



# Axial spondyloarthritis in the USA: diagnostic challenges and missed opportunities

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## Abstract

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease that primarily affects the sacroiliac joints and spine. Delayed or inadequate treatment may decrease quality of life and lead to poor long-term outcomes, including irreversible loss of spinal function. In this review, we discuss clinical practice related to axSpA within the USA, including prevalence, diagnosis, reasons for delayed/missed diagnosis, and suggestions for making early diagnosis. The US population prevalence of axSpA (0.9–1.4%) is higher than the diagnostic prevalence (0.2–0.7%). Although the estimated diagnostic delay for axSpA is 14 years in the USA, the disease can be identified earlier if appropriately preselected patients are quickly referred to rheumatologists. Only 37% of patients with ankylosing spondylitis in the USA are diagnosed by rheumatologists; the remaining 63% are diagnosed by primary care (26%), chiropractic/physical therapy (7%), orthopedic surgery (4%), pain clinics (4%), acute care (3%), and other settings (19%). To help reduce diagnostic delay, non-rheumatologist-healthcare professionals are urged to refer patients with back pain and  $\geq 1$  of 3 SpA features (HLA-B27 positivity, current inflammatory back pain, or x-ray/MRI evidence of sacroiliitis) to a rheumatologist. Prevalence and diagnosis rates of axSpA are disparate in the USA due to the lack of awareness and knowledge among non-rheumatologists. Progress has been made in identifying hurdles causing diagnostic delays. Public health initiatives are needed to guide primary care physicians, physical therapists, chiropractors, and other specialists seeing patients with chronic back pain on methods for suspecting or identifying axSpA and early referral to rheumatologists.

**Keywords** Ankylosing spondylitis · Axial spondyloarthritis · Clinical practice in the USA · Inflammatory back pain · Non-radiographic axial spondyloarthritis · Referral strategy

## Introduction

Axial spondyloarthritis (axSpA), a chronic inflammatory rheumatic disease primarily affecting the sacroiliac joints (SIJs) and spine, commonly presents in patients aged <40 years, with inflammatory back pain (IBP) as a presenting symptom [1–4]. The term axSpA encompasses both ankylosing spondylitis (AS) and non-radiographic axSpA (nr-axSpA), which are distinguished by the presence or absence of definitive sacroiliitis on plain radiographs [5]. Disease activity and

impairment in quality of life (QOL) are similar between patients with AS and nr-axSpA [6]. Hence, treating both conditions with equal priority is important because early treatment improves symptoms, function, and inflammation as viewed by magnetic resonance imaging (MRI) [7]. Distinguishing between AS and nr-axSpA can be important for scientific and clinical research purposes, but this differentiation is generally not necessary or practical for diagnostic or treatment purposes in daily clinical practice [5, 8]. Although the natural history of nr-axSpA is not fully understood, studies indicate that patients with nr-axSpA can experience progression to AS over time [9].

Many studies on prevalence, diagnosis, and prognosis of axSpA originate from Europe, and the clinical situation regarding these issues is less well understood in the USA. Interestingly, back pain, one of the cardinal symptoms of axSpA, is extremely prevalent in the USA [10], but there is limited information about which healthcare providers (HCPs) treat patients with back pain. The prevalence rates of

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rheumatoid arthritis (RA) and axSpA in the USA are similar [11, 12]. As RA presents with pain and swelling of hand joints, it is easily recognizable by non-rheumatology HCPs. However, it is difficult to examine the back and SIJs of patients with axSpA. Also, axSpA is more challenging to diagnose because chronic back pain is highly prevalent in the general population and patients with axSpA account only for 5% of these individuals [13, 14]. These factors cause underrecognition of axSpA that can result in a missed or late diagnosis, which, in turn, leads patients to have prolonged pain, stiffness, fatigue, and decreased mobility. Additional poor long-term outcomes include irreversible new bone formation in the axial skeleton, loss of spinal function, and reduced QOL [1, 15, 16].

A few characteristics of back pain in axSpA and associated laboratory and imaging features can provide clues to the presence of the condition. Using these criteria as filters in patients with back pain may help non-rheumatology HCPs identify patients with suspected axSpA early and appropriately refer them to rheumatologists.

