

Understanding Axial Spondyloarthritis: A Primer for Managed Care

Atul A. Deodhar, MD

Spondyloarthritis (SpA) represents a family of several heterogeneous and related chronic, immune-mediated, inflammatory conditions that share common clinical features. SpA can be classified as axial or peripheral, based on the predominant features of the clinical presentation, including anatomic distributions and manifestations.¹⁻³

Peripheral SpA conditions, including psoriatic arthritis (PsA), reactive arthritis, inflammatory bowel disease (IBD)-related arthritis, and unspecified SpA, are marked by predominant peripheral joint manifestations. These include inflammatory arthritis in peripheral joints, enthesitis (inflammation of the sites where tendons, muscles, or ligaments insert into the bone), and dactylitis.¹

Patients with axial spondyloarthritis (axSpA) have predominantly axial involvement, characterized by inflammation of 1 or both of the sacroiliac (SI) joints (sacroiliitis, where inflammation typically appears first), inflammation of the spine, or both.^{1,3} Other associated manifestations include inflammatory back pain (IBP), peripheral joint and enthesal manifestations, and extra-articular manifestations such as anterior uveitis (inflammation of the uvea), psoriasis, and IBD (Figure 1^{2,3}).

Approximately 1.5 million Americans are affected by axSpA, with estimates of axSpA's prevalence ranging from 0.9% to 1.4%.^{4,5} Typically, axSpA affects the younger SpA patient population, with an average age of symptom onset of 28 years.⁶ AxSpA consists of 2 subsets of patients: those with nonradiographic axial spondyloarthritis (nr-axSpA) and those with ankylosing spondylitis (AS), also known as radiographic axSpA.^{1,7} Results from current studies indicate that approximately half of all patients with axSpA are patients with nr-axSpA.^{8,9} Patients with AS are more likely to be male, whereas nr-axSpA is equally prevalent in both sexes.¹⁰

AxSpA is marked by a long diagnostic delay compared with other SpA conditions; on average, there is a 9-year period between symptom onset and diagnosis of AS compared with 9 months for rheumatoid arthritis.^{11,12}

Modified New York Criteria

The modified New York criteria for AS (originally developed in 1984) include clinical and radiographic features for diagnosis.¹³ A diagnosis

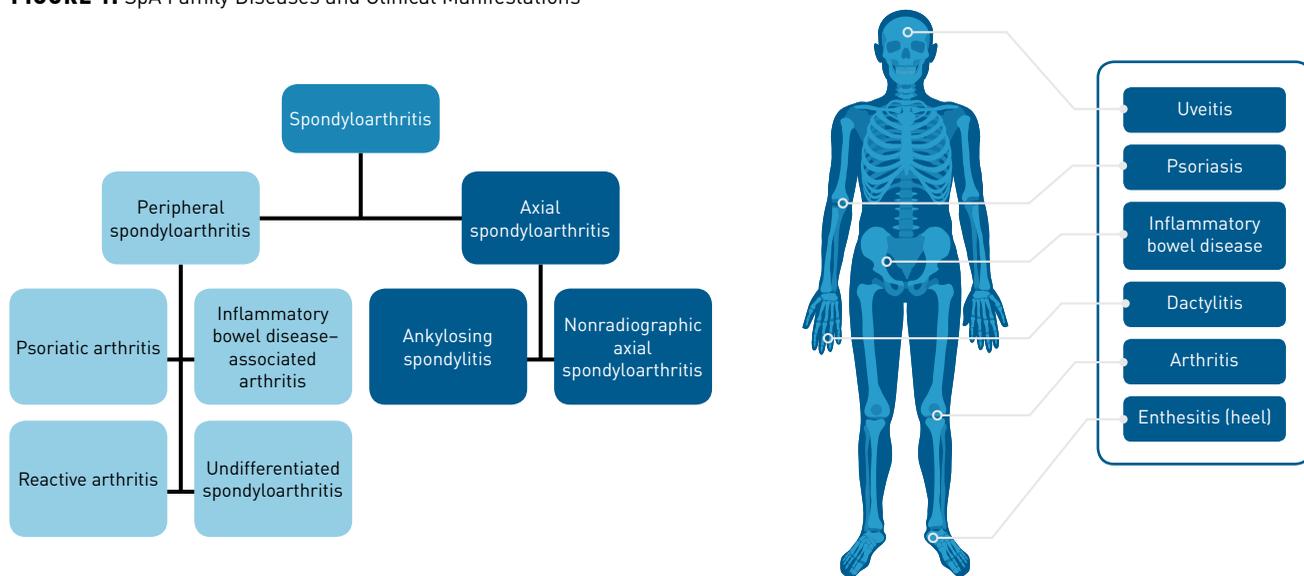
ABSTRACT

Axial spondyloarthritis (axSpA) is a chronic, immune-mediated, inflammatory condition consisting of 2 subsets that have been clinically defined as ankylosing spondylitis (AS) and nonradiographic axial spondyloarthritis (nr-axSpA). It is important to note that nr-axSpA is defined clinically by the absence of definitive x-ray evidence of structural damage to the sacroiliac (SI) joint by plain x-ray. Since the SI joint x-ray interpretation is subjective, the distinction between nr-axSpA and AS is not absolute. Sacroiliitis (inflammation of the SI joint) and inflammation of the spine are predominant features of axSpA, hence patients typically present with inflammatory back pain. Other manifestations, such as enthesitis, dactylitis, peripheral arthritis, anterior uveitis, psoriasis, and inflammatory bowel disease, are common. Despite an increased understanding of axSpA, unmet needs remain: most essentially, to improve the lengthy time to diagnosis after the onset of symptoms and to appropriate treatment. Patients and healthcare systems may incur substantial burden during the prolonged time to diagnosis or while patients are not receiving appropriate treatment for their axial disease. Prolonged time to diagnosis is related to difficulty in differentiating axSpA from common mechanical back pain, and absence of diagnostic criteria adversely affects the quality of care for axSpA. In addition, there are currently no diagnosis or billing codes for nr-axSpA, which poses an administrative challenge to identify and study patients affected. Patients with nr-axSpA have experienced a personal and societal disease burden similar to those of patients with rheumatoid arthritis and SpA conditions (AS and psoriatic arthritis). Healthcare costs of axSpA are substantial, and the costs of lost productivity due to illness are estimated to be even greater. More options are needed in the management of the disease to prevent possible conversion of nr-axSpA to AS; to avoid structural changes that limit spinal range of motion and increase the risk of fracture and spinal fusion; and to reduce the economic burden to patients, healthcare systems, payers, and society overall.

