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## Primer on Psoriatic Arthritis

**Oliver FitzGerald<sup>1</sup>, Alexis Ogdie<sup>2</sup>, Vinod Chandran<sup>3</sup>, Laura Coates<sup>4</sup>, Arthur Kavanaugh<sup>5</sup>, William Tillett<sup>6</sup>, Ying Ying Leung<sup>7</sup>, Maarten deWit<sup>8</sup>, Jose U Scher<sup>9</sup> and Philip Mease<sup>10</sup>.**

<sup>1</sup>Conway Institute for Biomolecular Research, University College Dublin, Ireland.

<sup>2</sup>Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

<sup>3</sup>Schroeder Arthritis Institute, Krembil Research Institute, University Health Network, Toronto, Canada and Departments of Medicine and Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada.

<sup>4</sup>Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK

<sup>5</sup>Center for Innovative Therapy, Division of Rheumatology, Allergy, Immunology, University of California, San Diego Medical School

<sup>6</sup>Royal National Hospital for Rheumatic Diseases, Pharmacy and Pharmacology, University of Bath, Bath, United Kingdom

<sup>7</sup>Singapore General Hospital, Duke-NUS Medical School, Singapore

<sup>8</sup>GRAPPA Patient Research Partner, Netherlands

<sup>9</sup>Department of Medicine, Division of Rheumatology, NYU Grossman School of Medicine, New York, NY, USA

<sup>10</sup> Swedish Medical Center/Providence St. Joseph Health and University of Washington, Seattle, WA, USA

Address correspondence to:

Prof Oliver FitzGerald MD FRCPI FRCP(UK)

Conway Institute for Biomolecular Research,

University College Dublin,

Ireland.

Email: [oliver.fitzgerald@ucd.ie](mailto:oliver.fitzgerald@ucd.ie)

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## 67 Introduction

68 Psoriatic Arthritis (PsA) is a complex inflammatory disease with heterogenous clinical features  
69 which complicates skin/nail psoriasis (Pso) in up to 30% of cases. There are no diagnostic criteria  
70 or tests. Diagnosis is most commonly made by identifying inflammatory musculoskeletal (MSK)  
71 inflammation of the joints, entheses or the spine in the presence of skin and/or nail Pso and in the  
72 usual absence of rheumatoid factor (RF) and anti-Cyclic Citrullinated Peptide (aCCP). The main  
73 clinical, laboratory and radiographic features which distinguish PsA from other forms of arthritis  
74 are shown in **Table 1**.

75 As depicted in **Figure 1** the evolution from psoriasis to the point at which the patient meets the  
76 CIASsification criteria for Psoriatic ARthritis (CASPAR) classification criteria (described in  
77 classification section below) for PsA may occur in stages. PsA complicates Pso in up to 30%  
78 attending dermatology clinics. The link between skin and MSK inflammation is certainly  
79 established but the mechanism is unclear. Many PsA patients with active disease may have very  
80 little Pso and the same may be said in reverse relating to severe Pso. One hypothesis is that this  
81 heterogeneity may be explained by differences in genotype, especially in the HLA region (referred  
82 to in section on Mechanisms/Pathophysiology below).

83 In recent years, new targeted therapies for PsA have been approved with additional therapies in  
84 development. These developments have substantially improved both short-and long-term  
85 outcomes including a reduction in MSK and skin manifestations as well as radiographic damage.  
86 These new treatments are at least in part related to improved understanding of the genetic basis of  
87 PsA and the underlying molecular pathways which are activated and contribute to disease  
88 expression. For example genetic studies have confirmed the association of PsA with single  
89 nucleotide polymorphisms (SNPs) in the IL17/IL23 pathway<sup>1,2</sup> with added significance of these  
90 findings being supported by immunopathologic studies which demonstrate the predominance of  
91 IL17-expressing CD8+T-cells in PsA synovial fluid.<sup>3</sup> Treatments targeting IL17  
92 and IL23 have proven particularly effective for skin Pso but are also effective and licensed for  
93 MSK manifestations. It is hoped that with efforts underway aimed at improving our understanding  
94 of the molecular basis for the heterogeneity of PsA, that a precision medicine approach to treating  
95 PsA may not be too far away.

## 96 Epidemiology

97 While the prevalence of PsA among patients with Pso has been estimated as 23.8% in a recent  
98 meta-analysis when CASPAR (described in classification section below) is applied, the incidence  
99 of PsA among patients with Pso ranges from 0.27 to 2.7 per 100 person years, depending on the  
100 study and outcome definition.<sup>4</sup> PsA is relatively uncommon in the general population (0.10-0.25%  
101 of adults).<sup>5</sup> The prevalence of PsA is highest among patients within the age range of 30-60 and is  
102 overall equally common among men and women.<sup>6</sup> The majority of patients with PsA are white. It  
103 is unclear whether this is related to a specific genetic underpinning or perhaps in part related to the  
104 difficulty in identifying Pso among patients with darker skin colours.<sup>7</sup> Of interest, the reported

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105 prevalence of PsA is lower in Asia than in Europe and North America, potentially suggesting  
106 differences by race and/or ethnic group or by environment.<sup>5</sup>

107 The prevalence and phenotype of PsA is quite different among children, in part related to  
108 differences in classification criteria. Within the International League of Associations for  
109 Rheumatology (ILAR), classification criteria for PsA and enthesitis-related arthritis are analogous  
110 to the CASPAR and ASAS criteria used in adults but they are quite different in that a variety of  
111 exclusion criteria move patients to other categories depending on certain factors.<sup>8,9</sup> For example,  
112 a patient with HLA-B27, a first degree relative with HLA-B27-associated disease, a positive  
113 rheumatoid factor, or a systemic presentation of JIA would be excluded from having a diagnosis  
114 of PsA<sup>9</sup> (Table 2). The ILAR criteria are the most commonly used criteria, however, an alternative  
115 juvenile PsA, the Vancouver Criteria, were developed in 1989 though are rarely used today.<sup>10,11</sup>  
116 Additionally, limitations with the ILAR criteria include that: (1) patients are required to have a  
117 diagnosis of psoriasis to be classified as juvenile PsA. This is not withstanding the fact that  
118 approximately half of patients with juvenile PsA develop their arthritis first and later develop  
119 psoriasis, further complicating classification criteria development in children;<sup>12</sup> and (2) the criteria  
120 refer to boys/men when we know that PsA affects both sexes in equal proportion. Treatment for  
121 JIA may differ from treatment of adult PsA. Methotrexate remains the first line therapy as of 2019,  
122 although a 2021 update of the ACR JIA treatment guidelines are in progress.<sup>13</sup> Many therapies  
123 used to treat adult disease have not yet been approved for use in children.

