

Module 3

Diagnosis and Disease Classification



Learning Objectives



- Explain how axSpA (AS and nr-axSpA) is diagnosed in practice
- Outline the differences between classification criteria and diagnostic tools
- Describe the most currently used classification criteria for AS and axSpA

Content Flow



- The challenges in the diagnosis of axSpA
- Classification and Diagnostic Criteria and Tools
 - Classification versus Diagnosis
 - Definition of AS/r-axSpA and nr-axSpA in Clinical Trials and Clinical Practice
 - The most common symptoms: IBP, fatigue, and stiffness
 - Modified New York Criteria for Classification and Diagnosis of AS
 - ASAS Classification Criteria for axSpA
 - X-Ray Imaging of Sacroiliac Joint and Spine
 - MRI Assessment
- Summary

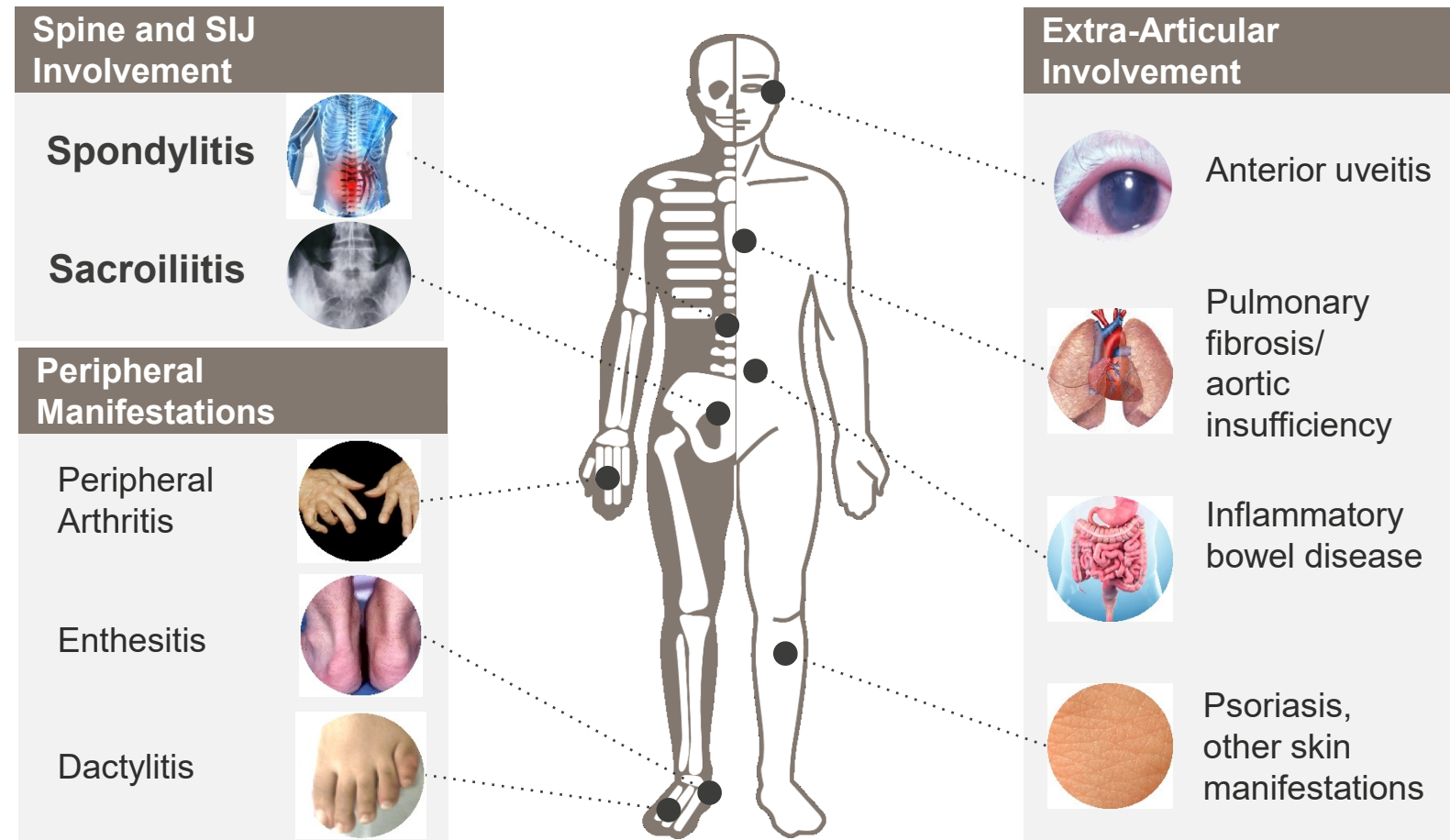
Challenges in Diagnosis



axSpA Clinical Manifestations

axSpA Clinical Manifestations

- axSpA refers to the **inflammation of the axial skeleton**^{1-3*}
- The spondyloarthritis (SpA) features are similar for AS/r-axSpA and nr-axSpA, but the frequencies of some manifestations vary^{4,5}
- Most common symptoms include inflammatory back pain, stiffness, fatigue¹



*Vertebral column, ribs, sternum, and skull.

