Spondyloarthritis Update
New Insights Regarding Classification, Pathophysiology, and Management

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Abstract
There has been a burgeoning interest in the spondyloarthritides (SpAs) due to a confluence of elements. Basic science research has provided new insight into the unique pathophysiology of synovium, enthesis, and bone, highlighting the important differences from rheumatoid arthritis (RA). Through collaborative research of international working groups, classification criteria for psoriatic arthritis (PsA) and ankylosing spondylitis (AS) have been developed or are being refined to aid characterization and diagnosis of SpAs and aid in research. These same working groups, under the umbrella of Outcome Measures in Rheumatology Clinical Trials (OMERACT), have developed domain core sets to be measured in clinical trials and registries, which allow validation of reliable outcome measures. Both through clinical trials and observational data from national clinical registries, the relative effectiveness and safety of old and new therapies are being demonstrated. This has been particularly shown with long-term data on anti-TNF therapy. Never anti-TNF therapies are being developed, as are treatments with different mechanisms of action in order to treat patients who do not have long-term effectiveness or develop side effects to older disease modifying therapy and anti-TNFs. International treatment recommendations have been or are being developed based on the evidence base from clinical trials.

A convergence of interest in epidemiology, classification, clinical characterization, pathophysiology, assessment, and management has occurred in the spondyloarthritides, leading to new findings in this field. This has occurred partly as a result of the significant efficacy of targeted biologic immunotherapies and increased funding for research that has come from the biopharmaceutical industry, as well as national research agencies. These funding sources and researchers understand the need for more precise knowledge about the following: the incidence and prevalence of the spondyloarthritides; classification schema; specific cellular and cytokine pathways involved in the disease states; natural history; demonstration of efficacy and safety of drugs; and the consequent need for accurate and reliable disease activity measures. Some of this research activity has been focused through international research consortia, such as the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), the Assessments in Ankylosing Spondylitis working group (ASAS), and research methodology associations, such as Outcome Measures in Rheumatology Clinical Trials (OMERACT). The following report provides brief updates on recent work in the disease states of psoriatic arthritis (PsA) and ankylosing spondylitis (AS).

Classification
Psoriatic Arthritis
Historically, the principle classification criteria for PsA have been the Moll and Wright criteria, based on their observations with a large cohort of patients from their clinic in Leeds, England, United Kingdom, published in the early 1970s (Table 1). Because this criteria set has not been validated using patient data nor tested in different populations, a consortia of 31 experts conducted the Classification Criteria for the Study of Psoriatic Arthritis study (CASPAR), involving extensive investigation of 588 patients evaluated definitively to have PsA. A second group of 536 control patients were similarly evaluated to have another form of inflammatory arthritis. The resultant criteria set, shown in Table 1, yields a sensitivity of 98.7% and specificity of 91.4% for the diagnosis of PsA. The criteria set has now been validated in...
several different patient populations and is being applied as entry criteria for current clinical trials in PsA.

**Ankylosing Spondylitis**

The classic criteria set used for the classification of AS is the modified New York Criteria (Table 2). This is more stringent in terms of specificity than the European Spondylarthropathy Study Group (ESSG) criteria and more feasible than the Amor criteria (Table 2). The current issue with the New York criteria is the necessity that there be significant plain radiographic changes of the sacroiliac (SI) joints, thus excluding numerous patients who may not yet have such clear-cut changes, which may take years to develop. These patients may either represent a pre-AS state, including the demonstration of significant inflammatory changes of the SI joints or spine, as well as other compelling clinical features of the presence of a spondylarthropathy or a positive HLA-B27, or both. The ASAS working group is currently

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**Table 1** Classification Criteria for Psoriatic Arthritis