124 A number of potential risk factors for the development of PsA have been identified among patients  
125 Defining PsA in a population is challenging and one of the potential reasons that prevalence  
126 estimates vary by study. CASPAR criteria are ideal for studies in which patients are being  
127 examined.<sup>16</sup> However, studying small samples (i.e., a dermatology clinic) can be associated with  
128 selection bias, leading to biased prevalence estimates. On the other hand, studying large,  
129 population-based datasets are complicated by misclassification bias as they rely on codes for  
130 defining PsA (i.e., missing diagnoses that have not been recorded in the dataset and simultaneously  
131 misdiagnoses of PsA as having conditions unrelated to Pso such as osteoarthritis).<sup>15,17,18</sup> The truth  
132 may be somewhere in the middle. Thus, both study designs must be interpreted in light of these  
133 potential limitations although they are helpful in understanding not only prevalence and incidence  
134 but also outcomes and risk factors for PsA.

## 136 Comorbidities

137 PsA is associated with several chronic conditions that may impact both quality and quantity of  
138 life.<sup>19</sup> While most studies show that the overall mortality in PsA is not higher compared to the  
139 general population, mortality from CV comorbidities and psychiatric disease seem to be higher.<sup>20</sup>

140 Obesity is particularly common in PsA, significantly more prevalent than in patients with psoriasis,  
141 rheumatoid arthritis or compared to those in the general population.<sup>20</sup> Obesity can  
142 significantly impact function, quality of life and response to therapy.<sup>21</sup> In addition, PsA is  
143 associated with a higher prevalence of cardiovascular risk factors such as hypertension,  
144 hyperlipidemia, diabetes, and the combination of these, metabolic syndrome. It should come as no

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145 surprise then that PsA is also associated with an increased incidence of cardiovascular events such  
146 as myocardial infarction, even after adjusting for traditional risk factors.<sup>22</sup> Similarly, patients with  
147 PsA are at significantly increased risk for diabetes and fatty liver disease.<sup>23,24</sup> These  
148 cardiometabolic conditions may also be associated with increased disease activity.<sup>20</sup> Beyond  
149 cardiometabolic disease, depression and anxiety are common in PsA, affecting 10-30% each,<sup>25</sup>  
150 and fibromyalgia/central sensitization is also common, affecting nearly 30% as well.<sup>26,27</sup>  
151 Depression, anxiety and fibromyalgia have a substantial impact on treatment outcomes and should  
152 be identified and managed so as to improve outcomes.<sup>28,29</sup>  
153 PsA is also associated with extra-articular manifestations including uveitis and inflammatory  
154 bowel disease (i.e., Crohn's disease and ulcerative colitis).<sup>30</sup> In a recent meta-analysis, the  
155 prevalence of uveitis and IBD were each approximately 3%.<sup>31</sup> These conditions can have a  
156 significant impact on treatment selection as not all therapies for PsA cover these manifestations  
157 (see treatment section below).

## 158 Mechanisms/Pathophysiology

### 159 *PsA is a complex genetic disease*

160 There is a strong genetic contribution to both Pso and PsA. While epidemiologic evidence suggests  
161 that the recurrence rate of PsA among first degree relatives of PsA probands ( $\lambda$ s 30 to 48) is greater  
162 than the recurrence of psoriasis among first degree relatives of Pso probands ( $\lambda$ s 4 to 10)<sup>32</sup>, a more  
163 recent study, which interrogated SNPs from large-scale genotyping arrays, while confirming  
164 strong heritability, concluded that there is perhaps a stronger contribution coming from Pso.<sup>33</sup> The  
165 genetic associations in PsA are with both HLA- and non-HLA-region genes with the strongest  
166 association being within the HLA region. HLA-C\*06:02 is found in ~60% of those with Pso but  
167 the frequency is significantly lower at 28% in those with PsA.<sup>34</sup> This same study reported that 18%  
168 of PsA cases were HLA- B\*27 positive, with the frequency of B\*27 in PsC (Pso patients where  
169 PsA has been excluded) no different from the normal controls. HLA- B\*08 was the major allele at  
170 37% in PsA but interestingly, its frequency was significantly reduced in PsC to 15%. When HLA  
171 alleles and amino acid sequences were compared between PsA and PsC directly  
172 , the most significant association was found at HLA-B amino acid  
173 position 45. Of the amino acid residues at this position, glutamine (HLA-B Glu45) most  
174 significantly increased risk for PsA compared to PsC. Although, among the HLA alleles, HLA-  
175 B\*27 had the lowest p value, the association was much less significant than the association with  
176 HLA-B Glu45. It is interesting that HLA-B  
177 alleles previously associated with PsA including HLA-B\*27, -B\*38, -B\*39 have Glu at position  
178 45.<sup>35</sup> Another study that also controlled for age of psoriasis onset, showed that HLA-C\*06:02 is  
179 not associated with PsA and that amino acid position 97 (asparagine or serine) of HLA-B  
180 differentiates PsA from PsC. Of note, HLA-B\*27 has asparagine at position 97, and HLA-B\*07  
181 and HLA-B\*08, serine.<sup>36</sup>  
182 HLA-class I molecules play a critical role in our immune responses, particularly to viruses, by  
183 presenting viral peptides to CD8+T cells. There is accumulating evidence for a role of CD8+T

184 cells in PsA pathogenesis<sup>37</sup> with clonally expanded populations found in synovial fluid and tissue.  
185 The amino acid residues associated with PsA are in the antigen binding groove of the HLA-B  
186 molecule. The peptides driving clonal expansions of CD8+T cells in PsA have not been identified  
187 but given the structural similarity of the binding (B) pockets of each of the HLA-B molecules  
188 associated with PsA producing a negative charge, it is highly likely that the peptide sitting in the  
189 B pocket has positively charged amino acids at position 45.<sup>38</sup> It has further been suggested that the  
190 heterogenous nature of this T cell response determines the molecular pathways which are activated  
191 and which ultimately result in characteristic diverse clinical disease expression and perhaps  
192 treatment responses. In support of this concept, studies have shown associations of HLA genotypes  
193 not just with susceptibility to disease but also with certain disease features such as [the interval](#)  
194 [between the onset of Pso and PsA \( HLA-B\\*27 being associated with a short interval between skin](#)  
195 [and musculoskeletal disease and HLA-C\\*06 with a longer interval\), dactylitis \(B\\*27:05:02-](#)  
196 [C\\*01:02:01, B\\*08:01:01-C\\*07:01:01 haplotypes\), enthesitis \(B\\*27:05:02-C\\*01:02:01 haplotype\)](#)  
197 [and sacroiliitis \(symmetric- B\\*27:05:02-C\\*01:02:01 and B\\*27:05:02-C\\*02:02:02 haplotypes;](#)  
198 [asymmetric \(B\\*08:01:01-C\\*07:01:01 haplotype\).](#)<sup>39</sup>

