Axial Spondyloarthritis: Why Should the Internists Care?

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Conflicts of Interest

Research Grants, and/or Advisory Boards, and/or consultant for the following:

AbbVie, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Glaxo Smith Klien, Eli Lilly, Janssen, Novartis, Pfizer, UCB

Why Should the Internists Care About Axial Spondyloarthritis (axSpA)?

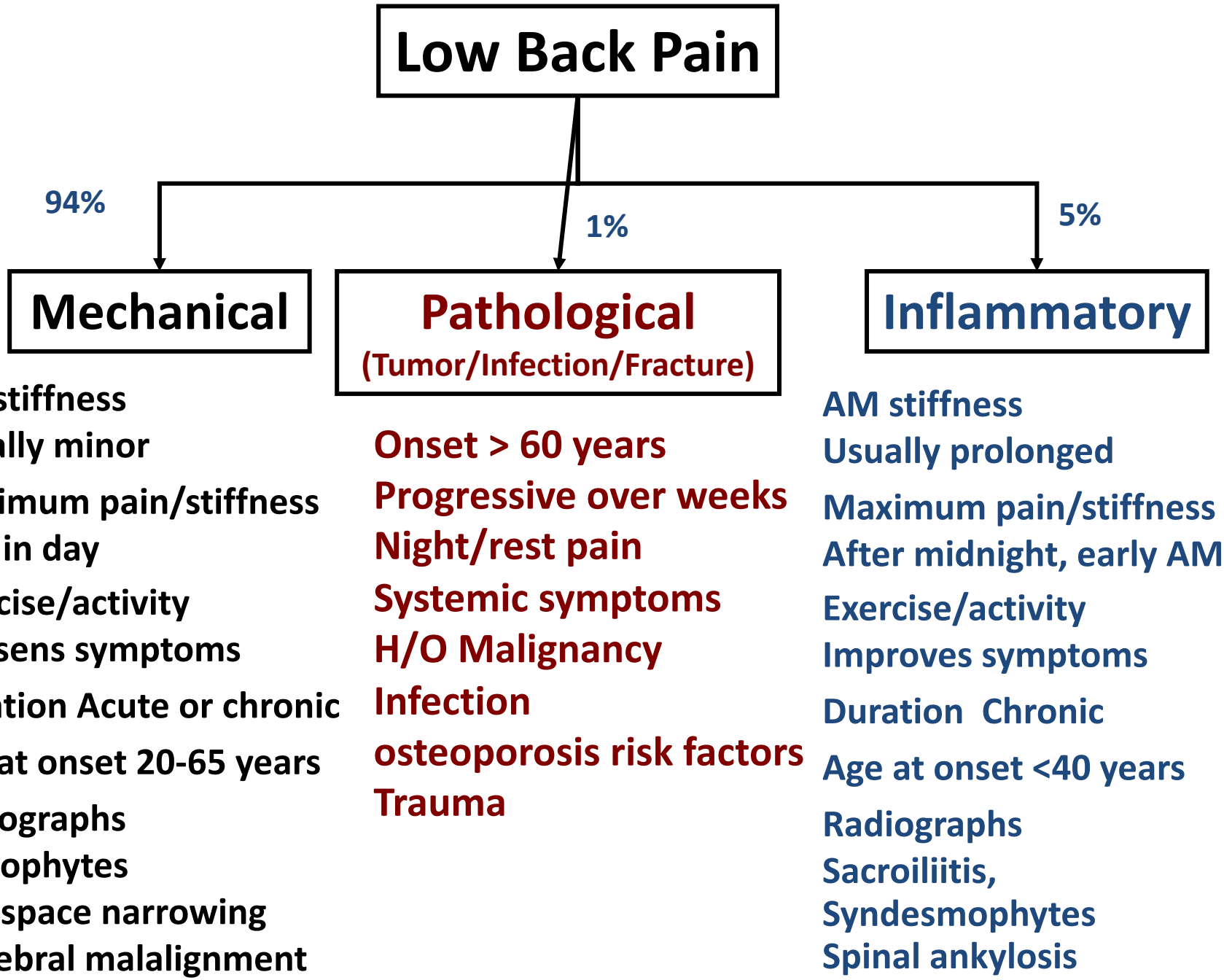
1. Because not every back pain is ‘mechanical’
2. Because axSpA is much more common than you think
3. Because axSpA is (*probably frequently*) missed in internists’ offices
4. Because axSpA has great treatment options, and if treated early it may prevent future progression
5. Because axSpA is rewarding to diagnose and treat

Case History

- 44-year old lawyer, very healthy & active – completed Ironman Canada in July 2013
- Post Ironman, C/O pain in the left buttock
- Next 18 months multiple visits to PCP, sports medicine, PT
- Tried rest, PT, acupuncture, massage, analgesics, muscle relaxers, US guided triamcinolone injection, prolotherapy – all failed, though NSAIDs worked
- MRI Pelvis: “Minimal tendinopathy of the origin of the left conjoint Hamstring tendon, no tear, left SI joint normal”
- Arthritis panel HLA B27+, Referral to rheumatology

Case History

- Rheum Fellow's note:
  - "Developed low back & left buttock pain in mid 20's, pain would awaken him at night, rest would worsen the pain & activity would improve it. Ibuprofen & naproxen relived the pain completely. Morning stiffness 30 minutes, also suffered from chronic bilateral Achilles tendon pains without swelling
  - No uveitis, psoriasis, IBD
  - O/E: Tender on bilateral Achilles tendon insertions, tender on bilateral SI joints & on left ischeal tuberosity & piriformis area
- X-ray SI joints: Normal


Low Back Pain
94%
1%
5%
Mechanical
Pathological
(Tumor/Infection/Fracture)
Inflammatory
AM stiffness
Usually minor
Maximum pain/stiffness
Late in day
Exercise/activity
Worsens symptoms
Duration Acute or chronic
Age at onset 20-65 years
Radiographs
Osteophytes
Disc space narrowing
Vertebral malalignment
Onset > 60 years
Progressive over weeks
Night/rest pain
Systemic symptoms
H/O Malignancy
Infection
osteoporosis risk factors
Trauma
AM stiffness
Usually prolonged
Maximum pain/stiffness
After midnight, early AM
Exercise/activity
Improves symptoms
Duration Chronic
Age at onset <40 years
Radiographs
Sacroiliitis,
Syndesmophytes
Spinal ankylosis

Inflammatory Back Pain

Feature	Odds Ratio
Age at onset < 40	9.9
Insidious Onset	12.7
Pain at night (with improvement upon getting up)	20.4
Improvement with exercise	23.1
No improvement with rest	7.7

Best trade-off if four or more of the above five parameters are fulfilled (sensitivity 79.6%; specificity 91.7%)
Positive Likelihood Ratio = 79.6/(100-91.7) = 9.6

