# Insights into a Timely and Appropriate Diagnosis of axSpA

# Objectives

1 **Review**
prevalence, classification, and symptoms of axial spondyloarthritis (axSpA)

2 **Identify**
multiple factors leading to diagnostic delay

3 **Explain**
contributing factors leading to overdiagnosis or underdiagnosis of axSpA

4 **Introduce**
a path toward increased awareness and identification of axSpA

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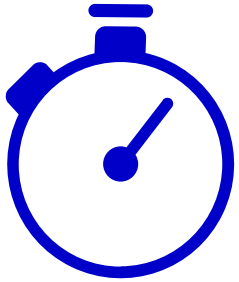
# Contents

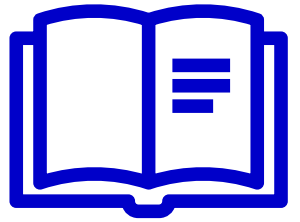
*Introduction*



*Delayed Diagnosis*

*Over Diagnosis*

*Outcomes*



*Increasing Awareness*

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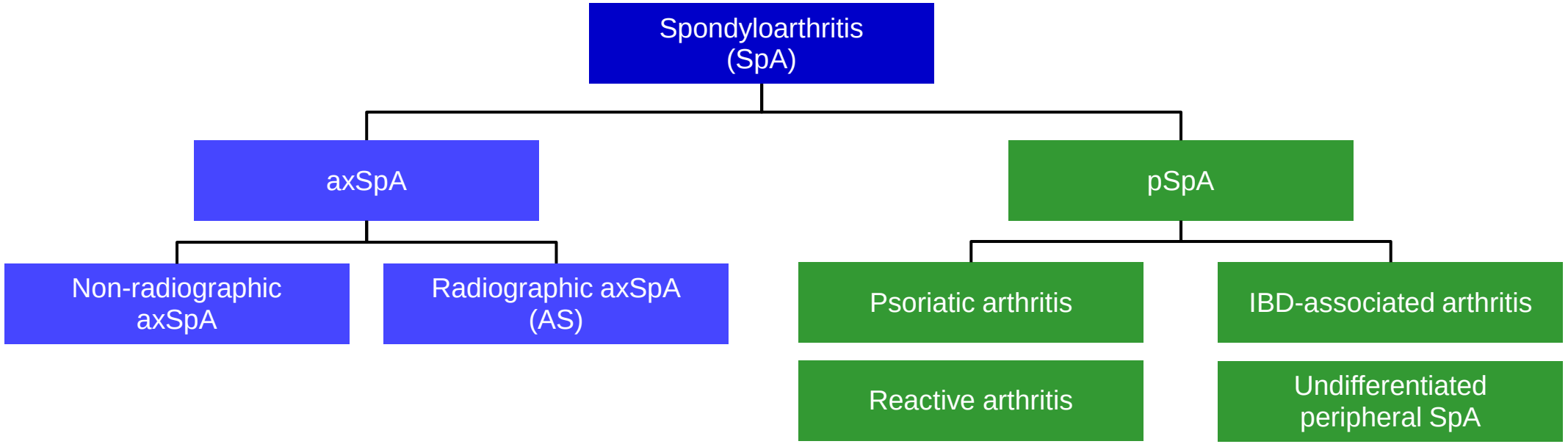
# Classification of SpA*

- SpA designates a group of immune-mediated inflammatory rheumatic diseases sharing common clinical and genetic features
  - axSpA can encompass the axial and peripheral skeleton, as well as the skin, gut, and eyes
  - AS classification is limited to definitive sacroiliitis and spinal features
  - pSpA does not require axial involvement




*Classification criteria is used for research studies and not meant to be used as diagnostic criteria.
AS, ankylosing spondyloarthritis; axSpA, axial spondyloarthritis; IBD, inflammatory bowel disease; pSpA, peripheral spondyloarthritis.
Raychaudhuri SP, et al. *J Autoimmun*. 2014;48-49:128-133.

# axSpA is an Under-recognized Disease

**High prevalence of back pain in the general population, variable symptoms, and lack of awareness surrounding axSpA leads to delayed diagnosis and treatment, which may result in lower quality of life for patients[1]**

