Psoriatic arthritis

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Abstract | Psoriatic arthritis (PsA) is a complex inflammatory disease with heterogeneous clinical features, which complicates psoriasis in 30% of patients. There are no diagnostic criteria or tests available. Diagnosis is most commonly made by identifying inflammatory musculoskeletal features in joints, entheses or the spine in the presence of skin and/or nail psoriasis and in the usual absence of rheumatoid factor and anti-cyclic citrullinated peptide. The evolution of psoriasis to PsA may occur in stages, although the mechanisms are unclear. In many patients, there may be little or no relationship between severity of musculoskeletal inflammation and severity of skin or nail psoriasis. The reason for this disease heterogeneity may be explained by differences in genotype, especially in the HLA region. New targeted therapies for PsA have been approved with additional therapies in development. These developments have substantially improved both short-term and long-term outcomes including a reduction in musculoskeletal and skin manifestations and in radiographic damage. With efforts underway aimed at improving our understanding of the molecular basis for the heterogeneity of PsA, a personalized approach to treating PsA may become possible.

Psoriasis
Psoriasis is a skin disease that causes itchy, scaly patches commonly on the extensor aspects of the knees and elbows and in the scalp.

Entheses
The enthesis is the site of attachment of ligament to bone.

Rheumatoid factor
Rheumatoid factor is an anti-immunoglobulin antibody found commonly in patients with rheumatoid arthritis.

Anti-cyclic citrullinated peptide
This peptide is an antibody found commonly in patients with rheumatoid arthritis.

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Psoriatic arthritis (PsA) is a complex inflammatory disease with heterogeneous clinical features that complicates skin or nail psoriasis in up to 30% of patients. No diagnostic criteria or tests are available for PsA. Diagnosis is most commonly made by identifying inflammatory musculoskeletal features in the joints, entheses or the spine in the presence of skin and/or nail psoriasis, and in the usual absence of rheumatoid factor and anti-cyclic citrullinated peptide[1] (TABLE 1). PsA is thought to be the result of interplay between environmental factors, an individual's phenotype and genotype and the adaptive and innate immune systems[2].

The evolution from psoriasis to the point at which the patient meets the criteria for PsA of the Classification Criteria for Psoriatic Arthritis (CASPAR) (described in the section Classification) may occur in stages (FIG. 1). PsA may develop in up to 30% of patients with psoriasis attending dermatology clinics[3]. The link between skin and musculoskeletal inflammation is certainly established but the underlying mechanisms are yet unclear. Many patients with PsA with active disease may have mild psoriasis and many patients with severe psoriasis may have only mild musculoskeletal features associated with PsA. The differences in genotype, especially in the HLA region, are considered to explain the heterogeneity of the disease[2].

Several new targeted therapies have been approved for use in PsA, with additional therapies in development. These advances have substantially improved the short-term and long-term outcomes, including reductions in musculoskeletal and skin manifestations and radiographic damage. These new treatments are at least in part related to an improved understanding of the genetic basis of PsA and the underlying molecular pathways that are activated and contribute to disease expression. For example, genetic studies have confirmed the association between PsA and single-nucleotide polymorphisms in the IL-17/IL-23 pathway[4,5]. In addition, immunopathological studies have demonstrated the predominance of IL-17-expressing $CD8^+$ T cells in the synovial fluid of patients with PsA, providing further evidence for the IL-17/IL-23 pathway in PsA pathogenesis[6]. Furthermore, treatments targeting IL-17 and IL-23 have not only proven particularly effective for skin psoriasis but are also effective and licensed for musculoskeletal manifestations. With efforts underway aimed at improving our understanding of the molecular basis for the heterogeneity of PsA, a precision medicine approach to treating PsA may not be too far away.

In this Primer, we discuss the epidemiology and pathogenesis of PsA and focus on the challenges in its diagnosis, screening and prevention. In addition, we discuss in detail the current treatment approaches as well as the impact of PsA on the quality of life (QoL) and well-being of patients. The Primer concludes with a glimpse at what the future holds in terms of unmet needs and opportunities to address them.

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Epidemiology

Incidence and prevalence in adults

The incidence of PsA among patients with psoriasis ranges from 0.27 to 2.7 per 100 person-years, depending on the study and outcome definition[7]. However, a meta-analysis found a prevalence of PsA defined using CASPAR of 23.8% among patients with psoriasis. PsA is relatively uncommon in the general population (0.10–0.25% of adults)[8]. The prevalence of PsA is highest among patients 30–60 years of age and affects men and women equally[9]. The majority of patients with PsA are white; whether this increased incidence is related to a specific genetic underpinning or is in part related to the difficulty in diagnosing psoriasis in patients with darker skin colours is unclear[10]. Of interest, the reported prevalence of PsA is lower in Asia than in Europe and North America, potentially suggesting differences by race and/or ethnic group or by environment[8].

Incidence in children

The prevalence and phenotype of PsA is quite different among children, in part related to differences in the criteria used in different classification systems. In the International League of Associations for Rheumatology (ILAR) classification, the criteria for PsA and enthesitis-related arthritis are analogous to those in the CASPAR and the Assessment of SpondyloArthritis international Society systems used in adults; however, they are quite different in that a variety of exclusion criteria classify patients to other categories depending on certain factors[11,12]. For example, a patient with HLA-B27, a first-degree relative with HLA-B27-associated disease, a positive rheumatoid factor or a systemic presentation of juvenile idiopathic arthritis would be excluded from having a diagnosis of PsA[12] (TABLE 2). The ILAR classification is the most commonly used; however, an alternative system for classifying juvenile PsA, the Vancouver criteria, was developed in 1989 but is rarely used today[13,14]. Additionally, there are several limitations with the use of the ILAR system. First, patients are required to have a diagnosis of psoriasis to be classified as having juvenile PsA. This is not withstanding the fact that ~50% of patients with juvenile PsA develop arthritis first and develop psoriasis later, further complicating the development of classification systems for use in children[15]. Second, the criteria refer to boys or men, although we know that PsA affects both sexes equally. Third, treatment for juvenile idiopathic arthritis may differ from the management of adult PsA. Methotrexate remains the first-line therapy as of 2019, although a 2021 update of the American College of Rheumatology juvenile idiopathic arthritis treatment guidelines is in progress[16]. Many therapies used to treat adult disease have not yet been approved for use in children.

Risk factors for PsA

Studies have identified a number of potential risk factors for the development of PsA among patients with psoriasis[17]. These include the following: genetic susceptibility within the HLA region; variants in genes involved in interferon signalling and NF-κB signalling[18]; comorbidities such as obesity and hyperlipidaemia; and psoriasis-related factors such as psoriasis severity, nail dystrophic changes and potentially psoriasis location[19]. Understanding the role of these risk factors is an active area of investigation.

Defining PsA in a population is challenging and might be one of the potential reasons for the variability in prevalence estimates across studies. The CASPAR classification can only be applied in studies in which patients are being examined[20]. However, studying small samples (for example, in a dermatology clinic) can be associated with selection bias, leading to biased prevalence estimates. On the other hand, analysing large, population-based datasets is complicated by misclassification bias as classification in this setting relies on codes for defining PsA (that is, missing diagnoses that have not been recorded in the dataset and simultaneously misdiagnosis of PsA as conditions unrelated to psoriasis (for example, osteoarthritis))[19,21,22]. The truth might be somewhere in the middle. Thus, both study designs must be interpreted in light of these potential limitations, although they are helpful in understanding not only prevalence and incidence but also outcomes and risk factors for PsA.

Comorbidities

PsA is associated with several chronic conditions, which may affect lifespan and QoL[23]. Although most studies have shown that the overall mortality among patients with PsA is not higher than in the general population, cardiovascular comorbidities have a higher prevalence and can impact lifespan and QoL[17]. Obesity is particularly common in patients with PsA, and is significantly more prevalent than in patients with psoriasis or rheumatoid arthritis and the general population[17]. Obesity has a particular impact on function, QoL and response to therapy[24]. In addition, PsA is associated with an increased prevalence of cardiovascular risk factors such as hypertension, hyperlipidaemia, type 2 diabetes mellitus, and the combination of these (that is, the metabolic syndrome) compared with the prevalence in the general population[25]. Indeed, PsA is associated with an increased incidence of cardiovascular events such as myocardial

Uveitis
Uveitis is inflammation of the uveal tract of the eye.

infarction, even after adjusting for traditional risk factors[26]. Similarly, patients with PsA are at significantly increased risk of type 2 diabetes mellitus and fatty liver disease[27,28]. These cardiometabolic conditions may also be associated with increased disease activity[17]. In addition, depression and anxiety are common in patients with PsA, each affecting 10–30% of patients[29], and fibromyalgia or central sensitization is also common, also affecting ~30% of patients[30,31]. Depression, anxiety and fibromyalgia have a substantial impact on treatment outcomes and, therefore, these comorbidities should be identified and managed so as to improve outcomes[32,33].

PsA is also associated with extra-articular manifestations including uveitis and inflammatory bowel disease (that is, Crohn's disease and ulcerative colitis)[34]. A meta-analysis showed a prevalence of ~3% of uveitis and ~3% of inflammatory bowel disease in patients with PsA[35]. These conditions can have a major impact on treatment selection as not all therapies for PsA cover these manifestations.

Mechanisms/pathophysiology

The exact sequence of events leading to the onset and progression of human PsA has not yet been delineated. Nevertheless, arthritis has been suggested to be triggered by a complex interplay between an individual's genetic predisposition and environmental influences that triggers an immune response, leading to entry and proliferation of immune cells at articular, periarticular and extra-articular sites. The mediators for musculoskeletal inflammation may be skin-derived or there may be a common trigger causing skin and joint disease (FIG. 2).