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For author information and disclosures, see end of text.

FIGURE 1. SpA Family Diseases and Clinical Manifestations^{1,2}



Adapted from Raychaudhuri SP, Deodhar A. *J Autoimmun.* 2014;48-49:128-133. doi: 10.1016/j.jaut.2014.01.015.

TABLE 1. Radiographic Sacroiliitis Grading¹⁴

Grade	Definition of radiographic evidence
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 the following: erosions, evidence of sclerosis, widening, narrowing, or partial ankylosis
4	Severe abnormality—total ankylosis

Adapted from Goie The HS, Steven MM, van der Linden SM, Cats A. *Br J Rheumatol.* 1985;24(3):242-249.

of AS requires the presence of 1 or more clinical criteria: These include low back pain and stiffness, lasting longer than 3 months, that improve with exercise but do not improve at rest; limited lumbar spinal movement (sagittal and frontal planes); and/or limited chest expansion for age and sex. The diagnosis also requires meeting one of the radiographic criteria: sacroiliitis on radiographic imaging of at least grade 2 bilaterally or grade 3 to 4 unilaterally or bilaterally.¹³ Sacroiliitis criteria present a barrier to early diagnosis because often the defined radiologic features of AS may not be evident for years after symptom onset.¹³ A substantial proportion of patients with nr-axSpA will not convert to AS; some, however, do.¹⁴

Radiologic and Imaging Assessments

The distinguishing characteristic of nr-axSpA is inflammation in the axial skeleton without definitive sacroiliitis on radiographic (x-ray)

imaging, defined as a combination of erosive damage, joint space widening and narrowing, sclerosis, and bony fusions of the SI joint.^{2,13,15}

X-rays may show structural/radiographic abnormalities from early stages of damage, such as indistinctness of the SI joint margins (widening and narrowing), that do not meet radiographic grading criteria (Table 1¹⁶).^{13,16} In patients with nr-axSpA, inflammation and pain often precede evidence of radiographic sacroiliitis, which may reflect the consequences of inflammation rather than inflammation itself.^{13,17} As opposed to those with nr-axSpA, patients with AS present with definitive radiographic sacroiliitis representing irreversible structural damage.^{13,15,17}

Advancements in imaging with magnetic resonance imaging (MRI) allow detection of early changes to the SI joints in patients with axSpA, including active inflammatory lesions and structural changes.^{13,15,17} Noting that not all nr-axSpA patients convert to AS, MRI abnormalities may often be detected years before the appearance of radiographic sacroiliitis. However, MRI is costlier than x-ray and may not always be available.^{3,13,18}

AxSpA Classification

Physicians consider multiple parameters, including a combination of clinical features, laboratory findings, and imaging assessments, as they look for patterns characteristic of nr-axSpA to establish diagnosis while eliminating other possible diagnoses. Although classification criteria have been established to assist in enrolling patients with axSpA in clinical trials, there are no diagnostic criteria or definitive diagnostic tests.¹³ In the absence of published diagnostic criteria, axSpA is diagnosed through a combination of specific symptoms (inflammatory back pain), extraspinal manifestations,

laboratory abnormalities, genetic characteristics, and findings on imaging.

HLA-B27

A genetic marker, human leukocyte antigen-B27 (HLA-B27), has been useful in the classification of axSpA; however, its presence alone is not sufficient to make a diagnosis.^{18,19} HLA-B27 is a predictor of development of AS in patients with IBP and is also useful for identifying patients with nr-axSpA.^{19,20} Although most patients (between 70% and 95%) with AS have expression of HLA-B27, only 7% to 8% of HLA-B27 carriers in the general population develop AS.^{20,21} HLA-B27 is associated with the following disease features in patients with AS: (1) younger age at disease onset, (2) development of anterior uveitis, and (3) a positive family history of SpA.²⁰

Additional features of axSpA used in the classification of disease include response to NSAIDs, family history of SpA, and elevated C-reactive protein (CRP).³ Notably, patients with AS more commonly have elevated CRP than those with nr-axSpA.²²

Clinical Features

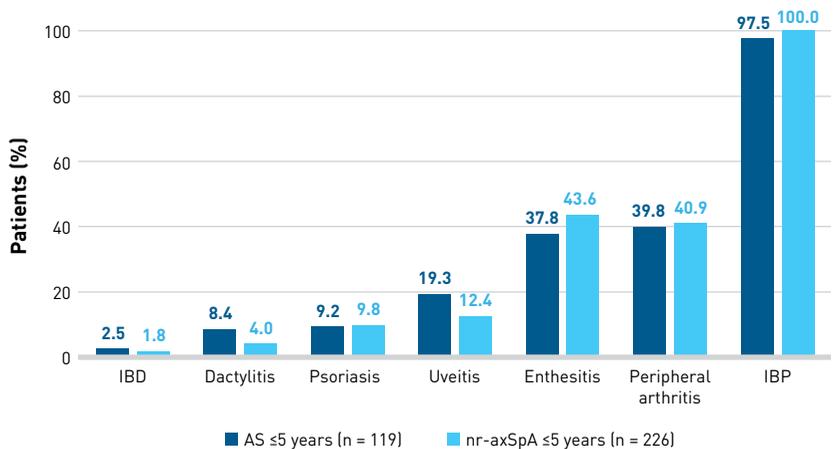
Patients with nr-axSpA and AS share common extraspinal and peripheral manifestations, which can include psoriasis, uveitis, enthesitis, and Crohn disease.^{3,10,19,22,23} In a cross-sectional analysis of patients with axSpA in the German Spondyloarthritis Inception Cohort, the frequency of clinical manifestations (IBD, dactylitis, psoriasis, uveitis, enthesitis, peripheral arthritis, and IBP) were directly compared in patients with AS (n = 119) and nr-axSpA (n = 226) (Figure 2).²⁴ IBP was the most common clinical manifestation observed in both axSpA populations, occurring in 100% and 97.5% of patients with nr-axSpA and AS, respectively.²⁴

IBP and stiffness, hallmarks of axSpA, are caused by inflammation of the SI joint and spine.²⁵ AxSpA occurs in up to 15% of patients with IBP.²⁰ IBP is usually characterized by onset in late adolescence to early adulthood, improves with exercise and worsens at rest, and is associated with prolonged morning stiffness (more than 30 minutes).³ IBP contributes to disability and functional impairments in patients with axSpA.²⁵

Assessment of Spondyloarthritis International Society (ASAS)

The ASAS classification criteria for axSpA were developed to facilitate earlier identification of patients with clinical manifestations of axSpA without definitive sacroiliitis on radiographic imaging.^{3,13} Unlike the modified New York classification criteria for AS, the

FIGURE 2. Clinical Manifestations in Patients With nr-axSpA and AS, GESPIC^{24,a}



AS indicates ankylosing spondylitis; GESPIC, German Spondyloarthritis Inception Cohort; IBD, inflammatory bowel disease; IBP, inflammatory back pain; mNY criteria, modified New York criteria; nr-axSpA, nonradiographic axial spondyloarthritis; SpA, spondyloarthritis.