#### 200 **Genetic and genomic risk factors- genes proteins and pathways**

201 While the strongest genetic associations with PsA are with genes within the HLA region, non-  
202 HLA gene associations are also well described. Many of these genetic risk loci reported as  
203 associated with PsA susceptibility are shared with psoriasis such as *IL12B* and *TRAF3IP2*,  
204 involved in IL17 signalling<sup>40</sup>, perhaps reflecting shared molecular pathways mediated by the  
205 presence of cutaneous psoriasis in both phenotypes. It is also possible that the number of shared  
206 susceptibility alleles relates to inadequate exclusion of MSK inflammation in patients designated  
207 as PsC. A number of PsA-specific loci have however been identified thus beginning to explain the  
208 additional MSK burden. These loci include the presence of glutamic acid at the amino acid position  
209 45 in HLA-B, a risk locus at chromosome 5q3, distinct PsA variants at the *IL23R* locus, *PTPN22*  
210 which is a potent inhibitor of T cell activation and *RUNX3* which is involved in CD8+ T  
211 lymphocyte differentiation and is therefore, a good candidate for involvement in PsA.<sup>41</sup> It is  
212 noteworthy that all of these PsA-specific loci involve genes which are involved in immune  
213 activation emphasising the importance of immune dysfunction PsA pathogenesis.

214 The exact mechanism which results in over-expression of pro-inflammatory mediators, including  
215 cytokines, is poorly understood. We do know however that active PsA is associated with  
216 production of a cascade of cytokines including TNF $\alpha$ , IL17 and IL23.<sup>42</sup> The importance of these  
217 cytokines in disease expression is supported by the significant efficacy of inhibitors of these  
218 cytokines on clinical disease expression. As not all patients respond to cytokine inhibition and as  
219 some disease features, such as Pso, respond better to strategies targeting cytokines of the IL17 or  
220 IL23 pathway, it has been suggested that improved understanding of the molecular pathways  
221 associated with specific disease features may help to better guide treatment choices.<sup>37</sup>

#### 222 **Environmental factors**



223 A number of environmental factors are thought to be associated with the development of PsA.  
224 These include [musculoskeletal injury](#), obesity and infection; evidence for association with  
225 stress or anxiety, alcohol consumption or with smoking is controversial. For years, support for a  
226 role of [musculoskeletal injury](#) was poor with case reports or series providing anecdotal  
227 evidence only. A recent matched cohort study using data from The Health Improvement Network  
228 showed that patients with PsO exposed to trauma, especially bone and joint trauma, had an  
229 increased risk of PsA compared with controls.<sup>43</sup> Association with trauma is not confined to major  
230 trauma consistent with the hypothesis that microtrauma at enthesal sites may be a critical disease  
231 initiating factor.<sup>44</sup> It is possible that this may explain the association of PsA with increasing BMI  
232 <sup>45</sup> with higher mechanical load at enthesal sites being a consequence of high BMI. It is also  
233 possible that the effects of excess adipose tissue, which includes abundant pro-inflammatory  
234 mediators, may spill over to other tissue sites.

235 A role for infection in triggering PsA has been suggested in particular with the well-known  
236 association between streptococcal infection and guttate PsO. Both PsO and PsA also occur more  
237 commonly and severely in the presence of HIV disease which targets CD4+ and not CD8+T cells.  
238 There have been some studies too which have examined changes in microbiome and onset of PsA  
239 <sup>46</sup> which to date have been inconclusive. This is clearly an area for further research focus as  
240 microbial-driven populations of IL17-producing innate immune cells have been identified in other  
241 tissues <sup>47</sup> and a recent study very nicely demonstrated the considerable influence of the gut  
242 microbiota—together and over time—on systemic immune cell dynamics.<sup>48</sup>

#### 243 ***PsA pathogenetic mechanisms***

244 Although the sequence of events leading to the onset and progression of human PsA has not yet  
245 been delineated, it is proposed that the arthritis is triggered by a complex interplay between a  
246 subject's genetic predisposition and environmental influences described above [that](#)  
247 [trigger](#) an immune response leading to entry and proliferation of immune cells at articular, peri-  
248 articular, and extra-articular sites. Given the strong association with HLA class I alleles and Th17  
249 immune response, a model for pathogenesis of PsA was recently proposed whereby primed  
250 antigen-presenting cells at sites such as the skin or entheses engage with innate lymphoid cells and  
251 naive T cells, leading to local clonal expansion of type 1 cells (T helper 1 (TH1) and type 1 CD8+  
252 (Tc1) cells) and type 17 cells (TH17 and type 17 CD8+ (Tc17) cells).<sup>49</sup> The interplay between the  
253 effector T cell subsets, stromal cells, and the cytokine milieu at the local sites determines disease  
254 features including enthesitis, synovitis, bone and cartilage loss as well as new bone formation in  
255 the axial and peripheral musculoskeletal (MSK) system.<sup>49</sup>

256 The strong relationship between skin and MSK inflammation begets the question whether the  
257 relationship between inflammation at the two sites is successive (changes in the skin triggering  
258 MSK inflammation) or synchronous (a common trigger leading to skin and MSK inflammation).  
259 In 70% of patients with PsA, skin inflammation predates MSK inflammation by many years. This  
260 latency is associated with certain HLA alleles- HLA C\*0602 is associated with a long duration  
261 between skin and MSK inflammation.<sup>50</sup> Thus, mediators originating in the inflamed skin could  
262 trigger MSK inflammation. This theory is supported by a recent study that demonstrated increased

263 circulatory skin derived tissue resident memory CCR10+ CD8+ T cells in the peripheral circulation  
264 of PsA patients compared to patients with PsC.<sup>51</sup> However, these cells were not enriched in the  
265 synovial fluid.<sup>51</sup> Another study has demonstrated a high proportion of synovial Tc17 cells  
266 expressing markers typically associated with homing to the skin or gut.<sup>52</sup> Injury to sites of  
267 biomechanical stress may be the underlying mechanism driving synchronous skin and MSK  
268 inflammation. It has been demonstrated that in 30% of patients, joint disease occurs simultaneously  
269 or prior to onset of skin disease.<sup>42</sup>  
270 HLA- B\*27 is associated with such short skin-joint disease latency.<sup>34,39</sup>  
271 Microtrauma at sites of significant biomechanical stress leading to enthesitis may underlie this  
272 form of PsA with skin disease limited to sites of microtrauma such as behind the elbows and knees  
273 and joint disease triggered at the enthesis. In fact, it is believed that ‘enthesitis’ may be the  
274 mechanism underlying the diverse MSK manifestations of PsA/SpA including eye and gut  
275 inflammation. The association between HLA-B\*27 and more severe sonographic enthesitis in PsA  
276 supports this hypothesis.<sup>53</sup>