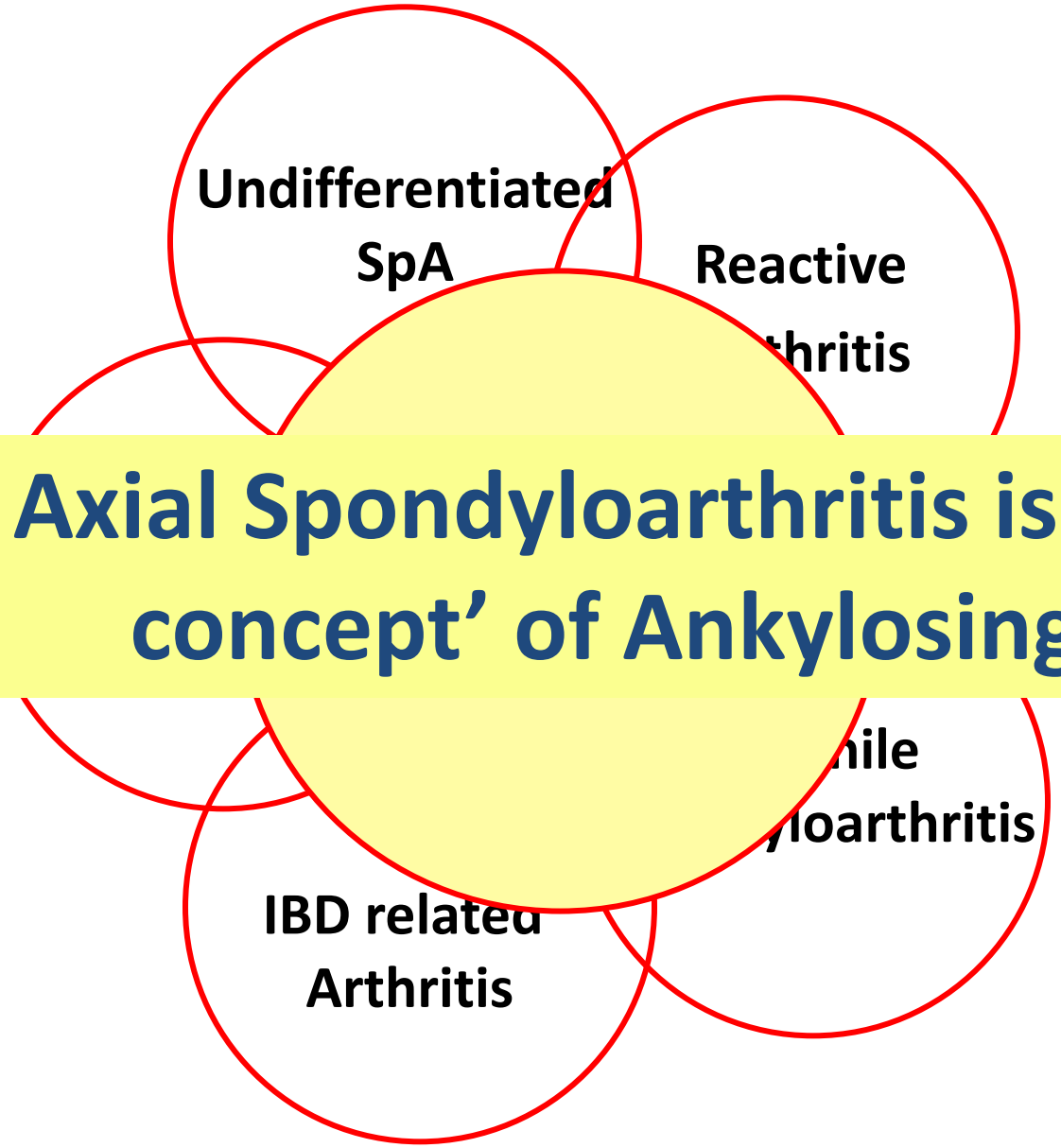
Sieper J. et al. Ann Rheum Dis. 2009 Jun;68(6):784-8.

- While IBP should raise the suspicion of spondyloarthritis, it does ***not*** make the diagnosis
- Only 15% of IBP patients have axial spondyloarthritis

So, what is '**Axial** Spondyloarthritis'?

Clarification of Nomenclature

What is Spondyloarthritis?



SpA are a group of rheumatic disorders that share several common factors:

1. **Synovitis *and***
2. **HLA-B27**
3. **Usually RF -ve**

Axial Spondyloarthritis is the 'Expanded concept' of Ankylosing Spondylitis

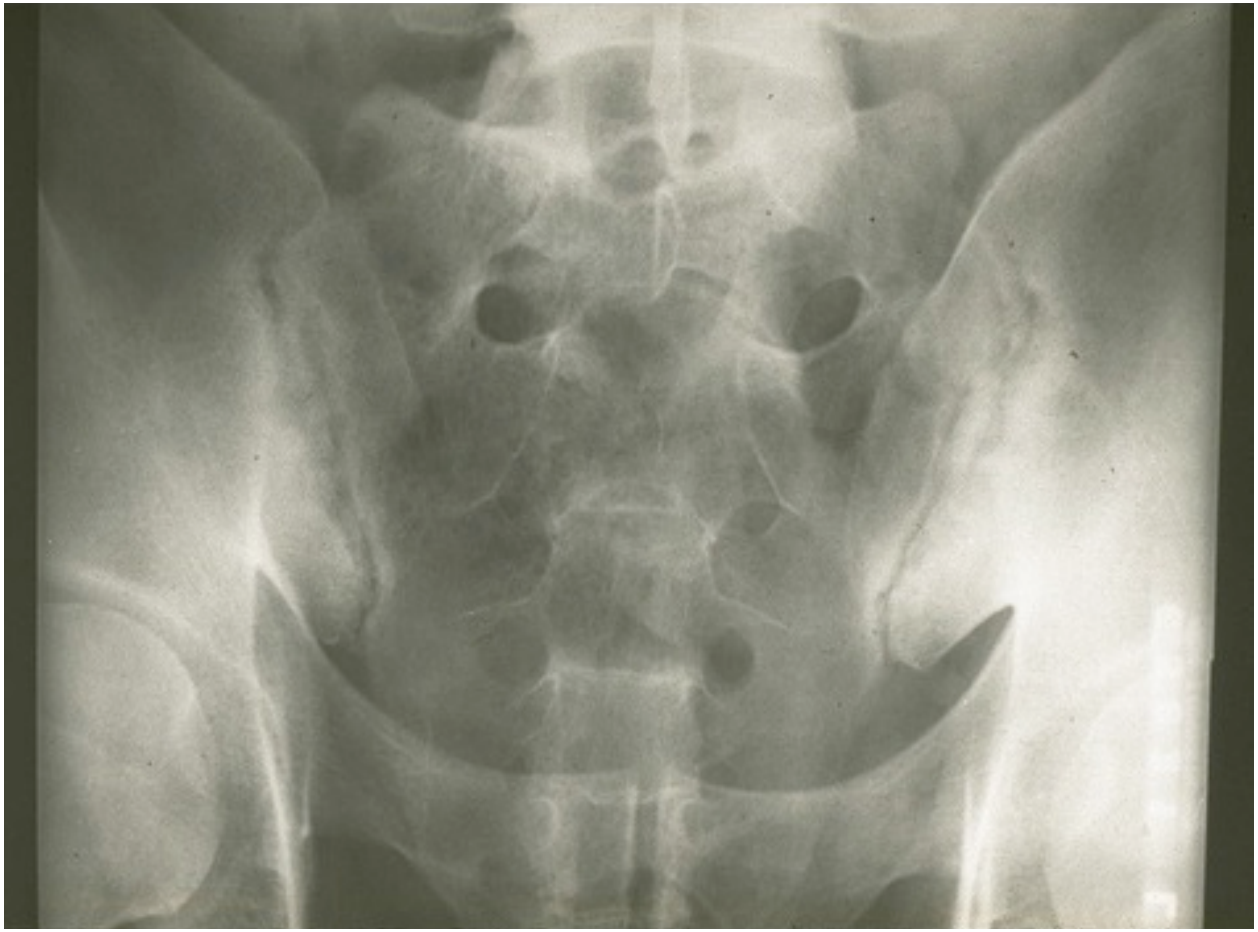
Ankylosing Spondylitis: Definition

- A chronic, systemic, inflammatory disorder involving the SI joints, spine & often hips
- Axial joints are *always* involved, peripheral joints are frequently affected
- Characterized by 'inflammatory' back pain, loss of spinal mobility

- In severe cases, extensive fusion (ankylosis) of vertebrae can increase the risk of spinal deformity, fracture, & disability

