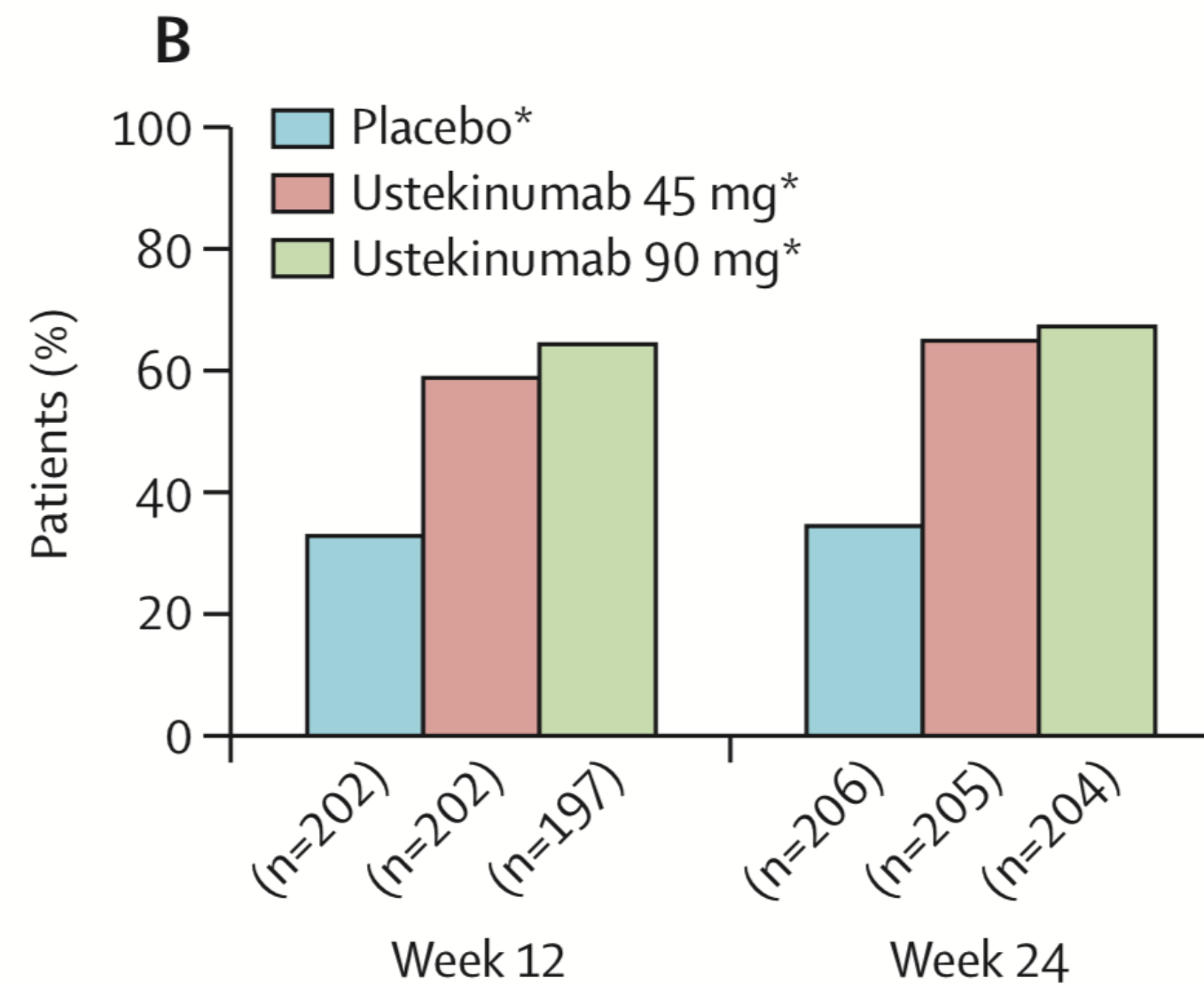
arthritis



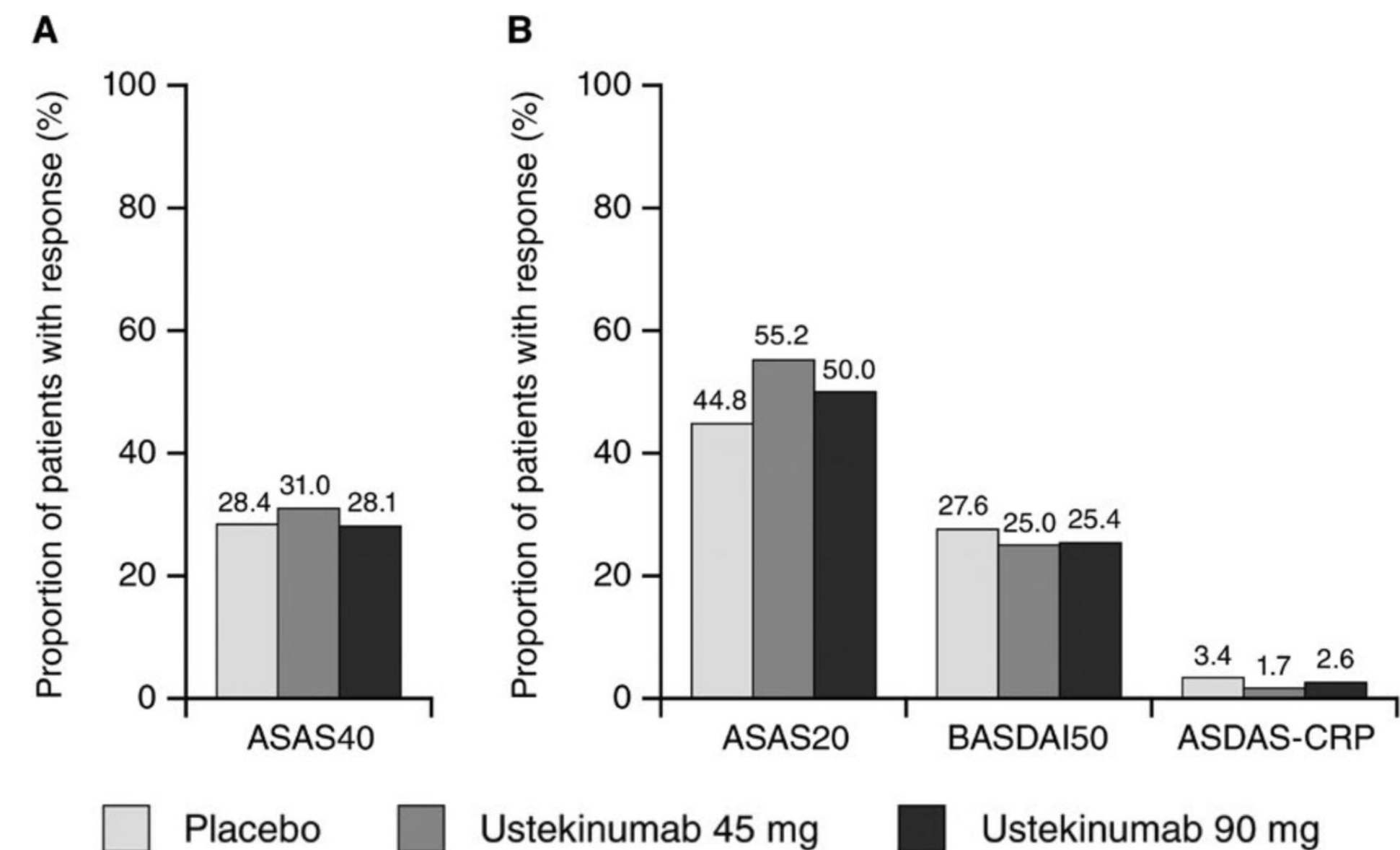
SPIRIT H2H: RCT in active PsA
IL-17A inhibitor (Ixekizumab) vs. TNF inhibitor (Adalimumab)

IL-23 inhibitors are effective in treating peripheral arthritis in PsA but not axial inflammation axSpA/AS

Psoriatic arthritis (week 12, 24)



AS (week 24)

