In the US, about 7.5 million people have psoriasis, a chronic immune-mediated, inflammatory disease. As with many chronic conditions, there is often a delay in diagnosis. Patients may be slow to seek treatment, and providers often overlook the severity and true burden of the disease, especially in mild to moderate cases. Despite being an immune-mediated condition that has many systemic effects, it is often considered to be simply a cosmetic or skin disorder. As with many autoimmune diseases, there isn't a specific immune biomarker to rule it in or out. Diagnosis is primarily made on physical exam and patient history, although skin biopsy to look for inflammation can be done to differentiate from other skin conditions such as eczema. For patients with mild to moderate psoriasis vulgaris/plaque psoriasis (the most common form), the primary conventional treatments are often topical: corticosteroids, retinoids, vitamin D analogues, salicylic acid, coal tar, and moisturizers. These treatments, while often effective at reducing itching, scaling, and redness, don't address the underlying immune dysfunction, are rated poorly on patient compliance, and are widely overutilized. Topical therapies also fail to reduce the underlying pathophysiology, which can lead to more serious symptoms and damaging comorbidities, including psoriatic arthritis (PsA), cardiovascular disease, and inflammatory bowel disease (IBD).

Approximately 30% of patients with psoriasis will also develop psoriatic arthritis, when the inflammatory process moves beyond the skin and affects the joints. The time between a diagnosis of psoriasis and a diagnosis of PsA is an average of 4 years, during which irreversible joint damage can occur. Because of similar presentation, it is often difficult to differentiate PsA from other inflammatory arthropathies, including rheumatoid arthritis (RA) and anklyosing spondylitis (AS). PsA and RA both cause inflamed joints that are often red or warm to the touch and both are commonly found in the hands, feet, and axial skeleton. PsA, however, is more likely to be asymmetric and to present with enthesopathy (inflammation of tendons at their insertion sites that can often cause confusion with fibromyalgia), dactylitis (inflammation of a digit), and iritis (inflammation in the iris of the eye). Some characteristic radiographic markers seen with PsA include "pencil-in-cup" changes of digital joints, especially the distal interphalangeal joint (DIP), periostitis, joint ankylosis, osteolysis, and sacroiliac changes; however, these are more likely to be seen with advanced disease. Laboratory values, including inflammatory markers such as sedimentation rate and C-reactive protein, are often elevated, but not consistently enough to contribute to a defined diagnosis. Furthermore, rheumatoid factor and anti-CCP antibodies (both used in the diagnosis of RA) are usually negative, but not always, which confuses the issue.

So how is PsA typically defined? There have been various methods used over the years, although the standard that is currently considered the most specific is the ClASsification of Psoriatic ARthritis (CASPAR) criteria, which require the presence of inflammation in a joint, the spine, or entheses plus at
least 3 points from the following factors: presence of current psoriasis (2 points) or a personal or family history of psoriasis (1 point), dactylitis (1 point), pitting or ridging of the nails (1 point), a negative rheumatoid factor (1 point), and radiographic evidence of new bone formation (1 point).\(^1\)

**Figure 1: CASPAR group criteria for diagnosis of psoriatic arthritis.**

The presence of inflammation in a joint, the spine or entheses, **plus three points** from the following:

Current psoriasis.......................................................................................... 2 points
A personal or family history of psoriasis..................................................... 2 points
Dactylitis (swelling of digits)........................................................................ 1 point
Nail dystrophy (pitting or ridging of nails).................................................... 1 point
Negative rheumatoid factor.......................................................................... 1 point
Radiographic evidence of new bone formation......................................... 1 point

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Important to note in these criteria is the fact that psoriasis may not be present. A first degree family history of psoriasis (along with 2 other criteria) is sufficient for diagnosis of PsA. This is a primary difference from diagnostic criteria that have been used to define PsA in the past, but the requirement of psoriasis can be problematic, because skin lesions may occur prior to, concomitant with, or after the onset of arthritis symptoms.\(^2\) Additionally, psoriasis may be present, but limited to locations that are less visible and more likely overlooked, such as beneath the breasts or on the scalp and covered by hair; and some forms of psoriasis mimic other conditions and are therefore overlooked. Intertriginous psoriasis appears fungal in nature and guttate psoriasis often occurs after infection, which can cause it to be confused with a drug reaction or other rash. Understanding the diagnostic criteria is important because the pathophysiology of PsA differs from RA. While both are inflammatory conditions and share some common cytokine pathways, there does appear to be a slightly different immune response between the two, presenting the opportunity for varying treatments.\(^3\) A correct diagnosis is instrumental to direct the appropriate treatment and minimize future joint destruction.