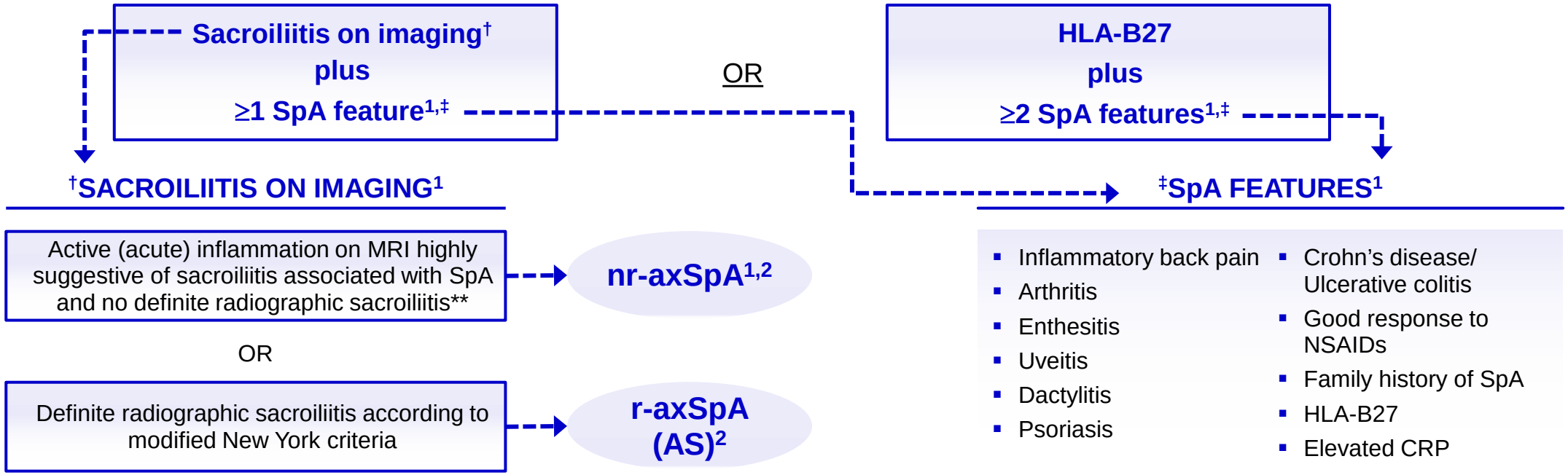
- **The prevalence of axSpA is estimated to be between 0.9% and 1.4%** in the United States[2,*]
- axSpA is an **immune-mediated inflammatory rheumatic disease** with **no clear etiology**[3]
- Inflammatory back pain associated with axSpA has the potential to **progress to structural damage to the sacroiliac joints and spine**[1]
- Symptoms **persist and worsen** in the **absence of treatment**[3]
- Diagnostic delay of axSpA ranges from **~8–11 years**[1]

*Based on 2009–2010 NHANES data using either the Amor or European Spondyloarthritis Study Group classification criteria.
axSpA, axial spondyloarthritis.
1. Danve A, et al. *Clin Rheumatol*. 2015;34:987-993. 2. Curtis JR, et al. *Perm J*. 2016;20(4):15-151. 3. Furst D, et al. *Arthritis Res Ther*. 2019;21:135.

# Classification of axSpA

## ASAS Classification Criteria[1,*]

In patients with back pain ≥3 months and age at onset <45 years

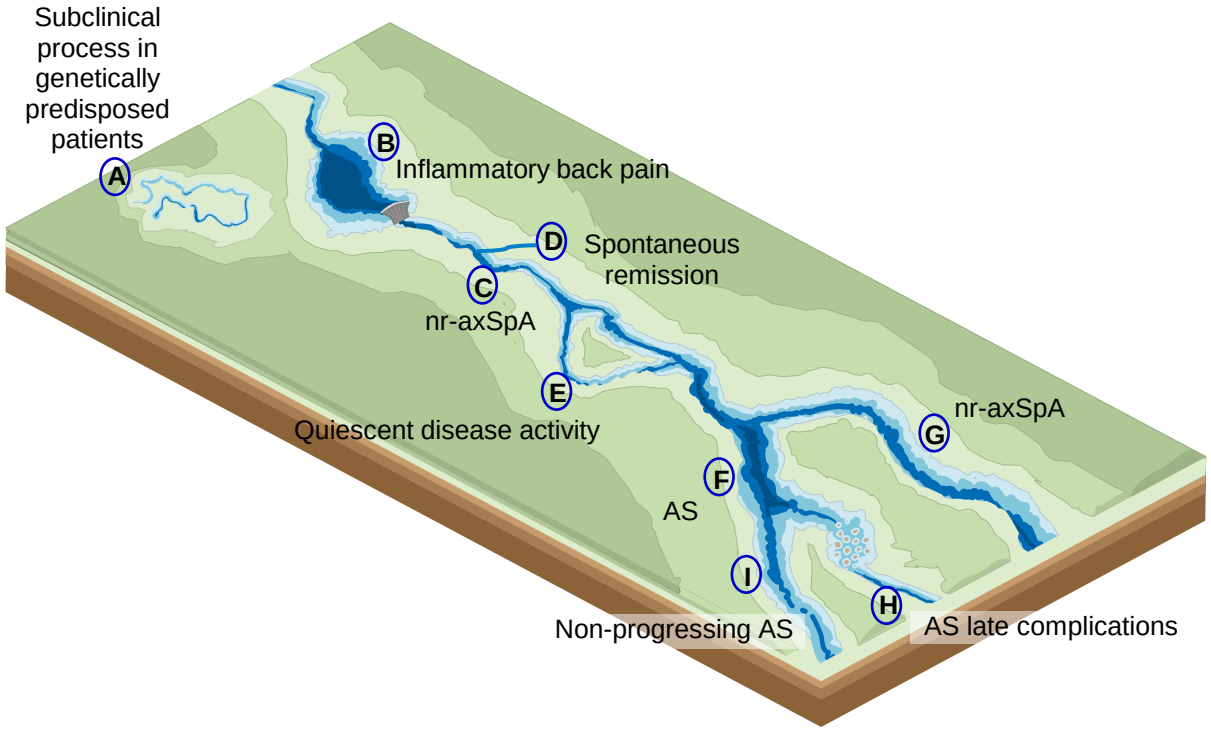



*Classification criteria is used for research studies and not meant to be used as diagnostic criteria. **Definite radiographic sacroiliitis means bilateral grade 2, or unilateral or bilateral grade 3 or 4.