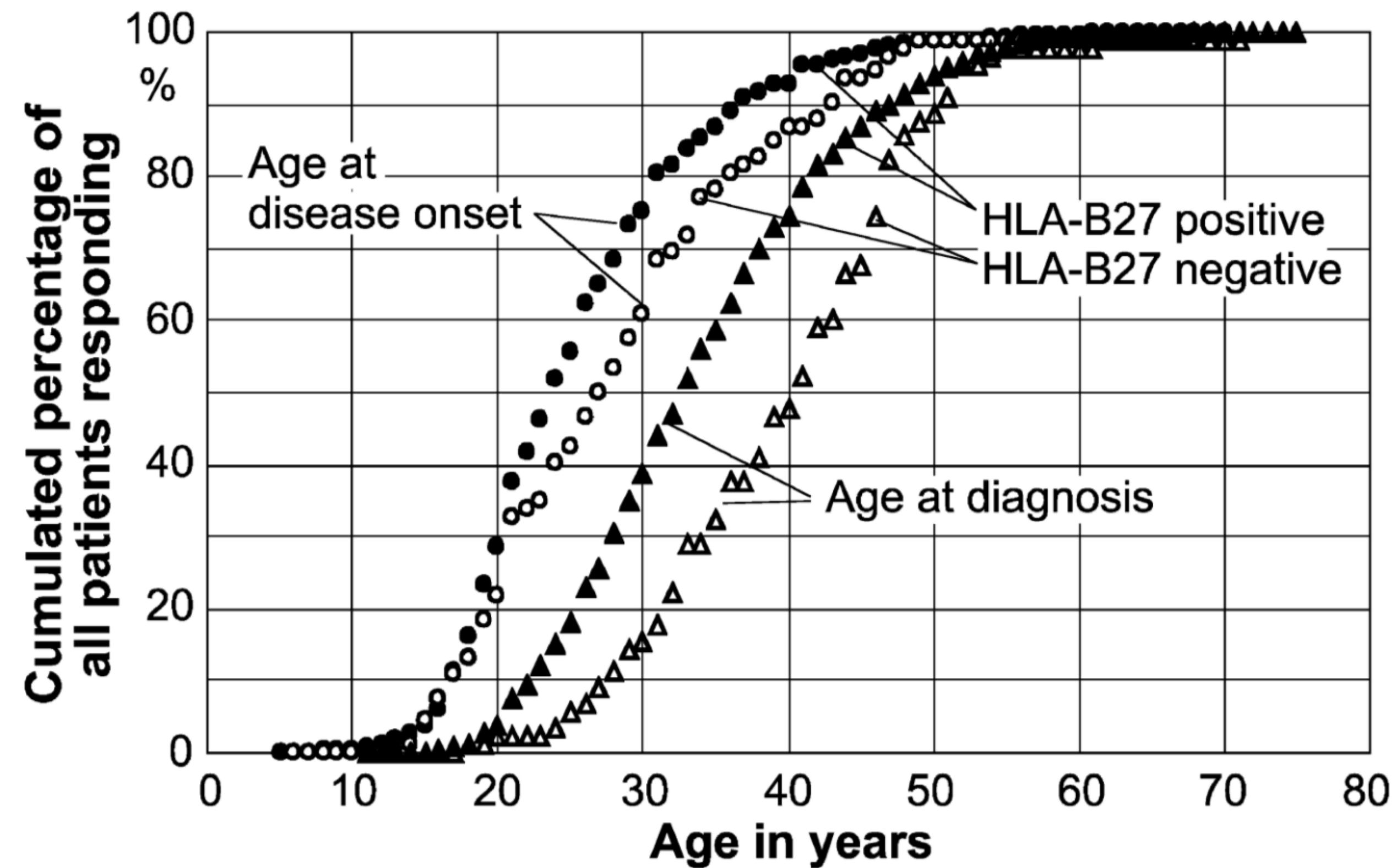


RCTs of Ustekinumab (anti-IL-12/23) in active SpA and active AS
same dosing: 45 mg, 90 mg or placebo SC at week 0, 4, 16

Treatment of SpA

- non-pharmacological interventions:
 - physical therapy (important role in axial SpA/AS)
 - weight loss (improves treatment responses in PsA)
 - smoking cessation (risk factor for radiographic progression in AS)
- management of risk factors for cardiovascular disease
- care for SpA patients on biologics and JAK inhibitors
 - vaccinations
 - baseline pneumococcal and shingles vaccines, annual flu shot
 - no live vaccines
 - awareness of specific drug side effect profiles
 - TNFi - mycobacterial infections, MS and lupus-like disease
 - IL-17Ai - candida infections
 - JAKi - shingles