This review examines the US clinical situation of axSpA delayed/missed diagnosis and provides practical guidance on strategies for improving early diagnosis.

## Methods

We included original articles concerning human studies published between January 1984 and June 2018. A targeted PubMed literature review used all possible combinations of the following terms: nr-axSpA, AS, diagnosis, prevalence, classification criteria, comorbidities, practitioners, imaging, x-ray, MRI, computed tomography, and IBP. Titles, abstracts, and full reports of the resulting articles were screened for relevance. Search results were enhanced by reference citations in articles identified in initial searches and based on the authors' familiarity with the published literature. Articles were selected if they provided insight into the US clinical practice situation regarding the prevalence or diagnosis of axSpA or reasons for delayed/missed diagnosis.

## US prevalence of AxSpA

Varying diagnostic and population prevalence findings for axSpA have been reported by US studies. A retrospective chart review of Mayo Clinic (Rochester, MN, USA) records from 1935 to 1973 found the prevalence of AS to be 129 per 100,000 in a predominately white population [17]. An updated study of patients from Rochester, MN, which examined records from 1935 to 1989, reported the incidence of AS to be 7.3 per 100,000 person-years [18]. In 2008, the National Arthritis Data Workgroup reported the prevalence of AS in a

US population sample to be 520 per 100,000 [19]. Data from the 2009–2010 National Health and Nutrition Examination Survey (NHANES; a cross-sectional survey of the civilian, non-institutionalized US population) indicated that the population prevalence of axSpA is 0.9 to 1.4% (i.e., 1.7–2.7 million persons) [20]. A retrospective review of medical records of a random sample of 514 patients from US rheumatology practices who were identified as being at risk for axSpA (defined as age 18–44 years with chronic back pain) estimated the prevalence of axSpA to be 0.7% [11]. A recent analysis from the Northern California Kaiser Permanente database estimated that the diagnostic prevalence of axSpA in US healthcare settings is 0.2% and the diagnostic prevalence of AS is 0.1% [21].

The marked differences between estimates of diagnostic prevalence and population prevalence are concerning despite the fact that in almost any population, some patients with a particular disease remain undiagnosed or may not seek care [22]. Accounting for additional reasons for differences in prevalence are studies that were performed in different geographic regions, reporting of crude versus adjusted rates, and variability in classification criteria or case definitions used in different studies [20–22].

Other characteristics observed in patients with axSpA in the USA include a slightly lower mean age in women compared to men at AS disease onset (21.5 vs 23.6;  $P = 0.03$ ) [23]. Women were also more likely to have a family history of AS (41.0 vs 24.6%;  $P = 0.002$ ) and had less radiographic progression as measured by Bath Ankylosing Spondylitis Radiology Index (6.5 vs 10.0;  $P < 0.001$ ) [23]. In a comparison of racial/ethnic groups, axSpA was more common in non-Hispanic whites (1.5%) and Mexican Americans (1.5%) than in blacks/African Americans (0.9%) [20]. This difference may be attributed to the lower frequency of human leukocyte antigen (HLA)-B27 in blacks/African Americans (1.1%) than in non-Hispanic whites (7.5%) or Mexican Americans (4.6%) [24].

Data from national surveys, including NHANES and the National Health Interview Survey, estimate that the US prevalence of RA is 0.6% (~1.3 million persons) [19]. The higher reported US prevalence of axSpA versus RA is paradoxical given that the number of patients treated for axSpA in rheumatology practices is much lower than the number of patients treated for RA. For example, in a recent cross-sectional study of 573 patients seeking care at a university-based rheumatology practice in Oregon, 18% of patients had been diagnosed with RA, whereas only 5% had been diagnosed with AS [25].