Table 1 | **Distinguishing clinical, laboratory and radiographic features of PsA**

Feature	Psoriatic arthritis	Rheumatoid arthritis	Osteoarthritis	Ankylosing spondylitis
Polyarticular	Common	Very common	Common	Rare
Oligoarticular	Common	Occasional	Common	Occasional
Distal interphalangeal joint involvement	Common	Rare	Common	Rare
Axial spondyloarthritis	Common	No	No	Nearly always
Dactylitis	Common	No	No	Rare
Enthesitis	Common	Rare	No	Common
Psoriasis	Very common	Rare	Rare	Occasional
Nail dystrophy	Very common	No	No	Occasional
Rheumatoid factor-positive	Occasional	Very common	Rare	Rare
aCCP-positive	Rare	Very Common	Rare	Rare
Elevated ESR or elevated CRP	Common	Very common	Rare	Common
HLA-B27 positivity	Occasional	Rare	Rare	Very common
Joint erosion[a]	Common	Very common	Occasional	Occasional
Osteoproliferation[a]	Common	Rare	Common	Very common[b]
Sacroiliitis on radiographs[a]	Occasional	No	No	Nearly always

aCCP, anti-cyclic citrullinated peptide; common, 30–60%; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; nearly always, >90%; no, not found; occasional, 10–30%; PsA, psoriatic arthritis; rare, <10%; very common, 60–90%. [a]In disease of >2 years duration. [b]Very common in spine or sacroiliacs; occasional in peripheral skeleton.

HLA-associated genetic factors

Studies have revealed a strong genetic contribution to the development of psoriasis and PsA. Epidemiological evidence suggests that the recurrence of PsA among first-degree relatives of PsA probands (λs 30–48) is greater than the recurrence of psoriasis among first-degree relatives of psoriasis probands (λs 4–10)[36]. However, a new study that investigated single-nucleotide polymorphisms from large-scale genotyping arrays, while confirming strong heritability, concluded that there is a stronger contribution from psoriasis[37]. The genetic associations in PsA are found in HLA and non-HLA region genes, with the strongest association being within the HLA region. *HLA-C*06:02* is found in ~60% of those with psoriasis but the frequency is significantly lower than in those with PsA (28%)[38]. This same study found that 18% of patients with PsA were *HLAB*27*-positive, with the frequency of B*27 in patients with psoriasis in whom PsA has been excluded (cutaneous-only psoriasis; PsC) similar to that in normal controls. *HLA-B*08* was the major allele in patients with PsA (37%) but, interestingly, its frequency was significantly less in those with PsC (15%)[38]. A comparison of HLA alleles and amino acid sequences in patients with PsA or PsC revealed that the association was most significant for HLA-B amino acid position 45. Of the amino acid residues at this position, the presence of glutamine (HLA-B Glu45) was associated with the highest risk of developing PsA rather than PsC. Although, among the HLA alleles, *HLA-B*27* had the lowest *P* value, the association was less significant than the association with HLA-B Glu45. Interestingly, HLA-B alleles that associated with PsA, including *HLA-B*27*, *HLA-B*38* and *HLA-B*39*, have glutamine at position 45 (REF.[39]). Another study that controlled for age of psoriasis onset showed that *HLA-C*06:02* is not associated with PsA and that amino acid position 97 (asparagine or serine) of HLA-B differentiates PsA from PsC. Of note, *HLA-B*27* has asparagine at position 97 and *HLA-B*07* and *HLA-B*08* have serine[40].

HLA class I molecules play a critical role in immune responses, particularly to viruses, by presenting viral peptides to $CD8^+$ T cells. Studies have demonstrated the presence of clonally expanded $CD8^+$ T cell populations in synovial fluid and tissue of patients, indicating a role for $CD8^+$ T cells in PsA pathogenesis[2]. The amino acid residues associated with PsA are in the antigen-binding groove of the HLA-B molecule. The peptides driving clonal expansions of $CD8^+$ T cells in PsA have not been identified. But given the structural similarity of the binding pockets of each of the HLA-B molecules associated with PsA producing a negative charge, the peptide sitting in the B pocket is highly likely to have positively charged amino acids at position 45 (REF.[41]). The heterogeneous nature of this T cell response has been suggested to further determine the molecular pathways that are activated, which ultimately result in characteristic diverse clinical disease expression and possibly

Sacroiliitis
Inflammation of the sacroiliac joints

treatment responses. In support of this concept, studies have shown associations of HLA genotypes not just with susceptibility to disease but also with certain disease features, such as the interval between the onset of psoriasis and PsA. For example, *HLA-B*27* is associated with a short interval between skin manifestations and musculoskeletal disease and *HLA-C*06* is associated with a longer interval. In addition, *B*27:05:02,C*01:02:01* and *B*08:01:01,C*07:01:01* haplotypes are associated with dactylitis; *B*27:05:02,C*01:02:01* haplotype is associated with enthesitis; *B*27:05:02,C*01:02:01* and *B*27:05:02,C*02:02:02* haplotypes are associated with symmetrical sacroiliitis and *B*08:01:01,C*07:01:01* haplotype with asymmetrical sacroiliitis[42].

Non-HLA-associated genetic factors

Although the strongest genetic associations with PsA are with genes within the HLA region, non-HLA gene associations are also well described. Many of the genetic risk loci reported as associated with PsA susceptibility are shared with psoriasis, such as *IL12B* and *TRAF3IP2*, which are involved in IL-17 signalling[43]. This finding reflects shared molecular pathways mediated by the presence of cutaneous psoriasis in both phenotypes. The number of shared susceptibility alleles might possibly relate to inadequate exclusion of musculoskeletal inflammation in patients designated as having PsC. However, studies have identified a number of PsA-specific loci, which explains the additional musculoskeletal burden. These loci include the following: the presence of glutamic acid at amino acid position 45 in HLA-B; a risk locus at chromosome 5q3; and distinct PsA variants at *IL23R*, *PTPN22* (which encodes a potent inhibitor of T cell activation) and *RUNX3* (which is involved in $CD8^+$ T lymphocyte differentiation)[44]. Notably, all of these PsA-specific loci involve genes that are involved in immune activation, emphasizing the importance of immune dysfunction in PsA pathogenesis.

The exact mechanism that results in over-expression of pro-inflammatory mediators, including cytokines, is poorly understood. We do, however, know that active PsA is associated with production of a cascade of cytokines including TNF, IL-17 and IL-23 (REF.[1]). The importance of these cytokines in disease pathogenesis is supported by the efficacy of inhibitors targeting these cytokines in affecting clinical disease expression. As not all patients respond to cytokine inhibition, an improved understanding of the molecular pathways associated with specific disease features may help to better guide treatment choices[2].

Environmental factors

A number of environmental factors have been hypothesized to be associated with the development of PsA. These factors include musculoskeletal injury, obesity and infection; evidence for the association of PsA with stress or anxiety, alcohol consumption or smoking is controversial[45]. For years, support for a role of musculoskeletal injury in disease pathogenesis was poor, with case reports or series providing anecdotal evidence only. A matched cohort study using data from the Health Improvement Network showed that

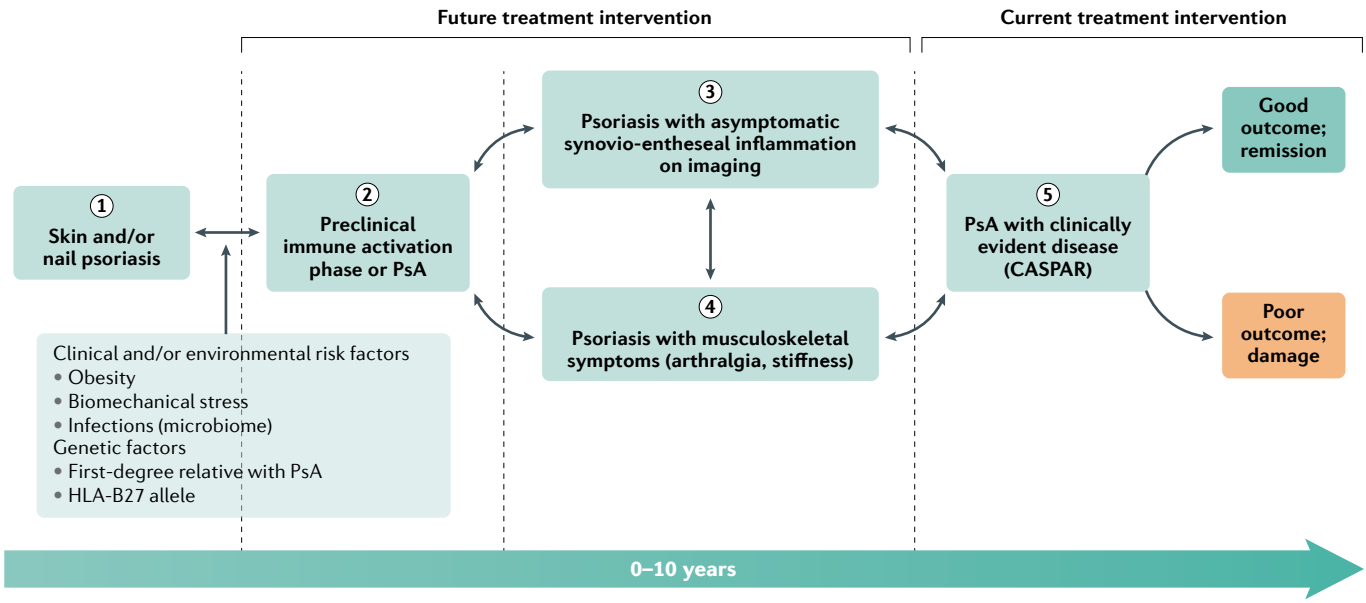

Fig. 1 | **Stages in the evolution of psoriasis to psoriatic arthritis.** This figure illustrates the stages in the evolution of psoriasis to psoriatic arthritis (PsA). These stages include: (1) patients with skin and/or nail psoriasis only but with risk factors, at present undetermined, for subsequent development of PsA; (2) musculoskeletal immune activation phase when cytokines such as IL-23/IL-17 and/or TNF are over-expressed at a cellular or tissue level; (3) an asymptomatic stage with evidence of synovio-entheseal inflammation on imaging such as MRI or ultrasonography; (4) a 'prodromal' stage in which patients with psoriasis may have musculoskeletal symptoms such as arthralgia and/or stiffness but without sufficient signs to make a diagnosis of PsA; and (5) the stage in which patients meet the criteria of the Classification Criteria for Psoriatic Arthritis (CASPAR). The bidirectional arrows reflect the important possibility that some of these stages may be reversible. At present, treatment is focused on those patients who receive a diagnosis of psoriatic arthritis (stage 5) and have ongoing inflammatory disease and evidence of radiographic damage. Future treatment intervention strategies may target patients at earlier disease stages (stages 1–4).