^aIn GESPIC, all patients had a definite clinical diagnosis of axSpA, and they were classified as having either AS or nr-axSpA based on fulfillment of the mNY criteria.

Adapted from Rudwaleit M, Haibel H, Baraliakos X, et al. *Arthritis Rheum.* 2009;60(3):717-727. doi: 10.1002/art.24483.

ASAS classification includes MRI positivity for active inflammation in the SI joints; it also includes the presence of the HLA-B27 gene.

According to the ASAS criteria, patients with back pain lasting longer than 3 months and an age of onset of less than 45 years can be classified as having axSpA with either (1) the presence of HLA-B27 and 2 or more clinical features of SpA; or (2) definite sacroiliitis on imaging (x-ray or MRI) and 1 or more clinical features of SpA as follows: IBP, arthritis, enthesitis, uveitis, dactylitis, psoriasis, Crohn disease or ulcerative colitis, response to NSAIDs, family history of SpA, HLA-B27, or elevated CRP (Figure 3).^{3,13}

These are classification criteria and are not diagnostic criteria. Use of the ASAS classification criteria for diagnosis could result in misdiagnosis due to the broad inclusion criteria. Objective signs of inflammation help to provide confidence in diagnosis; these include imaging, with no evidence of structural damage at the SI joints evident on x-ray (which, if present, would indicate an AS diagnosis) but evidence of active inflammation on MRI; laboratory tests indicating a high level of systemic inflammation (ie, elevated CRP); and associated extraspinal and peripheral manifestations such as active uveitis, psoriasis, IBD, dactylitis, peripheral arthritis, and enthesitis.¹⁴

AxSpA Disease Progression and Associated Risk Factors

Radiographic Progression of nr-axSpA

Prevention of inflammation is key in the management of axSpA. Ultimately, the prevention of progressive structural damage is the aspirational goal. Although both active inflammation and resulting

structural damage may contribute to impaired spinal function and mobility, the component of disability due to structural damage is not reversible.^{17,25} Nr-axSpA may progress to AS in some patients; however, not all patients with nr-axSpA will show signs of progression with radiographic changes leading to development of AS.²⁶

The rate of radiographic progression of nr-axSpA (ie, development of definitive structural changes of the SI joint) is variable. In a literature review of several longitudinal studies investigating radiographic progression in patients without structural damage in

the SI joint, approximately 10% to 40% of patients with nr-axSpA converted to AS over 2 to 10 years.¹⁴

Risk Factors for Conversion From nr-axSpA to AS

Limited data are available to predict which patients with nr-axSpA will develop structural changes in the SI joints and experience progression to AS.^{14,23} Signs of active systemic inflammation, as indicated by elevated CRP levels, correlate with progression of radiographic damage to the spine.¹⁴ Additional risk factors for disease conversion include objective signs of inflammation on imaging (ie, presence of active or chronic inflammatory changes on MRI of the SI joints). The presence of low-grade structural damage on radiographs or MRI is also a risk factor.¹⁴

Irreversible Progression of AS

The progression of spinal damage of AS begins with bone inflammation, which may be visible as osteitis, typically seen on a short tau inversion recovery (STIR) image of the MRI.^{13,17} To repair the tissue, subchondral bone marrow is replaced with fatty metaplasia, which may present as a fatty lesion on a T1 weighted MRI scan.^{13,17} Presence of either inflammation or intermediate stage of fatty lesions may play an important role in the development of new bone formation (structural damage), highlighting the need for early abrogation of inflammation to reduce risk.¹⁷

Approximately 60% to 70% of patients with AS develop irreversible structural changes that result in spinal fusion and reduced spinal mobility.^{17,26} Although patients with AS usually present with compromised physical and spinal function due to structural damage and inflammation, in patients with nr-axSpA, this functional impairment is typically due to inflammation alone.^{15,27}

Risk Factors for Radiographic Progression of AS

Risk factors for progression of spinal disease, in those patients already known to have AS, include male sex, presence of syndesphophytes at baseline, elevation of CRP, and smoking (in men).^{20,28}

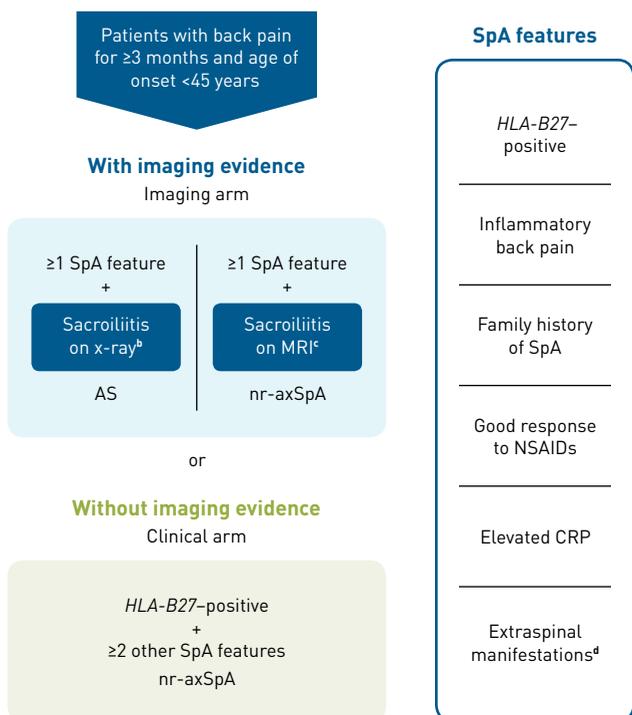
Clinical and Economic Burden of axSpA

Productivity Losses and Employment Limitations

AxSpA is associated with substantial clinical and economic burden for patients and healthcare systems. Patients with axSpA have physical limitations that can adversely affect employment, work productivity, leisure activities, mood, and interpersonal relationships.