ASAS, Assessment of Spondyloarthritis International Society criteria; axSpA, axial spondyloarthritis; CRP, C-reactive protein; HLA, human leukocyte antigen; NSAIDs, nonsteroidal anti-inflammatory; SpA, spondyloarthritis.

1. Raychaudhuri SP, et al. *J Autoimmun*. 2014;48-49:128-133. 2. Michelena X, et al. *Rheumatology*. 2020:59:iv18-iv24.

# Development of r-axSpA and nr-axSpA[1]




**r-axSpA**

Definitive evidence of sacroiliitis on x-ray[2]

**nr-axSpA**

No definitive sacroiliitis on plain radiographs[2]

A. Some people can be genetically predisposed to develop axSpA, but may never develop any clinical manifestations[3]
B. Patients develop inflammatory back pain[3]
C. A small portion with IBP will develop nr-axSpA[3]
D. A small portion of these patients may have spontaneous remission[3]
E. Others may have quiescent disease course for a time[3]
F. Studies have shown that up to 12% of patients with nr-axSpA develop AS (radiographic sacroiliitis) within 2 years[3]
G. Some patients may continue as nr-axSpA[3]
H. A portion of patients progress to develop long-term complications[3]
I. Others may have a relatively benign but chronic course[3]

## Complexities of the disease course leads to delayed diagnosis[4]

AS, ankylosing spondylitis; axSpA, axial spondyloarthritis; IBP, inflammatory back pain; nr-axSpA, non-radiographic axial spondyloarthritis; r-axSpA, radiographic axial spondyloarthritis; SpA, spondyloarthritis.

Image adapted from Garg N, et al. Best Pract Res Clin Rheumatol. 2014;28:663-672.

1. Garg N, et al. *Best Pract Res Clin Rheumatol*. 2014;28:663-672. 2. Michelena X, et al. *Rheumatology*. 2020;59:iv-18-iv24. 3. Deodhar A. *The Rheumatologist*. May 1, 2014. Accessed October 6, 2021. https://www.the-rheumatologist.org/article/rheumatologists-make-progress-defining-spectrum-of-axial-spondyloarthritis/3/. 4. Danve A, et al. *Clin Rheumatol*. 2015;34:987-993.

# Factors in Delayed Diagnosis of axSpA

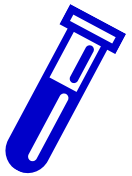
## Lack of validated diagnostic criteria to use in clinical practice[1]

Classification criteria used in clinical trials should not be used for diagnosis due to inherent limitations*

## Limitations on physical exams

- Clinicians cannot manually assess SI joints and spine for inflammation[1]
- Signs and symptoms of axSpA may be overlooked or misinterpreted in patients of young age and female gender[2]

## Lack of reliable biomarkers and imaging tests



### HLA-B27[3,4]

- 6.1% of US adults ages 20-69 years old are HLA-B27+
- Prevalence varies according to race
- >80% sensitivity
- ~90% specificity

### C-reactive protein[4]

- Low sensitivity
- Low specificity

### X-ray[4]

- Low sensitivity
- >90% specificity

### CT scans[4]

- Cannot depict active inflammation
- Conventional CT scans can have high radiation dose

### MRI[4]

- Cost prohibitive
- Low specificity of inflammation seen on MRI of the SI joints or spine

*Modified New York (mNY), Amor, European Spondyloarthropathy Study Group, Assessment of Spondyloarthritis International Society (ASAS) criteria.[1]

axSpA, axial spondyloarthritis; CT, computed tomography; HLA-B27, human leukocyte antigen; MRI, magnetic resonance imaging; SI, sacroiliac.

1. Danve A, et al. *Clin Rheumatol*. 2019;38:625-634. 2. Kiwalkar S, et al. Presented at: ACR Convergence: American College of Rheumatology Annual Meeting. November 5-9, 2020. Virtual. Abstract 1869.
3. Reveille JD, et al. *Arthritis Rheum*. 2012;64:1407-1411. 4. Poddubnyy D. *Rheum*. 2020;59:iv6-iv17.

# Patient Factors for Delayed Diagnosis in nr-axSpA[1] and r-axSpA[2,3]

## Patients initially attribute back pain to normal wear and tear or age-related processes[1,*]

- Activity or injury
- Aging
- Growing pains due to young age

## Patients may not interact frequently with the healthcare system[2,*]

- Less access to healthcare due to socioeconomic status
- Delay seeing a physician
- Insurance limitations[3]

## Lack of continuity of care[2]

- Patients doctor shop when they feel they are not being properly treated
- Younger patients frequent urgent care centers instead of consistently visiting a single primary care physician

*Reported from HCP and patient interviews.