277  
278 Clonal expansion of T cells in the psoriatic joint is well described.<sup>54,55</sup> A recent study demonstrated  
279 a 3-fold expansion of memory CD8 T cells in the joints of PsA patients compared to peripheral  
280 blood, as well as pronounced CD8 T cell clonal expansion.<sup>56</sup> These cells express cycling,  
281 activation, tissue-homing and tissue residency markers, including the skin/gut-homing marker  
282 ITGA1 (CD49a) and granulysin. The chemokine receptor CXCR3 is upregulated in the expanded  
283 synovial CD8 T cells, and its two receptors CXCL9 and CXCL10, are elevated in PsA synovial  
284 fluid.<sup>56</sup> Elevated CXCL10 is known to predict future development of PsA in patients with PsC.<sup>57</sup>  
285 To summarize, inflammation in the MSK structures in patients with Pso is most likely triggered in  
286 genetically susceptible hosts by environmental factors such as trauma, infections or even changes  
287 in the microbiome that then leads to expansion of immune cells of both the innate and adaptive  
288 systems. The mediators for MSK inflammation may be skin derived or there may be a common  
289 trigger causing skin and joint disease. These events may lead to expansion of CD8 T cells well as  
290 other effector cells of the innate and adaptive systems. The local tissue milieu likely drives the  
291 specific disease manifestations synovitis, bone and cartilage loss as well as new bone formation.  
292 These concepts are illustrated in Figure 2.  
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## 295 **Diagnosis, Screening and Prevention.**

296 The first step in caring for patients with PsA is to make an accurate and timely  
297 diagnosis allowing future therapy. The process of diagnosing PsA brings multiple pieces of  
298 evidence together to assign a particular disease label. Typically, these may include patient history,  
299 physical examination and results of laboratory and imaging results. Although the diagnostic  
300 process may end in a clinician making a binary decision (either the disease is present or not), this

301 is often associated with a level of probability of the diagnosis and other potential differential  
302 diagnoses.

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

307 Unfortunately, there is a well-recognised delay in diagnosis typically seen in patients with PsA.  
308 Recent data from a United Kingdom (UK) national audit in 2015 estimated this to be a median of  
309 29 weeks, and significantly longer than matched patients presenting with RA.<sup>58</sup> This delay has  
310 also been shown to have significant implications. A further UK study found that a delay in  
311 diagnosis of 12 months was associated with increased physical function impairment at 10 years  
312 follow up despite active treatment.<sup>59</sup> A subsequent study in Ireland showed that even a delay in  
313 diagnosis of 6 months was associated with a higher chance of peripheral erosive disease and poorer  
314 physical function.<sup>60</sup>

### 315 **Clinical presentation**

316 There is relatively little data concerning the signs and symptoms that aid diagnosis of PsA. In  
317 2013, a nominal group exercise was performed with health care professionals interested in  
318 rheumatology, but also patient research partners to identify descriptive elements of inflammatory  
319 joint disease. Symptoms identified included early morning stiffness (EMS) >30 minutes, joint  
320 tenderness, pain aggravated by rest and relieved by exercise, symptoms improved by non-steroidal  
321 anti-inflammatory drugs (NSAIDs) or corticosteroid use, joint erythema or warmth and related  
322 fatigue. Possible clinical signs included joint swelling, limited motion and joint deformity.<sup>61</sup>

323 In terms of peripheral arthritis, presentation is similar to most forms of inflammatory arthritis  
324 although the pattern of joint involvement can vary with oligoarticular and polyarticular patterns  
325 described. DIP joint involvement is more common than in other forms of inflammatory arthritis.

326 The clinical presentation of MSK inflammation can be helpful to differentiate between PsA and  
327 other forms of inflammatory arthritis (table 1). In addition to peripheral arthritis, patients often  
328 present with inflammation in other musculoskeletal tissues including at the insertion of a tendon  
329 into the bone (enthesitis), seen in up to 67% of presenting cases,<sup>62-67</sup> fusiform swelling of a digit  
330 with inflammation typically seen in multiple tissues (dactylitis), seen in 12-39% of cases<sup>62-68</sup>  
331 and axial involvement within the axial spondyloarthritis (AxSpA) phenotype  
332 seen in 5-28% of cases at diagnosis, but potentially up to 70% in late stage disease.<sup>62-67</sup> Although  
333 the vast majority of patients presenting with PsA have peripheral MSK involvement, a few cohorts  
334 have reported a prevalence of axial disease in isolation with psoriasis at 7-17%.<sup>66,69</sup>

### 335 **Investigations**

336 Part of the reason accounting for this diagnostic delay compared to RA may be related to a lack of  
337 specific investigations to confirm the diagnosis (table 1). Primary care physicians typically use  
338 inflammatory markers like C reactive protein (CRP) and specific antibodies like rheumatoid factor  
339 (RF) or anti-citrullinated peptide antibodies (ACPA) to screen patients with possible inflammatory  
340 arthritis. PsA is usually seronegative, although a positive RF or ACPA does not exclude the

341 condition. At presentation, 33-89% are identified as having a raised CRP<sup>62,64,69,70</sup>; thus, a  
342 significant proportion of patients do not have raised blood markers despite active disease.  
343 Although typical imaging features in PsA have been identified, and are included in the  
344 classification criteria, these are more prevalent with increasing disease duration. In early disease,  
345 radiographs are often normal as bony damage has not occurred, so often do not assist in diagnosis.  
346 A study in 2003 of peripheral arthritis identified that 27% of patients had erosions at presentation,  
347 and 10 years later in the Tight Control of PsA (TICOPA) study, results were similar.<sup>71</sup> However,  
348 in both studies, the amount of erosive disease seen is relatively small and affecting only a few  
349 joints in most of the patients imaged.

350 Given the potential for axial involvement, imaging of the spine and sacroiliac joint can also show  
351 abnormalities in PsA. Again this is more prevalent with increasing disease duration with limited  
352 value in early diagnosis.<sup>72,73</sup> Sacroiliac joint involvement in PsA appears similar to that seen in  
353 AS although asymmetrical sacroiliac involvement is more common.<sup>74,75</sup>

#### 354 **Classification**

355 Related but independent from diagnosis, is the issue of classification. Classification is the method  
356 of defining a disease for research. This allows standardisation across the field, rather than taking  
357 into account multiple different inputs which may feed into diagnosis. In classification, it is  
358 specificity that is key to ensure homogeneity in clinical studies even though sensitivity may suffer  
359 in this situation.