Patients with axSpA and other inflammatory rheumatic diseases (PsA and RA) share a similar burden of disease on health-related quality of life, demonstrated by Short Form-36 physical and mental function scores (Figure 4).²⁹ Results from a study that evaluated patients with axSpA (N = 324) according to ASAS criteria found that 42.1% (n = 178) of patients with AS and 35.4% (n = 146) of patients with nr-axSpA required help with their daily activities from relatives, friends, or

FIGURE 3. ASAS Classification for axSpA^{3,13,a}



AS indicates ankylosing spondylitis; ASAS, Assessment of SpondyloArthritis International Society; axSpA, axial spondylitis; CRP, C-reactive protein; HLA, human leukocyte antigen; mNY criteria, modified New York criteria; MRI, magnetic resonance imaging; nr-axSpA, nonradiographic axial spondyloarthritis; NSAIDs, nonsteroidal anti-inflammatory drugs; SpA, spondyloarthritis; STIR, short tau inversion recovery.

^aASAS criteria are used for classification and are not typically used for diagnosis.

^bDefinite sacroiliitis on x-ray is defined according to the mNY criteria (at least grade 2 bilaterally or grade 3-4 unilaterally).

^cThe ASAS definition of positive MRI for sacroiliitis of sacroiliac joint includes: active inflammation of subchondral or periarticular bone marrow; active inflammation is defined as bone marrow edema on STIR sequences or osteitis on gadolinium-enhanced T1-weighted sequences; or 2 or more lesions must be present on the same coronal slice or a single lesion must be visible on 2 consecutive slices. Other inflammatory features of axSpA, such as synovitis, enthesitis, and capsulitis are believed to be rare in the absence of bone marrow edema and in isolation are not sufficient for diagnosis.^{3,13}

^dExtraspinous manifestations may include current or history of arthritis, enthesitis (heel), uveitis, dactylitis, psoriasis, Crohn's, or ulcerative colitis.

Adapted from Rudwaleit M, Van der Heijde D, Landewé R, et al. *Ann Rheum Dis*. 2009;68(6):777-783. doi: 10.1136/ard.2009.108233.

paid caregivers, and those patients reported higher household and workplace activity losses than those who did not require assistance.³⁰

It has been suggested that costs related to productivity losses constitute the largest part of the total cost of illness of AS.³¹ The economic impact of work limitations and lost productivity related to axSpA is likely compounded by the typically young age at diagnosis (28 years).³¹ A survey for the British Society for Rheumatology Biologics Register of patients with axSpA (N = 577) found that up to 41% of patients reported an at-work productivity loss due to their disease.³² A reason for the amount of work loss from axSpA is that back pain is the primary symptom³¹; this causes more disability than any other condition and is among the most common reasons that people miss work.³³

The CORRONA registry evaluated the characteristics of patients with AS and nr-axSpA in the United States, and it demonstrated similar disease-related burdens in both groups of clinical pain and fatigue scores, disease activity, and function, with impacts on absenteeism, presenteeism, work productivity loss, and overall activity impairment (Figure 5).²³ Patients with nr-axSpA, versus patients with AS, had a significantly greater mean percentage of presenteeism (32.6% vs 24.2%; $P = .02$) and overall activity impairment (36.6% vs 28.6%; $P = .04$). On average, patients with AS and nr-axSpA missed 6.3% of work time because of disease-related problems.²³ In a phase 3 double-blind study evaluating the effects of axSpA on work productivity, patients with nr-axSpA reported approximately 8 days of paid work affected by their disease every month.³¹ Similar trends in absenteeism and presenteeism were observed in patients with AS and nr-axSpA (Figure 6).³¹

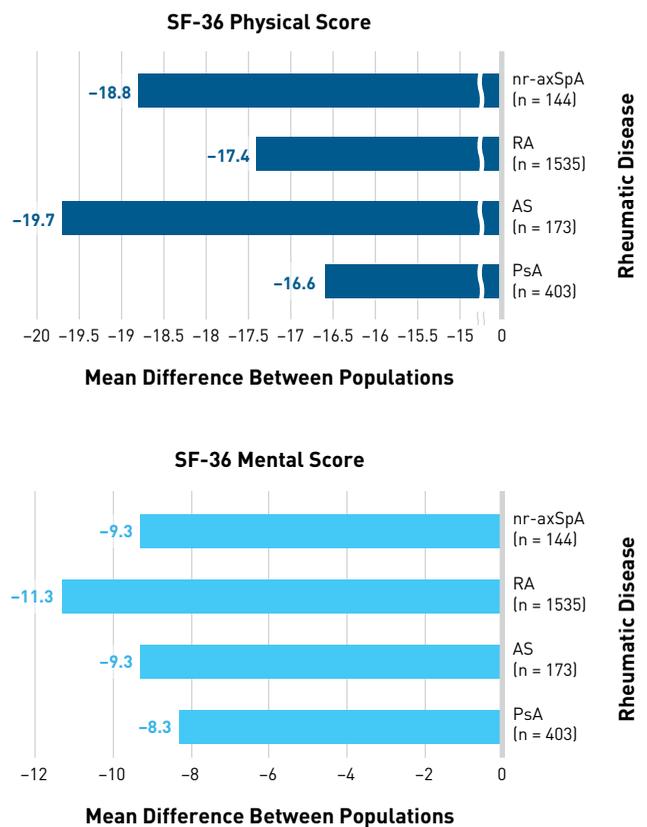
Patients may experience work instability, may be unable to meet the physical demands of a job, and may be forced into early retirement.³⁴ The financial and clinical burden associated with axSpA is significant and affects patients, healthcare systems, and society overall.