Underrepresentation of axSpA in US rheumatology practices raises an important question: Where are these patients, and who is managing them? A retrospective analysis of data from 2000 to 2012 showed that only 37% of patients with AS were diagnosed by a rheumatologist [26]. The remaining 63% of patients were diagnosed

by other providers, such as practitioners in primary care (26%), chiropractic/physical therapy (7%), orthopedic surgery (4%), pain clinics (4%), acute care (3%), and other settings (19%) [26]. Of the patients who were diagnosed with AS by other providers and subsequently saw a rheumatologist, 42% had their diagnosis of AS confirmed by the rheumatologist; the remaining 58% were found to have other disorders, such as joint effusion, unspecified back disorder, RA, rheumatism not otherwise specified, osteoarthritis, and spondylosis [26]. A study by Hurwitz et al. looked at claims data for low back pain from 2000 to 2009 and examined patterns of care among different providers [27]. This study reported that patients with low back pain were most often seen by physicians, chiropractors, and physical therapists; the number of patients seen by each type of provider increased during the study [27]. Taken together, these studies indicate that patients with suspected axSpA in the USA commonly receive care from providers other than rheumatologists and that these providers may be unfamiliar with differentiating this condition from other common causes of back pain and, hence, miss the diagnosis of axSpA in a substantial proportion of patients.

Delayed diagnosis of axSpA is a major problem in the USA and other countries [28–30]. Recent data estimate that average US diagnostic delays may be as long as 14 years; however, early referral to a rheumatologist can significantly reduce these delays [26, 28]. In an insurance claims database analysis of patients with back pain referred to a rheumatologist with suspicion of axSpA, a diagnosis of AS was typically made within 1 month [26]. Thus, timely referral to a rheumatologist is recommended for all patients at the earliest signs of suspected axSpA [31]. Results from the Prevalence of axSpA (PROSpA) study indicated that US rheumatologists also frequently missed the diagnosis of axSpA in their existing patients who were being followed for other reasons [28]. Notably, ~40% of patients in this study with a new diagnosis of axSpA were existing patients in rheumatology practices [28].

### Reasons for missed or delayed axSpA diagnosis in the USA

Among the many reasons that axSpA is so commonly missed is that spinal pain, the primary symptom of axSpA, affects approximately 80% of all adults at some point in their lifetimes [32]. Additionally, chronic low back pain affects 13% of adults [33]. AxSpA accounts for only 5% of all chronic back pain [13, 14]. The commonality of mechanical causes of back pain in the USA has led to an uncommon diagnosis such as axSpA being missed or considered late in the disease.

### Lack of validated diagnostic criteria

Perhaps the simplest, most selective initial criteria for making the diagnosis of axSpA are patients' age and the nature of back pain at disease onset. In most (90–95%) patients with axSpA, the disease starts with an insidious onset of back pain before 45 years of age (average age at disease onset: ~25–28 years) [34, 35]. Therefore, onset age and type of back pain are especially important considerations as part of a differential diagnosis. However, after screening patients based on age and type of back pain, differential diagnosis becomes challenging because no validated diagnostic criteria are in place [36, 37].

Several classification criteria have been developed for the identification of axSpA, including the modified New York (mNY), Amor, European Spondyloarthropathy Study Group, and the most recent Assessment of Spondyloarthritis International Society (ASAS) criteria [37–40]. These classification criteria were developed mainly to have uniform patient populations for clinical research and clinical trials; they should not be used for making the diagnosis of axSpA due to intrinsic limitations. The mNY criteria are limited by poor sensitivity and the inability to identify patients in the non-radiographic stage of disease [4, 38, 41]. Additionally, although ASAS classification criteria have very good sensitivity and specificity [41], there are various reasons why they should not be used for diagnostic purposes. Specifically, certain parts of the criteria, including IBP, family history of SpA, good response to non-steroidal anti-inflammatory drugs, and the presence of enthesitis, lack objectivity and may lead to the misclassification of mechanical back pain or fibromyalgia as nr-axSpA [42]. Additionally, the “positive MRI” definition of the ASAS classification criteria is quite non-specific because mild inflammatory changes of the SIJs can be seen in healthy individuals and athletes, as well as in a wide range of pathologies (e.g., mechanical stresses, trauma, degenerative arthritis of SIJs) [43–45]. Hence, the use of positive MRI findings by ASAS criteria alone as a diagnostic test can result in a substantial overdiagnosis of axSpA [43, 45]. Additionally, inter-observer differences in the interpretation of x-ray images and MRIs of SIJs and a lack of formal training of rheumatologists and radiologists in reading these images can also contribute to misclassification.