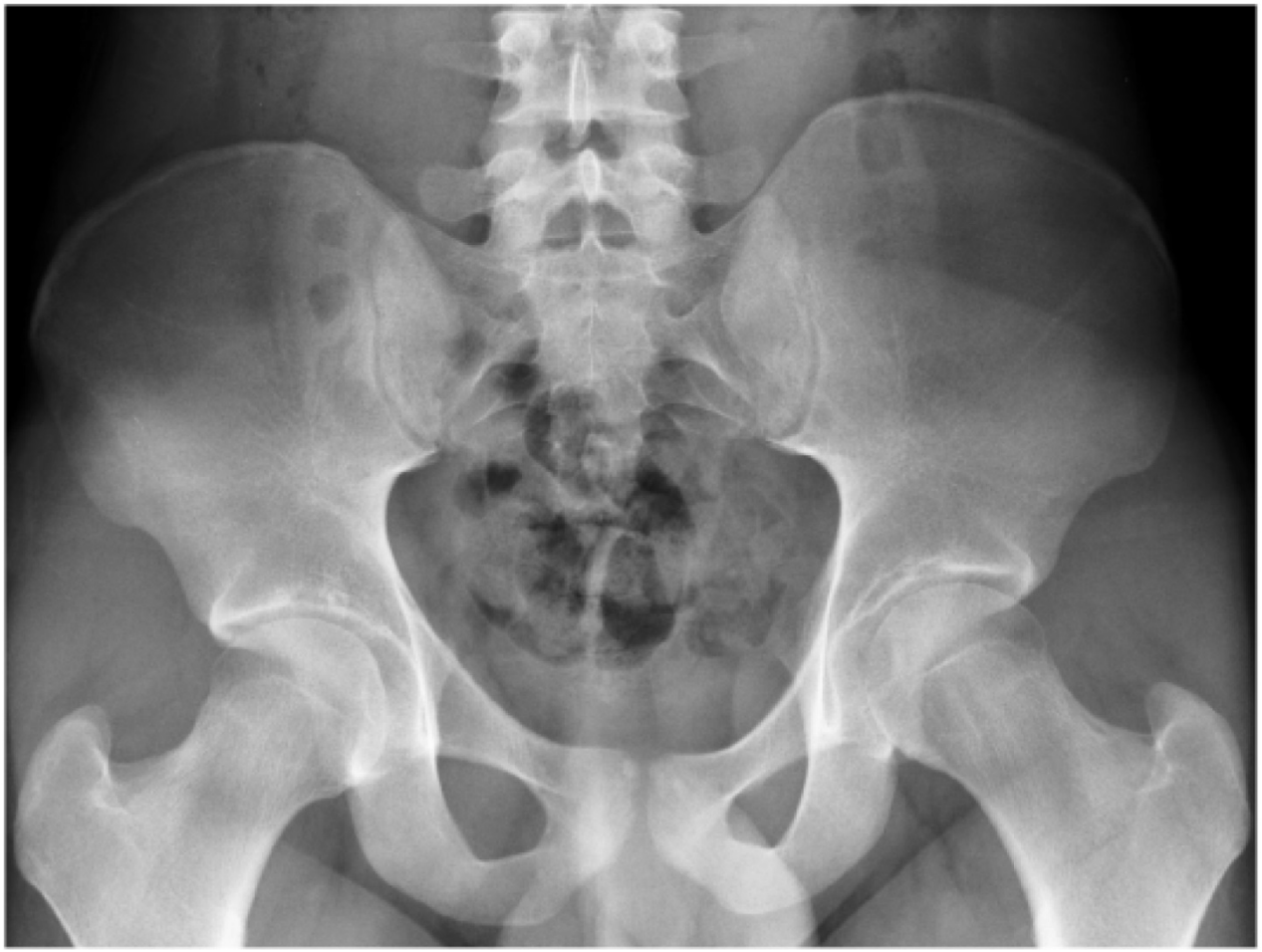
Sacroiliitis on X-Ray is Essential for the Diagnosis of AS

- 'Definitive sacroiliitis' may take up to 10 years to appear on x-ray[1]
- Thus, AS can not be diagnosed by NY criteria for several years after onset