Increased Prevalence of Comorbidities and Healthcare Costs

Patients with axSpA show an increased prevalence of comorbidities and extraspinal manifestations of their disease, driving axSpA-associated healthcare costs. In a retrospective observational study using a large US-based healthcare claims database, patients with AS had a higher prevalence of comorbidities compared with a matched population, including asthma, cardiovascular disease, depression, dyslipidemia, multiple sclerosis, osteoporosis, spinal fracture, IBD, and psoriasis.³⁵

Patients with AS also have an increased risk of vascular mortality. An updated meta-analysis of 12 longitudinal studies demonstrated the risk of myocardial infarction (MI) to be significantly higher in patients with AS compared with a matched control population (risk ratio [RR], 1.44; 95% CI, 1.25-1.67; $P < .00001$).^{36,37} Similarly, a meta-analysis of 7 studies showed a significant increase in the risk of stroke

FIGURE 4. Patient HRQOL: Mean Differences in SF-36 Scores Between Rheumatic Disease Population and Age- or Gender-Matched Population^{29,a}



AS indicates ankylosing spondylitis; HRQOL, health-related quality of life; nr-axSpA, nonradiographic axial spondyloarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SF-36, short form (36) health survey.

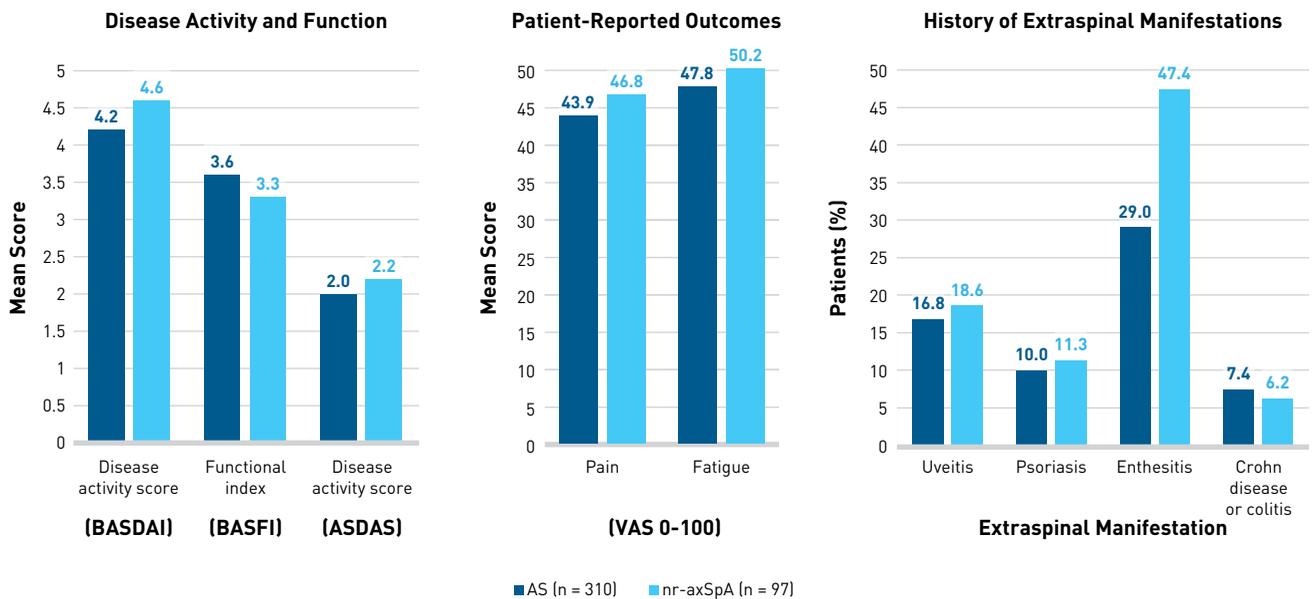
^aHRQOL scores were derived from a comparison of patients with the particular rheumatic disease versus patients without a rheumatic disease that were age- and gender-matched.

Adapted from Mease PJ, van Tubergen A, Deodhar A, Coteur G, Nurminen T, van der Heijde D. *Ann Rheum Dis*. 2013;72(3 suppl):A766-A767. doi: 10.1136/annrheumdis-2013-eular.2269.

(RR, 1.37; 95% CI, 1.08-1.73; $P < .008$).³⁶ Patients with AS (n = 21,473) had a 43% higher risk of vascular death than those without AS (adjusted HR, 1.36; 95% CI, 1.13-1.65) in an analysis of administrative health data from a Canadian population-based retrospective cohort study.³⁷

Increased comorbid conditions with AS contribute to higher healthcare costs, as shown in an analysis of a large US claims database. Patients with AS and comorbid conditions had higher rates of all-cause inpatient readmission, emergency department (ED) visits, and hospital-based outpatient visits than a matched population without AS ($P < .001$).³⁵ Patients in the population with AS also had higher mean total all-cause healthcare costs than the matched control population (\$33,285 vs \$8310), with a mean healthcare cost of \$16,337 per patient with AS. Total all-cause healthcare costs were driven by

FIGURE 5. Relative Disease Burden in AS and nr-axSpA, Corrona Registry^{23,a}

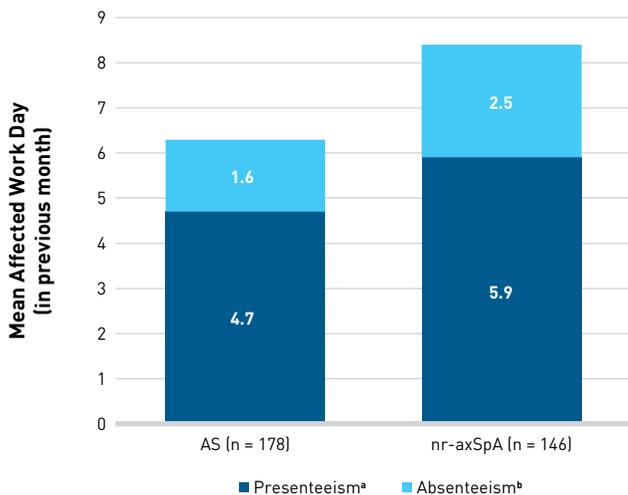


AS indicates ankylosing spondylitis; ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; nr-axSpA, nonradiographic axial spondyloarthritis; VAS, visual analogue scale.

^aThe Corrona Psoriatic Arthritis/Spondyloarthritis Registry is a prospective, multicenter, observational disease-based registry designed to collect data in the United States to better understand axSpA.

Adapted from Mease PJ, van der Heijde D, Karki C, et al. *Arthritis Care Res.* 2018;70(11):1661-1670. doi: 10.1002/acr.23534.

FIGURE 6. Burden of Disease on Workplace Productivity in Patients With AS and nr-axSpA³¹



AS indicates ankylosing spondylitis; nr-axSpA, nonradiographic axial spondyloarthritis.

^aPresenteeism was defined as days with work productivity reduced by at least 50% due to arthritis in the previous month (does not include days counted in absenteeism).