360 The first classification criteria developed for PsA were the Moll & Wright criteria, which were  
361 developed based on clinical observation. They have been the key criteria used until around 2006  
362 and are simple stating that PsA is an inflammatory arthritis (peripheral arthritis and/or sacroiliitis  
363 or spondylitis) in the presence of psoriasis and with the (usual) absence of serological tests for  
364 rheumatoid factor (RF).<sup>76</sup> However they focused on peripheral arthritis rather than other aspects  
365 of the musculoskeletal disease such as enthesitis and required a negative rheumatoid factor test  
366 which was an issue for a minority of patients.<sup>77</sup>

367 Over the decades, there have been a number of other classification criteria developed but until the  
368 advent of the CASPAR criteria, none of these were utilised widely in clinical research.

369 In 2000, a large international consortium of rheumatologists came together to develop new robust  
370 and data-driven classification criteria which were finally published in 2006. The CASPAR criteria  
371 bring together a wider range of items for inclusion, overlapping with the Moll & Wright criteria  
372 but also allowing classification of people without PsO (approximately 10%) or with a positive RF  
373 (approximately 15%) provided they have other key features of the disease.<sup>16</sup> In the development  
374 cohort, these had high sensitivity and specificity,<sup>16</sup> and this has been confirmed in numerous  
375 independent studies subsequently.<sup>78-80</sup>

376 In early disease, the classification may not be quite as straightforward but still specificity has been  
377 confirmed as typically over 95%. The issue in early inflammatory arthritis is that there seems to  
378 be lower sensitivity as some typical features may not yet be present.<sup>65,81</sup> In particular, typical new  
379 bone formation is not common at presentation therefore limiting the ability to identify the disease.

380 Another issue raised with the CASPAR criteria is the heavy weighting given to current Pso. Whilst  
381 the majority of patients do fulfil this criteria, it does make the criteria much harder to fulfil if a  
382 patient's Pso has been treated and gone into remission. Potentially, a clear diagnosis of psoriatic  
383 skin or nail disease by a dermatologist could be given similar weighting as current active psoriasis.  
384 The next step proposed for the CASPAR criteria is most likely to involve clarification of the "stem"  
385 of the criteria which state that patients must have Inflammatory articular disease (joint, spine, or  
386 enthesal). From the rheumatology perspective, where we are trying to identify PsA amongst other  
387 patients with inflammatory arthritis, this is straightforward. However, for dermatologists and  
388 primary care physicians, the key issue is how to identify inflammatory articular disease in patients  
389 who have known psoriasis.

### 391 **Prognosis**

392 Predicting prognosis in PsA is also based on limited data with significant individual variation.  
393 Multiple studies have shown that the evolution of PsA can vary over time with different joint and  
394 extra-articular involvement. The pattern of peripheral joint disease does seem to change over time,  
395 with oligoarthritis more common in early disease cohorts. In most cases, increased joint  
396 involvement is seen over time with increasing disease duration with a high proportion of mono or  
397 oligoarthritis progressing to polyarthritis.<sup>82,83</sup> Involvement of other domains can also change over  
398 time, in particular axial involvement is increasingly common with increasing disease duration.<sup>84,85</sup>  
399 However axial spondyloarthritis, and specifically axial PsA can be difficult to identify and clear  
400 evidence of axial involvement with radiographic change and restriction of mobility is likely to take  
401 many years to develop.

402 A number of treatment recommendations have noted potential poor prognostic markers based on  
403 the literature to aid treatment decisions. In terms of peripheral arthritis, in particular, these relate  
404 the number of joints involved (polyarthritis or  $\geq 5$  joints), presence of dactylitis, high inflammatory  
405 markers (CRP) or baseline erosive disease.<sup>86,87</sup> However, there is insufficient evidence around  
406 these risk factors and it is not easy to predict prognosis for individual patients. Many of these  
407 studies have focused solely on radiographic damage as the poor outcome of interest which also  
408 affects the predictors of prognosis. Overall, while oligoarthritis is less likely to cause radiographic  
409 damage within the hands or feet, it may have a significant impact on quality of life and functional  
410 ability.<sup>88</sup>

### 411 **Screening**

412 Unfortunately, there is often a significant delay in the diagnosis of PsA even though the majority  
413 of patients have a preceding condition in the form of skin Pso. Up to 30% of patients with Pso  
414 may go on to develop PsA. Although predicting this accurately at the individual level is not  
415 currently possible, studies have identified key predictors of PsA development including severity  
416 and site of psoriasis (nails, scalp), obesity, smoking and trauma.<sup>15</sup> Delay in diagnosis may be a  
417 particular issue in patients presenting with limited disease (e.g. oligoarthritis) or involvement in  
418 other domains e.g. axial disease or enthesitis.

419 Given awareness of the delay in diagnosis and the associated consequences, there has been a push  
420 to support early diagnosis with education and interventions focusing on primary care physicians,  
421 dermatologists and patients. In particular, studies have attempted to address this using screening  
422 questionnaires to identify potential PsA patients usually amongst a Pso population. There are a  
423 number of screening questionnaires developed but their sensitivity and specificity can be  
424 problematic.<sup>89,90</sup> Comparative studies, for example the CONTEST study, have shown similar  
425 levels of sensitivity (74.5-76.6%) and specificity (29.7-38.5%) across different questionnaires,<sup>89</sup>  
426 and the CONTEST questionnaire, developed from a combination of the best performing questions  
427 within each questionnaire did not outperform the PEST questionnaire in a subsequent study.<sup>91</sup>  
428 Most studies show higher sensitivity and lower specificity as joint symptoms related to other  
429 diagnoses are common. Studies have also shown that it seems harder to identify patients with pure  
430 axial disease. Whilst screening tools are not perfect, some studies have found a reasonable benefit  
431 to using them and the PEST questionnaire, which is the shortest questionnaire available, is  
432 recommended annually for Pso patients in the UK.<sup>92</sup> They also indirectly provide education  
433 to patients with Pso who are then aware of the potential for development of a related arthritis.

#### 434 ***Potential to prevent the evolution to psoriatic arthritis***

435 In addition to supporting earlier diagnosis of PsA, recent research has also focused on the concept  
436 of a spectrum from psoriasis to PsA (Figure 1). This raises the potential of identifying disease or  
437 the high likelihood of disease before it clinically manifests. In collaboration between  
438 dermatology and rheumatology, studies monitoring patients with only psoriasis, aiming to predict  
439 development of PsA are underway. To date, these studies have predominantly confirmed known  
440 predictors of PsA development<sup>93</sup> but in larger populations, they might be used to develop  
441 predictive models that could be applied to individuals. This would allow in depth study of the  
442 pathogenesis of disease in a high-risk population and may elucidate the triggers involved in this  
443 continuum. Potentially, as in RA, interventional studies trying to prevent the development of  
444 disease could be established in high risk populations. Studies such as these will require  
445 collaborative efforts so as to recruit suitably sized populations and should include patient  
446 representation to ensure that individual patients are educated about their potential risk and what  
447 this may mean for them in the future.