<table>
<thead>
<tr>
<th>Moll and Wright Classification</th>
<th>CASPAR Diagnostic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis with:</td>
<td>Established inflammatory musculoskeletal disease</td>
</tr>
<tr>
<td>Inflammatory arthritis (peripheral arthritis and/or spondylitis)</td>
<td>(joint, spine or enthesal with three or more of the following:</td>
</tr>
<tr>
<td>Negative for rheumatoid factor (usually)</td>
<td>1. Psoriasis: (a) current psoriatic skin or scalp</td>
</tr>
<tr>
<td>Five clinical subsets:</td>
<td>disease currently present, as judged by a qualified</td>
</tr>
<tr>
<td>Oligoarticular</td>
<td>health professional and/or (b) a history of psoriasis that</td>
</tr>
<tr>
<td>Polyarticular</td>
<td>may be obtained from patient, or qualified health</td>
</tr>
<tr>
<td>DIP predominant</td>
<td>professional and/or (c) a history of psoriasis in a first</td>
</tr>
<tr>
<td>Spine predominant</td>
<td>or second degree relative according to patient report.</td>
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<tr>
<td>Arthritis mutilans</td>
<td>2. Nail changes: typical psoriatic nail dystrophy,</td>
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<tr>
<td></td>
<td>including onycholysis, pitting, and hyperkeratosis</td>
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<tr>
<td></td>
<td>observed on current physical examination.</td>
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<tr>
<td></td>
<td>3. Negative test for RF.</td>
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<td></td>
<td>4. Dactylitis (a) current swelling of an entire digit</td>
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<tr>
<td></td>
<td>and/or (b) a history of dactylitis recorded by a</td>
</tr>
<tr>
<td></td>
<td>qualified health professional.</td>
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<tr>
<td></td>
<td>5. Radiological evidence of juxta-articular new bone</td>
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<td></td>
<td>formation: Ill-defined ossification near joint margin (but</td>
</tr>
<tr>
<td></td>
<td>excluding osteophyte formation) on plain radiographs</td>
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<tr>
<td></td>
<td>of hand or foot.</td>
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</tbody>
</table>

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**Table 2** Classification Criteria for Spondyloarthritis and Ankylosing Spondylitis

<table>
<thead>
<tr>
<th>Modified New York Criteria for Ankylosing Spondylitis</th>
<th>European Spondylarthropathy Study Group</th>
<th>Amor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitive diagnosis</td>
<td>Inflammatory spinal pain or synovitis (asymmetric or predominantly in the lower limbs), together with at least one of the following:</td>
<td>Diagnosis of SpA if 6 or more points are amassed (exclusion criteria not included):</td>
</tr>
<tr>
<td>Radiologic criteria</td>
<td>• Positive family history</td>
<td>• Inflammatory back pain (1 point)</td>
</tr>
<tr>
<td></td>
<td>• Psoriasis</td>
<td>• Unilateral buttock pain (1 point)</td>
</tr>
<tr>
<td></td>
<td>• Inflammatory bowel disease</td>
<td>• Alternating buttock pain (2 points)</td>
</tr>
<tr>
<td></td>
<td>• Urethritis</td>
<td>• Enthesitis (2 points)</td>
</tr>
<tr>
<td></td>
<td>• Alternating buttock pain</td>
<td>• Peripheral arthritis (2 points)</td>
</tr>
<tr>
<td></td>
<td>• Enthesopathy</td>
<td>• Dactylitis (sausage digit) (2 points)</td>
</tr>
<tr>
<td></td>
<td>• Sacroiliitis</td>
<td>• Acute anterior uveitis (2 points)</td>
</tr>
<tr>
<td></td>
<td>Sacroiliitis (bilateral with a grade of 2-4 or unilateral with a grade of 3-4)</td>
<td>• HLA-B27 positive</td>
</tr>
<tr>
<td></td>
<td>Sacroiliitis (bilateral with a grade of 2-4 or unilateral with a grade of 3-4)</td>
<td>• History of SpA (2 points)</td>
</tr>
<tr>
<td></td>
<td>Sacroiliitis (bilateral with a grade of 2-4 or unilateral with a grade of 3-4)</td>
<td>• Good response to NSAIDs (2 points)</td>
</tr>
</tbody>
</table>

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*Criteria yield specificity 98.7%, sensitivity 91.4%. †Current psoriasis awarded 2 points.
in the process of developing updated criteria that will take into account these more current imaging approaches and understanding about the positive predictive value of a variety of clinical features. This will be important from a regulatory and payer perspective regarding access to effective yet costly therapies that can improve symptoms, signs, function, and quality of life, as well as potentially prevent destructive disease progression.

**Pathophysiology**

**Psoriatic Arthritis**

There are key distinctions between rheumatoid arthritis (RA) and PsA synovitis. In PsA, a lesser degree of cellular infiltrate, increased vascularity, number of polymorphonuclear cells, CD163+ macrophages, and lymphocytes have been noted. PsA patients have a greater likelihood of having “ray” involvement (inflammation of each joint in a digit, while potentially sparing adjacent digits) and dactylitis (involvement of joints and intervening ligament, tendon, and fascial attachments (enthesitis)). These features suggest more subtle differences in antigenic and cytokine signaling factors in PsA and in associated SpAs than in RA, which may influence clinical features and response to therapies. The prominent role of key pro-inflammatory cytokines, including TNFα and IL-1, however, is a common denominator in synovial inflammation.