^bAbsenteeism was defined as work days missed due to arthritis in the previous month.

Adapted from van der Heijde D, Braun J, Rudwaleit M, Purcaru O, Kavanaugh AF. *RMD Open.* 2018;4(1):e000659. doi: 10.1136/rmdopen-2018-000659.

the increased use of outpatient medical services and pharmacy costs, and AS-specific costs were driven by the costs of AS medications.³⁵

Because the clinical burden of nr-axSpA is similar to that of AS, healthcare costs associated with nr-axSpA and AS are likely similar.³⁸ A retrospective cohort review of an administrative claims database assessed healthcare resource use and direct costs of AS. During the 12-month follow-up, 11.1% of all-cause healthcare resource use by patients with AS was due to hospitalizations and 22% was due to ED visits.³⁹ Unadjusted mean annual all-cause direct costs during 12-month follow-up included \$6514 for medical costs, \$4185 for hospitalizations, and \$11,214 for prescription drugs.³⁹ Additionally, several factors may indirectly drive the healthcare costs and total economic burden of axSpA. As discussed previously, the long duration to axSpA accurate diagnosis from symptom onset (9 years) may be associated with increased costs and healthcare resource utilization prior to diagnosis, such as multiple follow-up visits and treatments.

Considerations in the Management of nr-axSpA

Opioid use is common among patients with axSpA. A retrospective analysis of commercial and Medicaid claims data from a US claims database evaluated opioid use among patients with AS. In this study, investigators defined “chronic” opioid use as 90 or more days of opioid use within a 12-month period. The study results showed that approximately two-thirds of patients who used opioids

chronically had at least a 270-day supply during the 12-month evaluation period. Of the patients with axSpA who use opioids chronically to manage pain (26%), 44% use opioids exclusively, which fails to address underlying inflammation.⁴⁰ Early diagnosis and appropriate management are important because most function loss occurs within the first 10 years of disease.³³ Appropriate treatment of nr-axSpA can limit the impact of disease; however, treatment options for nr-axSpA are limited. Studies have shown a trend in the overtreatment (including opioids) of chronic back pain without an overall improvement in patient outcomes.³³

2019 ACR/SAA/SPARTAN Recommendations

Evidence-based recommendations in 2015 from the American College of Rheumatology (ACR), Spondylitis Association of America (SAA), and Spondyloarthritis Research and Treatment Network (SPARTAN) provided treatment goals for AS and nr-axSpA, including preventing inflammation and progressive structural damage; reducing symptoms and decreasing disease complications; reducing functional limitations; maintaining spinal flexibility and normal posture; preserving/normalizing function and social participation; and restoring ability to work.²⁶ In 2019, updated recommendations provided evidence-based guidance on the use of imaging, treat-to-target strategy, pharmacotherapy, and nonpharmacologic treatment options for the management of patients with AS and nr-axSpA.⁴¹

Imaging

The ACR/SAA/SPARTAN guidance recommends MRI imaging for patients who have unclear disease activity, or if a patient's MRI results could potentially change the course of their treatment. MRI imaging may focus on the spine or pelvis for patients with AS, and on the SI joints for those with nr-axSpA.⁴¹ The guidance also conditionally recommends against an MRI for patients with AS or nr-axSpA who have clearly clinically active or clinically stable disease, or if the results of the MRI do not have the potential to change treatment decisions. This recommendation was based on testing burdens, the potential for overtreatment, limitations in the detection of axSpA activity with MRI, and limited evidence that MRI results can help enhance clinical outcomes for stable patients. MRI imaging may be warranted if the patient and clinician disagree about whether the condition is stable.⁴¹

Radiographs may be limited to diagnosing axSpA, identifying the extent of spinal fusion, and exploring the possible cause of new spinal pain in patients with AS.⁴¹ The ACR/SAA/SPARTAN guidance recommends that regular radiographs be avoided, as no known clinical evidence indicates benefit that would offset the health risks to the patient that would come with repeated radiation exposure. The treat-to-target approach for active AS or active nr-axSpA, which places more importance on reaching a target Ankylosing Spondylitis Disease Activity Score of less than 1.3 (or 2.1) than physician assessment, is not endorsed.⁴¹

Treatment

Nonsteroidal anti-inflammatory drugs (NSAIDs) and physical therapy are strongly recommended as first-line management strategies for patients with active axSpA.⁴¹ Although NSAIDs can effectively control pain and improve physical function,^{41,42} not all patients respond to or tolerate NSAIDs.⁴³ Furthermore, treatment with NSAIDs does not always lead to adequate control of symptoms.⁴⁴

For patients with AS or nr-axSpA who do not respond to or tolerate at least 2 different NSAIDs at maximal doses over 1 month, or for patients who have partial response to 2 different NSAIDs over 2 months, treatment with a tumor necrosis factor (TNF) inhibitor (such as infliximab, etanercept, adalimumab, certolizumab, or golimumab) is strongly recommended.⁴¹ In patients with nr-axSpA, this recommendation was based on the evidence from several phase 3 clinical trials investigating the efficacy and safety of numerous TNF inhibitors (**Table 2**).⁴⁵⁻⁵³ TNF inhibitors are associated with global improvement in health-related quality of life by inhibiting the progression of disease; decreasing mean quarterly lost work days; improving function, spinal mobility, peripheral arthritis, enthesitis, bone density, and acute inflammation; and reducing pain and fatigue.^{33,42,54}

Notably, at the time of publication, the TNF inhibitor certolizumab pegol is the sole FDA-approved treatment for nr-axSpA.⁵⁵ The ACR/SAA/SPARTAN guidance does not recommend a specific TNF inhibitor for the treatment of AS or nr-axSpA.⁴¹ Given the limited evidence comparing the relative safety and efficacy of TNF inhibitors in patients with nr-axSpA,⁴¹ treatment recommendations for nr-axSpA were largely extrapolated from available evidence in the AS population; they were based on the results of indirect comparisons of network meta-analyses of short-term efficacy of different TNF inhibitors for active AS.⁴¹