axSpA, axial spondyloarthritis; HCP, Health Care Provider

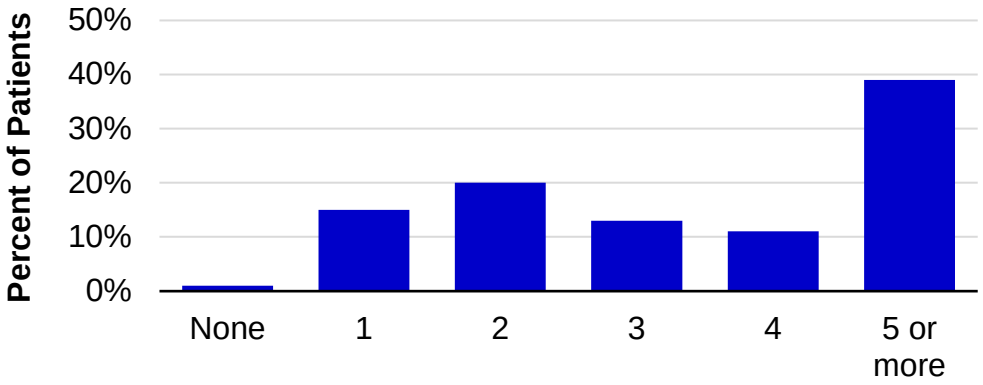
1. Kiwalkar S, et al. Presented at: ACR Convergence: American College of Rheumatology Annual Meeting. November 5-9, 2021. Virtual. Abstract 1869. 2. Lapane KL, et al. *BMC Family Practice*. 2020;21:204. 3. Yi E, et al. *Rheumatol Ther*. 2020;7:65–87.

# Patients Often See Multiple HCPs Before nr-axSpA Diagnosis

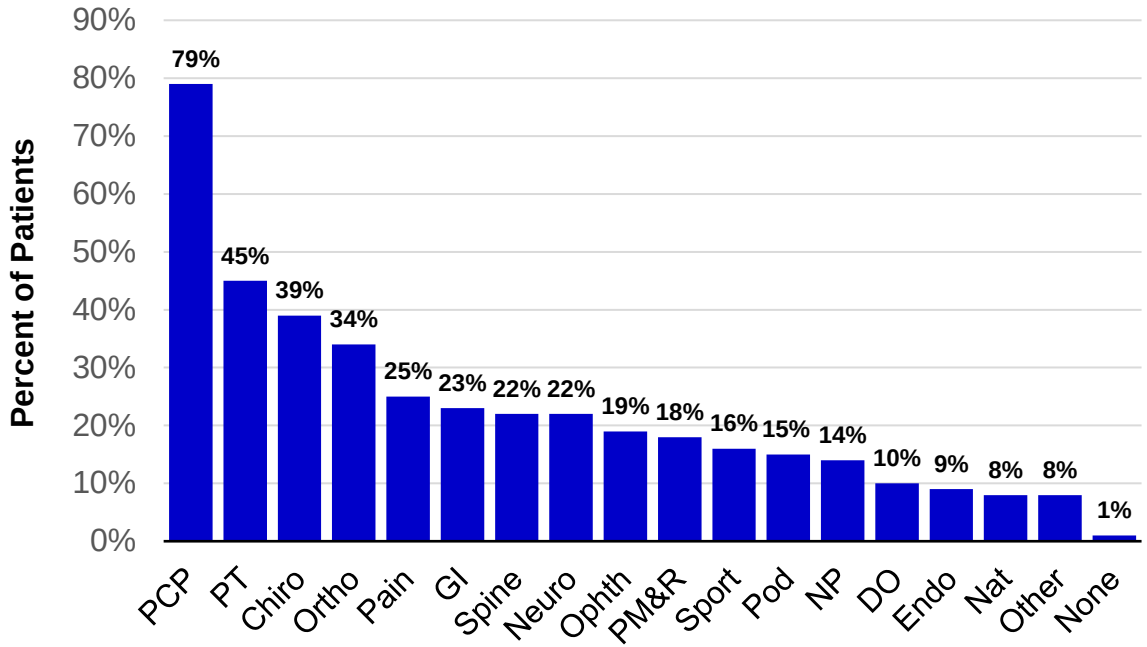
## Disease recognition by clinicians in specialties other than rheumatology is key for early referral and timely diagnosis

- Of patients with rheumatologist-confirmed nr-axSpA (n = 125)[1]
  - 50% saw 4 or more different healthcare providers before seeing a rheumatologist
  - 50% saw ≥2 rheumatologists before receiving nr-axSpA diagnosis