Further differentiation between SpAs and RA is seen in the clinical prominence of enthesitis, bone changes, and axial disease. Enthesitis, which can occasionally be present even in patients without synovitis, may yield symptoms in most joint areas, the thorax, pelvis, heels, and spine. Oftentimes, both patient and clinician are not aware of the source of pain, and only become aware through MR or ultrasound images that show characteristic changes in the connective tissue attachment and edema in the adjacent bone; as well, there can be a response to effective therapies. McGonagle and colleagues have emphasized the central role of the “synovio-enthesial complex” in SpA clinical symptoms and damage through imaging studies, as well as suggested a role for microtrauma and bacterial immunogenicity in the etiology of enthesitis.

Research in the field of osteoimmunology has shed light on bone pathology in the SpAs. Ritchlin and associates have noted the interesting phenomenon of “nests” of CD4+/CD8+ lymphocytes, osteoclasts, and increased vascularity in the subendosteal and subcartilaginous areas of bone marrow in the femoral heads of AS patients undergoing hip replacement surgery, distinct from patients with RA or osteoarthritis (OA). Sieper has noted the correlation of these cellular changes with bone edema changes, often prominently noted on MRI in SpA patients. In peripheral joints, such pathological changes may be precursors of sites of erosion in bone. However, paradoxically, in PsA, patients may also display periarticular periostitis, and in AS and to a lesser extent PsA, prominent syndesmophyte formation in the spine, leading to bridging ankylosis in its most severe form. The balance of these phenomena and the role played by the WNT signaling pathway, DKK-1 and BMPs, in addition to the role of inflammatory cytokines, such as TNFα, is reviewed by Schett and coworkers. Perhaps TNF inhibition may be highly useful in the early stage effort to inhibit syndesmophyte formation but may not be as helpful once ankylosis is further established.

**Ankylosing Spondylitis**

The pathologic role of the gene marker HLA-B27 in AS is being further unraveled. Of the various alleles of this gene, certain ones appear especially associated with disease, including B*2705. This subtype shares sequence homologies with enterobacterial antigens such as Klebsiella pneumoniae nitrogenase. It has been suggested that disease may result from the presentation of “arthritogenic” peptides to CD4+ and CD8+ T cells in the context of “triggering” by enterobacterial infection. Another observation in what is often used as an animal model for AS, the HLA-B27 transgenic rat, is the propensity for the B27 molecule to misfold during assembly in the endoplasmic reticulum. This, in turn, leads to an “unfolded protein response,” which can be pro-inflammatory.

What is less clear is why the pathophysiologic features of disease occur predominantly in the spine and particularly involve enthesium and bone, and not as frequently in the periphery, as is seen in PsA, and vice versa. Common to both diseases are increased

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**Figure 1** Domains for PsA. PGA, physician global assessment; MRI, magnetic resonance imaging; CT, computer tomography; US, ultrasound.
expression of CD163+ cells in the colon and uveal tract, as well as synovium, with not infrequent subclinical intestinal disease and occasional uveitis.17

Assessment

Psoriatic Arthritis

The GRAPPA group, working within the context of an OMERACT workshop and module,9,20 has developed a core set of domains that should be assessed in all PsA clinical trials and in long-term registry studies (Fig. 1). These domains include the joints, skin, patient global assessment, pain, physical function, and health-related quality of life. Desirable but not essential symptom domains to measure include enthesitis, dactylitis, nails, and fatigue. Imaging (radiographs as well as MRI, or ultrasound, or both) to measure effect of therapy on disease activity and joint damage also should be assessed at some point. Measures for these domains have been largely derived from studies in RA, such as by the American College of Rheumatology and Disease Activity Scores (DAS), as well as by the Health Assessment Questionnaire (HAQ), and in psoriasis, for example, by the Psoriasis Area and Severity Index (PASI). These measurement tools have been shown to be reliable and discriminative of treatment effect.19,24 Metrics for disease severity and numeric thresholds defining “remission” and “low disease state” are currently being developed by the GRAPPA group, as well as simplified disease activity measures, that can be used in standard clinical settings. Based on the disparate number of domains involved in PsA, determination of disease activity and therapeutic effect of various interventions is complex and requires a broad perspective that ideally involves both rheumatologists and dermatologists, as well as other health practitioners.25

Ankylosing Spondylitis

The ASAS working group has established specific measures of disease activity, including definition of remission.26 These include the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the Bath Ankylosing Spondylitis Function Index (BASFI), and the Bath Ankylosing Spondylitis Metrology Index (BASMI). Radiographic and MRI measures have been established [modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) and MRI measures]. Measures for second-

ary outcomes have been developed, including enthesitis scoring systems, such as the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) and quality of life measures, such as the Ankylosing Spondylitis Quality of Life questionnaire (ASQoL), a disease-specific measure that is often used along with a more general instrument, such as the SF-36. Composite measures, such as the ASAS 20 and 40, and definitions of remission have been developed and validated. Since measures like the BASDAI and BASFI are patient-reported outcome measures, they are feasible to use in a regular clinical setting as part of standard record-keeping.