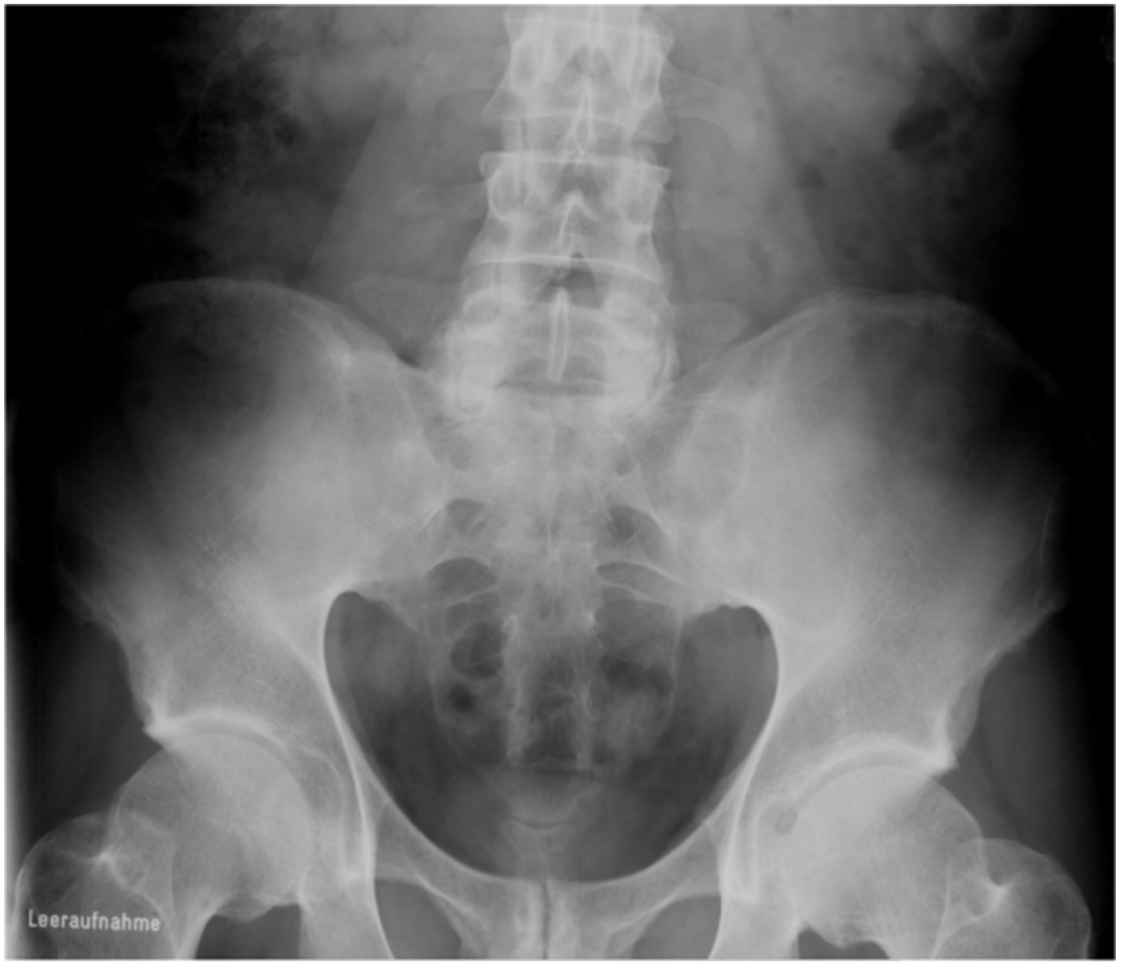


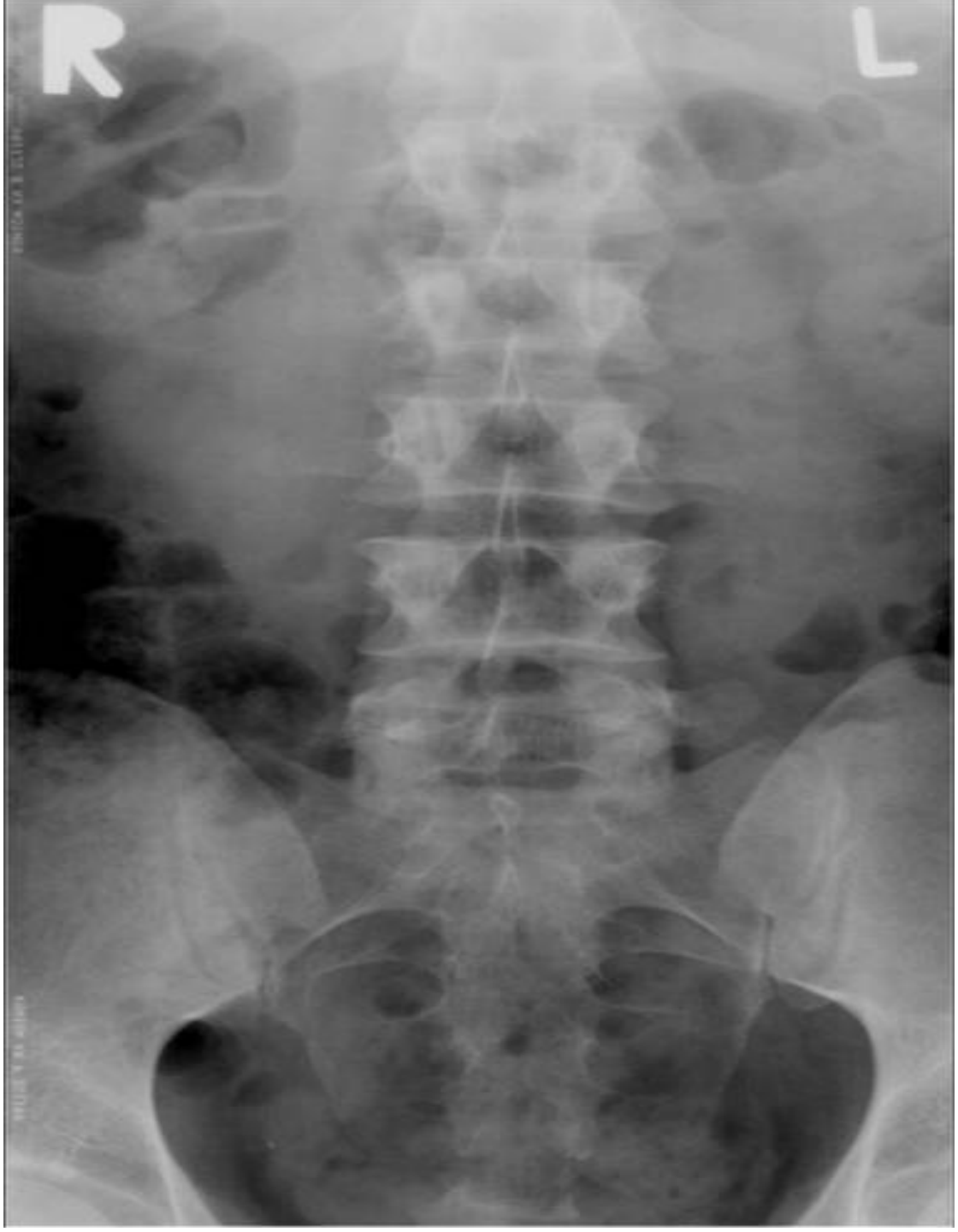
[1] Mau W., et al., *J Rheum* 1988; 15:1109-14.

Sacroiliitis Grade 0 (Normal)



Sacroiliitis Grade 4 Bilaterally





Does this person have sacroiliitis?

R Grade 1
L Grade 0

Variability in Sacroiliac Joint X-ray Reading

- Large inter and intra-observer variability in interpreting SI joint x-rays[1-3,4]
- Discordance between readers most likely between grades 1-2[4]
- Variability reported between central and local readers[5]

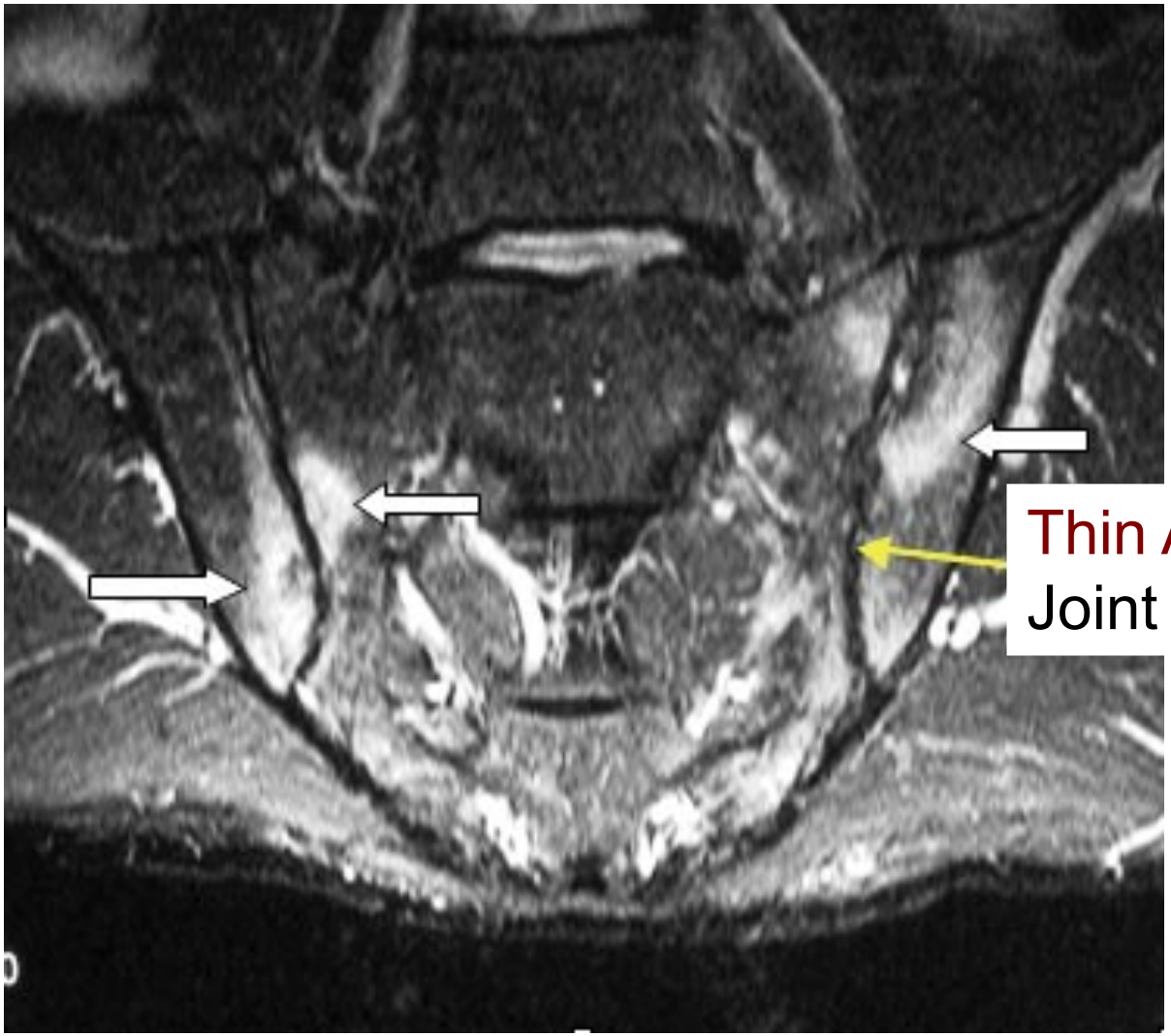
	Re-classified by Central Read	
Local Rheumatologist Read	**"Not AS"**	**AS**
AS patients (N=181)	**11.4%**	**88.6%**
"Not AS" patients (N=148)	**84.5%**	**15.5%**

The 'Kappa' (agreement) for x-ray sacroiliitis grade 1-2 between 'experts' is 0.35-0.45

[1]Hollingsworth,et al. J Rheumatol 1983;10:247-54. [2]Yazici et al. Ann Rheum Dis 1987; 46:139-45. [3]Taylor et al. Br J Rheumatol 1991; 30:330-5. [4]van Tubergen et al. Ann Rheum Dis 2003;62:519–525 [5]Poddubnyy et al. Ann Rheum Dis 2011;70:1369-74.