AS=Ankylosing Spondylitis; axSpA=Axial Spondyloarthritis; nr-axSpA=Nonradiographic Axial Spondyloarthritis; r-axSpA=Radiographic Axial Spondyloarthritis; SpA=Spondyloarthritis; SIJ=Spinal Iliac Joint.

1. Taurog JD, et al. *N Engl J Med*. 2016;374(26):2563-2574. 2. Ward MM, et al. *Arthritis Rheumatol*. 2016;68(2):282-298. 3. van der Linden S, et al. *Arthritis Rheum*. 1984;27(4):361-368. 4. de Winter JJ et al. *Arthritis Res Ther*. 2016;18:196. 5. Proft F et al. *Ther Adv Musculoskel Dis*. 2018;10(5-6):129-139. 6. van der Heijde D. *Primer on the Rheumatic Diseases*. 13th ed. New York, NY: Springer; 2008:193,194,196.

Diagnosis of axSpA Can at Times Be Challenging

- Some patients present with less common symptoms, such as isolated uveitis or enthesitis, before other more common symptoms develop¹
- HCPs face challenges when trying to obtain appropriate diagnostic imaging, such as MRI¹
- There is a long delay between the onset of symptoms and referral to a rheumatologist by other practitioners¹
- Some populations, such as female patients, face extra challenges as a result of inaccurate perceptions of disease prevalence²

HCP=Healthcare Provider; MRI=Magnetic Resonance Imaging.

1. Danve A, Deodhar A. *Clin Rheumatol*. 2019;38(3):625-634. 2. Rusman T et al. *Curr Rheumatol Rep*. 2018;20(6):35.

Diagnosis of axSpA in Clinical Practice

- In clinical practice, diagnosis can be based on a range of different assessments and information:¹⁻³
 - Personal and family history, and physical examination
 - Symptoms, such as chronic inflammatory back pain, fatigue, stiffness
 - Evaluation of other causes of back pain, and differentiation between inflammatory and mechanical back pain
 - Imaging including X-rays of the sacroiliac joint, in some cases also of the spine, and possibly MRIs
 - Laboratory tests (e.g., HLA-B27, CRP)



Other causes of back pain confound diagnosis¹

axSpA=Axial Spondyloarthritis; CRP=C-Reactive Protein; HLA=Human Leukocyte Antigen; MRI=Magnetic Resonance Imaging.

1. van den Berg R, de Hooge M, Rudwaleit M, et al. *Ann Rheum Dis*. 2013;72:1646-1653. 2. Sieper J, et al. *Nat Rev Dis Primers*. 2015;9;1:15013. 3. Wolters Kluwer, UpToDate website. <https://www.uptodate.com/contents/axial-spondyloarthritis-including-ankylosing-spondylitis-beyond-the-basics/print>. (Accessed March 12, 2019).

Diagnosis and Classification Criteria



Diagnosis versus Classification

Diagnosis

- **Diagnostic criteria** developed to be highly **sensitive** to identify as many patients with the disease as possible
- The value of diagnostic tests/parameters **depends on the prevalence of the disease** (pretest probability)
- Should allow for flexibility in diagnostic confidence (definite, probable, possible)
- Applied to an **individual** patient (ICD code – clinical diagnosis)

Classification

- **Classification criteria** are developed to define a homogeneous group for the purpose of research
- High **specificity** to avoid misclassification
- No dependence on disease prevalence as patients are already diagnosed
- Applied to a **group**
- **Evidence-based**

Defining AS/r-axSpA and nr-axSpA in Clinical Trials and Clinical Practice

Clinical Practice	Clinical Trials
<p>Diagnosis</p> <ul style="list-style-type: none">AS is diagnosed based on history, physical examination, imaging findings and careful diagnostic considerations¹⁻⁴- Classification criteria used to diagnose patients³ <p>Imaging</p> <ul style="list-style-type: none">Most HCPs rely on imaging interpretations by radiologists and/or their own interpretation^{3,4}	<p>Diagnosis</p> <ul style="list-style-type: none">Patients are required to fulfill accepted classification criteria such as the mNY and/or the ASAS criteria^{5,6}Sometimes, an expert interpretation system is used to decrease intra- and inter-reader variability and assure a more accurate diagnosis, including defined criteria to identify sacroiliitis

AS=Ankylosing Spondylitis; ASAS= Assessment of SpondyloArthritis International System; axSpA=Axial Spondyloarthritis; HCP=Health Care Practitioner; mNY=Modified New York Criteria; nr-axSpA=Nonradiographic Axial Spondyloarthritis; r-axSpA=Radiographic Axial Spondyloarthritis.