Table 2 | **Classification systems for psoriatic arthritis and enthesitis-related arthritis**

ILAR enthesitis-related arthritis	ILAR psoriatic arthritis	Vancouver psoriatic arthritis
Arthritis and enthesitis or arthritis or enthesitis plus at least two of the following: sacroiliac joint tenderness or inflammatory back pain; HLA-B27 positivity; family history (first-degree relative) of HLA-B27-associated disease; acute and symptomatic anterior uveitis; arthritis in boys >6 years of age	Arthritis and psoriasis or arthritis and at least two of the following: dactylitis; nail pitting or onycholysis; family history of psoriasis (first-degree relative)	Arthritis and psoriasis or arthritis plus at least two of the following: dactylitis; nail pitting; family history of a first-degree or second-degree relative with a psoriasis-like rash
Exclusions: psoriasis in self or first-degree relative, rheumatoid factor positivity, systemic JIA	Exclusions: onset of arthritis in an HLA-B27-positive male beginning after the sixth birthday, family history (first-degree relative) of HLA-B27-associated disease, rheumatoid factor positivity, systemic JIA	Exclusions: none

ILAR, International League of Associations for Rheumatology; JIA, juvenile idiopathic arthritis.

patients with psoriasis exposed to trauma, especially bone and joint trauma, had an increased risk of PsA compared with controls[46]. Association with trauma is not confined to major trauma, which is consistent with the hypothesis that microtrauma at entheseal sites may be a critical disease-initiating factor[47]. This finding might possibly explain the association between PsA and increasing BMI[45], with higher mechanical load at entheseal sites being a consequence of high BMI. The effects of excess adipose tissue, which includes abundant pro-inflammatory mediators, might spill over to other tissue sites, triggering immune activation.

Studies have suggested a role for infection in triggering PsA, in particular the association between streptococcal infection and guttate psoriasis is well established[48]. In addition, psoriasis and PsA also occur more commonly and severely in individuals with HIV infection, which targets $CD4^+$ T cells but not $CD8^+$ T cells, than in the general population[49]. Studies have examined changes in the microbiome and onset of PsA[50]; however, the findings from these studies have been inconclusive. Understanding the role of the microbiota in PsA pathogenesis is an area for further research as microbiota-driven populations of IL-17-producing innate immune cells have been identified in other tissues, such as the gastrointestinal tract and periodontal tissue[51]. Furthermore, one study has demonstrated the important influence of the gut microbiota — together and over time — on systemic immune cell dynamics[52].

Immune mediators in PsA

Given the strong association with HLA class I alleles and T helper 17 (T_H17) immune response, a model for pathogenesis of PsA has been proposed whereby primed antigen-presenting cells at sites such as the skin or enthesis engage with innate lymphoid cells and naive T cells, leading to local clonal expansion of T_H1 and T_H cells and $CD8^+$ cytotoxic T (T_C1 and T_C17) cells[53]. The interplay between the effector T cell subsets, stromal cells and the cytokine milieu at the local sites determines disease features including enthesitis, synovitis, bone and cartilage loss, and new bone formation in the axial and peripheral musculoskeletal system[53].

The strong relationship between skin and musculoskeletal inflammation raises the question as to whether the relationship between inflammation at the two sites is successive (that is, changes in the skin trigger musculoskeletal inflammation) or synchronous (that is, a common trigger leads to skin and musculoskeletal inflammation). In 70% of patients with PsA, skin inflammation predates musculoskeletal inflammation by many years. This latency, if associated with certain HLA alleles, such as *HLA-C*0602*, is associated with a long interval between the onset of skin inflammation and musculoskeletal inflammation[54]. Thus, mediators originating in the inflamed skin could trigger musculoskeletal inflammation. This theory is supported by the findings of one study, which demonstrated increased circulatory skin-derived tissue-resident memory $CCR10^+CD8^+$ T cells in the peripheral circulation of patients with PsA compared with the levels in patients with PsC[55]. However, these cells were not enriched in the synovial fluid[55]. Another study demonstrated a high proportion of synovial T_C17 cells expressing markers typically associated with homing to the skin or gut[56]. Injury to sites of biomechanical stress may be the underlying mechanism driving synchronous skin and musculoskeletal inflammation. Joint disease has been demonstrated to occur simultaneously with or prior to the onset of skin disease in 30% of patients[1]. Furthermore, *HLA-B*27* is associated with short skin–joint disease latency[38,42]. Microtrauma at sites of increased biomechanical stress leading to enthesitis may underlie this form of PsA, with skin disease limited to sites of microtrauma (such as behind the elbows and knees) and joint disease triggered at the enthesis. In fact, enthesitis is hypothesized to be the mechanism underlying the diverse musculoskeletal manifestations of PsA or spondyloarthritis including eye and gut inflammation, which is further supported by the association between *HLA-B*27* and more severe sonographic enthesitis in PsA[57].

Clonal expansion of T cells in the psoriatic joint is well described[58,59]. Indeed, one study demonstrated a threefold increase in the population of memory $CD8^+$ T cells as well as pronounced $CD8^+$ T cell clonal expansion in the joints of patients with PsA compared with the population in peripheral blood[60]. These cells express cell-cycle activation, tissue-homing and tissue residency markers, including the skin or gut-homing

Synovitis
Synovitis is inflammation of the synovial tissue, which is normally a thin layer of tissue lining the inside of joints.

marker ITGA1 (also known as CD49a) and granulysin. CXC-chemokine receptor 3 (CXCR3) is upregulated in the expanded synovial CD8⁺ T cells, and its two ligands, CXCL9 and CXCL10, are elevated in PsA synovial fluid[60]. Elevated CXCL10 is known to predict the future development of PsA in patients with PsC[61].

Diagnosis, screening and prevention

The first step in caring for patients with PsA is to make an accurate and timely diagnosis to allow prompt therapy. Multiple factors are considered in the process of diagnosing PsA. Typically, these factors may include patient history, physical examination, laboratory findings and imaging results. Although the diagnostic process may end in a clinician making a binary decision (that is, the disease is present or not), this process is often associated with a level of probability of the diagnosis in relation to other potential differential diagnoses.

The majority of patients manifest psoriasis before developing PsA, although this may not have been previously diagnosed. In patients with psoriasis, the key issue is to identify whether inflammatory musculoskeletal disease (arthritis, enthesitis or spondylitis) is present. The majority of patients with inflammatory arthritis and psoriasis are likely to have PsA[62].

Unfortunately, there is a well-recognized delay in the diagnosis of PsA even though the majority of patients have a preceding condition in the form of skin psoriasis. Data from a UK national audit in 2015 estimated a median delay of 29 weeks, which was substantially longer than in matched patients presenting with rheumatoid arthritis[63]. This delay in diagnosis has also been shown to have major implications. For example, another UK study found that a delay in diagnosis of 12 months was associated with increased physical function impairment at 10 years despite active treatment[64]. A subsequent study in Ireland showed that a delay in diagnosis of even 6 months was associated with a higher chance of peripheral erosive disease and poorer physical function than a shorter diagnostic delay[65].