A TNF inhibitor is recommended over an interleukin (IL)-17A as the first biologic treatment. For patients who do not experience symptom control with a TNF inhibitor, an IL-17A (secukinumab or ixekizumab) is recommended over switching to another TNF inhibitor. This recommendation is conditional, with the assumption that symptoms are unresponsive because TNF is not the key inflammatory mediator.⁴¹ In patients with AS, treatment with secukinumab or ixekizumab is strongly recommended over no treatment with secukinumab or ixekizumab; however, this is conditionally recommended in patients with nr-axSpA given that the trials for secukinumab and ixekizumab are currently being conducted and preliminary results have not been published (**Table 2**).⁴⁵⁻⁵³⁴¹ For patients with active AS or nr-axSpA despite NSAID treatment who are contraindicated for treatment with TNF inhibitors, IL-17A inhibitors are conditionally recommended over certain conventional synthetic antirheumatic drugs.⁴¹

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TABLE 2. Selected Efficacy Outcomes From Phase 3 Clinical Trials in Patients With nr-axSpA⁴⁵⁻⁵³

Agent (Trial)	Patient Population	Design	Treatment	Efficacy Outcomes		
				Primary endpoint	Secondary endpoint	
Anti-TNF				ASAS40^b (week 12)	ASAS20^c (week 12)	
Adalimumab (ABILITY-1 [NCT00939003])	N = 185 Patients: <ul style="list-style-type: none"> were ≥18 years of age had active nr-axSpA met the 2009 ASAS classification criteria^a did not meet the mNYC criteria for AS had an active disease (BASDAI ≥4 and total back pain ≥4) responded inadequately to or could not tolerate ≥1 NSAID (or NSAIDs were contraindicated) 	Patients were randomized to receive adalimumab 40 mg SC or placebo Q2W during a 12-week double-blind period (N = 185). This was followed by a 144-week open-label extension in which all patients received adalimumab 40 mg SC Q2W for a total of 3 years (N = 179).	Adalimumab (n = 91)	36%	52%	
			Placebo (n = 94)	15%	31%	
					<i>P</i> <.001	<i>P</i> <.001
					ASAS40 (year 3)	ASAS20 (year 3)
				43.8%	54.6%	
				Outcomes reached through the nonresponder imputation method.		
				ASDAS-MI^d (week 52)	ASAS40 (week 12)	
Certolizumab pegol (C-AXSPAND [NCT02552212])	N = 317 Patients: <ul style="list-style-type: none"> were ≥18 years of age had adult-onset active nr-axSpA for at least 12 months had objective signs of inflammation (positive CRP and/or positive MRI) responded inadequately to or could not tolerate ≥1 NSAID or could not tolerate a maximal dose of NSAIDs for 30 days 	Patients were randomized (1:1) to receive a loading dose of certolizumab pegol 400 mg SC or placebo SC at weeks 0, 2, and 4 followed by certolizumab pegol 200 mg SC or placebo SC Q2W for 52 weeks.	Certolizumab pegol (n = 159)	47%	48%	
			Placebo (n = 158)	7%	11%	
					<i>P</i> <.0001	<i>P</i> <.0001
				ASAS40 (week 12)	ASAS20 (week 12)	
Etanercept (EMBARK [NCT01258738])	N = 215 Patients: <ul style="list-style-type: none"> were ≥18 years to <50 years of age had active nr-axSpA met the 2009 ASAS classification criteria had an active disease (BASDAI ≥4) had symptoms that lasted >3 months and <5 years had chronic back pain that hadn't adequately responded to ≥2 NSAIDs taken separately for a total combined time of >4 weeks. received a stable, tolerated dose of NSAIDs for ≥14 days before study baseline 	During the initial 12-week period, patients were randomized (1:1) to either etanercept 50 mg SC weekly or a matching placebo. This was followed by an open label extension in which all patients received etanercept 50 mg SC weekly and a background NSAID for an additional 92 weeks.	Etanercept (n = 106)	32%	52%	
			Placebo (n = 109)	16%	36%	
					<i>P</i> = .006	
					ASAS40 (week 104)	ASAS20 (week 104)
				61%	75%	

(continued)

TABLE 2. Selected Efficacy Outcomes From Phase 3 Clinical Trials in Patients With nr-axSpA (Continued)⁴⁵⁻⁵³

Agent (Trial)	Patient Population	Design	Treatment	Efficacy Outcomes	
				Primary endpoint	Secondary endpoint
Anti-TNF (Continued)				ASAS20 (week 16)	ASAS40 (week 16)
Golimumab* (GO-AHEAD [NCT01453725])	<p>N = 98</p> <p>Patients:</p> <ul style="list-style-type: none"> were ≥18 to ≤45 years of age had active nr-axSpA met the 2009 ASAS classification criteria had an active disease (BASDAI ≥4 and total back pain ≥4) were diagnosed within the previous 5 years had experienced chronic back pain for ≥3 months responded inadequately to or could not tolerate ≥1 NSAID or could not tolerate a maximal dose of NSAIDs for 30 days 	<p>Patients were randomized (1:1) to receive either golimumab 50 mg SC or placebo SC Q4W for 16 weeks.</p>	Golimumab (n = 93)	71%	57%
			Placebo (n = 97)	40%	23%
				<i>P</i> <.0001	<i>P</i> <.0001
Anti-IL-12/IL-23				ASAS20 (week 24)	ASAS40 (week 24)
Ustekinumab (NCT02407223)	<p>N = 250</p> <p>Patients:</p> <ul style="list-style-type: none"> were 18 to 50 years of age had active nr-axSpA met the 2009 ASAS classification criteria had experienced onset of disease by age 45 had back pain for ≥3 months responded inadequately to or could not tolerate ≥1 NSAID or could not tolerate a maximal dose of NSAIDs for 30 days 	<p>Patients were randomly assigned (1:1:1) to receive either ustekinumab 45 mg or 90 mg SC at weeks 0, 4, 16 and then every 12 weeks or placebo at weeks 0, 4, and 16.</p> <p>Placebo-treated patients were rerandomized at week 24 to receive ustekinumab 45 mg or 90 mg SC at weeks 24 and 28 and then every 12 weeks.</p>	Ustekinumab 45 mg (n = 83)	55%	34%
			Ustekinumab 90 mg (n = 85)	49%	28%
			Placebo (n = 82)	48%	26%
				NS	NS
Anti-IL-17				ASAS40 (week 16)	ASAS40 (week 52)
Ixekizumab (COAST-X [NCT02757352])	<p>N = 305</p> <p>Patients:</p> <ul style="list-style-type: none"> were ≥18 years had active nr-axSpA met the 2009 ASAS classification criteria were biologic disease-modifying antirheumatic drug (bDMARD)-naïve had active disease (BASDAI ≥4 and total back pain ≥4 at screening and baseline) had objective signs of inflammation (positive CRP and/or positive MRI) responded inadequately to ≥2 NSAIDs for 4 weeks or could not tolerate NSAIDs 	<p>Patients were randomized (1:1:1) to receive either ixekizumab SC Q2W, ixekizumab SC Q4W, or placebo Q2W for up to 52 weeks.</p>	<p>Ixekizumab Q2W</p> <p>Ixekizumab Q4W</p> <p>Placebo Q2W</p>	<p>The trial was completed on May 7, 2019. No results have been published.</p>	