### Limitations of physical examination

There are significant limitations to the physical examination of patients with suspected axSpA. It is simply not possible for clinicians to examine SIJs and the spine for presence of inflammation in the same way that peripheral joints are examined in RA. Thus, manual clinical assessments are limited to physical maneuvers (e.g., pain provocation, spinal mobility, functional tests) [46, 47]. However, none of these physical examination techniques, including spine mobility measurements, reliably

**Table 1** Overview of studies evaluating referral strategies for patients with CBP and age at onset < 45 years

Study	Referred, <i>n</i>	Referral strategy	Referred diagnosed with axSpA, %	axSpA diagnosed with nr-axSpA, %	axSpA diagnosed with AS, %
PROSpA [28] (USA)	751	IBP or HLA-B27+ or sacroiliitis on imaging	46.8	32.0	14.5
Brandt 2007 [66] (Germany)	350	IBP or HLA-B27+ or sacroiliitis on imaging	45.4	49.7	50.3
Hermann 2009 [67] (Austria)	92	IBP (Calin criteria)	29.3	29.6	59.3
MASTER [68] (Germany)	318 (strategy 1) 242 (strategy 2)	IBP or HLA-B27+ or sacroiliitis on imaging ≥ 2 of 5 features: IBP, HLA-B27+, sacroiliitis on imaging, good response to NSAIDs, family history of AS	41.8 36.8	38.3 38.2	61.6 61.8
Braun 2011 [69] (Germany)	322	CBP with age at onset < 45 years and duration < 10 years	35.1	58.4	41.6
RADAR [70] (International)	504 (strategy 1) 568 (strategy 2)	IBP or HLA-B27+ or sacroiliitis on imaging ≥ 2 of 6 features: IBP, HLA-B27+, sacroiliitis on imaging, good response to NSAIDs, family history of axSpA, extra-articular manifestations	35.6 39.8	NA NA	NA NA
Braun 2013 [71] (Germany)	325	CBP with age at onset < 45 years and duration < 10 years	35.9	57.0	43.0
Brandt 2013 [72] (Germany)	97	CBP, online questionnaire using diagnostic algorithm	14.4	NA	NA
van den Berg 2013 [73] (Netherlands)	157	CBP	41.4	NA	NA
van Hooften 2014 [74] (Netherlands)	364	IBP (ASAS criteria), good response to NSAIDs, family history of SpA	24	65	22
OptiRef 2018 [75] (Germany)	162 (strategy 1) 177 (strategy 2)	Physician-reported IBP or HLA-B27+ or sacroiliitis on imaging Self-reported IBP symptoms or good response to NSAIDs or peripheral symptoms suggestive of arthritis/enthesitis or HLA-B27+ or elevated CRP or psoriasis or inflammatory bowel disease or uveitis or family history	37.0 18.6	NA NA	NA NA

AS ankylosing spondylitis, ASAS Assessment of SpondyloArthritis international Society, axSpA axial spondyloarthritis, CBP chronic back pain, CRP C-reactive protein, HLA-B27 human leukocyte antigen-B27, IBP inflammatory back pain, NA not-applicable, nr non-radiographic, NSAID non-steroidal anti-inflammatory drug