1. Rudwaleit M, et al. *Ann Rheum Dis*. 2009;68:777-783. 2. van der Linden, et al. *Arthritis Rheum*. 1984;27(4):361-368. 3. Khmelinskii N, et al. *Front Med (Lausanne)*. 2018;5:106. 4. Taurog JD, et al. *N Engl J Med* 2016;374:2563-2574. 5. van den Berg R, et al. *Ann. Rheum Dis*. 2013;72,1646-1653. 6. Ghosh N, Ruderman EM. *Arthritis Res Ther*. 2017;19:286.

Most Typical Symptom is Inflammatory Back Pain

Characteristics of Inflammatory Back Pain (IBP)^{1,2}

- Age of onset <45 years
- Duration >3 months
- Insidious onset
- Morning stiffness >30 min
- Improvement with exercise
- No improvement with rest
- Awaking from pain (especially during second half of night), with improvement on arising
- Alternating buttock pain

The presence of ≥ 2 of these features should arouse suspicion for IBP, and the presence of ≥ 4 features can be considered diagnostic¹

The sensitivity of inflammatory back pain for the diagnosis of axial spondyloarthritis is 70-80%¹

The specificity varies, depending on the population being studied¹⁻³

Assessing IBP

- In clinical trials, IBP is assessed using BASDAI Q2 or ASAS pain questions on a NRS or VAS^{4,5}
- In clinical practice, patients are generally asked to rate the severity of the pain and compare to the severity from previous visits⁶

ASAS=Assessment in Spondyloarthritis International Society; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; IBP=Inflammatory Back Pain; NRS=Numeric Rating Scale; VAS=Visual Analog Scale.

1. Taurog JD et al. *N Engl J Med*. 2016;374:2563-2574. 2. Sieper J, et al. *Ann Rheum Dis*. 2009;68:784-788. 3. van den Berg R, et al. *Ann Rheum Dis*. 2013;72:1646-1653. 4. Landewé R, van Tubergen A. *Curr Rheumatol Rep*. 2015;17(7):47. 5. Sieper J, et al. *Ann Rheum Dis*. 2009;68 Suppl 2:ii1-44. 6. Haefeli M, Elfering A. *Eur Spine J*. 2006;15(Suppl 1):S17-S24.

Modified New York Criteria for Classification and Diagnosis of AS

1. Clinical criteria¹:

- a) **Low back pain and stiffness** for >3 months, which improves with exercise but is not relieved by rest
- b) **Limitation of motion** of the lumbar spine in both the sagittal and frontal planes
- c) **Limitation of chest** expansion relative to normal values corrected for age and sex

2. Radiologic criterion¹:

Sacroiliitis grade ≥ 2 bilaterally or sacroiliitis grade 3-4 unilaterally (sacroiliitis grading can be achieved using plain radiographs)

Definite diagnosis of AS if the radiologic criterion is associated with ≥ 1 clinical criterion²

AS=Ankylosing Spondylitis.

1. van der Linden S, et al. *Arthritis Rheum.* 1984;27(4):361-368. 2. Knipe H, Gaillard F. Sacroiliitis grading (New York criteria). Radiopaedia. <https://radiopaedia.org/articles/sacroiliitis-grading>. Accessed February 2019.

ASAS Classification Criteria for axSpA

In patients with chronic back pain
(≥ 3 months) and age at onset < 45 years:

IMAGING ARM

Sacroiliitis on imaging:

Acute inflammation on
MRI highly suggestive
of sacroiliitis

OR

Definite sacroiliitis according
to modified New York criteria

+
 ≥ 1 SpA
features

OR

CLINICAL ARM

HLA-B27-positive

+
 ≥ 2 SpA
features

SpA Features:

- Inflammatory back pain
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- Ulcerative colitis/Crohn's disease
- Good response to NSAIDs
- Family history of SpA
- HLA-B27 positive
- Elevated CRP

nr-axSpA classification is based on a positive MRI (imaging arm) OR on the clinical arm without imaging

ASAS=Assessment of SpondyloArthritis International Society; axSpA=Axial Spondyloarthritis; CRP=C-Reactive Protein; HLA=Human Leukocyte Antigen; IBD=Inflammatory Bowel Disease; MRI=Magnetic Resonance Imaging; NSAID=Nonsteroidal Anti-Inflammatory Drug; SpA=Spondyloarthritis.