(continued)

TABLE 2. Selected Efficacy Outcomes From Phase 3 Clinical Trials in Patients With nr-axSpA (Continued)⁴⁵⁻⁵³

Agent (Trial)	Patient Population	Design	Treatment	Efficacy Outcomes	
				Primary endpoint	Secondary endpoint
Anti-IL-17 (Continued)				ASAS40 (week 16)	ASAS40 (week 52)
Secukinumab (PREVENT [NCT02696031])	<p>N = 555</p> <p>Patients:</p> <ul style="list-style-type: none"> • were ≥18 years of age • had active nr-axSpA • met the 2009 ASAS classification criteria • had an active disease (BASDAI ≥4 and total back pain ≥4) • had objective signs of inflammation (positive CRP and/or positive MRI) • responded inadequately to ≥2 different NSAIDs • responded inadequately to a TNFα inhibitor (not more than 1) 	Patients were assigned to 1 of 3 treatment groups: secukinumab 150 mg SC with loading dose (induction of 150 mg secukinumab SC weekly for 4 weeks, then maintenance with 150 mg secukinumab monthly), secukinumab 150 mg no loading dose (150 mg secukinumab SC monthly), or placebo (induction of placebo SC weekly for 4 weeks, followed by maintenance once monthly).	<p>Secukinumab 150 mg with loading dose</p> <p>Secukinumab 150 mg no loading dose</p> <p>Placebo</p>	The estimated trial completion date is December 16, 2020. No results have been published.	

ASAS indicates Assessment in Spondyloarthritis International Society; ASDAS-MI, Ankylosing Spondylitis Disease Activity Score-Major Improvement; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; nr-axSpA, nonradiographic axial spondyloarthritis; MI, major improvement; mNYC, modified New York Criteria; MRI, magnetic resonance imaging; NS, not significant; NSAID, nonsteroidal anti-inflammatory drug; Q2W, every 2 weeks; Q4W, every 4 weeks; SC, subcutaneously; TNFα, tumor necrosis factor alpha.

*The 2009 ASAS classification criteria are sacroiliitis (by radiography or by MRI) in addition to ≥1 SpA feature or the presence of HLA-B27 plus ≥2 SpA features.

^aASAS20 is an improvement of ≥20% and absolute improvement of ≥10 units on a 0-100 scale in ≥3 of the 4 domains.

^bASAS40 is an improvement of >40% and absolute improvement of >10 units on a 0-100 scale in ≥3 of the 4 domains.

^cASDAS-MI is defined as a ≥2.0-point decrease from the baseline score in the ASDAS or achievement of the lowest possible ASDAS value (0.6).

^dGolimumab met the primary endpoint among all patients, but in a subanalysis the TNFα inhibitor was significantly better than placebo only among patients with evidence of inflammation on MRI or an elevated CRP at baseline (76.9% vs 37.5%; $P < .0001$).

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Unmet Needs in the Management of axSpA

The advent of advanced imaging with MRI scanning and the employment of genetic testing for *HLA-B27* have contributed to the recognition of nr-axSpA in its earlier stages.^{13,19} However, prevalence of *HLA-B27* is dependent on the racial background of the patients studied, and utility of advanced imaging is affected by operator experience.^{56,57} And, despite these advancements in detection, substantial unmet needs in the management of axSpA must be addressed, namely improving the delayed diagnosis of nr-axSpA with better identification of the disease at symptom onset and earlier treatment to prevent long-term suffering and to improve quality of life.⁶

One factor contributing to the delay in diagnosis is the difficulty in distinguishing patients with axSpA from patients with chronic low back pain of mechanical origin. Chronic low back pain is common and affects approximately 19% of the general population in the United States.⁵⁸ Of those patients with chronic low back pain, just 5% have axSpA.²¹ A multicenter, single-visit study was conducted to determine the proportion of patients with nr-axSpA, AS, and axSpA among 751 patients who had had chronic back pain for at least 3 months, whose age of onset was less than 45 years, and who had

at least 1 of the following features: *HLA-B27* positivity, current IBP, and evidence of sacroiliitis on MRI or radiographic imaging. The age of onset of chronic low back pain in patients who received a diagnosis of axSpA from a rheumatologist for AS or nr-axSpA was reported to be 28.1 and 27.3 years, respectively, with a mean duration of back pain of 14 years prior to diagnosis.⁶

Early identification is important to prevent the incapacity the axSpA diseases can cause, with early treatment intervention.^{17,59,60} However, prolonged time to diagnosis invariably results in critical delays in these therapeutic interventions.⁶¹

Unlike AS and the other SpA conditions, nr-axSpA does not have an *International Classification of Diseases, Version 10 (ICD-10)* code, which is needed for its classification as a disease and for reimbursement of healthcare services. A specific *ICD-10* code for nr-axSpA would address the administrative challenge of identifying patients and classifying disease, and would facilitate the generation of key research in real-world clinical databases.^{62,63}

Conclusions

Increased awareness among patients, healthcare systems, and payers about axSpA is necessary to prevent delay in diagnosis, improve patient outcomes, prevent structural damage, and control direct and

indirect costs for all stakeholders. Chronic back pain and reduced physical function cause substantial loss of productivity for patients with axSpA and contribute to its high associated healthcare costs. Special care should be taken to identify younger patients presenting with symptoms, because they bear a substantial part of the burden of this disease and represent a window of opportunity for treatment. It is important to understand that the healthcare burden of nr-axSpA is similar in terms of pain and disability to that of SpA conditions (AS and PsA) and of RA. Further complicating disease management is the fact that there are no diagnosis/billing codes for nr-axSpA, which poses an administrative challenge in identifying and classifying the disease and the patients affected. ■

Author Affiliation: Rheumatology Clinics, Division of Arthritis & Rheumatic Diseases, Oregon Health & Science University, Portland, OR.

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Address Correspondence to: deodhara@ohsu.edu.

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