### Number of HCPs Seen Before a Rheumatologist




### HCP Specialty Type Seen Before a Rheumatologist

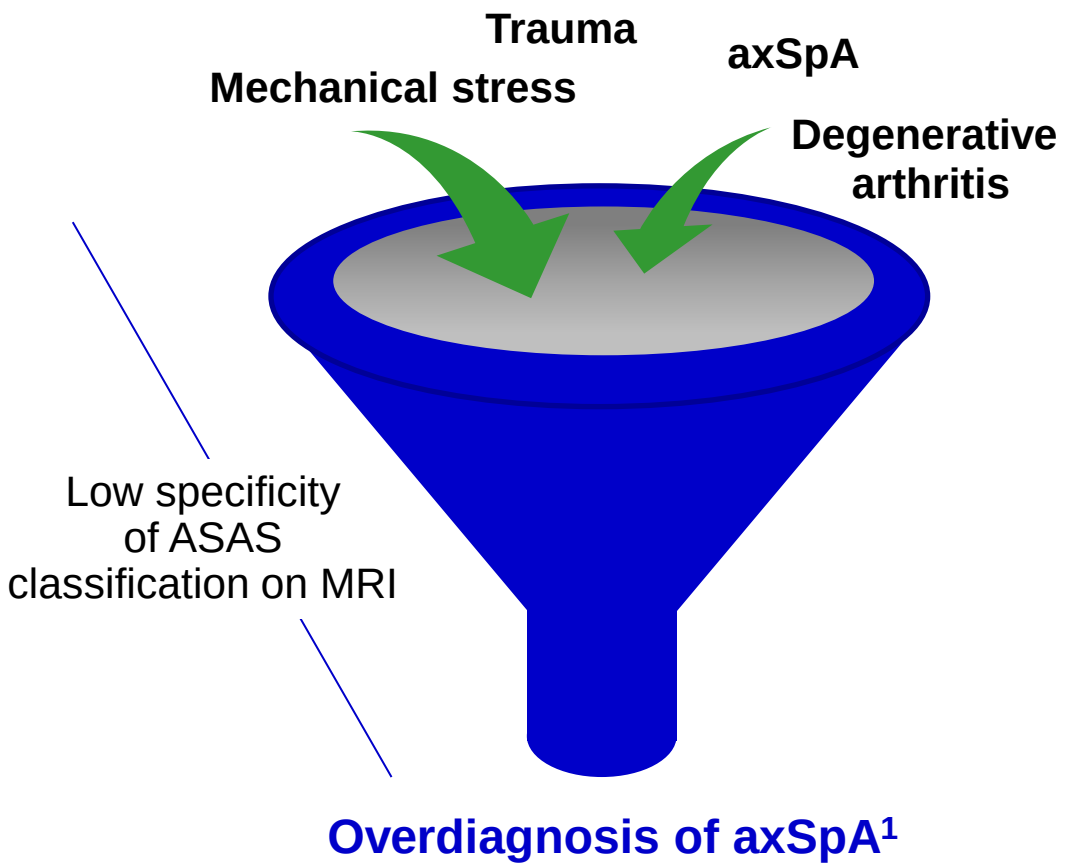



axSpA, axial spondyloarthritis; Chiro, chiropractor; DO, osteopath; Endo, endocrinologist; GI, gastroenterologist; HCP, healthcare provider; Nat, naturopath; Neuro, neurologist; NP, nurse practitioner; nr-axSpA, non-radiographic axial spondyloarthritis; Ophth, ophthalmologist; Ortho, Orthopedist; Pain, pain specialist; PCP, primary care physician; PM&R, physical medicine and rehabilitation; Pod, podiatrist; PT, physical therapist; Spine, spine specialist; Sport, sports medicine.

Kiwalkar S, et al. Presented at: ACR Convergence: American College of Rheumatology Annual Meeting. November 5-9, 2021. Virtual. Abstract 1869.

# Factors in Overdiagnosis of axSpA

- A major advance in the diagnosis of axSpA is the ability to detect inflammation of SI joints using MRI[2]
- Specificity of finding inflammation of SI joints on MRI is low[1]
  - Positive MRI definition of ASAS classification criteria is non-specific
- Mild inflammatory changes of the SI joints can be seen in healthy individuals and athletes[1]
  - Mechanical stress
  - Trauma
  - Degenerative arthritis




ASAS, Assessment of Spondyloarthritis International Society; axSpA, axial spondyloarthritis; SI, sacroiliac.

1. Danve A, et al. *Clin Rheumatol*. 2019;38:625-634. 2. Maksymowych WP, et al. *Rheumatology*. 2021;60:4778-4789.

# New Definitions for MRI Lesions May Aid in the Prevention of Overdiagnosis of axSpA[1]

- **Current ASAS definition includes:**
  - Presence of 2 BME lesions on a single semicoronal slice through the SI joint

  OR
  - Single lesion on 2 consecutive semicoronal slices
- The ASAS-MRI working group conducted investigations to **develop data-driven definitions of various lesions seen on MRI of the SI joints and spine in patients with axSpA**
  - Developed definitions for “positive MRI” for diagnosis
- New optimal definition for active lesion and ASAS positive MRI
  - Presence of BME in ≥4 SI joint quadrants or in ≥3 consecutive slices
- New optimal definition for definite structural lesion typical of axSpA
  - Presence of erosion in ≥3 SI joint quadrants or ≥2 consecutive slices or the presence of fat lesions in ≥5 SI joint quadrants or ≥3 consecutive slices

Musculoskeletal radiologists need training on new developments in MRI definitions of ‘positive MRI’[2]

**Study Limitations:** Higher MRI lesion cut-offs for specific lesions did not necessarily eliminate cases that were negative for a diagnosis of axSpA, because such patients had other MRI lesions that contributed to diagnostic ascertainment. These cut-offs will require further validation in different practice settings where the prevalence of axSpA, which influences PPV, may differ from that observed in the ASAS-CC. The follow-up of the ASAS-CC incurred substantial patient drop-out, and a higher proportion of patients assessed at follow-up had MRI inflammation than those lost to follow-up. This channeling bias may inflate PPVs for MRI parameters.

ASAS, Assessment of Spondyloarthritis International Society; axSpA, axial spondyloarthritis; BME, bone marrow edema; PPV, positive predictive value; SI, sacroiliac.

1.Maksymowych WP, et al. *Rheumatology*. 2021;60:4778-4789. 2. Deodhar, A. *Arthritis Rheumatol*. 2016;68(4):775-778.