Clinical presentation

There are relatively few data concerning the signs and symptoms that aid diagnosis of PsA. In 2013, a nominal group exercise was performed with health-care professionals interested in rheumatology and with patient

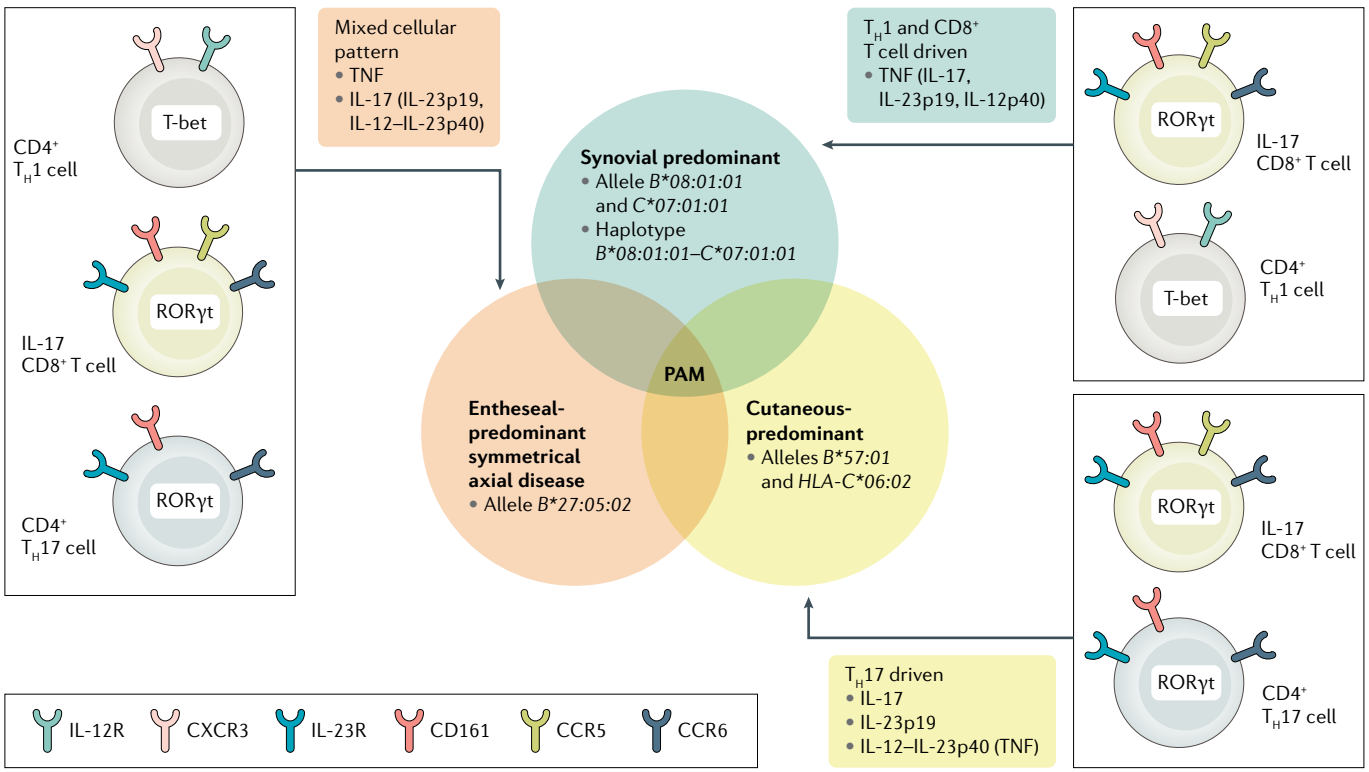

Fig. 2 | **Proposed pathogenetic pathways activated in key subtypes of psoriatic disease.** Distinct clinical phenotypes of psoriatic disease (PsD) occur as a consequence of genetic predisposition, environmental triggers (such as biomechanical or metabolic stress, infections and obesity) and local factors according to disease site (joints, skin, spine or entheses). Amplification of the IL-23–IL-17 axis is initiated via activation of innate cells in the skin, entheses and gastrointestinal tract, ultimately resulting in the expansion of CD4⁺ and CD8⁺ T helper 1 (T_H1) and T_H17 cells, which are expanded by IL-23 and IL-12 and produce TNF and IL-17. Different HLA alleles and/or haplotypes, T cell subsets and treatment response profiles are associated with different PsD phenotypes. Synovial-predominant PsD is associated with *HLA-B*08:01:01*, *HLA-C*07:01:01* and haplotype *HLA-B*08:01:01–HLA-C*07:01:01*, CD8⁺ engagement with T_H1 cells and responsiveness to TNF inhibition. Cutaneous-predominant PsD is associated with *HLA-B*57:01* and *HLA-C*06:02*, is T_H1 cell-driven and is responsive to IL-17 and IL-23 inhibition. Entheseal-predominant psoriasis with or without axial disease, which is associated with the *HLA-B*27:05:02* allele, involves engagement of both T_H1 and T_H17 cells that produce both TNF and IL-17, and is responsive to TNF and IL-17 inhibition. Psoriatic arthritis mutilans (PAM) probably represents a combination of these host genetic factors and T cell interactions. CXCR3, CXC-chemokine receptor 3; CCR, CC-chemokine receptor; IL-12R, IL-12 receptor; IL-23R, IL-23 receptor. Reprinted from REF.[53], Springer Nature Limited.

Joint erythema
Joint erythema is one of the features of an inflamed joint or arthritis when the joint is red in appearance.

Dactylitis
Dactylitis is sausage-like swelling of a finger or toe.

research partners to identify descriptive elements of inflammatory joint disease. The symptoms identified included early morning stiffness for >30 min, joint tenderness, pain aggravated by rest and relieved by exercise, symptoms improved by NSAIDs or corticosteroid use, joint erythema or warmth and related fatigue. Possible clinical signs included joint swelling, limited motion and joint deformity[66].

In terms of peripheral arthritis, the presentation is similar to that in most forms of inflammatory arthritis, although the pattern of joint involvement can vary, with oligoarticular and polyarticular patterns described. Distal interphalangeal joint involvement is more common in patients with PsA than in those with other forms of inflammatory arthritis[67]. The clinical presentation of musculoskeletal inflammation can be helpful in differentiating between PsA and other forms of inflammatory arthritis (TABLE 1). In addition to peripheral arthritis, patients often present with inflammation in other musculoskeletal tissues including the following: enthesitis, observed in up to 67% of patients on presentation[68–73]; dactylitis, observed in 12–39% of patients[68–74]; and axial involvement within the axial spondyloarthritis phenotype, observed in 5–28% of patients at diagnosis but potentially in up to 70% of patients with late-stage disease[68–73]. Although the vast majority of patients presenting with PsA have peripheral musculoskeletal involvement, the prevalence of axial disease in isolation with psoriasis has been reported to be 7–17% in a few cohorts[72,75].

Laboratory testing

The reason for the diagnostic delay in PsA compared with rheumatoid arthritis may be partly related to the lack of specific investigations to confirm the diagnosis (TABLE 1). Primary care physicians typically use inflammatory markers including CRP, specific antibodies, such as rheumatoid factor, or anti-citrullinated peptide to screen patients with possible inflammatory arthritis. Patients with PsA are usually seronegative, although a positive rheumatoid factor or anti-citrullinated peptide does not exclude the condition. At presentation, only 33–89% of patients demonstrated elevated CRP levels[68,70,75,76]; thus, a substantial proportion of patients do not have raised blood markers despite active disease.

Studies have identified typical imaging features in PsA, which are included in the classification criteria. These imaging features are more prevalent with increasing disease duration. In early disease, radiographs often appear normal as bone damage has not occurred and therefore radiographs often do not assist in diagnosis. A 2003 study in patients with peripheral arthritis found that 27% of patients had erosions at presentation, and the findings were similar in the 2015 Tight Control of PsA (TICOPA) study[77]. However, in both studies, the amount of erosive disease observed was relatively small, affecting only a few joints in most of the patients imaged.

Given the potential for axial involvement, imaging of the spine and sacroiliac joint can also show abnormalities in patients with PsA. Again, axial involvement is more prevalent in late disease stages, with limited value in early diagnosis[78,79]. Sacroiliac joint involvement in PsA seems similar to that observed in ankylosing spondylitis, although asymmetrical sacroiliac involvement is more common[80,81].

Classification

The first classification system developed for PsA was that of Moll and Wright, which was developed based on clinical observation, and was the key classification used until 2006 (REF.[62]). In the Moll and Wright classification, PsA is defined as an inflammatory arthritis (peripheral arthritis and/or sacroiliitis or spondylitis) in the presence of psoriasis with the (usual) absence of serological tests for rheumatoid factor[62]. However, the criteria focus on peripheral arthritis rather than on other aspects of the musculoskeletal disease, such as enthesitis, and require a negative rheumatoid factor test, which is an issue in a minority of patients[82].

Over the decades, a number of other classification systems have been developed but none of these classifications was utilized widely in clinical research until the introduction of the CASPAR system. In 2000, a large international consortium of rheumatologists came together to develop a new, robust and data-driven classification, which was finally published in 2006. The CASPAR system considers a wider range of items for inclusion, overlapping with the criteria of Moll and Wright but also allows classification of people without psoriasis (~10% of patients) or with a positive rheumatoid factor (~15% of patients), provided the patients have other key features of the disease[20]. In the development cohort, CASPAR had a high sensitivity and specificity[20], and these findings have been confirmed in numerous independent studies subsequently[83–85].

In early disease, classification according to CASPAR may not be as straightforward as in established disease but specificity has been confirmed to be >95%. There is an issue of lower sensitivity in early inflammatory arthritis as some typical features may not yet be present[71,86]. In particular, typical new bone formation is not common at presentation, thereby limiting the ability to identify the disease. Another issue raised with CASPAR is the heavy weighting given to ongoing psoriasis. Whilst the majority of patients do fulfil this criterion, the criteria are difficult to meet if a patient's psoriasis has been treated and gone into remission. Potentially, a clear diagnosis of psoriatic skin or nail disease by a dermatologist should be given a weighting similar to ongoing active psoriasis.

The next step proposed for the CASPAR classification is most likely to involve clarifying the 'stem' of the criteria, which state that patients must have inflammatory articular disease (joint, spine or enthesis). From a rheumatology perspective, where we are trying to differentiate PsA from other types of inflammatory arthritis, this is straightforward. Rheumatologists are confident in identifying inflammatory arthritis and can then use CASPAR to confirm if this is likely to be PsA. However, for dermatologists and primary care physicians, the key issue is the diagnosis of inflammatory articular disease in patients who have known psoriasis. Here, the psoriasis is often clear, but it may be difficult for non-rheumatologists to accurately differentiate inflammatory articular disease (as required for CASPAR)

PEST questionnaire
A questionnaire designed to screen for psoriatic arthritis in patients with psoriasis.

from other causes of musculoskeletal pain, for example, osteoarthritis and mechanical joint pain.