Psoriasis and psoriatic arthritis are primarily mediated by T cells (rather than B cells). T cells have both a direct effect, and work through the release of associated cytokines, including tumor necrosis factor alpha (TNF-α).\(^4\) RA patients also exhibit elevated TNF-α levels, although when quantified, the elevations are significantly higher in PsA.\(^5\) Analysis of synovial fluid and tissue of PsA patients indicates elevated levels of Th1 cytokines TNF-α, IFN-γ, IL-12, IL-17, and several others compared with RA patients.\(^6\) Increased levels of both interleukin-12 (IL-12) and interleukin-23 (IL-23) have been detected in the serum of PsA patients when compared with healthy controls.\(^7\) As with many autoimmune conditions, the inflammation seen in psoriasis and psoriatic arthritis is due to hyperreaction of the immune response. One of the important concepts with immune-mediated disease is loss of immunological tolerance. This is primarily due to alterations in T regulatory (Treg) cells, a type of T cell that modulates the immune system by suppressing the immune responses of other cells.\(^8\) Without this "self-check" system, the inflammatory cells and signals proliferate.

Despite the differences in specific pathophysiology, many of the treatments used to treat psoriatic arthritis are shared with other inflammatory arthropathies, including RA. Mild PsA may be successfully treated with NSAIDs or intra-articular injections of corticosteroids; however, NSAID therapy has caused worsening of skin disease in many cases and glucocorticoids must be used judiciously to avoid inducing bone demineralization and immune flare on withdrawal.\(^9\) In moderate to severe PsA, conventional disease modifying antirheumatic drugs (DMARDs) are generally considered first-line therapy. These drugs include methotrexate, which inhibits the metabolism of folate; leflunomide, a pyrimidine synthesis inhibitor; and sulfasalazine, which inhibits eicosanoid and cytokine production, among others. While these medications can be effective at limiting joint damage and reducing inflammation and improving symptom pictures, they have significant side effects, including kidney and liver damage and increased risk of infection. Additionally, these traditional DMARDs have not been shown to have a significant impact on several aspects of PsA, including axial involvement, dactylitis, or enthesitis.\(^10\)
New medications used in the treatment of PsA include those that fall into the biologic category, which means that they are protein-based substances manufactured in a microorganism, not created through chemical synthesis. These drugs target very specific parts of the immune response, rather than affecting the entire immune system. Because this class of medication is expensive, prescription guidelines often dictate that patients must fail a more traditional systemic therapy first, or suffer from a condition that would preclude them from using a DMARD such as alcoholism, compromised liver or kidney function, or GI issue. Most of the biologic drugs available for treating PsA work by inhibiting the binding of TNF-α to its receptor: etanercept, adalimumab, infliximab, and golimumab. Ustekinumab is another biosimilar used to treat PsA; it works by blocking the cytokines IL-12 and IL-23 rather than TNF-α. These drugs have shown significant efficacy in treating psoriatic arthritis; however, like the DMARDs, their administration requires close monitoring and there are significant risks of side effects, including infection due to compromised immune function. In the past year, a new advanced oral systemic was approved for use with PsA: apremilast is a phosphodiesterase 4 (PDE4) inhibitor that modulates mRNA expression and blocks the synthesis of TNF-α, IL-23 and several pro-inflammatory chemokines. Tofacitinib, a janus kinase inhibitor, is expected to be approved for PsA by the end of this year. While technically neither of these medications are biologics, they target more specific immune pathways than traditional DMARDs.

Understanding the pathophysiology of a condition provides better framework to investigate the origin of the disease. There are multiple factors involved in the pathogenesis of psoriasis and psoriatic arthritis, including genetic variations, lifestyle components, history of infection, and altered gut flora. Psoriasis is 19 times more likely to be found among first-degree relatives of psoriatic arthritis patients, although the pattern of inheritance is multifactorial. There are several major histocompatibility complex (MHC) alleles consistently associated with PsA. These molecules are involved in the activation of T cells and identification of immune targets. Specifically, the HLA-B27, HLA-B38, and HLA-B39 alleles are associated with PsA, with HLA-B27 related to spinal involvement and HLA-B38 and HLA-B39 occurring more frequently in cases of peripheral polyarthritis.