# Outcomes of Delayed Diagnosis and Overdiagnosis

**Delay** of diagnosis leads to higher economic burden for patients[1]

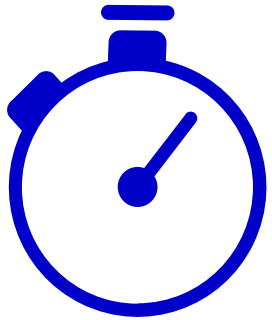
Costs associated with a delayed diagnosis can include:

**Doctor visits**

**Specialist services**

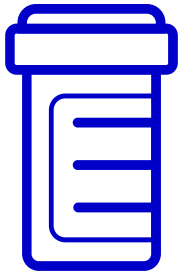
**Treatments**

**Delay** in diagnosis has a negative impact on patient quality of life[2]



- Intermittent pain
- Inflammation
- Fatigue
- Numerous medical tests
- Uncertainty
- Anxiety
- Depression
- Unnecessary visits to specialists

Limitations in diagnostic features and imaging can lead to **overdiagnosis**[3]



Misdiagnosing axSpA can lead to overtreatment with medications that have potential risks for patients

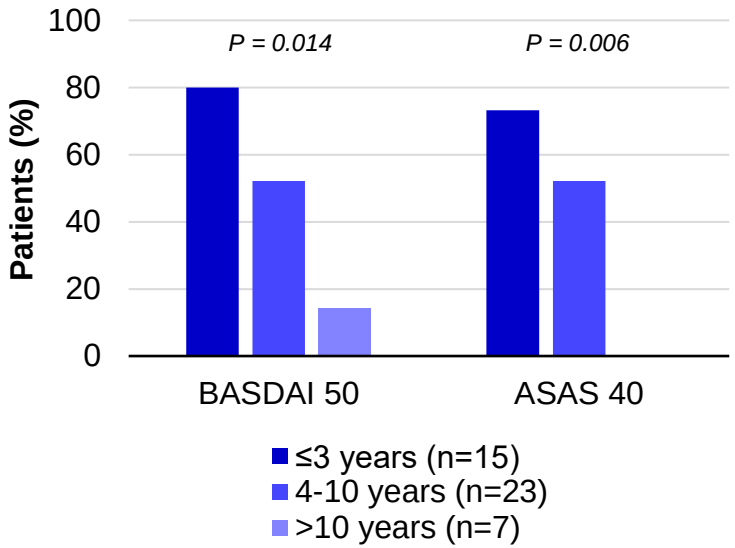
axSpA, axial spondyloarthritis.

1. Yi E, et al. *Rheumatol Ther*. 2020;7:65–87. 2. Garrido-Cumbrera M, et al. *Rheumatology*. 2021;keab369. 3. Garg N, et al. *Best Pract Res Clin Rheumatol*. 2014;28:663-672.

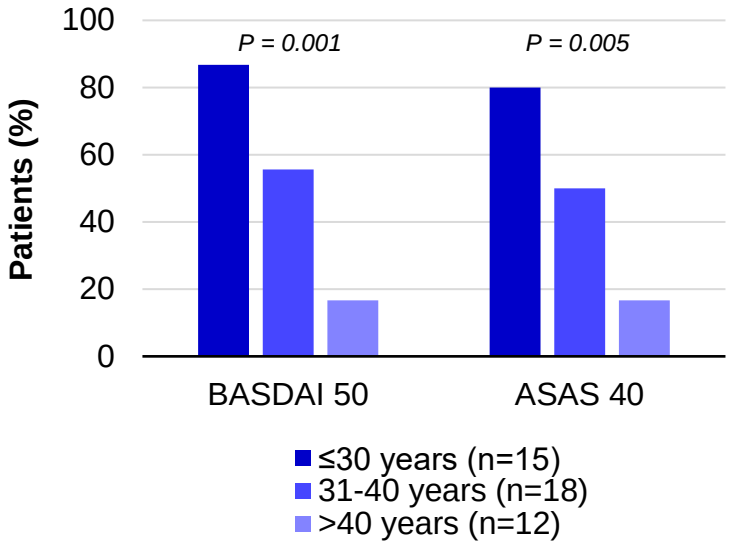
# Factors Leading to Better Treatment Response

- Patients with axSpA without radiographically defined sacroiliitis received 40 mg of a TNF inhibitor or placebo every other week for 12 weeks, then continued to an open-label extension for up to 52 weeks

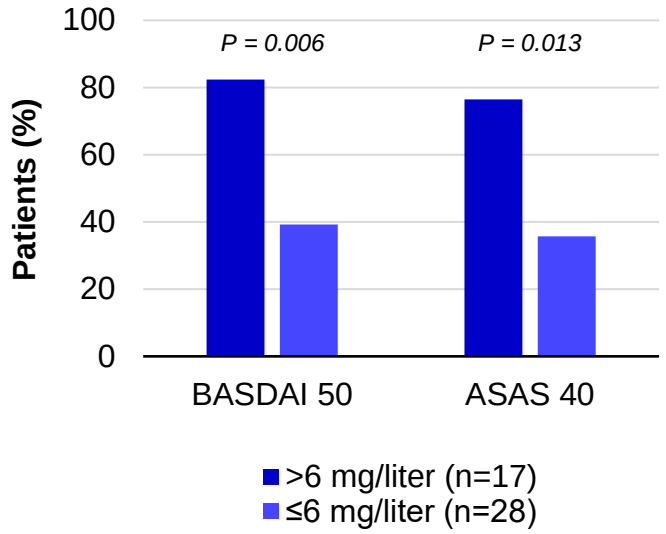
## Disease Duration




## Age at Study Entry




## C-Reactive Protein




**Patients with shorter disease duration, younger age at study entry, and higher C-reactive protein at baseline have better BASDAI 50 and ASAS 40 responses at 52 weeks of TNF-inhibitor treatment***

**Study Limitation:** Only 45 patients were analyzed; 1 patient was excluded from the study (before treatment with adalimumab for at least 8 weeks after switching from placebo. Logistic regression analysis was performed on HLA-B27 status, MRI status, sex, disease duration, age at study entry, and CRP levels; only statistically significant findings are shown.