Prognosis

Predicting outcomes in patients with PsA is based on limited data with substantial individual variation. Multiple studies have shown that the evolution of PsA can vary over time with different joint and extra-articular involvement[87]. The pattern of peripheral joint disease does seem to change over time, with oligoarthritis more common in patients with early disease than in those with late disease. In most cases, increased joint involvement is observed over time with increasing disease duration, with a high proportion of patients with monoarthritis or oligoarthritis showing progression to polyarthritis[87,88]. Involvement of other domains can also change over time, in particular axial involvement is increasingly common with increasing disease duration[78,89]. However, axial spondyloarthritis and specifically axial PsA can be difficult to diagnose as clear evidence of axial involvement with radiographic changes and restriction of mobility is likely to take many years to develop.

Previous studies have identified a number of poor prognostic markers in PsA. These markers are often included in published treatment recommendations to potentially aid treatment decisions, advising that more urgent or aggressive therapy should be started if the poor prognostic markers are present. In terms of peripheral arthritis, in particular, these markers relate to the number of joints involved (polyarthritis or five or more joints), or the presence of dactylitis, high levels of inflammatory markers (for example, CRP) or baseline erosive disease[90,91]. However, evidence around these risk factors is insufficient and it is not easy to predict outcomes in individual patients. Many of these studies have focused solely on radiographic damage as the poor outcome of interest, which also affects the prognosis. Overall, although oligoarthritis is less likely than polyarthritis to cause radiographic damage in the hands or feet, it may have a marked impact on QoL and functional ability[92].

Screening

Up to 30% of patients with psoriasis may go on to develop PsA. Although predicting this progression accurately at an individual level is not currently possible, studies have identified key predictors of PsA development including severity and site of psoriasis (for example, nails, scalp), obesity, smoking and trauma[19]. Delay in diagnosis may be a particular issue in patients presenting with limited disease (for example, oligoarthritis) or involvement in other domains, such as axial disease or enthesitis.

Given awareness of the delay in diagnosis and the associated consequences, education and interventions focusing on primary care physicians, dermatologists and patients to promote early diagnosis is ongoing. In particular, studies have employed screening questionnaires to identify potential patients with PsA, usually from amongst patients with psoriasis. A number of screening questionnaires have been developed but their sensitivity and specificity are limited[93,94]. Comparative studies, for example the CONTEST study, have shown similar levels of sensitivity (74.5–76.6%) and specificity (29.7–38.5%) across different questionnaires[93]. The CONTEST questionnaire, developed from a combination of the best-performing questions in each questionnaire did not out-perform the Psoriasis Epidemiology Screening Tool (the PEST questionnaire) in a subsequent study[95]. Most studies have shown high sensitivity and low specificity as joint symptoms related to other diagnoses are common. Studies have also shown difficulty in identifying patients, in particular those with pure axial disease. Whilst screening tools are not perfect, some studies have found a reasonable benefit in using them. It is recommended that the PEST questionnaire, which is the shortest questionnaire available, is used annually in patients with psoriasis in the UK[96]. The questionnaires also indirectly provide education to patients with psoriasis who are then aware of the potential for the development of psoriasis-related arthritis.

Prevention

In collaboration between dermatology and rheumatology, studies monitoring patients with psoriasis aiming to predict the development of PsA are underway. To date, these studies have predominantly confirmed known predictors of PsA development[97]. In large populations, these findings might be used to develop predictive models that could be applied to individuals, which would allow in-depth study of the pathogenesis of disease in a high-risk population and may elucidate the triggers involved in this continuum. Potentially, similar to the studies performed in rheumatoid arthritis, interventional studies trying to prevent the development of disease could be established in high-risk populations. Studies such as these would require collaborative efforts to recruit suitably sized populations and should include patient representation within their design to ensure that the studies are acceptable to patients and that individual patients are educated about their potential risk and what this may mean for them in the future.

Management

Prior to the year 2000, the pharmacological treatment options for PsA were essentially limited to NSAIDs, glucocorticoids, methotrexate, sulfasalazine and cyclosporine. Only a few randomized therapeutic trials specifically investigated PsA. Despite known clinical differences between the conditions, it was assumed that evidence from clinical trials in rheumatoid arthritis could be extrapolated to PsA. Since the year 2000, the management of PsA has been revolutionized as a result of several developments. These advances include the development of numerous immunologically targeted biological disease-modifying drugs (bDMARDs) and targeted synthetic drugs (tsDMARDs). Although these drugs were originally developed for the treatment of rheumatoid arthritis, they have shown efficacy in other conditions, including psoriasis, PsA and axial spondyloarthritis. In addition, by identifying the importance of pro-inflammatory mediators and pathways, research on the immunopathogenesis of PsA has helped reinforce the rationale for the effectiveness of targeted immunotherapies, and has also suggested new treatments. Furthermore, research on the clinical aspects of PsA

Table 3 | **Outcome measures in clinical trials in PsA**

Domains	Instruments
Arthritis	68/66 T/S joint count, ACR20/50/70 response, DAS28, PsARC, PsAJAI, DAPSA, cDAPSA
Enthesitis	Leeds Enthesitis Index, SPARCC, MASES, four-point[a]
Dactylitis	Leeds Dactylitis Index, Dactylitis Count, Dactylitis Severity Score
Axial spondyloarthritis	BASDAI, BASFI, BASMI
Skin, nails	PASI, target lesion, physician global, PSI, PSD, NAPSI, mNAPSI, nail VAS
Composite — multidomain	MDA, VLDA, PASDAS, CPDAI, GRACE
Pain	VAS, NRS
Patient global	VAS (joint global, skin + joints global), NRS
Physician global	VAS (joint global, skin + joints global), NRS
Physical function	HAQ, HAQ-S, SF-36 PF, PROMIS-PF
HRQoL	SF-36, PSAID, PsAQoL, DLQI, EQ5D, PROMIS-Profiles
Fatigue	FACIT-Fatigue, VAS, PROMIS-Fatigue
Participation	PROMIS-Social roles and participation
Acute phase reactant	ESR, CRP
Structural damage	Plain radiography (modified Sharp or van der Heijde–Sharp), MRI, US
Work or home productivity	WPAI, WPS

Data from REFS[81–83]. ACR, American College of Rheumatology; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; cDAPSA, clinical Disease Activity in Psoriatic Arthritis; CPDAI, Composite Psoriatic Disease Activity Index; CRP, C-reactive protein; DAPSA, Disease Activity in Psoriatic Arthritis; DAS, Disease Activity Score; DLQI, Dermatology Life Quality Index; EQ5D, EuroQol five dimensions; ESR, erythrocyte sedimentation rate; FACIT, Functional Assessment of Chronic Illness Therapy; GRACE, GRAPPA Composite Exercise; GRAPPA, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; HAQ, Health Assessment Questionnaire; HAQ-S, Health Assessment Questionnaire–Spondyloarthritis; HRQoL, health-related quality of life; MASES, Maastricht Ankylosing Spondylitis Enthesis Score; MDA, minimal disease activity; mNAPSI, Modified Nail Psoriasis Severity Index; NAPSI, Nail Psoriasis Severity Index; NRS, numeric rating scale; PASDAS, Psoriatic Arthritis Disease Activity Score; PF, physical functioning; PROMIS, Patient-Reported Outcomes Measurement Information System; PsA, psoriatic arthritis; PSAID, Psoriatic Arthritis Impact of Disease; PsAJAI, Psoriatic Arthritis Joint Activity Index; PsAQoL, Psoriatic Arthritis Quality of Life Index; PsARC, Psoriatic Arthritis Response Criteria; PASI, Psoriasis Area and Severity Index; PSI, Psoriasis Symptom Inventory; PSD, Psoriasis Symptom Diary; SF-36, Short-Form 36; SPARCC, Spondyloarthritis Research Consortium of Canada; T/S, tender/swollen; US, ultrasonography; VAS, visual analogue scale; VLDA, very low disease activity; WPAI, Work Productivity and Activity Index; WPS, Work Productivity Survey. [a]Used in the impact study.

has led to an increased appreciation of the complex and heterogeneous nature of the disease in individual patients including peripheral arthritis, axial arthritis, enthesitis, dactylitis, spondylitis, skin and nail psoriasis, iritis and inflammatory bowel disease. These domains need to be assessed individually to ensure that different manifestations are being treated appropriately.

In addition, since the early 2000s, the development of reliable and validated outcome measures to assess PsA clinical domains has helped optimize assessment in clinical trials[98–101] (TABLE 3). Advances in imaging, including ultrasonography and MRI, have allowed more precise visualization of tissue inflammation and joint damage. Besides standard randomized controlled trials (RCTs), strategy trials such as treatment to target of remission and head-to-head comparative trials are increasingly being performed. In this section, we summarize the pharmacological treatment of PsA, focusing on specific classes of drugs, followed by a summary of treatment recommendations and treatment strategies. A review of non-pharmacological therapies, including physical and occupational therapy, psychotherapy and dietary approaches including weight reduction is beyond the scope of this Primer. These non-pharmacological treatments should be pursued in parallel with pharmacological treatment.

Treatment to target of remission
Treatment to target of remission is where treatment is escalated according to patient response until a target of remission has been achieved.