Sacroiliitis Can Be Diagnosed By MRI Scan Before Seen on X-rays

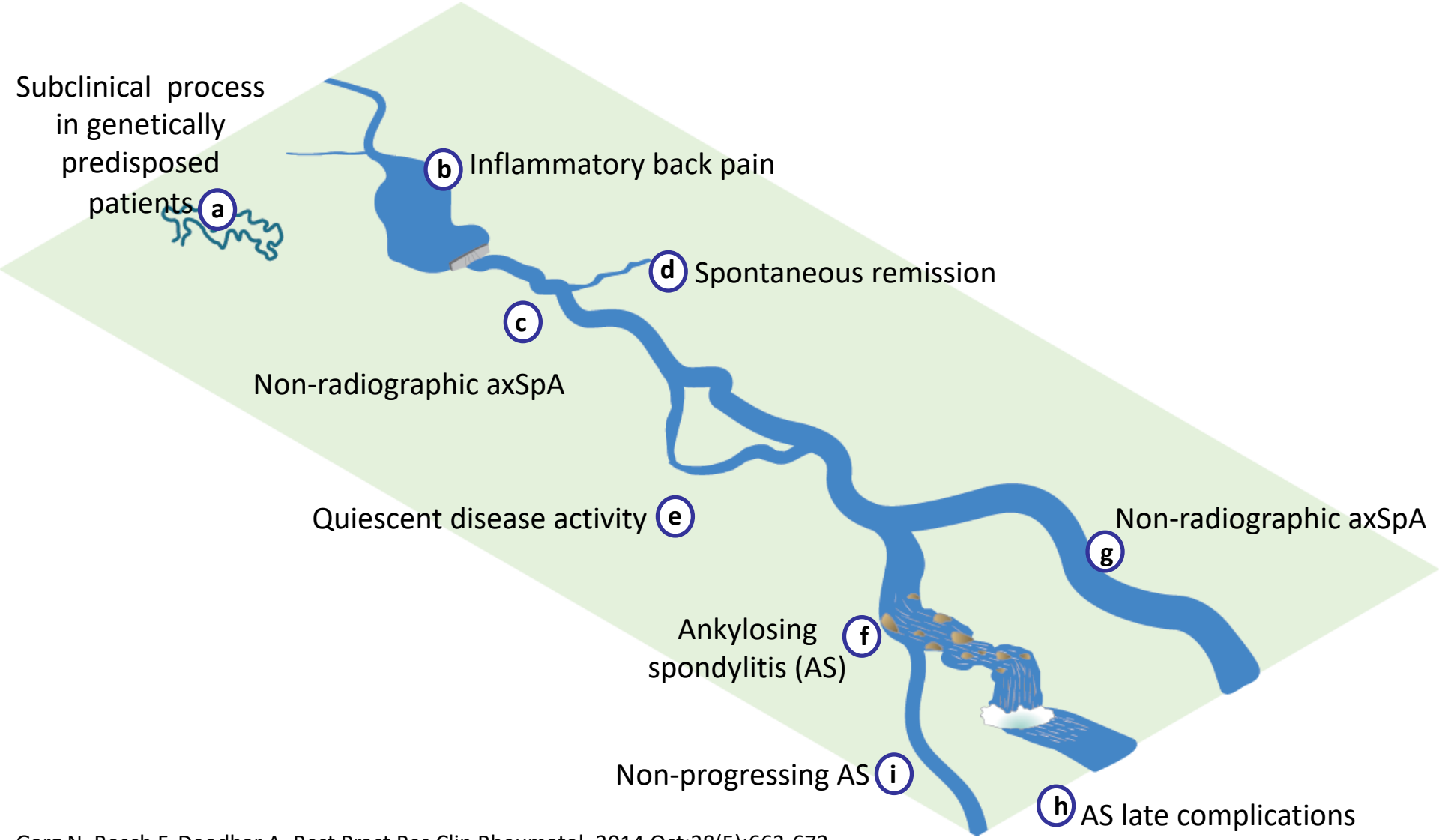
Thick Arrows: Subchondral marrow inflammation shown by increased MRI signal on fat suppressed T2 weighted image (STIR)



Diagnosis of axSpA Depends on History, PE & Targeted Investigations

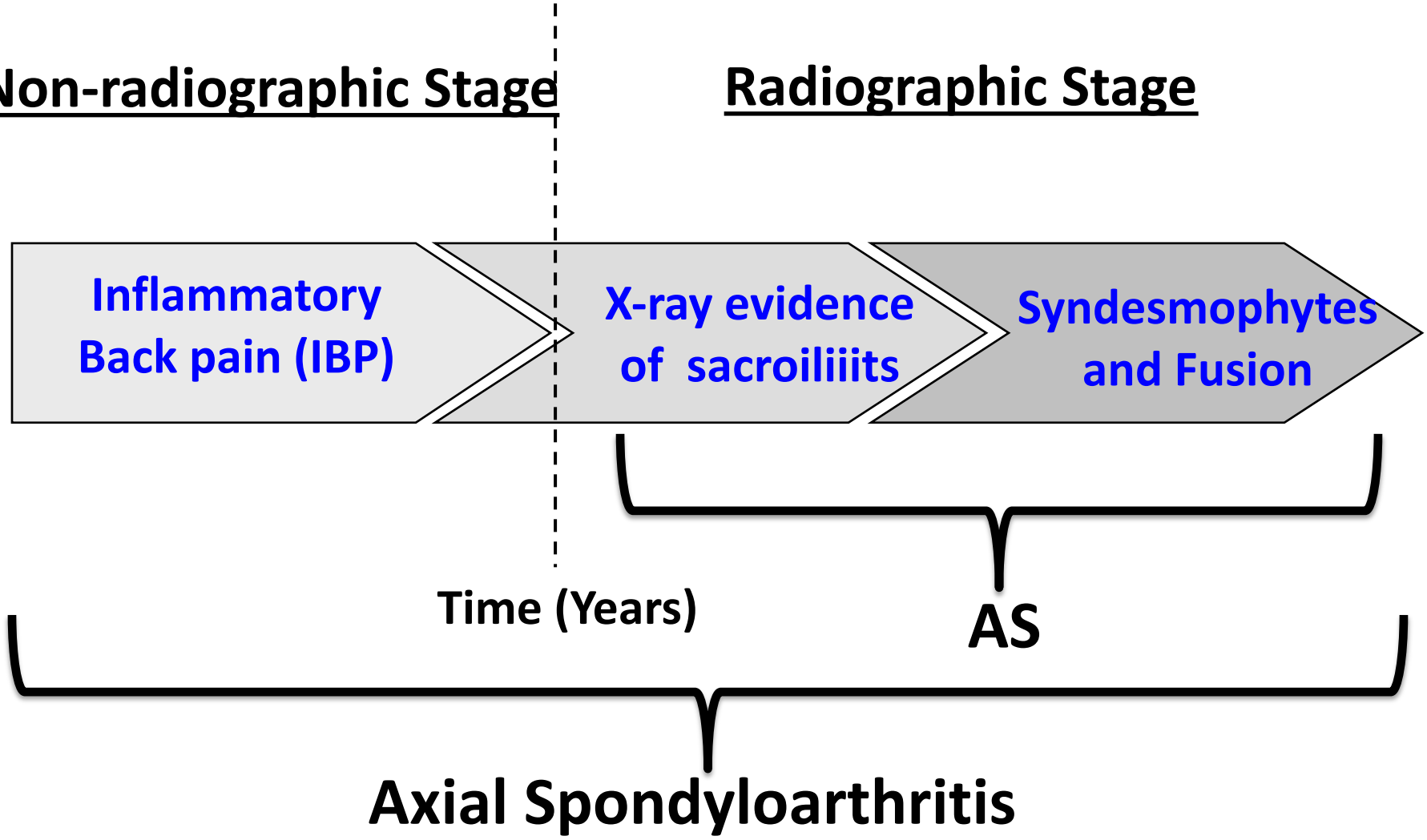
- History:
  - Inflammatory back pain
  - Inflammatory peripheral arthritis: asymmetric, oligoarticular, LL > UL
  - Inflammatory Bowel Disease, Psoriasis, Uveitis
  - Non-traumatic plantar fasciitis, Achilles tendonitis
- Physical Exam:
  - Inflammatory arthritis (*true* swelling), asymmetric, oligoarticular, LL
  - Uveitis, psoriasis, *true* enthesitis
  - (Spinal examination is not very helpful)
- Targeted Investigations
  - CRP
  - Plain X-ray pelvis to look foir sacroiliitis
  - HLA-B27
  - (*Rarely* MRI SI joints)