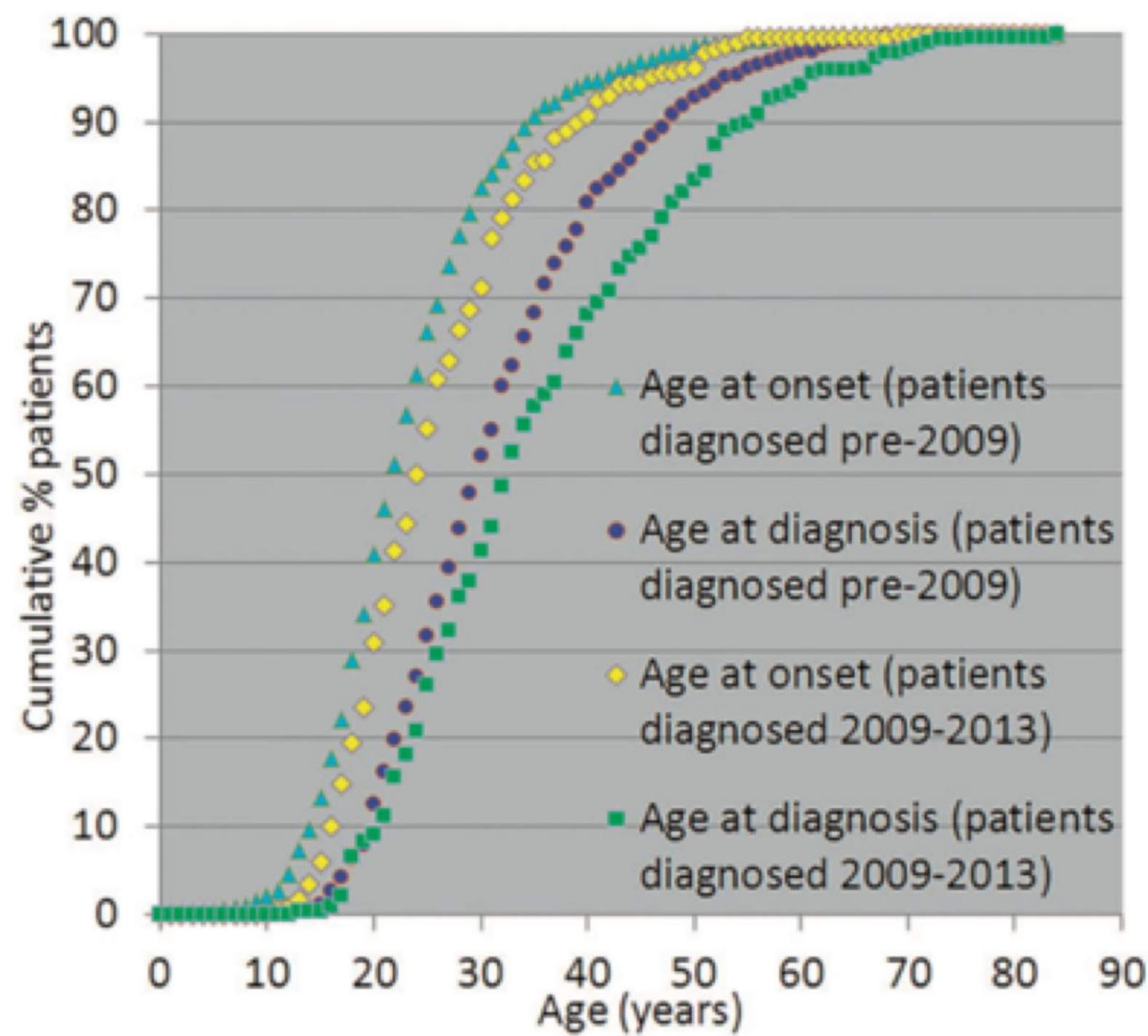
Time from symptom onset to diagnosis of axial SpA/AS: 5-10 years



Is the diagnostic delay getting shorter? No.