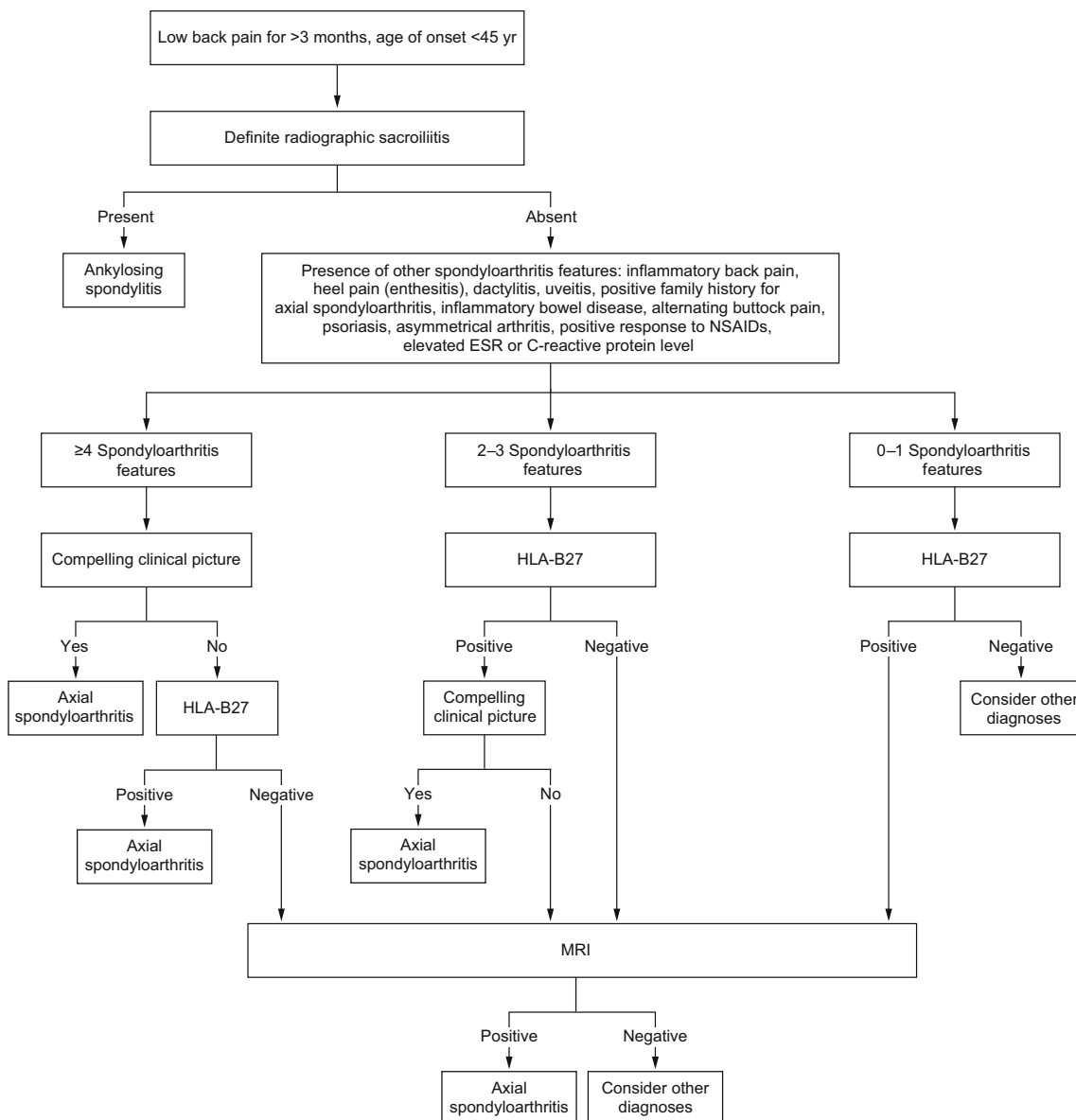
distinguish inflammatory diseases of the spine, such as axSpA, from common degenerative diseases of the spine.

### Lack of reliable biomarkers

The availability and utility of serum and imaging biomarkers are limited in axSpA, especially compared with other rheumatic conditions (e.g., RA) [48, 49]. Currently, HLA-B27 and C-reactive protein are the two most commonly used serum biomarkers, and MRI scans of the SIJs are the most sensitive imaging biomarker [50, 51]. NHANES data indicate that 6.1% of the general US population is HLA-B27 positive [24], but a prevalence of 0.5% [52] for AS would account for only 8% of

HLA-B27-positive individuals. Traditional radiography is an inexpensive way to identify joint damage caused by sacroiliitis, and radiographic findings can inform decisions about the need for more advanced imaging [14, 53]. However, traditional radiography is associated with intra- and inter-reader variability and poor sensitivity in axSpA [14, 51, 53–55].