## 448 **Therapy of Psoriatic Arthritis**

### 449 ***Introduction.***

450 Prior to the year 2000, the pharmacologic treatment options for PsA were essentially limited to  
451 non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids methotrexate, sulfasalazine and  
452 cyclosporine. There had been few randomized therapeutic trials specifically in PsA. Despite  
453 known clinical differences between the conditions, there was a general assumption that the  
454 evidence from rheumatoid arthritis (RA) clinical trials could be extrapolated to PsA. Since the year  
455 2000, the field of PsA therapeutics has been revolutionized due to several developments. These  
456 include 1) Numerous immunologically targeted biologic disease modifying drugs (bDMARDs)

457 and targeted synthetic drugs (tsDMARDs) have been developed for the treatment of systemic  
458 inflammatory autoimmune diseases, usually initially in RA. Testing of these therapies in other  
459 conditions, including psoriasis, PsA and axial spondyloarthritis (axSpA) also demonstrated  
460 significant efficacy. 2) Research on the immunopathogenesis of PsA has helped reinforce the  
461 rationale for effectiveness of targeted immunotherapies, and also suggested new treatments. 3)  
462 Research on the clinical aspects of PsA has led to increased appreciation of the complex and  
463 heterogeneous nature of the disease, with potential involvement in individual patients in peripheral  
464 arthritis, axial arthritis, enthesitis, dactylitis, spondylitis, skin and nail psoriasis, iritis and  
465 inflammatory bowel disease. These domains need to be assessed individually in order to assure  
466 that all are being treated adequately. 4) Development of reliable and validated outcome measures  
467 to assess PsA clinical domains has helped optimize assessment in clinical trials through the last  
468 two decades.<sup>94</sup> (Domains that are assessed and commonly used measures are noted in **Table 3**.)<sup>95-</sup>  
469 <sup>97</sup> 5) Advances in imaging, including ultrasound and MRI, have allowed more precise visualization  
470 of tissue inflammation and joint damage. 6) In addition to standard randomized controlled trials,  
471 strategy trials such as treatment to target of remission and head-to-head (H2H) comparative trials  
472 are increasingly being performed. The following is a focused summary of PsA pharmacologic  
473 treatment organized by specific classes of drugs, followed by a summary of treatment  
474 recommendations and treatment strategies. Review of non-pharmacologic therapies, including  
475 physical and occupational therapy, psychotherapy, and dietary approaches including weight  
476 reduction is beyond the scope of this manuscript. These treatments should be pursued in parallel  
477 with pharmacologic treatment.

#### 478 ***Adjunctive Treatments: NSAIDs and glucocorticoids***

##### 480 **NSAIDs.**

481 NSAIDs are frequently used for symptomatic improvement of pain associated with arthritis and  
482 periarticular manifestations of PsA. Interestingly, and in distinction to the case with RA, there is  
483 very little evidence addressing NSAID efficacy specifically in PsA. In one 12 week randomized  
484 controlled trial (RCT) of celecoxib 200 or 400 mg statistical superiority over placebo was not  
485 demonstrated.<sup>98</sup> Nevertheless, many years of clinical experience suggests that they can be a useful  
486 adjunct for various domains of PsA, including peripheral arthritis, axial arthritis, enthesitis, and  
487 dactylitis. Indeed, in axial disease, the lack of efficacy of conventional synthetic DMARDs  
488 (csDMARDs) leaves NSAIDs as the mainstay of therapy. Before biologic agents, NSAIDs were  
489 commonly included as concomitant therapies in trials of DMARDs in PsA.

##### 490 **Glucocorticoids.**

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495 Whereas topical steroid medications are commonly used to treat psoriasis and intra-articular  
496 steroids used to treat flares in one or a few joints, systemic steroids are not as commonly used in

497 PsA as in RA. In PsA, there is a need for caution when considering steroids for local  
498 tendon/entheseal injection, as efficacy over the longer term is questionable and tendon rupture has  
499 been reported. Part of the concern for steroid use in PsA comes from is the anecdotal  
500 experience wherein skin psoriasis can flare dramatically upon abrupt  
501 discontinuation of steroids, usually at very high doses.

#### 502 **Conventional Synthetic DMARDs (csDMARDs) (refer to Table 4<sup>99</sup>)**

503 **Methotrexate.** Although methotrexate (MTX) has been one of the most widely used medications  
504 for PsA in the last four decades, there have been very few studies of MTX in PsA.<sup>100,101</sup>

505 Assessment of these few studies raised the suggestion that doses of MTX of 15 mg/week or higher  
506 may be more effective in PsA. In the Methotrexate in Psoriatic Arthritis (MIPA) trial published in  
507 2012, no differentiation from placebo in the primary endpoint was observed.<sup>102</sup> However, design  
508 issues including the dose of MTX used impacted assessment of the data from that study, and MTX  
509 was effective in subset analysis of PsA patients who were more ‘RA like’ (i.e. polyarticular  
510 disease, with elevated acute phase reactants). In the Study of Etanercept and Methotrexate in  
511 Combination or as Monotherapy in Subjects with Psoriatic Arthritis (SEAM-PsA) trial, MTX  
512 appeared to perform well, achieving levels of articular, enthesial and skin responses, numerically  
513 close to those achieved with TNF inhibition; of note, there was no placebo comparator.<sup>103</sup> Based  
514 on evidence from the SEAM study, as well as experience from global clinical practice, MTX  
515 remains an important therapy, especially in parts of the world with more limited health care

516 resources. An additional benefit from MTX is that when used with certain biologic therapies, it  
517 can reduce immunogenicity. MTX can be associated with tolerability issues (e.g. nausea,  
518 diarrhoea, fatigue) and laboratory monitoring for safety issues (liver, hematologic) is necessary

519 **Sulfasalazine.** Sulfasalazine is an older oral medication that has shown to have modest efficacy in  
520 arthritis but no significant benefit for psoriasis was demonstrated in an RCT.<sup>104</sup> Gastrointestinal  
521 tolerability issues as well as allergic reactions may limit its utility, and laboratory monitoring (e.g.  
522 hematologic, liver) is standard.

523 **Leflunomide.** Leflunomide is an oral pyrimidine antagonist that has shown efficacy in arthritis  
524 endpoints in a single placebo-controlled study involving 190 PsA patients.<sup>105</sup> Less robust results  
525 were demonstrated in other domains of PsA, especially skin. Lab monitoring for liver function  
526 tests and blood counts is required.