Rudwaleit M, et al. *Ann Rheum Dis*. 2009;68(6):777-783.

Grading of Radiographic Sacroiliitis: The New York Grading Scale

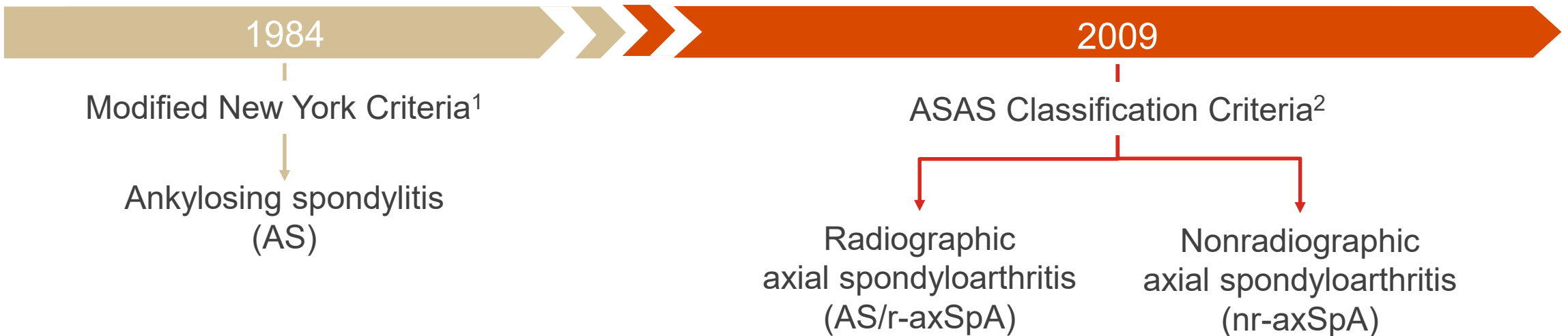
Grade	Description ^{1,2}
0	Normal
1	Suspicious changes
2	Minimal abnormality – small localized areas with erosion or sclerosis, without alteration in the joint width
3	Unequivocal abnormality – moderate or advanced sacroiliitis with 1 or more of: <ul style="list-style-type: none">• Erosions• Evidence of sclerosis• Widening, narrowing, or partial ankylosis
4	Severe abnormality – total ankylosis

The New York grading scale for radiographic sacroiliitis was defined in 1968 and is still in use today^{1,3}

1. Bennet PH, Burch, TA. In: *Population Studies of the Rheumatic Diseases: Proceedings of the Third International Symposium*; New York, NY; 5-10 June, 1966;1968:456-457. 2. SPA-imaging.org. Diagnosis of sacroiliitis by radiography. http://www.spa-imaging.org/default.asp?MainMenuId=394&PageId=397&Sub=397&Desc=Sacroiliitis_-_radiography. Accessed February 2019. 3. van der Heijde D, et al. *Ann Rheum Dis*. 2017;76(6):978-991.

AS/r-axSpA and nr-axSpA Classification

- Diagnosis and classification of AS has been based on the modified New York (mNY) criteria, which require the presence of radiographic sacroiliitis¹
- The ASAS criteria allow for the classification of patients without radiographic changes as nr-axSpA²
 - Positive MRI of the sacroiliac joints (based on specific definitions) is used to identify this subtype
 - The criteria also contains a clinical arm, which enhances the capability to identify patients without MRI findings as it requires the presence of positive HLA-B27 and two SpA features
- The imaging arm of the ASAS classification criteria includes sacroiliitis on X-rays (as per mNY criteria) as one of its criterion and therefore, identifies patients with AS/r-axSpA²