Adjunctive treatments

NSAIDs. NSAIDs are frequently used for symptomatic improvement of pain associated with arthritis and periarticular manifestations of PsA. Interestingly, and in contrast to rheumatoid arthritis, there is very little evidence addressing NSAID efficacy specifically in PsA. One 12-week RCT investigating the efficacy of celecoxib did not demonstrate statistical superiority of celecoxib over placebo[102]. Nevertheless, many years of clinical experience suggests that NSAIDs can be a useful adjunct in the management of various domains of PsA, including peripheral arthritis, axial arthritis, enthesitis and dactylitis. Indeed, in axial disease, the lack of efficacy of conventional synthetic DMARDs (csDMARDs) leaves NSAIDs as the mainstay of therapy. Before the advent of biological agents, NSAIDs were commonly included as concomitant therapies in trials of DMARDs in PsA.

Glucocorticoids. Although topical steroid medications are commonly used to treat psoriasis and intra-articular steroids used to treat flares in one or a few joints, systemic steroids are not as commonly used in PsA as in rheumatoid arthritis. In PsA, there is a need for caution when considering steroids for local tendon or entheseal injection, as longer-term efficacy is questionable owing to reports of tendon rupture[103]. The concern for steroid use in PsA partly comes from anecdotal experience showing that skin psoriasis can flare dramatically upon abrupt discontinuation of steroids, usually at very high doses[104].

Conventional synthetic DMARDs

Methotrexate. Although methotrexate has been one of the most widely used medications for PsA since the 1980s, very few studies have investigated the efficacy of methotrexate in PsA[105–107] (BOX 1). Assessment of the findings of these few studies suggested that doses of methotrexate of 15 mg/week or higher may be more effective than lower doses in PsA. In the Methotrexate in Psoriatic Arthritis (MIPA) trial published in 2012, the primary end point was not significantly different between patients receiving methotrexate and those receiving placebo[108]. However, design issues including the dose of methotrexate used affected assessment of the data from that study. In addition, a subset analysis showed that methotrexate was effective in patients with PsA whose disease was similar to rheumatoid arthritis (that is, polyarticular disease, with elevated acute phase reactants). In the study of etanercept and methotrexate in combination or as monotherapy in patients with psoriatic arthritis (SEAM-PsA) trial, methotrexate seemed to perform well, achieving levels of articular, entheseal and skin responses numerically close to those achieved with TNF inhibition; of note, there was no placebo comparator[109]. Based on evidence from the SEAM

Box 1 | **PsA therapeutic groups**[5]

Adjunctive therapies

- NSAIDs, glucocorticosteroids (oral, intra-articular, intramuscular or topical administration)
- Conventional synthetic DMARDs (cs-DMARDs)
- Methotrexate, sulfasalazine, leflunomide, cyclosporine
- biological DMARDs (bDMARDs)
- TNF inhibitors
  - Etanercept[a], infliximab[a], adalimumab[a], golimumab, certolizumab
- IL-12/IL-23 inhibitors
  - Ustekinumab
- IL-17 inhibitors
  - Secukinumab, ixekizumab, brodalumab[b], bimekizumab[c]
- IL-23 inhibitors
  - Guselkumab, risankizumab[b], tildrakizumab[b]
- T cell modulator
  - Abatacept

Targeted synthetic DMARDs

- PDE4 inhibitor (apremilast)
- JAK inhibitors (tofacitinib, upadacitinib; baricitinib[c], filgotinib[c])

[a]Biosimilars available in 2021. [b]Approved for the treatment of psoriasis but not psoriatic arthritis (PsA) at the time of publication. [c]In development.

study as well as experience from global clinical practice, methotrexate remains an important therapy, especially in parts of the world with limited health-care resources. When used with certain biological therapies, methotrexate can reduce immunogenicity. Nevertheless, methotrexate can be associated with tolerability issues, such as nausea, diarrhoea and fatigue, and laboratory monitoring for safety issues (for example, liver, haematological) is necessary.

Sulfasalazine. Sulfasalazine is an oral medication that has been shown to have modest efficacy in arthritis but no significant benefit was demonstrated in psoriasis in an RCT[110]. Gastrointestinal tolerability issues as well as allergic reactions may limit its utility, and laboratory monitoring (for example, haematological, liver) is standard.

Leflunomide. Leflunomide is an oral pyrimidine antagonist, which has shown efficacy in arthritis end points in a single placebo-controlled study involving 190 patients with PsA[111]. Studies have demonstrated less robust results in other domains of PsA, especially skin. Laboratory monitoring for liver function tests and blood counts is required.

Cyclosporine. Cyclosporine is a calcineurin inhibitor that has demonstrated greater benefit in skin psoriasis than in PsA but can also be effective for articular manifestations. Laboratory monitoring for renal toxicity is needed, and hypertension can limit its use in some patients[112].

Biological DMARDs

TNF inhibitors. TNF is a pro-inflammatory cytokine with myriad impacts on various aspects of the inflammatory and immune responses. TNF inhibitors (TNFi) are a landmark breakthrough in the therapy of PsA. Following success observed in rheumatoid arthritis, the first evidence for this benefit in PsA came from a trial demonstrating the effectiveness of etanercept in both articular and psoriasis domains[113]. Soon after, one study showed improvement in articular and psoriasis domains as well as physical function, dactylitis and enthesitis with infliximab therapy; in addition, the treatment slowed the progression of radiographic damage to peripheral joints in PsA[114]. Subsequently, studied TNFi, including adalimumab, golimumab and certolizumab, also showed efficacy across all PsA domains. All TNFi have also demonstrated benefit in ankylosing spondylitis, used as surrogate evidence for efficacy in the axial component of PsA. With the introduction of biosimilar versions of several TNFi in many countries around the world, the acquisition costs have decreased, an important consideration that affects the utilization of biological agents. Important, albeit infrequent, serious side effects with TNFi include infection, including opportunistic infection (particularly tuberculosis), and autoimmune reactions[115].

IL-12 or IL-23 inhibition. Ustekinumab is a human IgG1 monoclonal antibody that binds to the common p40 subunit of IL-12 and IL-23, the former involved in differentiation and activation of T_H1 cells and the latter in differentiation and activation of T_H17 cells. Downregulating these pathways can lead to reduction of several key cytokines in the pathogenesis of psoriasis and PsA, including IL-23, IL-17 and TNF. The efficacy of ustekinumab in PsA was confirmed in two phase III trials, across domains[116,117]. Of note, in dermatology, ustekinumab was the first biological agent that showed efficacy in skin psoriasis greater than that of TNFi. Ustekinumab failed to show benefit in ankylosing spondylitis[118], although previously subjective axial symptoms did improve in a subset of patients with PsA[119]. Whether axial arthritis in PsA differs from ankylosing spondylitis or whether the outcome measures used can detect improvement in extra-axial domains is a matter of discussion. The safety profile of ustekinumab is benign overall, with low rates of serious infection.

IL-17 inhibitors. IL-17 includes a family of related cytokines; IL-17A and IL-17F seem to be the most involved in pathogenesis of inflammatory disease. IL-17 is produced by a wide variety of cells in the innate immune system including natural killer cells, γδ T cells, neutrophils and mast cells, which line barrier sites such as the gut, skin and lung. Several, but not all, of these cell types are activated by IL-23 produced by keratinocytes, macrophages and dendritic cells in response to microbial agents. IL-17 plays a key part in preserving barrier function in the gut and integrity of the epithelium. Two IL-17A inhibitors are currently approved for the treatment of PsA in many jurisdictions. Secukinumab is a human monoclonal IgG1 antibody that binds to

IL-17A. All clinical domains of PsA demonstrated significant improvement, including particularly robust improvement in psoriasis and in axial disease in PsA[120]. Ixekizumab is an IgG4 humanized monoclonal antibody to IL-17A that has also shown efficacy in all clinical domains of PsA, similar to that of secukinumab. In head-to-head trials of both these agents against adalimumab, skin psoriasis improved more with IL-17 inhibitors and articular domains were comparable[121,122]. Brodalumab is a human antibody that binds to the IL-17 receptor, thereby resulting in broad inhibition of the IL-17 family. Brodalumab has been approved for the treatment of psoriasis in many countries. Brodalumab has shown efficacy in PsA similar to that of the other IL-17 inhibitors[123,124]. Bimekizumab, a humanized IgG1 monoclonal antibody that binds to IL-17A and IL-17F, has shown efficacy in all clinical domains of PsA in a phase II study and is currently in phase III development[125].

IL-23 inhibitors. The first IL-23 inhibitor to be approved worldwide for the treatment of PsA is guselkumab, a p19 IL-23 inhibitor that specifically targets IL-23 (distinct from ustekinumab, which binds to the p40 unit and inhibits IL-12 and IL-23). IL-23 is a key pro-inflammatory cytokine in psoriasis and, indeed, its inhibition yields the most complete reduction of psoriasis manifestations compared with other biological agents[126]. Efficacy data in arthritis, enthesitis and dactylitis domains of PsA is robust, similar to the data from RCTs of TNFi and IL-17 inhibitors[127,128]. A sub-study of patients with back pain and radiographic evidence of sacroiliitis demonstrated symptomatic improvement of spinal pain (Bath Ankylosing Spondylitis Disease Activity Index, BASDAI question 2)[129]. This preliminary finding in patients with axial PsA will be further explored as studies of IL-23 inhibitors in ankylosing spondylitis failed to demonstrate efficacy compared with placebo, suggesting that IL-23 is not a driver of inflammation in that condition[130]. Phase II studies of risankizumab[131] and tildrakizumab[132] demonstrated results consistent with those of the phase III studies of guselkumab. Studies have shown minimal evidence of serious infection with IL-23 inhibitors.