Alternatively, the specificity of finding inflammation of SIJs on MRI is low; relying on MRI findings for diagnosis of axSpA can result in overdiagnosis or misclassification of axSpA [43, 56–58]. Therefore, it is necessary for biomarkers to be interpreted in the context of other clinical features that suggest a diagnosis of axSpA.



**Fig. 1** ASAS modification of the Berlin Algorithm for diagnosis of axSpA from Taurog et al. [77]. Reprinted with permission from Massachusetts Medical Society. ASAS Assessment of SpondyloArthritis

international Society, *axSpA* axial spondyloarthritis, *ESR* erythrocyte sedimentation rate, *HLA-B27* human leukocyte antigen-B27, *MRI* magnetic resonance imaging

## Patient and practitioner factors

Historically, US patients with low back pain seek medical care from primary care physicians, orthopedists, chiropractors, or complementary/alternative medicine practitioners (e.g., osteopaths, massage therapists, acupuncturists) [59, 60]. A 2016 survey of 7645 US adults found that if out-of-pocket costs were equal, people were most likely to choose physicians (53%) if they had neck or back pain, followed by chiropractors (28%), massage therapists (7%), physical therapists (6%), and acupuncturists (1%) [61]. A previous study showed that Americans are increasingly choosing to see chiropractors

for routine care if it is covered by health insurance, especially in rural areas where people may not have access to medical specialists [62, 63]. Complementary and alternative medicine is also gaining popularity, in part, because it can be less expensive than traditional care for many patients with back pain. Patients with axSpA may also seek initial care from specialists (e.g., ophthalmologists, gastroenterologists, dermatologists) regarding associated disease manifestations, including uveitis, inflammatory bowel disease, and psoriasis, respectively [64, 65]. In general, these practitioners and specialists may be unfamiliar with recognizing symptoms of back pain specific to axSpA [65].

**Table 2** Ankylosing spondylitis case ascertainment tool and scoring algorithm [79]

Question item	Response categories	Item score
What is your gender?	Male Female	1.2397 0
Have you experienced pain or stiffness that lasted for $\geq 3$ months? If so, please indicate the location(s).		
Neck	Yes/no	Yes = 1.2502
Hip	Yes/no	Yes = 1.2644
Other regions	Yes/no	Yes = 0.9421
Approximately how old were you when you first had pain or stiffness in your back that lasted $\geq 3$ months?	In years	$-0.0747 \times (\text{number of years})$
Approximately how long have you had back pain or stiffness?	In months	$0.00374 \times (\text{number of months})$
Have you felt numbness or tingling that spread into or down your leg(s) that you think or have been told might have been caused by your back pain or stiffness?	Yes/no	Yes = $-1.0214$
Is the pain or stiffness due to a fall, sprain, or other incidents, such as twisting or lifting?	Yes/no	Yes = $-1.3775$
How does exercise affect the pain or stiffness in your lower back or buttocks? Select the one that best describes your experience.	<ul style="list-style-type: none"> <li>• It decreases the pain or stiffness</li> <li>• It does not change the pain or stiffness</li> <li>• It increases the pain or stiffness</li> <li>• I do not have pain or stiffness in the lower back or buttocks</li> </ul>	<ul style="list-style-type: none"> <li><math>-1.5437</math></li> <li>0</li> <li><math>-2.6988</math></li> <li>0</li> </ul>
How does daily physical activity affect the pain or stiffness in your lower back or buttocks? Select the one that best describes your experience.	<ul style="list-style-type: none"> <li>• It decreases the pain or stiffness</li> <li>• It does not change the pain or stiffness</li> <li>• It increases the pain or stiffness</li> <li>• I do not have pain or stiffness in the lower back or buttocks</li> </ul>	<ul style="list-style-type: none"> <li>2.1178</li> <li>0</li> <li>1.0141</li> <li>0</li> </ul>
Do you take any NSAIDs? If so, do they help reduce your back pain or stiffness within 48 h?	<ul style="list-style-type: none"> <li>• Yes, they help reduce my back pain or stiffness within 48 h</li> <li>• No, they do not help reduce my back pain or stiffness within 48 h</li> <li>• I do not take an NSAID</li> </ul>	<ul style="list-style-type: none"> <li>0.3293</li> <li><math>-2.1489</math></li> <li>0</li> </ul>
Have you been diagnosed with iritis?	Yes/no	Yes = 3.4113
Scoring algorithm		
1 Assign an item score for each of the patient's responses.		
2 Take the sum of the patient's item scores. Let $x$ be the sum of the patient's item scores.		
3 Let $y$ be the patient's transformed score. We calculate $y$ as follows:		
$y = \frac{e^{x-1.0242}}{1+e^{x-1.0242}} \times 100$		
(Note: $-1.0242$ is the intercept of the logistic regression mode.)		
4 If $y \geq 66.86$ , then the case ascertainment tool result is positive for AS.		