527 **Cyclosporine.** Cyclosporine is a calcineurin inhibitor that has had greater use for skin psoriasis  
528 than in PsA, but can be effective for articular manifestations. Laboratory monitoring for renal  
529 toxicity is needed, and hypertension can limit its use in some patients.<sup>106</sup>

#### 530 **Biologic DMARDs**

531 **Tumour necrosis factor (TNF) inhibitors.** TNF is a pro-inflammatory cytokine with myriad  
532 impacts on various aspects of the inflammatory and immune responses. TNF inhibitors (TNFi)  
533 represented a landmark breakthrough in the therapy of PsA. Following success observed in RA,  
534 the first evidence for this in PsA came from a trial demonstrating the effectiveness of etanercept  
535 in both articular and psoriasis domains.<sup>107</sup> Soon after, infliximab therapy was shown to improve  
536 articular and psoriasis domains, as well as physical function dactylitis and enthesitis; in addition,



537 treatment was shown to slow the progression of radiographic damage to peripheral joints in PsA.<sup>108</sup>  
538 Subsequently studied TNFi, including adalimumab, golimumab and certolizumab also showed  
539 efficacy across all PsA domains. All TNFi have also demonstrated benefit in ankylosing  
540 spondylitis, used as surrogate evidence for efficacy in the axial component of PsA. With the  
541 introduction of biosimilar versions of several TNFi in many countries around the world, the  
542 acquisition costs have decreased, an important consideration that impacts the utilization of biologic  
543 agents. Significant albeit infrequent serious side effects with TNFi include the risk of infection,  
544 including opportunistic infection (particularly tuberculosis) and autoimmune reactions.

545 **IL-12/23 inhibition.** Ustekinumab is a human IgG1 monoclonal antibody which binds to the  
546 common p40 subunit of IL-12 and IL-23, the former involved in differentiation and activation of  
547 Th1 cells and the latter in differentiation and activation of Th17 cells. By downregulating these  
548 pathways, a decrease of several key cytokines in the pathogenesis of psoriasis and PsA, including  
549 IL-23, IL-17, and TNF, may be seen. Its efficacy in PsA was confirmed in two phase 3 trials,  
550 across domains.<sup>109,110</sup> Of note, in dermatology, ustekinumab was the first biologic agent showing  
551 efficacy for skin psoriasis greater than that of TNFi. Ustekinumab failed to show benefit in  
552 ankylosing spondylitis,<sup>111</sup> although previously subjective axial symptoms did improve in a subset  
553 of PsA patients.<sup>112</sup> Whether axial arthritis in PsA differs from AS or the outcome measures used  
554 can detect improvement in extra-axial domains is a matter of discussion. The safety profile of  
555 ustekinumab is benign overall, with low rates of serious infection.

556 **IL-17 inhibitors.** IL-17 includes a family of related cytokines; IL-17 A and F appear to be the  
557 most involved in pathogenesis of inflammatory disease. IL-17 is produced by a wide variety of  
558 cells in the innate immune system such as natural killer (NK) cells,  $\gamma\delta$ T cells, neutrophils, and  
559 mast cells which line barrier sites such as gut, skin and lung. Several, but not all of these cell types  
560 are activated by IL-23 produced by keratinocytes, macrophages and dendritic cells in response to  
561 microbial agents. IL-17 plays a role in preserving barrier function in the gut and integrity of the  
562 epithelium. Two IL-17A inhibitors are currently approved in PsA in many countries. Secukinumab  
563 is a human monoclonal IgG1 antibody that binds to IL-17A. All clinical domains of PsA  
564 demonstrated significant improvement, including particularly robust improvement in psoriasis and  
565 in axial disease in PsA.<sup>113</sup> Ixekizumab is an IgG4 humanized monoclonal antibody to IL-17A  
566 that has also shown efficacy in all clinical domains of PsA, similar to secukinumab. Both of these  
567 agents have conducted head-to-head trials against adalimumab, where skin psoriasis improved  
568 more with IL-17i and articular domains were comparable.<sup>114,115</sup> Brodalumab is a human antibody  
569 that binds to the IL-17 receptor, thus resulting in broad inhibition of the IL-17 family; it has been  
570 approved for psoriasis in many countries. PsA studies showed efficacy similar to the other IL-17  
571 inhibitors.<sup>116,117</sup> Bimekizumab is a humanized IgG1 mAb that binds to IL-17A and IL-17F. It has  
572 shown efficacy in all clinical domains of PsA in a phase 2 study and is currently in phase 3  
573 development.<sup>118</sup>

574 **IL-23 inhibitors.** The first IL-23i to be approved worldwide for PsA is guselkumab, a p19 IL-23  
575 inhibitor that specifically targets IL-23 (distinct from ustekinumab which binds to the p40 unit and  
576 inhibits both IL-12 and IL-23). IL-23 is a key proinflammatory cytokine in psoriasis, and indeed,

577 its inhibition yields the most complete reduction of psoriasis manifestations compared to other  
578 biologics. Efficacy data for arthritis, enthesitis, and dactylitis domains of PsA is robust, similar to  
579 the data from RCTs of TNFi and IL-17i.<sup>119,120</sup> A sub-study of subjects with back pain and  
580 radiographic evidence of sacroiliitis demonstrated symptomatic improvement of spinal pain  
581 (BASDAI question 2).<sup>121</sup> This preliminary finding in patients with axial PsA will be further  
582 explored since studies of IL-23 inhibitors in ankylosing spondylitis failed to demonstrate  
583 separation from placebo, suggesting that this mechanism of action was not effective in axial  
584 inflammation.<sup>122</sup> Phase 2 studies of risankizumab<sup>123</sup> and tildrakizumab<sup>124</sup>  
585 demonstrated consistent with the phase 3 studies of guselkumab. There has been  
586 minimal signal for serious infection with IL-23i.

587 **Costimulatory Blockade.** Abatacept (CTLA4-Ig) is a recombinant human fusion protein which  
588 binds to CD80/86 on antigen presenting cells (APCs), preventing interaction with CD28 on T cells  
589 In a phase 3 trial in PsA. in which the majority of patients had failed TNF inhibition, modest benefit  
590 in arthritis and minimal benefit in psoriasis were noted.<sup>125</sup> Even though effect is modest, one  
591 advantage of the medication is its relatively benign safety profile.