Costimulatory blockade. Abatacept (CTLA4 immunoglobulin) is a recombinant human fusion protein that binds to CD80/CD86 on antigen-presenting cells, preventing interaction with CD28 on T cells. A phase III trial in which the majority of patients had failed treatment with TNF inhibitors demonstrated modest benefit of abatacept in arthritis and minimal benefit in psoriasis compared with placebo[133]. Although the effects of abatacept are modest, one advantage of the medication is its relatively benign safety profile.

Targeted synthetic DMARDs

PDE4 inhibitor. The oral phosphodiesterase 4 (PDE4) inhibitor apremilast may downregulate a number of key pro-inflammatory cytokines involved in the pathogenesis of psoriasis and PsA, including TNF and IL-23. Studies have shown modest efficacy of apremilast in psoriatic skin lesions, arthritis, enthesitis and dactylitis[134–136]. Apremilast has a benign safety profile with no serious adverse effects such as infection, and does not need laboratory monitoring.

JAK inhibitors. The JAK–STAT kinase intracellular signalling system is critical for the induction of cellular activation by cytokines involved in PsA pathogenesis, including IL-23, IL-6 and IL-15. There are four JAK molecules — JAK1, JAK2, JAK3 and TYK2. The first JAK inhibitor to be approved for the treatment of PsA, tofacitinib (which inhibits JAK3 and JAK1 more than JAK2), is effective in musculoskeletal domains and modestly beneficial for skin lesions[137–139]. The safety profile is similar to that seen in the treatment of rheumatoid arthritis, which includes the risk of serious infection, the need for laboratory monitoring of liver function tests and blood counts, and rare adverse effect of lymphoma. Evidence suggests an increased risk of thromboembolic events if the medication is used at higher than the recommended dose, which may be a class effect[139]. Other JAK inhibitors in development for the treatment of PsA include the selective JAK1 inhibitors, upadacitinib and filgotinib[140,141], and the TYK2 inhibitor, deucravacitinib[142,143]. Whether differential selectivity for JAK isoforms impacts efficacy across domains of PsA or toxicity remains to be determined.

Treatment strategies

Treat-to-target. As in other fields of medicine, striving for a treatment target of remission has become common practice if possible, or low disease activity if not. Such a strategy yields optimal short-term and long-term outcomes for the patient. Numerous treat-to-target trials have been conducted in rheumatoid arthritis, utilizing quantifiable measures of disease activity, typically including numerically assessed physical examinations, such as joint counts, quantified patient self-assessment and laboratory measures of disease activity, such as CRP. The Tight Control of Psoriatic Arthritis (TICOPA) trial[77], conducted in patients with early-stage PsA, compared patients evaluated monthly and requiring intensification of treatment if a goal of Minimal Disease Activity (MDA) activity was not met with patients evaluated every 3 months without such a target of treatment. After 48 weeks, the patients in the treat-to-target group demonstrated superior treatment results, supporting this goal of treatment in clinical practice. Notably, many treat-to-target studies are tautological, in as much as the requirement to alter therapy to achieve a goal results in greater achievement of the goal using similar metrics. Factors such as longer-term outcomes, safety considerations and pharmacoeconomic assessments should also be taken into account in therapeutic decision-making.

Treatment recommendations. Four international organizations have published and updated PsA treatment recommendations — the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), the European League Against Rheumatism (EULAR), and the American College of Rheumatology and National Psoriasis Foundation in collaboration (ACR–NPF). The GRAPPA recommendations[144] were

BASDAI question 2
A questionnaire commonly used to assess disease activity in patients with ankylosing spondylitis.

developed by rheumatologists, dermatologists and patients with PsA and are organized across the domains of PsA, including peripheral arthritis, axial disease, enthesitis, dactylitis, skin psoriasis and nail psoriasis, as well as inflammatory bowel disease and uveitis. The EULAR guidelines[145] overall yield recommendations similar to the GRAPPA recommendations, but are arranged in an algorithm sequence from early and/or mild disease to more advanced disease in patients in whom previous treatments have failed. The ACR–NPF guidelines[146] used a strict Grades of Recommendation Assessment, Development and Evaluation (GRADE) approach. The guidelines choose one class or group of medicines ahead of another, allowing for variances depending on contextual factors, such as the presence of severe skin disease. One key difference among the three guidelines is the recommendation to use TNFi prior to csDMARDs, based on efficacy and safety data from clinical trials. In the absence of head-to-head trials available when these guidelines were developed, the majority of recommendations are considered 'conditional' as the comparative evidence is indirect. Importantly, there are also additional regional and societal guidelines, developed with less rigor, which present the clinician with a heterogeneous group of treatment guidelines to follow.

Overall, there are numerous biopharmacological therapeutic options for the management of PsA. Most treatment options have the potential to be effective in all clinical domains of the disease. However, in many patients, cross-domain efficacy can be variable, efficacy may not be achieved or may soon be lost, and true remission is not frequent. Clinicians must, therefore, assess each domain on a regular basis and aim to achieve remission or low disease activity across the different active domains, whilst being cognizant of potential adverse events. A greater understanding of the disease pathophysiology has allowed us to precisely target key cellular and cytokine pathways. Treatment effect with any single agent may wane; hence, multiple classes of medicine and choices of individual agents are needed to sustain treatment targets.

Box 2 | **Patient experience**

The statement provided has not been edited and the patient's emphases remain in place.

The advent of effective DMARDs has changed the perspective of people with psoriatic arthritis (PsA) for the better. When I was diagnosed with PsA after a delay of 5 years suffering from severe psoriasis and unexplained joint pain, I was left with indomethacin. It could not prevent serious damage of one knee, a radical synovectomy followed by a total knee replacement ten years later. I lost my job as a company trainer and became depressed, hardly able to take care of my family.

Starting anti-TNF became a life-changing event. I joined a local patient hydrotherapy group and became a volunteer at an arthritis patient organization. I got to know other patients and their stories inspired me to read information about rheumatology research. It made me aware about my responsibility for my own health. Too long I had unconditionally followed my rheumatologist's advice and still feeling isolated and loosing many friends. Receiving an effective treatment motivated me to give something back to society and changed my perspective on health care delivery and research. I learned the principles of self-management, which enabled me to cope better with residual symptoms and limitations. For me remission is not the ultimate goal if that means to further increase the methotrexate dose. Communication with my rheumatologist is improved, I dare to ask more questions and we discuss existing guidelines. Sometimes a specialized arthritis nurse monitors my disease, and it is good to see that she not only asks how my joints are doing but also asks for skin symptoms.

Over the years the diagnosis and care of people with PsA has improved. I have developed a positive outlook on my future and, despite the fact that we have not found the Holy Grail of curing the disease, I am optimistic about the perspective for newly diagnosed people who is promising.

-Anon

Quality of life

PsA has a substantial negative impact on physical function and QoL (BOX 2). The concept of QoL extends beyond the physical manifestations of disease to include emotional well-being, self-esteem, participation in work and activities as well as non-health issues such as financial security, spiritual well-being and environmental safety (FIG. 3). PsA has a similar effect on QoL to that observed in rheumatoid arthritis despite generally being a less destructive arthropathy. The negative effect of PsA seems to be due to the accumulated burden of skin, joint, entheseal, axial disease, comorbidities and flare[147,148]. Pain is ranked consistently in qualitative studies as the top priority in patients as an outcome of treatment, but fatigue, physical function, ability to work and social participation all rank highly[149,150]. An observational study in patients with early PsA and rheumatoid arthritis has shown that despite severe disease at diagnosis, near-normalization of health-related QoL is observed in patients with rheumatoid arthritis after 5 years but not in those with PsA, possibly owing to diagnostic delay[151]. The delay in diagnosis in PsA is longer than that in rheumatoid arthritis and is associated with worse clinical and functional outcomes[64,65].

Assessment of QoL

The understanding of treatment outcomes important to patients has advanced considerably since the 2010s. Improving QoL is clearly a high-priority outcome of treatment for patients[150]. All RCTs and observational studies of PsA have confirmed the importance of assessing QoL[152]. Instruments for measuring QoL may be generic, applicable across diseases or the general population, or disease-specific, attributing the measured effect to the particular disease under consideration. Disease-specific QoL instruments cover concerns that are specific and relevant to the group of patients with the condition. Generic measures of QoL commonly used in PsA include the Medical Outcome Study 36-item short form questionnaire (SF-36)[153] and the EuroQoL five dimensions questionnaire (EQ5D)[154]. The SF-36 scores eight subdomains and aggregates the score into two summary domains of physical and mental health, and there are data supporting its validity in PsA[100]. The EQ5D is available as an index (with country-specific adjustments) or visual analogue scale. Disease-specific instruments include the Psoriatic Arthritis Quality of Life (PsAQoL) index[155] and the Psoriatic Arthritis Impact of Disease (PSAID) score[149]. The PSAID has been provisionally recommended by the Outcome Measures in Rheumatology (OMERACT) for use in RCTs and observational studies in PsA[156]. The PSAID can be used in the 9-item or 12-item versions, and captures information in 0–10 numerical rating scales for pain, fatigue,