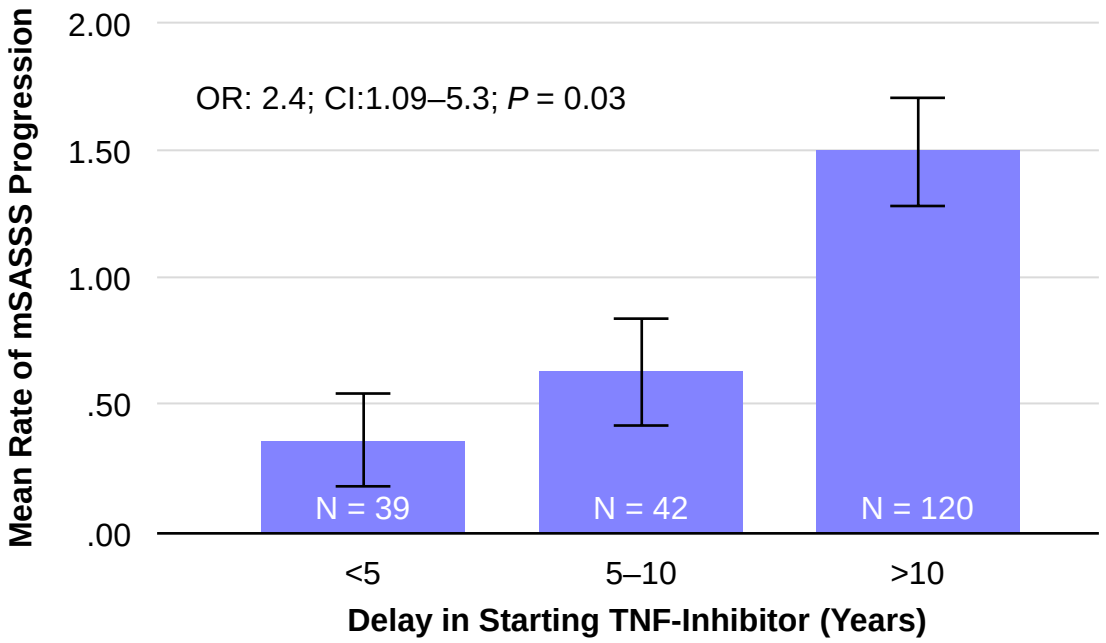
*Trial conducted in Germany; ex-US findings may not be applicable to US patients.

ASAS40, Assessment of Spondyloarthritis International Society criteria for 40% improvement; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; TNF, tumor necrosis factor.

Haibel H, et al. *Arthritis Rheum*. 2008; 58:1981-1991.

# Early Treatment of Patients With Shorter Disease Duration is Associated With Better Response

## Impact of delay of TNF-inhibitor treatment on mean rate of mSASSS progression




- Prospective study of radiographic disease progression in patients treated with TNF-inhibitors

**Early initiation of therapy resulted in lower rate of disease progression**

**Study Limitations:** This was not a randomized study; potential unmeasured confounders and potential bias cannot be adjusted for. TNF-inhibitors were given to patients who were not well controlled on NSAIDs and had high disease activity.

mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score; OR, odds ratio; TNF, Tumor Necrosis Factor.

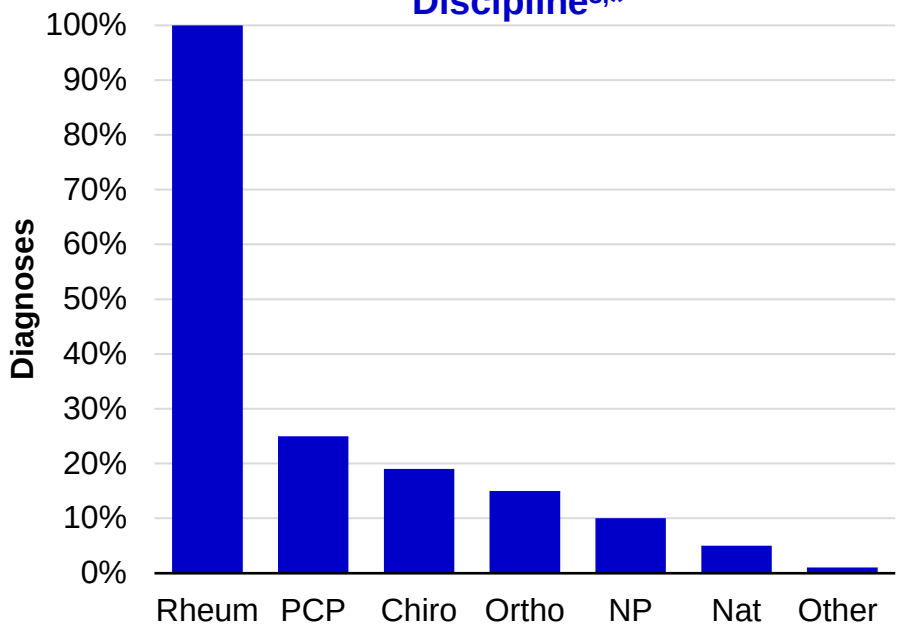
Haroon N, et al. *Arthritis Rheum*. 2013;65:2645-2654.