Natural History of Axial Spondyloarthritis



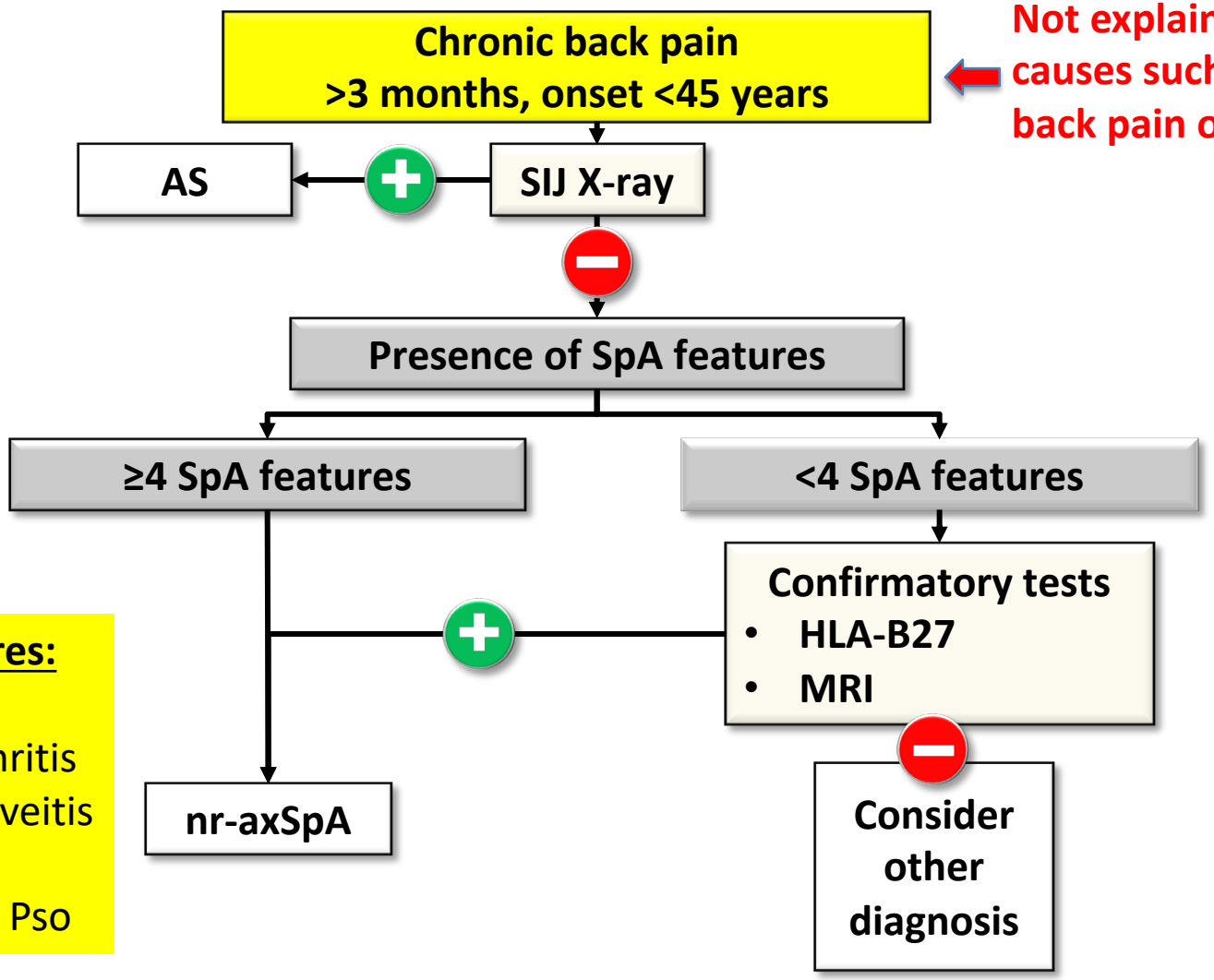
Garg N. Bosch F. Deodhar A. Best Pract Res Clin Rheumatol. 2014 Oct;28(5):663-672.

Axial Spondyloarthritis and AS: Clarification of the Nomenclature



Rudwaleit M. et al. *Arthritis Rheum*. 2005; 52:1000-1008.

How Do Rheumatologists Diagnose axial SpA in Practice?



SpA Features:
IBP
Inflam Arthritis
IBD, Pso, Uveitis
Enthesitis
F/H of IBD, Pso

van den Berg R, et al. Ann Rheum Dis 2013;72:646–653

How common is axial spondyloarthritis?

Studies on ‘Epidemiology of Axial SpA’

NHANES 2009-2010

National Health & Nutrition Examination Survey

NHANES: "To monitor the health & nutritional status of the civilian, non-institutionalized population of the US"

Mobile Examination Centers

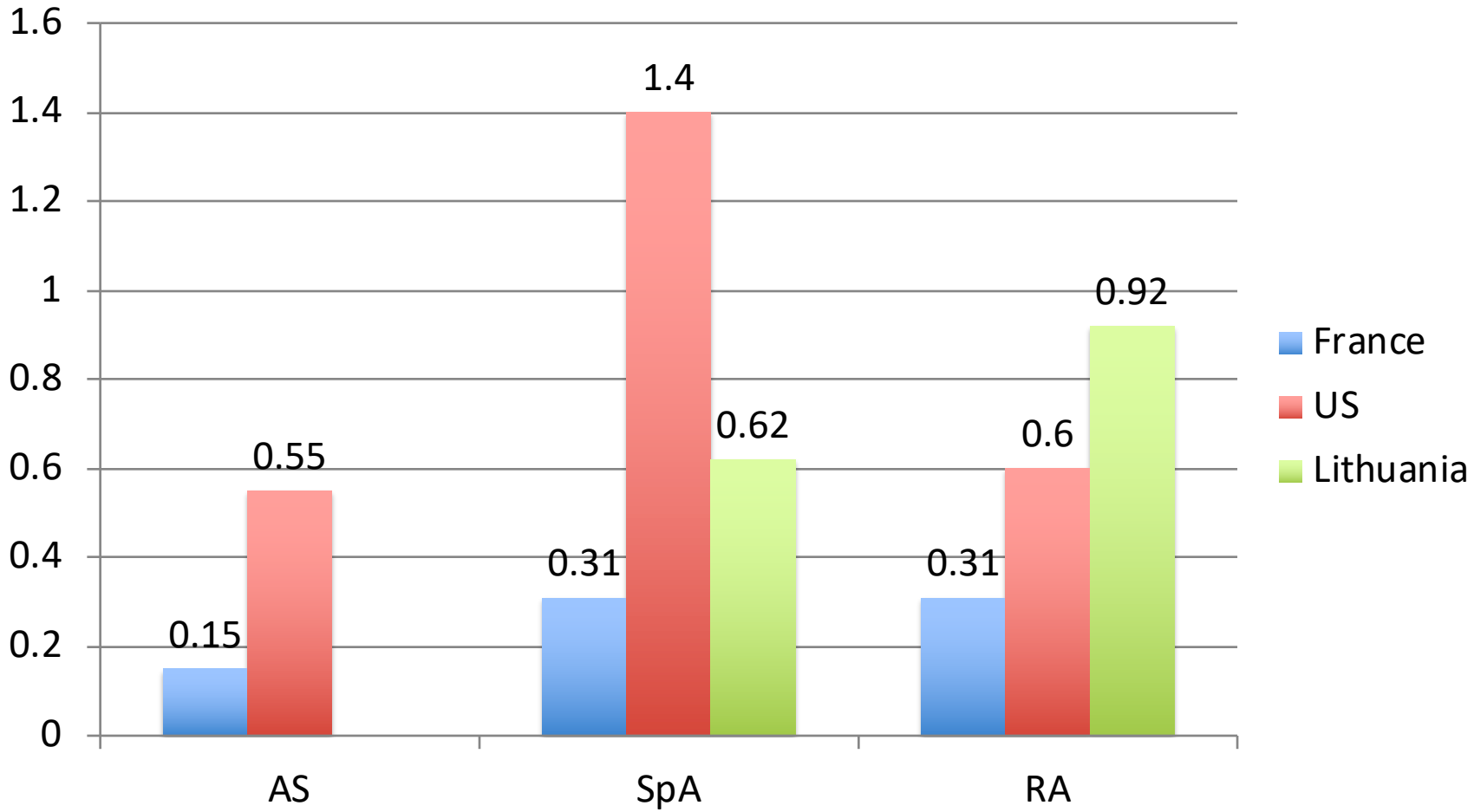
Centers for Disease Control and Prevention
National Center for Health Statistics