While genetics may set the stage, physical, emotional, or environmental stressors are often triggers for the expression or worsening of symptoms. Psoriatic patients often report flare-ups during or following a stressful event. A stress response typically involves activation of the hypothalamus-pituitary-adrenal (HPA) axis as well as the sympathetic adrenomedullary (SAM) axis; however, exposure to stress in psoriatic patients has been associated with a blunted HPA response and increased SAM activation, resulting in decreased cortisol and increased levels of epinephrine and norepinephrine. Stress may be psychological or physical. An increase in immune response following injury (cut, burn, etc.) to the skin in psoriatic patients is called the Koebner phenomenon. A similar reaction can occur following injury to the joint (sometimes referred to as a deep Koebner phenomenon), when the inflammation initially induced by trauma becomes uncontrolled. There have been several studies that link bacterial or viral agents with the onset of psoriatic disease including streptococcal infection, hepatitis C, and HIV. The varied microorganisms involved suggest that the trigger may not be a specific infectious agent, but an altered immune response following an infective trigger.

There is much ongoing research regarding gut bacteria and immune response. One of the primary functions of commensal bacteria is to shape the immune system and aid in the establishment of immunological tolerance. Approximately 70% of immune cells in the body are found in the intestine. Some types of resident bacteria induce T cells to differentiate into T regulatory cells, which control unwanted immune activation and dampen inflammation in target tissues. It is theorized that much of the loss of regulation or tolerance in the immune system may be due to alterations in intestinal microbes. Identification of specific bacterial strains that are beneficial has been difficult, as there are 100 trillion microorganisms in the human intestine representing over 400 bacterial species; however, this is an area that is currently being researched. Bifidobacterium infantis has been shown to downregulate intestinal inflammation and increase Treg cells. Bacteroides fragilis produces a polysaccharide (PSA) that stimulates expansion of Treg cells.
and differentiation of the immune system. Supplementation with these and other strains of bacteria, as well as a diet rich in soluble fiber or prebiotics, is an effective way to support a healthy immune system.

Controlling triggers and environmental factors contributing to inflammation can be a very effective treatment for the symptoms of psoriasis and psoriatic arthritis, and also addresses the underlying immune dysfunction, a key to preventing further joint damage and debilitation. The integrative or alternative healthcare practitioner may employ these therapies to complement conventional DMARD or biologic therapy, or use them in lieu of treatments that have significant side effects. Identification of allergenic foods through an IgG antibody test can guide dietary changes and the elimination of inflammatory triggers in the gut. Though food allergies are not thought to be the singular "cause" of inflammatory arthritis, the ongoing inflammation in the gut caused by increased immune activity can contribute significantly. There is an increased prevalence of celiac disease and anti-gliadin antibodies in PsA patients, although improvement in clinical measures and laboratory inflammatory markers have been seen with a gluten-free diet regardless of celiac status.

Diet changes shouldn't focus exclusively on what foods are eliminated but should also incorporate recommended foods, including those high in omega-3 polyunsaturated fatty acids such as coldwater fish, flax and chia seeds, walnuts, and fish-oil supplements. The omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are used in the formation of anti-inflammatory prostaglandins and leukotrienes that inhibit inflammation. In contrast, omega-6 fatty acids such as arachidonic acid are precursors to inflammatory signals.

There has been a deluge of research and information on vitamin D over the past few decades. Although it's long been known that vitamin D is central to the innate immune system, it has also been discovered that vitamin D is important to promote tolerance in the adaptive immune system through the enhancement of regulatory T cells. This is of particular importance in autoimmune disease when the primary pathophysiology is the loss of tolerance. Given these mechanisms of immune modulation, it is no surprise that there is a high prevalence of vitamin D insufficiency among patients with psoriatic arthritis.

Just as the mechanisms of many conventional therapies include targeting TNF-α, there are natural substances that work on this same pathway. The leaf (not the root as is used for prostate health) of the stinging nettle (Urtica dioica) plant inhibits the activation of TNF-α and the cytokine IL-1 in the synovial tissue. This action makes it a good choice for psoriatic arthritis specifically because of the significant involvement of TNF-α in the pathogenesis of PsA. Boswellia serrata, an Ayurvedic herb that has been used for thousands of years for arthritis symptoms, is another possible option for PsA, as it has also been shown to inhibit TNF-α and IL-1. Additionally, boswellic acids inhibit the synthesis of 5-lipoxygenase (5-LOX) and leukotriene B4 (LTB-4). LTB-4 can stimulate the pro-inflammatory cytokines IL-1, IL-2, IL-6, and IFN-γ.