From Weisman et al. [79]. Reprinted with permission from John Wiley & Sons, Inc.

AS ankylosing spondylitis, NSAID non-steroidal anti-inflammatory drug

## The way forward

Given the unfamiliarity regarding differences between mechanical back pain and IBP among HCPs, public health initiatives are needed to educate non-rheumatologists (primary care physicians and specialists such as in dermatology, gastroenterology, ophthalmology, orthopedics, spinal surgery) on ways to identify patients with axSpA [65]. Table 1 provides an overview of studies that have evaluated referral strategies for patients with chronic back pain and age at onset < 45 years. Application of these different referral strategies to the patients in the SPACE cohort showed that most of these models had good sensitivity and specificity [76]. Most of the studies listed in Table 1 were conducted in Europe, with only the PROSpA study providing data on US referral practices and patterns [28]. PROSpA was a study conducted at 68 rheumatology practices across the USA that enrolled 751 patients with chronic ( $\geq 3$  months) back pain that began at age < 45 years. Within this cohort, 46% (319 of 697) of patients with available data were diagnosed by the study investigator as having axSpA, and 46.8% (348 of 744) fulfilled ASAS axSpA classification criteria. These findings indicate that the presence of  $\geq 1$  of 3 SpA features (HLA-B27 positivity, current IBP, or MRI evidence of sacroiliitis) is an effective way to suspect possible axSpA, and these patients should be referred to a rheumatologist [28].

Recognizing the need for enhanced awareness and understanding of axSpA and AS, Taurog and colleagues recently published a modification of the ASAS algorithm for diagnosis of axSpA in patients with chronic back pain that initiated at age < 45 years (Fig. 1) [77]. When compared with an external standard rheumatologist diagnosis, the algorithm on which Fig. 1 is based resulted in an 8.9% false-negative and an 11.5% false-positive diagnosis rate in the SPACE cohort and a 12.7% false-negative and a 9.8% false-positive diagnosis rate in a larger ASAS cohort [73]. Algorithms such as this can be valuable tools when combined with a comprehensive diagnostic workup and consideration of alternative diagnoses [78].

Research efforts supported by the Spondylitis Association of America led to the development of a case ascertainment tool that patients can use for self-identification (Table 2) [79]. It was hoped that use of this tool would result in earlier and more accurate diagnosis of axSpA, but the instrument is cumbersome and, thus, has not been widely incorporated into daily clinical practice. A patient-reported clinical screening tool, such as a questionnaire without the use of imaging or laboratory tests with high sensitivity and reasonable specificity, is needed for use in non-rheumatologic practices to identify patients with suspected axSpA. An instrument of this type could facilitate easier decision-making regarding referral of appropriate patients to a rheumatologist for diagnosis of axSpA. Additionally, administrative healthcare codes for diagnosing AS have high predictive value for identifying these

patients, but, in general, the lack of specific diagnostic codes limits the utility of healthcare databases to study axSpA [80].

In conclusion, much progress has been made in recent years in understanding the importance of early axSpA diagnosis and in identifying many of the hurdles that contribute to diagnostic delays in the USA. By implementing the tools and strategies outlined in this review, it is hoped that future diagnostic delays will be reduced or eliminated in patients with axSpA.

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### Compliance with ethical standards

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