How common is axSpA in the US?

- National Health & Nutrition Examination Survey (NHANES) 2009-10 on 5103 participant US residents showed
  - Chronic low back pain in 19.4%
  - Inflammatory back pain in 7%
  - HLA-B27 prevalence of 6%
    - Non-Hispanic whites (Caucasians): 7.5%
    - Mexican Americans: 4.6%
  - Axial Spondyloarthritis in 1% (0.9 – 1.4%)
  - Ankylosing Spondylitis in 0.5%

Weisman MH et al. Ann Rheum Dis. 2013;72:369-73.
Reveille JD et al. Arthritis Rheum. 2012 May;64(5):1407-11.

Axial SpA may be more common than Rheumatoid Arthritis in the US



France: Saraux A, et al. Ann Rheum Dis 2005;64:1431-5. Guillemin F, et al. Ann Rheum Dis 2005;64:1427-30.

Lithuania: Adomaviciute D, et al. Scand J Rheumatol 2008;37:113-9.

USA: Helmick CG, et al. Arthritis Rheum 2008;58:15-25.

If axSpA is more common than RA in the US, why is it missed?

- axSpA patients are seen by others before rheumatologists
  - Family practice, *Internal medicine*
  - Chiropractors, Osteopaths, Physical therapy
  - Orthopedic surgeons, Spine surgeons, Neurosurgeons, Physiatrists
  - Dermatologists, Ophthalmologists, Gastroenterologists
- Commonest MRI scan ordered is L Spine: SI joints missed
- Lack of reliable biomarkers other than HLA-B27

Clin Rheumatol (2016) 35:1769–1776
DOI 10.1007/s10067-016-3231-z

ORIGINAL ARTICLE

Ankylosing spondylitis diagnosis in US patients with back pain: identifying providers involved and factors associated with rheumatology referral delay

Atul Deodhar[1,3] · Manish Mittal[2] · Patrick Reilly[2] · Yanjun Bao[2] · Shivaji Manthena[2] · Jaclyn Anderson[2] · Avani Joshi[2]

- Truven Healthcare Database: 127 million patients
- *63% of AS diagnosis is made by non-rheumatologists*
- When patients with AS diagnosis is referred to rheumatologists, the *diagnosis is confirmed only in 42%* of cases

Diagnostic Prevalence of Ankylosing Spondylitis Using Computerized Health Care Data, 1996 to 2009: Underrecognition in a US Health Care Setting

Jeffrey R Curtis, MD; Leslie R Harrold, MD, MPH; Maryam M Asgari, MD, MPH;
Atul Deodhar, MD; Craig Salman; Joel M Gelfand, MD, MSCE; Jashin J Wu, MD; Lisa J Herrinton, PhD

Perm J 2016 Fall;20(4):15-151

- Kaiser Permanante Northern California Database
- Point prevalence of 'any' spondyloarthritis: 0.2%, for AS 0.1%, *that is 1/10th of real prevalence*
- *Less than 50%* of those diagnosed, were *referred to rheumatology*

ARTHRITIS & RHEUMATOLOGY
Vol. 68, No. 7, July 2016, pp 1669–1676

Frequency of Axial Spondyloarthritis Diagnosis Among Patients Seen by US Rheumatologists for Evaluation of Chronic Back Pain

Atul Deodhar,[1] Philip J. Mease,[2] John D. Reveille,[3] Jeffrey R. Curtis,[4] Su Chen,[5] Kailash Malhotra,[5] and Aileen L. Pangan[5]

- *Referral Strategy*: If patients with CBP starting before age 45 with either a) Inflammatory back pain, b) HLA B27 positivity, or c) Sacroiliitis: *Prevalence of axSpA is 46%*
- There is a *14 year delay in axSpA diagnosis* in the US

Combined conclusions of US epidemiologic studies on axSpA

- Population-based studies show prevalence of axSpA is 1%, and prevalence of AS is 0.5% (RA is 0.6%)
- However, diagnostic prevalence of axSpA is 1/10th of population prevalence, indicating that axSpA ('diluted' amongst mechanical back pain) is under-recognized
- In the US, delay in diagnosis from onset of symptoms is 14 yrs
- 63% of AS in US are diagnosed by non-rheumatologists, and when re-examined by rheumatologists, only 40% are confirmed
- axSpA diagnosis is missed by rheumatologists too – 47% of patients were existing patients of rheumatologists who remained 'undiagnosed' for a long time

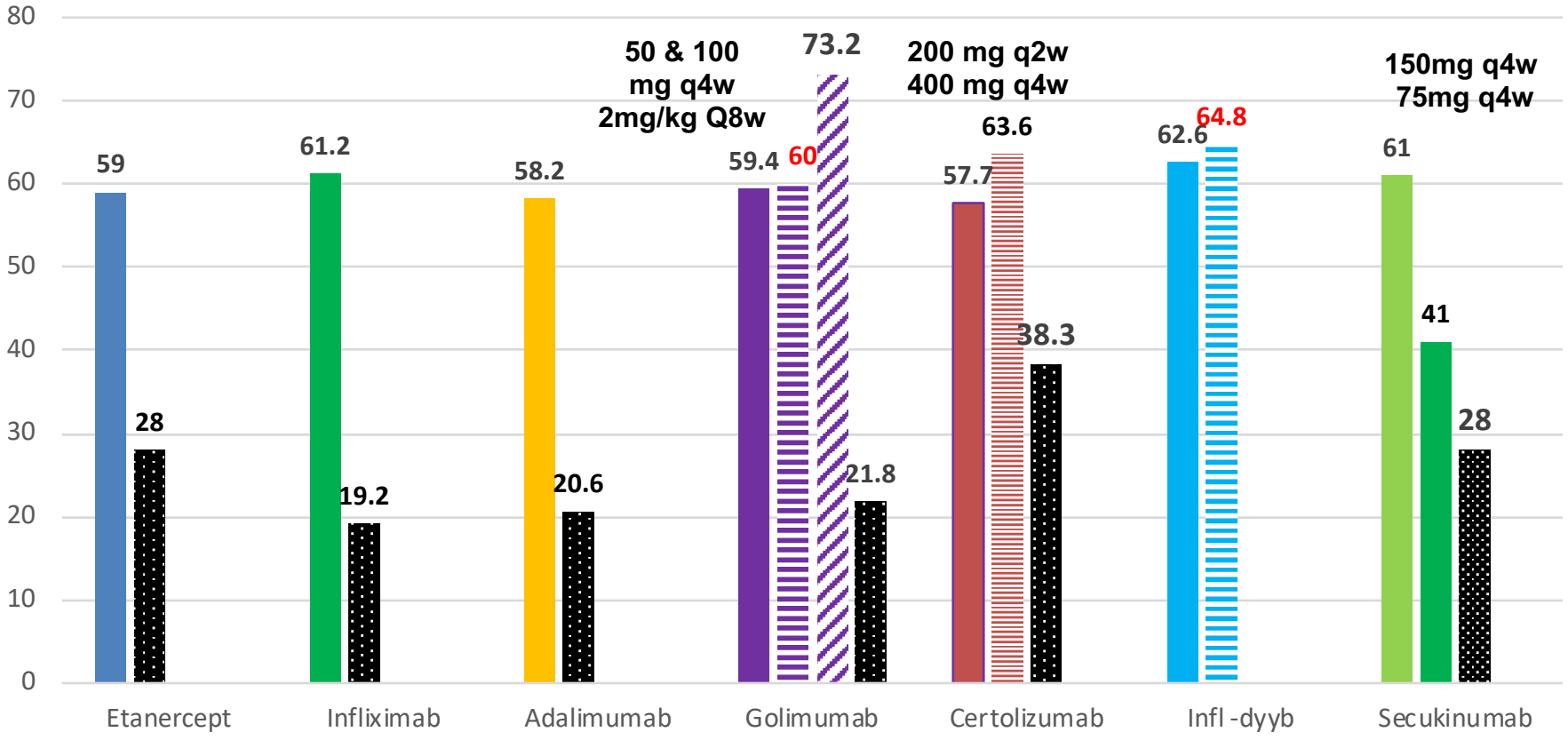
Deodhar A. et al. Clin Rheumatol 2016;35:1769-76
Curtis J….Deodhar A. et al. Per J. 2016;20(4):15-151
Deodhar A. et al. Arthritis Rheumatol. 2016;68:1669-76