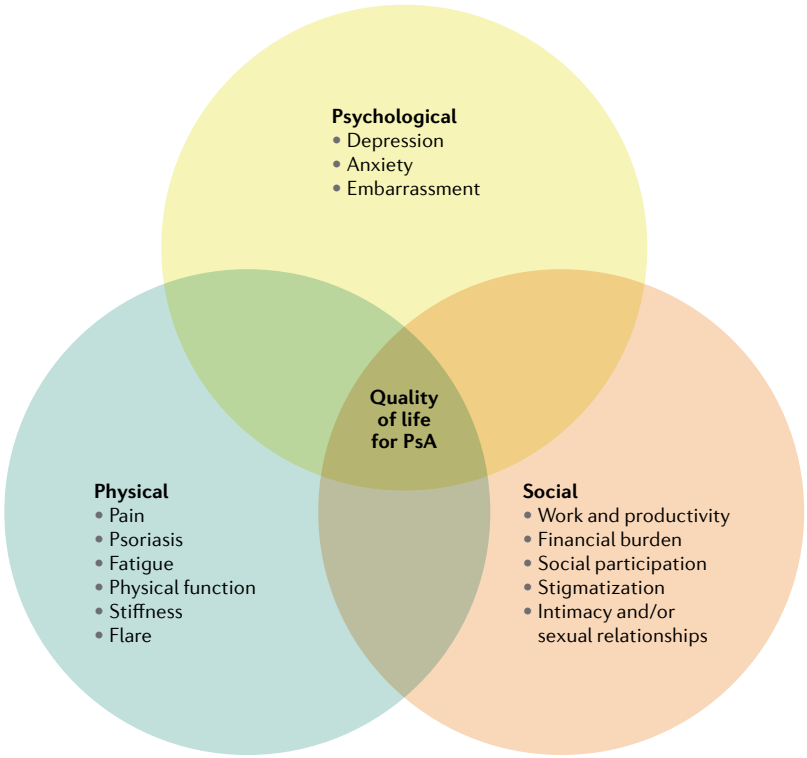

Fig. 3 | **The complex model of quality of life for patients with PsA.** The negative impact of psoriatic arthritis (PsA) on the quality of life (QoL) occurs through a complex interplay of physical, psychological and social domains. The Venn diagram lists the individual elements that impact QoL within each domain.

skin, work, function, discomfort, sleep, coping, anxiety, embarrassment, social participation and depression individually and as a summary score.

Personal and professional QoL

With the development of improved patient-reported measures of QoL, such as the PSAID, large observational studies to quantify the impact of disease on QoL have been feasible. Despite being on treatment, a global study in 1,286 patients from eight countries identified high levels of residual disease impact, including moderate or major impacts of PsA on physical activity (78%), ability to perform certain activities (76%), work productivity (62%) and career path (57%)[157]. Skin or nail symptoms occurred in 80% of patients. Overall, 69% of patients reported that PsA had a moderate to major impact on emotional or mental well-being, 56% on romantic relationships or intimacy, and 44% on relationships with family and friends. Social impacts included emotional distress (58%), social shame or disapproval (32%) and cessation of participation in social activities (45%)[157]. The relative impact of each domain of the disease is uncertain. Evidence suggests that joint pain is most strongly associated with reduced QoL in people with PsA but that resolution of skin disease is required for optimal QoL. Pain from joint disease is often ranked as the highest priority to patients and was the highest ranked outcome in the PSAID development studies and a UK multicentre study[149,150]. However, improving skin and joint disease symptoms is important to achieving optimal improvement in QoL[158,159].

Financial burden

Patients' experiences of the disease vary considerably. One of the concerns of patients is the financial impact of the disease[152,160]. Psoriasis alone has a considerable impact on socioeconomic status[161]. The impact of PsA on finances may be through lost work productivity[162,163], direct medical costs, and insurance and pension costs, and the broader financial impact on the family. Up to 50% of people with PsA become unemployed and those able to attend work report reduced effectiveness (presenteeism)[164]. A study of work disability found that treatment of active PsA was associated with a 40% improvement in work disability following 6 months of treatment with biological therapy[165]. In a Danish study of health-care and public transfer (allowance) costs in patients with PsA, the relative risk for being on disability pension 5 years prior to PsA diagnosis was 1.36 (95% CI 1.24–1.49) compared with the general population, rising to 1.60 (95% CI 1.49–1.72) at the time of diagnosis and 2.69 (95% CI 2.40–3.02) 10 years after diagnosis, where 21.8% of the patients with PsA received disability pension[166].

Psychological impact of PsA

People living with PsA suffer from a range of psychological impacts including disturbed sleep, fatigue, low-level stress, depression, mood and behavioural changes, and poor body image[162]. Responses to pain differ between individuals, depending on a variety of psychological factors including each individual's personality structure, cognition and attention to pain[162]. Fatigue is now recognized as one of the core domains to be measured in RCTs in PsA, and fatigue seems to negatively affect patients' QoL and work[167–169]. Anxiety and depression are known to be prevalent amongst people living with PsA. In a systematic literature review of 24 studies including 31,227 people with PsA, the pooled estimate of the proportion of individuals living with anxiety was 33% (95% CI 17–53%) and of those living with depression was up to 51%[170].

Multidisciplinary patient care

The burden of PsA beyond musculoskeletal manifestations has been increasingly recognized. This need highlights the importance of a patient-centred holistic approach in the care of patients living with PsA. Different models of multidisciplinary care led by rheumatologists or dermatologists, together with specialized nurses, psychologists and various therapists, have been explored[171]. The evidence showing favourable outcomes are preliminary[172], and further studies to better understand sustainable outcomes are required. Nonetheless, awareness of the multidimensional needs of these patients remains the key to improving their care.

Outlook

Although the field of PsA has continued to evolve substantially over the past two decades, a number of outstanding gaps in basic, translational and clinical research remain unmet. There are several knowledge-based needs for further basic or translational advances in the field. First, a more detailed characterization of genetic and environmental factors that determine disease initiation

is needed[1]. Although several genome-wide association studies have contributed to the understanding of disease pathogenesis, multiple questions are yet to be answered. For instance, why the concordance rate for PsA is <20% in monozygotic twins and the precise role of epigenetic modifications, environmental exposures, biomechanical stress and infections (including gut and skin dysbiosis) in the triggering of synovio-entheseal disease are yet to be determined. Furthermore, the cellular and molecular drivers of disease perpetuation remain to be fully elucidated. This understanding is of high relevance as most of the latest advances in therapeutics were derived from the discovery of a handful of unique, disease-specific targets, most notably IL-17 and IL-23 cytokines and/or their receptors. A more expansive and detailed characterization of T resident memory cells[56], innate cells (that is γδ T cells, innate lymphoid cells and natural killer cells)[173] and newly discovered players should include not only their molecular and functional capacity, but also their spatial interactions, homing features and migratory patterns so that their function or contribution in various compartments can be studied and therapeutically addressed.

Concomitantly, there are multiple challenges to be elucidated in the clinical realm. These include the need for further characterization of factors associated with the development of PsA and the common definition of states that precede clinically overt synovio-enthesitis (that is, what constitutes preclinical PsA). A related concept pertains to the adequate timing of potential immunomodulatory interventions and even preventive strategies[19]. Another issue that is yet to be addressed is the meaning of imaging abnormalities present in patients with psoriasis without musculoskeletal symptoms[174,175]. A third unmet need involves the distinction between various phenotypes of PsA and other forms of inflammatory arthritis (for example, axial PsA and axial spondyloarthritis)[176]. Critically, and despite the achievement of remarkable outcomes in clearance of the skin with the newer generation of biological agents (such as IL-23 and IL-17 blockers), the use of the same molecular strategies has not proven superior to TNF blockade in terms of ameliorating peripheral arthritis or axial disease[177].

To overcome these challenges, multiple complementary and potentially synergistic priorities are envisioned. First, incorporating digital biomarkers into the clinical journey of patients with psoriatic disease should help address progression from psoriasis to PsA, flares and treatment response. Second, an in-depth study of cells and associated inflammatory mediators that modulate disease in the synovial, entheseal and axial tissues is gradually materializing. Several platforms promise to aid in this endeavour, including spatial transcriptomics[178], ECCITE-seq[179] and other variations of single-cell resolution sequencing technologies. In turn, these technologies can aid in precision medicine approaches and treatment strategies based on synovial biopsy and/or synovial fluid cellular or molecular pathways. Critically, big data analytics that incorporate clinical, genetic, environmental and immunological variables into predictive algorithms for diagnostics and therapeutics are emerging and should serve as examples for bringing precision medicine initiatives into the management of PsA.

As these tools become available, applying the knowledge generated into avenues for new therapeutic paradigms will be essential. As discussed, the current approach of monotherapy strategies to improve the outcomes of a multidomain, multicytokine condition, such as PsA, may be inadequate. Altering the treatment strategies by implementing multitarget approaches may prove more efficacious[180]. Such combination therapy has shown efficacy in multiple neoplastic syndromes and is currently being tested in related conditions, such as inflammatory bowel disease. A concrete example is the VEGA trial, which is testing the hypothesis that the biological combination of a TNF inhibitor and an IL-23 inhibitor might be superior to monotherapy[181].

Ultimately, the success of these endeavours will be dependent on innovative work performed by clinical and translational researchers and industry partners, most likely through a team science approach. Multiple programmes have been launched that incorporate private–public partnerships to advance the field through collaborative efforts, using novel multidisciplinary strategies. These programmes include the NPF's Psoriasis Prevention Initiative; the European Union's Innovative Medicines Initiative (IMI)[182] and the Accelerating Medicines Partnership (AMP)[183]. IMI is a partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations. AMP is an NIH-led pre-competitive effort including government, industry, academia and non-profit organizations to harness collective capabilities, scale and resources towards the development of new therapies for complex, heterogeneous diseases. All three programmes have funded (or propose to fund) large consortia of investigators in the field, which, combined with individual efforts, will be fundamental to enhancing the understanding of PsA pathogenesis, diagnostics and new targets for better treatments as well as preventive strategies.

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