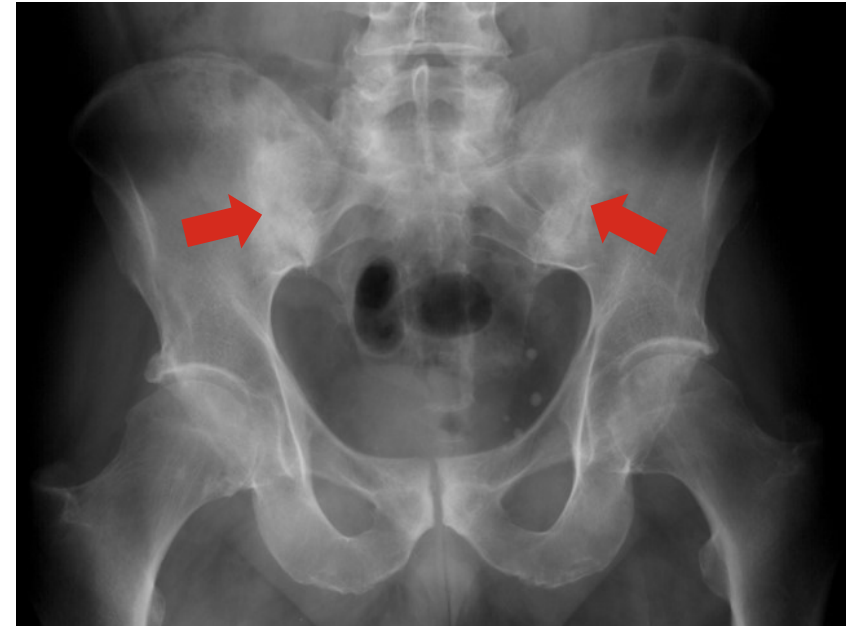
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Radiographs of Sacroiliac Joint and Spine to Confirm Sacroiliitis



No definite radiographic sacroiliitis
(grade 0)¹



Definite radiographic sacroiliitis
(grade 3 bilaterally)¹

X-ray is the main diagnostic method used to confirm presence of sacroiliitis¹
and to follow characteristic spinal changes in AS²

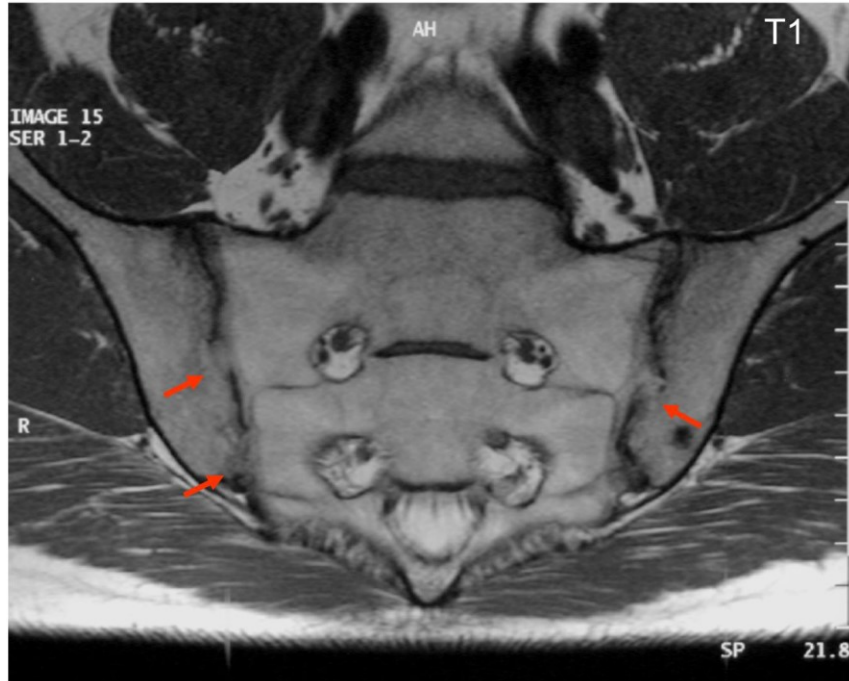
AS=Ankylosing Spondylitis.

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1. Sieper J, et al. *Ann Rheum Dis.* 2009;68:ii1-44. 2. Sieper J, Poddubnyy D. *Lancet.* 2017;390(10089):73-84. 3. Louie GH, Ward MM. *Curr Opin Rheumatol.* 2014;26(2):145-150.



MRI Assessment



- Some HCPs require an MRI where the X-ray findings are not clear¹
- This imaging technique is more sensitive and can help with classification and diagnosis¹
- “Acute inflammation on MRI highly suggestive of sacroiliitis” is included in the imaging arm of the ASAS Classification Criteria¹

Summary



- The diagnosis in patients with less common presentations can be challenging
- In clinical practice, the diagnosis of a patient is based on history and physical examination, evaluation of other diagnostic possibilities in the differential, imaging and laboratory tests if needed
- In clinical trials, classification criteria are used to identify eligible patients
- Classification criteria should not be used to diagnose patients
- Appropriate imaging techniques for the diagnosis of AS/r-axSpA and nr-axSpA include:
 - X-rays of the sacroiliac joints and spine
 - MRI of the sacroiliac joints, and possibly the spine if needed