Why does it matter to find these patients early?

ASAS20 Responses in AS Patients Treated with TNFi & IL-17i

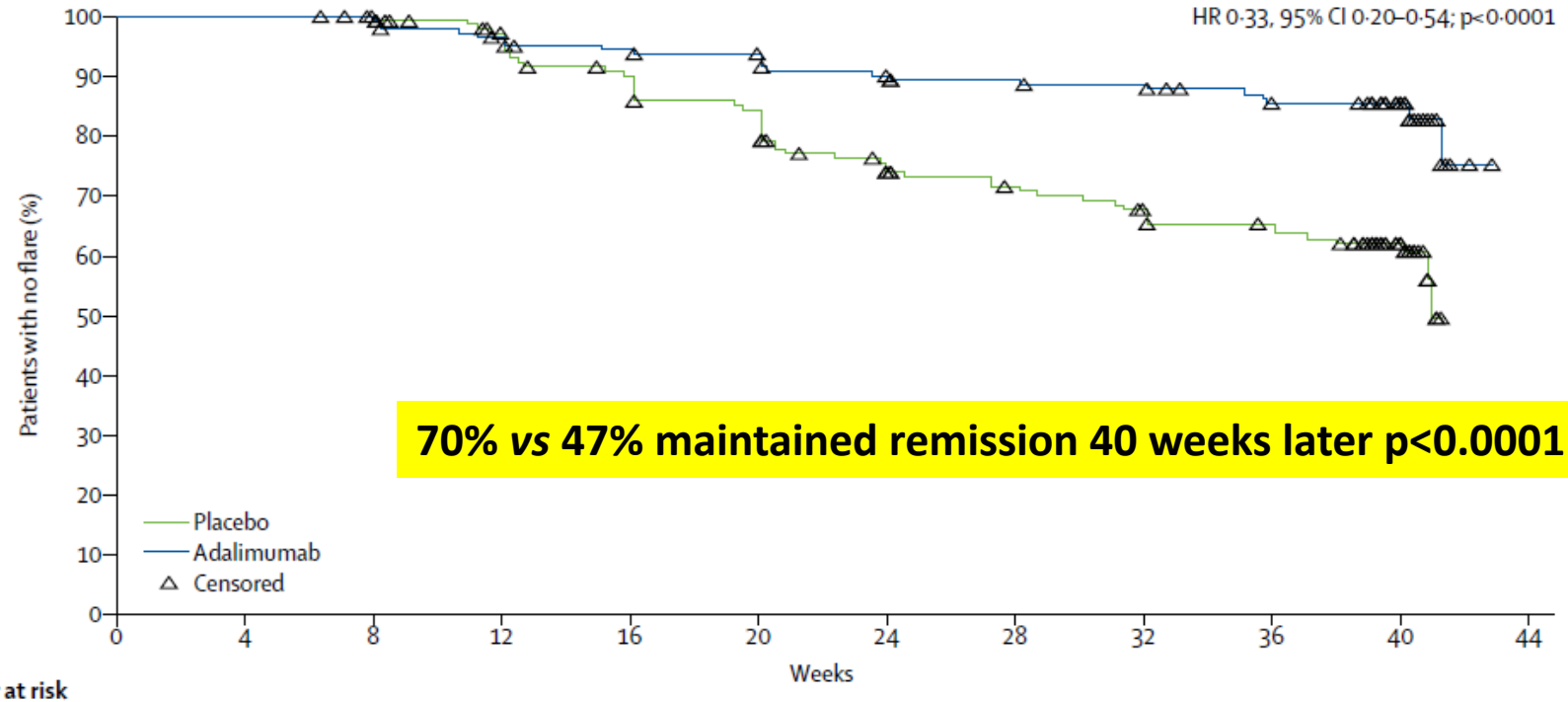
NOT H2H

ASAS20 response rates at Wk 24 for infliximab, Wk 14 for golimumab & Infliximab dyyb, at Wk 12 for adalimumab, certolizumab, & etanercept, Wk 16 for secukinumab & IV Golimumab



•1. van der Heijde D, et al. *Arthritis Rheum.* 2006;54:2136–46; 2. Davis Jr JC, et al. *Arthritis Rheum.* 2003;48:3230–6; 3. Inman RD, et al. *Arthritis Rheum.* 2008;58:3402–12; 4. van der Heijde D, et al. *Arthritis Rheum.* 2005;52:582–91; 5. Landewé R, et al. *Ann Rheum Dis.* 2014;73:39–47 6. Park W, et al. Ann Rheum Dis 2013;72:1605–1612. 7. Baeten D. et al. N Engl J Med 2015;373:2534-48.

Continuing vs Withdrawing Adalimumab in Maintaining Remission in nr-axSpA



70% *vs* 47% maintained remission 40 weeks later p<0.0001

Number at risk (number censored)												
Placebo	153 (0)	153 (0)	152 (0)	140 (4)	127 (14)	118 (22)	101 (36)	93 (39)	87 (44)	81 (47)	60 (51)	0 (54)
Adalimumab	151 (0)	151 (0)	149 (0)	139 (5)	134 (8)	132 (9)	125 (14)	121 (15)	119 (16)	112 (20)	92 (20)	0 (22)

In patients with active nr-axSpA who achieved sustained remission withadalimumab, continued therapy was associated with significantly fewer patients flaring than was treatment withdrawal.

Landewe R. …..Deodhar A. et al. Lancet 2018;392:134-44

What happened to our patient?

- We diagnosed him with axial spondyloarthritis based on
  - Inflammatory back pain starting at age of 20
  - Multiple episodes of verifiable enthesitis (Achilles tendon, hamstrings tendon – MRI proven)
  - History of very good response to NSAIDs
  - HLA B27+
- X-ray SI Joints: No sacroiliitis, hence he did not have AS, but had "non-radiographic axial SpA"
- He entered the clinical trial on adalimumab in nr-axSpA and underwent a repeat pelvic MRI scan that showed right sided sacroiliitis
- He was symptom-free within a month in the trial

Suspect axSpA if your back pain patient has any of these features:

- Chronic (>3 months) back pain starting before age 45, no precipitating cause, insidious onset
- Inflammatory back pain: Better with exercise, worse with rest, great response to NSAIDs
- Inflammatory bowel disease: Crohn's, Ulcerative Colitis, Uveitis, Psoriasis
- Inflammatory arthritis in the peripheral joints (knees, ankles, toes, dactylitis) or enthesitis
- High CRP (unexplained by other causes)
- HLA-B27

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Thank You