Management

Psoriatic Arthritis

The GRAPPA group has published a compendium of evidence-based reviews of therapy for the various disease domains (joints, skin, enthesium, dactylitis, and spine).22,27-34 Table 3 provides a general summary of therapeutic effectiveness of different classes of treatment, a “+” sign indicating the presence of evidence of effect.27-34 Since the spine has not been evaluated in PsA trials, it has been agreed that extrapolation from evidence in AS trials is warranted. For patients with mild disease, simpler medicines, such as nonsteroidal anti-inflammatory drugs (NSAIDs) for arthritis and topical creams or light therapy for the skin are reasonable and may be adequate. For moderate to severe disease, it is most likely that systemic disease-modifying anti-rheumatic drugs (DMARDs) will be needed to adequately control disease in the various domains. In general, most clinicians will use methotrexate, although sulfasalazine has also been shown to be efficacious, as has leflunomide.35 If methotrexate is not well tolerated or causes persistent elevation of liver function tests, or if there is persistent disease activity (evidenced by persistent swollen and tender joints, morning stiffness, enthesopathy, psoriatic plaques, and fatigue, and certainly imaging evidence of progressive joint damage), current practice, depending on local treatment patterns and financial coverage, would be to add one of the parenteral anti-TNF agents. The currently available agents are adalimumab, etanercept, and infliximab. These have been shown to have rapid and significant effect on all domains of disease activity, with or without background DMARD, and all have sustained

<table>
<thead>
<tr>
<th>Table 3: PsA Treatment27-34</th>
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<tbody>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>NSAIDs</td>
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<tr>
<td>Intra-articular steroids</td>
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<tr>
<td>Topical steroids and vitamin D</td>
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<tr>
<td>Physiotherapy</td>
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<tr>
<td>Psoralen UVA/UVB</td>
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<tr>
<td>DMARDs (MTX, CsA, SSZ, Lef)</td>
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<td>Biologics (anti-TNF antagonists)</td>
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</table>

*+* indicates the presence of evidence of effect; NSAIDs, nonsteroidal anti-inflammatory drugs; DMARDs, disease-modifying antirheumatic drugs; MTX, methotrexate; CsA, ciclosporin; SSZ, sulfasalazine; Lef, leflunomide.
efficacy data out to two years (ACR 20/50/70 responses in more than 60%, more than 40%, and approximately 20%, respectively)—including inhibition of progressive structural damage as measured radiographically.22,36-38 All are effective in clearing skin lesions, although it does appear that in standard doses, the monoclonal antibody constructs have somewhat greater efficacy on psoriasis lesions than does the soluble receptor agent, etanercept. However, with higher doses of etanercept used in the initial phase of psoriasis trials, there is not as much difference between the agents in terms of skin efficacy.39 The infliximab trials published formal data on assessment of enthesitis and dactylitis, and showed significant improvement in these domains.22,38 Measures of function, quality of life, and fatigue, all patient-reported outcomes, consistently demonstrated significant and sustained improvement with each therapy.22 There is some evidence that it is rational to “switch” from one anti-TNF agent to another if there is loss of efficacy or intolerability of a current anti-TNF.40 There have been no new safety concerns aside from those already noted in RA patients treated with anti-TNF therapy.

There are a number of caveats about methotrexate use in PsA. However, a paucity of controlled trial data about its effectiveness in PsA exists. The principle study supporting its use was published in 1984 and was essentially a negative trial, albeit in a small number of patients treated with low dosages.41 Clinical experience supports its effectiveness in arthritis and, to a certain extent, in the skin. However, there is greater caution about its hepatotoxic potential in psoriasis and PsA, as compared to RA. This is evidenced by worse hepatic scores in liver biopsy studies in psoriasis patients,42 which might be influenced by additional factors, such as differing administration regimens in psoriasis, a proclivity to obesity in psoriasis patients, corollary presence of hepatic steatosis (“fatty liver”), male gender, alcohol use, and so forth. The potential for adverse consequences to the liver has led to the recommendation, in dermatology, to monitor serial liver biopsies in methotrexate-treated patients, a practice not typically followed by rheumatologists. There is also more of a pattern of restricted dose and time course of use in psoriasis. Unlike with RA, a key question regarding methotrexate in PsA has not been studied. Does a combination of methotrexate and anti-TNF agents yield greater clinical or radiographic efficacy than either as monotherapy? Until this question is addressed, clinicians tend to be guided clinically, i.e., using combination therapy when monotherapy does not yield adequate clinical benefit.