Bath/Norwich

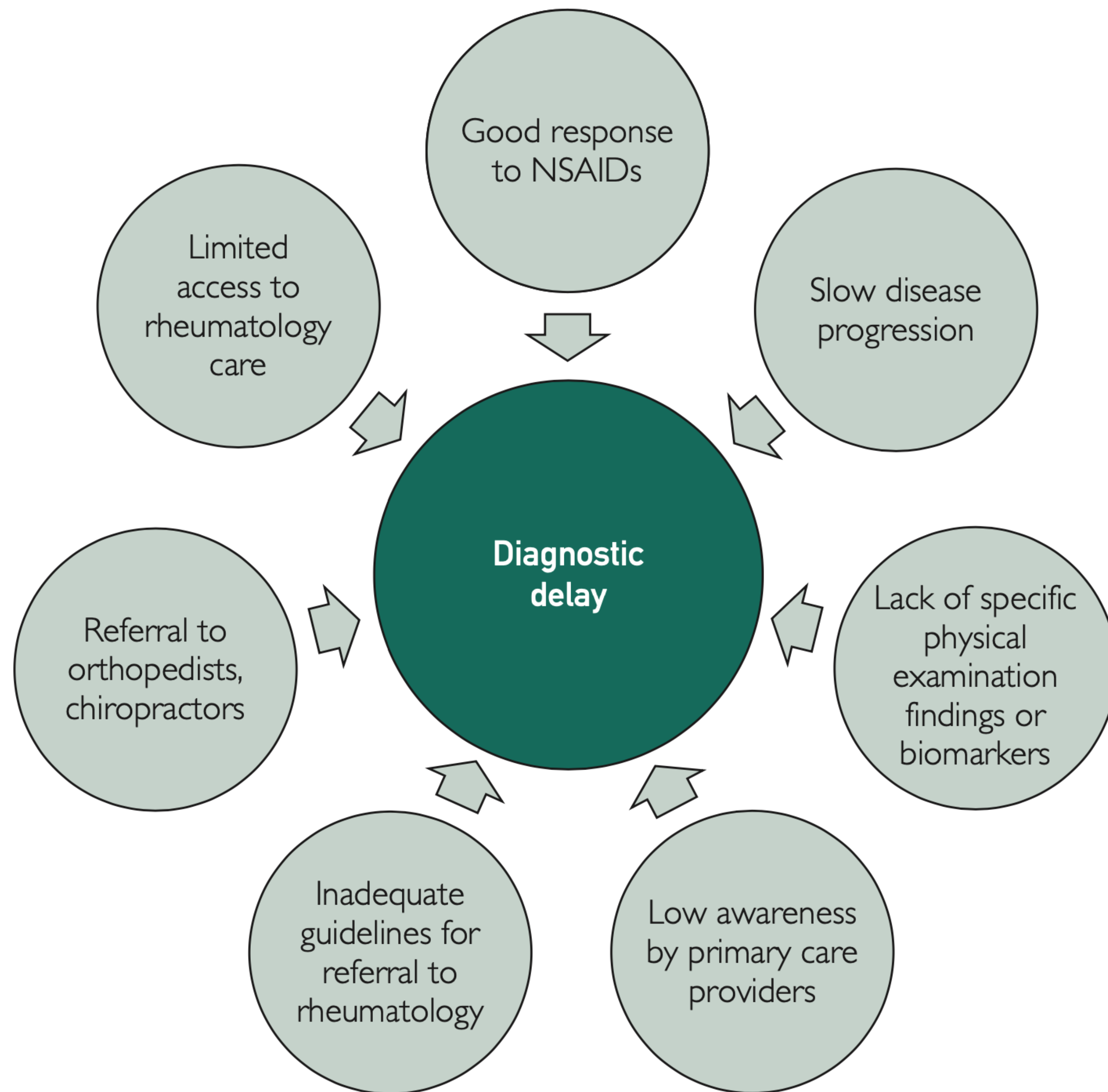
UK



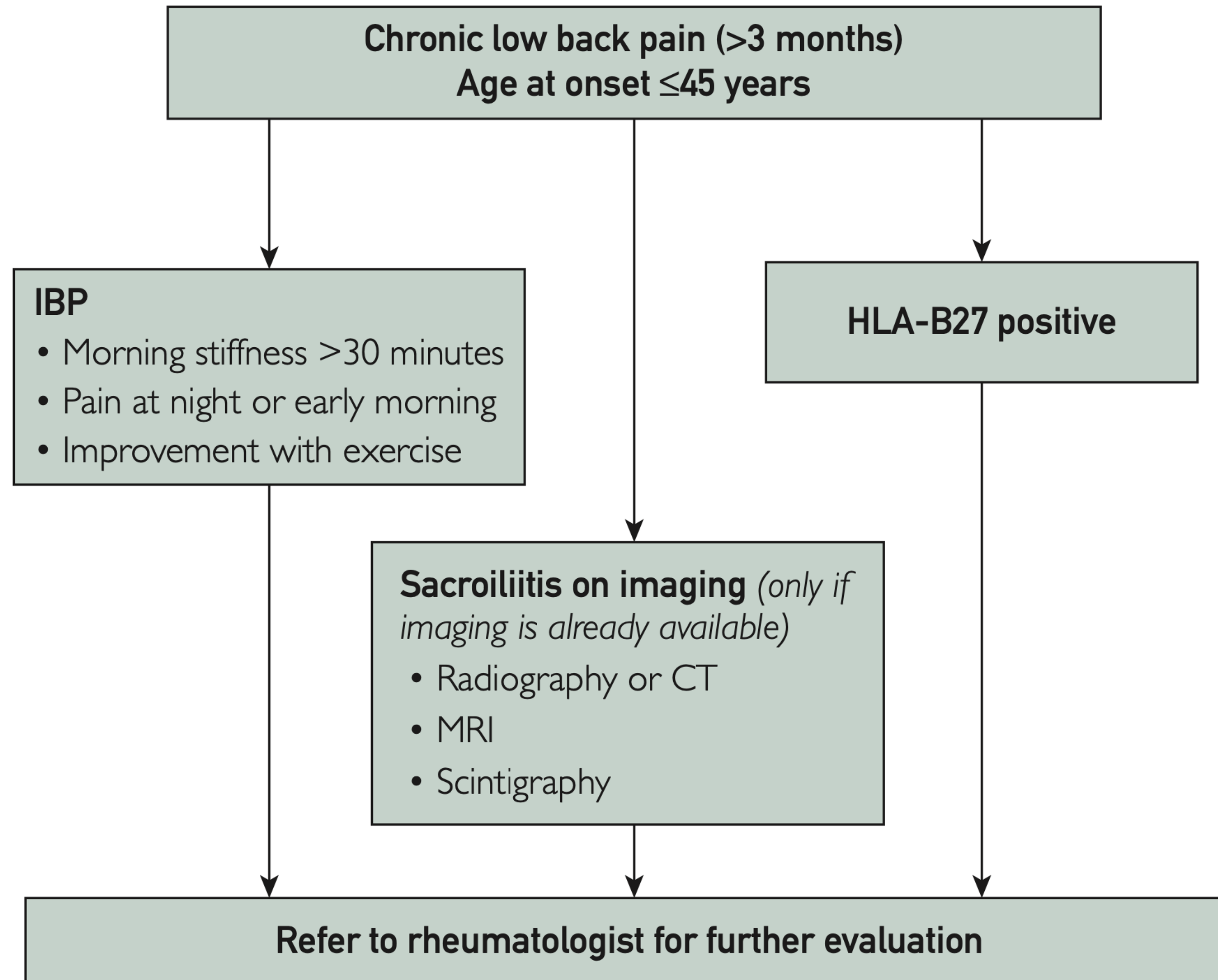
PROCLAIR

Patient-Reported Outcomes with CLAIMs data
for health services research in Rheumatology
Germany

axSpA diagnostic delay		
	mean [SEP][years]	median [SEP][years]
1996 - 2005	6.3	2.6
2006 - 2015	7.4	2.7



Pre-screening increases the likelihood of axial SpA/AS from ~5% to ~35%



MOC Reflective Statement

- SpA = family of inflammatory rheumatic diseases with overlapping clinical features,
AS and psoriatic arthritis are prototypic SpA diseases
- axial SpA:
 - includes AS + non-radiographic axial SpA
 - similar symptoms and disease burden
 - equally common in men and women
 - long diagnostic delay (5-10 years)
- SpA treatment differs from RA, established important therapies:
 - NSAIDs
 - TNF inhibitors
 - IL-23/IL-17A pathway inhibitors
 - JAK inhibitors
- in young adults with chronic back pain → consider axial SpA

References

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- Khmelinski N et al. (2018) The Role of Imaging in Diagnosing Axial Spondyloarthritis. *Front Med (Lausanne)* 5:106
- Coates L et al. (2022) Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021. *Nat Rev Rheumatol* 18:465-479
- Ramiro S et al. (2023) ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. *Ann Rheum Dis* 82:19-34
- Navarro-Compan et al. (2025) Axial spondyloarthritis. *Lancet* 405:159-72