# Education for HCPs Across Multiple Disciplines May Lead to Shorter Time to Diagnosis

**Researchers have demonstrated limited awareness of axSpA and limited diagnostic training among general practitioners[1]**

**Education is needed in the US to increase awareness, appropriate referral, and timely diagnosis for patients with axSpA[2]**

## nr-axSpA Diagnoses by HCP Discipline[3,*]




## Insights into referral strategies

- MASTER and RADAR studies showed that a simple referral strategy was reliable for identifying patients with axSpA[4,5]
  - Presence of chronic back pain for ≥3 months
  - Age at onset of <45 years
  - ≥1 of 3 SpA-related features
    - HLA-B27 positivity
    - Current inflammatory back pain
    - Evidence of sacroiliitis on imaging
- SPADE tool[6]
  - Resource for clinicians to aid in determining probability of SpA in patients age <45 years with chronic back pain and no definitive changes on radiographs

*125 patients completed a questionnaire regarding which HCP specialties were able to diagnose nr-axSpA.

axSpA, axial spondyloarthritis; Chiro, chiropractor; HCP, healthcare provider; HLA, human leukocyte antigen; Nat, naturopath; NP, nurse practitioner; nr-axSpA, non-radiographic axial spondyloarthritis; Ortho, orthopedist; PCP, primary care physician; r-axSpA, radiographic axial spondyloarthritis; Rheum, rheumatologist; SpA, spondyloarthritis; SPADE, Spondyloarthritis Diagnosis Evaluation.

1. van Onna M, et al. *J Rheumatol*. 2014;41:897-901. 2. Deodhar A, et al. *Arthritis Rheumatol*. 2016;68:1669-1676. 3. Kiwalkar S, et al. Presented at: ACR Convergence: American College of Rheumatology Annual Meeting. November 5-9, 2020. Virtual. Abstract 1869. 4. Sieper J, et al. *Ann Rheum Dis*. 2013;72:1621-1627. 5. Poddubnyy D, et al. *J Rheumatol*. 2011;38:2452-2460. 6. Habibi S, et al. *Rheumatology*. 2016;i144. Abstract 202.

# Increasing Education for HCPs and Patients can Lead to More Timely Diagnosis of axSpA

## HCP Education Resources

Educational symposia in the US[1]

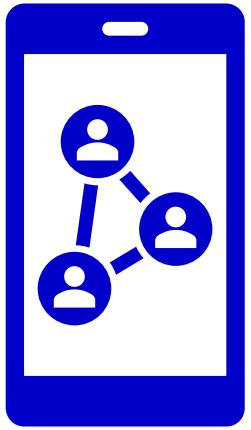
- Spondyloarthritis Research and Treatment Network (SPARTAN)
- Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)*

ASAS Case Library[2]

- Educational project of imaging findings in the context of clinical and laboratory test results

## Patient Education Resources

- Spondylitis Association of America (SAA)[3]
- Free Open Access Medical Education Movement (FOAM)[4]
  - Reduce the gap between medicine and patients
- Comparative effectiveness research[4,†]
- Currently, there are several studies researching the impact of social media and medical education regarding axSpA
  - Recruitment tool for clinical trials[4]
  - FaxSpA – education tool distributed via Facebook[5]



*GRAPPA resources require membership for use. †Resource not yet available for use as of 1/10/21.

ASAS, Assessment of Spondyloarthritis International Society; axSpA, axial spondyloarthritis; HCP, healthcare provider.

1. Danve A, et al. *Clin Rheumatol*. 2015;34:987-993. 2. Poddubnyy D. *Rheum*. 2020;59:iv6-iv17. 3. Spondylitis Association of America. Accessed October 20, 2021. https://spondylitis.org/. 4. Reuter K, et al. *Curr Op*in *Rheumatol*. 2019;31:321-328. 5. Afinogenova Y, et al. Presented at: ACR Convergence: American College of Rheumatology Annual Meeting. November 5-9, 2021. Virtual. Abstract 1894.

# Summary

- axSpA is a commonly under-recognized immune-mediated inflammatory rheumatic disease, accounting for 5% of all chronic back pain[1]
- Lack of clinical diagnostic tools and disease awareness among HCPs/patients contribute to delayed diagnosis[1,2]
- New definitions for positive MRI of the sacroiliac joint may provide support in the correct diagnosis of axSpA[3]
- Delayed and overdiagnosis can have adverse effects on patients' quality of life[4]
- Education is key in helping to reduce the time to axSpA diagnosis[5]

ASAS, Assessment of Spondyloarthritis International Society; axSpA, axial spondyloarthritis; HCP, healthcare provider.

1. Danve A, et al. *Clin Rheumatol*. 2019;38:625-634. 2. Kiwalkar S, et al. Presented at: ACR Convergence: American College of Rheumatology Annual Meeting. November 5-9, 2021. Virtual. Abstract 1869.
3. Maksymowych WP, et al. *Rheumatology*. 2021;60:4778-4789. 4. Garrido-Cumbrera M, et al. *Rheumatology*. 2021;keab369. 5. Deodhar A, et al. *Arthritis Rheumatol*. 2016;68:1669-1676.