**Ankylosing Spondylitis**

Zochling and associates analyzed four trials of NSAID therapy that noted benefit for spinal and peripheral joint pain and function in AS.43 Chen and Liu performed a Cochrane meta-analysis of 11 trials with sulfasalazine, showing some benefit for peripheral arthritis, morning stiffness, and erythrocyte sedimentation rate, but not for spinal pain or mobility, function, or patient or clinician global assessment. In the same meta-analysis, methotrexate was not shown to benefit any aspect of disease compared to control.44 On the other hand, all of the anti-TNF agents have shown significant benefit for pain, both spinal and peripheral, and function. Although resolution of bone edema findings on MRI has been noted, it is not yet clear whether spinal radiologic progression can be fully arrested as compared to the success of the anti-TNF agents in this regard in peripheral joints. Multi-year data sets with each of the anti-TNF medicines document sustained clinical efficacy in patients who respond. Patient-reported outcomes, including quality of life and function, have demonstrated significant benefit from anti-TNF agents as well. There have been no new safety concerns other than those noted in RA. The ASAS 2005 AS treatment recommendations are noted in Figure 2, illustrating the point of going from NSAIDs directly to anti-TNF agents, related to effects on spinal pain, mobility, and function.45

A conundrum is that all of the patients in clinical trials of AS fulfilled modified New York criteria. What about the more “undifferentiated” patient who has features of spondyloarthritis but does not have the “required” plain radiographic changes in the sacroiliac joints? Studies have recently been conducted with both adalimumab and infliximab in this patient group.45,46 In the infliximab study, patients had to have normal sacroiliac joint radiographs but abnormal light-up in the SI joints by MRI. In the adalimumab study, patients had normal SI joint radiographs and a combination of signs and symptoms suggestive of spondyloarthritis, such as abnormal SI MRI, characteristic symptoms, +HLAB27, and so forth. In both studies, patients did exceedingly well, demonstrating the efficacy of this class of therapy in more undifferentiated spondyloarthritis states.

**Emerging Therapies**

Trials of newer agents are currently underway, particularly in PsA. Golimumab, a new monthly subcutaneous anti-TNF agent, has shown significant benefit in all domains of PsA.47 Two T-cell modulatory agents, alefacept and efalizumab, which work through the inhibition of T-cell stimulation by other immune cells (“co-stimulatory blockade agents”), are
approved for the treatment of psoriasis. Alefacept, which blocks interaction between LFA-3 on the antigen presenting cell and CD2 on the T cell, has shown modest efficacy in joints and skin.\textsuperscript{48} Joint efficacy, however, has not been shown with efalizumab, which blocks ICAM-1 and LFA-1.\textsuperscript{49} Abatacept (CTLA4-Ig), which binds to the CD80/86 receptor on the antigen presenting cell (blocking interaction with CD28 on the T cell), has shown significant efficacy in RA and has previously shown efficacy in psoriasis.\textsuperscript{50} It is now being tested in PsA. An anti-IL1 agent, anakinra, has not shown efficacy in PsA.\textsuperscript{51} An anti-IL12/23/p40 agent, ustekinumab, has shown significant efficacy in psoriasis and modest efficacy in PsA.\textsuperscript{52} Anti-IL-15 has shown benefit in PsA.\textsuperscript{53} A number of other agents that are in development in RA, including oral intracellular signaling molecule inhibitors, such as the JAK3,\textsuperscript{54,55} JAK1-2,\textsuperscript{56} and SYK kinase inhibitors, may soon be tested in PsA. Finally, agents that inhibit osteoclastogenesis, including the RANK ligand inhibitor denosumab, may ultimately be shown to inhibit erosive damage of joints in RA and possibly PsA, and thus be used as adjunctive therapy along with immunomodulatory agents.\textsuperscript{57} Several of these agents, including abatacept, are being tested in AS.

**Conclusion**

Improved understanding about the classification, pathophysiology, and assessment of the spondyloarthritides, especially PsA and AS, has significantly deepened our knowledge about the prevalence of these conditions and their impact on patients and society. Coupled with the emergence of new and more targeted therapies, we are better able to effectively care for these patients, including the possibility of achieving low disease state or remission. For patients with inadequate responses, new treatments in development may broaden our effective therapeutic options.

**Disclosure Statement**

The author has no financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

**References**