#### 592 *Targeted Synthetic DMARDs*

593 **PDE4 inhibitor.** The oral phosphodiesterase 4 (PDE4) inhibitor apremilast may downregulate a  
594 number of key pro-inflammatory cytokines involved in the pathogenesis of psoriasis and PsA,  
595 including TNF and IL-23. By inhibiting PDE4 apremilast was shown to have modest efficacy in  
596 treating psoriatic skin lesions, arthritis, and enthesitis/dactylitis.<sup>126-128</sup> It has a benign safety profile  
597 with no serious safety issues such as infection, and no need for laboratory monitoring

598 **JAK inhibitors.** The Janus kinase (JAK) – STAT kinase intracellular signalling system is critical  
599 for the induction of cellular activation by a number of cytokines involved in the pathogenesis of  
600 PsA, including IL-23, IL-6, and IL-15. There are 4 JAK molecules: JAK1, 2, 3 and TYK2. The  
601 first JAKi to be approved, tofacitinib, inhibits JAK3 and JAK1 more than JAK2.<sup>129-131</sup> Tofacitinib  
602 was effective in musculoskeletal domains and modestly beneficial for skin lesions. The safety  
603 profile was similar to that seen in treatment of RA, i.e. the risk of serious infection, the need for  
604 laboratory monitoring of liver function tests and blood counts, and rare side effect of lymphoma.  
605 Recent evidence suggests that thromboembolic events may occur when the medication is used in  
606 higher than recommended dose.<sup>131</sup> This may be a class effect. Other JAK inhibitors in development  
607 for PsA include the selective JAK1i, upadacitinib and filgotinib,<sup>132,133</sup> and the Tyk2i  
608 deucravacitinib.<sup>134,135</sup> Whether differential selectivity for JAK isoforms impacts efficacy across  
609 domains of PsA or toxicity remains to be seen.

#### 610 *Treatment Strategies*

611 **Treat-to-target.** As in other fields of medicine, it has become commonplace to strive for a  
612 treatment target of remission, if possible, or low disease activity if not. Such a strategy yields  
613 optimal short and long term outcomes for the patient. Numerous “treat-to-target” (T2T) trials have  
614 been conducted in RA, utilizing quantifiable measures of disease activity, typically including  
615 numerically assessed physical examinations, such as joint counts, quantified patient self-  
616 assessment, and laboratory measures of disease activity, such as C-reactive protein. The TICOPA

Commented [AO1]: Place holder for phase III since that will likely be public by the time this is published?

Commented [PM2R1]: Phase 3 publications not out yet. Phase 2, including 1 year data, has been submitted for publication, thus the reference to the abstract

617 trial,<sup>71</sup> conducted in early PsA patients, compared patients evaluated monthly and requiring  
618 intensification of treatment if a goal of Minimal Disease Activity (MDA) activity was not met to  
619 patients seen every 3 months, without such a target of treatment. After 48 weeks, the patients in  
620 the T2T group demonstrated superior treatment results, thus supporting this goal of treatment in  
621 clinical practice. It is worth noting that many T2T studies are tautologic, insofar as the requirement  
622 to alter therapy to achieve a goal, results in greater achievement of the goal using similar metrics.  
623 Longer term outcomes, safety considerations, and pharmacoeconomic assessments should also be  
624 factors in therapeutic decision making.

625 **Treatment Recommendations.** Three international organizations have published and updated  
626 PsA treatment recommendations: the Group for Research in Psoriasis and Psoriatic Arthritis  
627 (GRAPPA), the European League Against Rheumatism (EULAR), and American College of  
628 Rheumatology/National Psoriasis Foundation (ACR-NPF). The GRAPPA recommendations<sup>136</sup>  
629 are developed by both rheumatologists and dermatologists as well as PsA patients and are  
630 organized across the domains of PsA: peripheral arthritis, axial disease, enthesitis, dactylitis, skin  
631 psoriasis and nail psoriasis, as well as IBD and uveitis. The EULAR guidelines<sup>137</sup> yield overall  
632 similar recommendations as GRAPPA, but arranged in an algorithmic sequence from early and/or  
633 mild disease to more advanced disease wherein previous treatments have failed. The ACR-NPF  
634 guidelines<sup>138</sup> used a strict Grades of Recommendation Assessment, Development and Evaluation  
635 (GRADE) approach. The guidelines chose one class/group of medicines ahead of another,  
636 allowing for variances depending on contextual factors, such as the presence of more severe skin  
637 disease. One key difference among the 3 guidelines is the recommendation to use TNFi  
638 prior to use of csDMARDs, based on both efficacy and safety data from clinical trials. In the  
639 absence of H2H trials available when these guidelines were developed, the majority of  
640 recommendations are considered “conditional”, since the comparative evidence is indirect. It  
641 should be noted that there are also additional regional and societal guidelines, developed with less  
642 rigor, which present the clinician with a heterogeneous group of treatment guidelines to follow.

643 **Conclusion.** There are now numerous biopharmacologic therapeutic options for the management  
644 of PsA. Efficacy, with most of the options, has the potential to be significant in all clinical domains  
645 of the disease. However, in many patients, cross-domain efficacy can be variable, efficacy may  
646 not be achieved or soon lost and true remission is not frequent. Clinicians must assess each domain  
647 on a regular basis and aim to achieve remission or low disease activity across the different active  
648 domains, whilst being cognisant of potential adverse events. Greater understanding of the  
649 pathophysiology of the disease has allowed us to more precisely target the appropriate cellular and  
650 cytokine pathways of disease. Treatment effect with any single agent may wane, thus the need for  
651 multiple classes of medicine and choices of individual agents to switch to in order to sustain  
652 treatments targets remains necessary.

## 653 Quality of life

654 **PsA** has a significant negative impact on physical function and Quality of Life (QoL). The concept  
655 of QoL extends beyond the physical manifestations of disease to include emotional well-being,

656 self-esteem, participation in work and activities as well as non-health issues such as financial  
657 security, spiritual well-being, and environmental safety (**Figure 3**). PsA has a similar impact on  
658 QoL to that seen in RA despite generally being a less destructive arthropathy. The impact in PsA  
659 appears to be due to the accumulated burden of skin, joint, enthesal, axial disease, comorbidities  
660 and flare.<sup>139,140</sup> A consistent finding across qualitative studies has been the ranking of pain as the  
661 top priority for patients as an outcome for treatment but fatigue, physical function, ability to work  
662 and social participation all rank highly.<sup>141,142</sup> A recent observational study in early PsA and RA  
663 has shown that despite more severe disease at diagnosis near normalisation of health related QoL  
664 is seen in patients with RA after five years but not PsA, possibly due to delay in diagnosis.<sup>143</sup>  
665 Despite the presence of psoriasis as a visible risk factor for developing PsA in the majority of cases  
666 delay to diagnosis of PsA is longer than RA and is associated with worse clinical and functional  
667 outcome.<sup>59,144</sup>

#### 668 ***Disease specific and generic assessment of QoL***

669 The understanding of treatment outcomes important to patients has advanced considerably in  
670 recent years. It is clear that improving QoL is a high priority outcome from treatment to patients.<sup>142</sup>  
671 The assessment of QoL is recommended in all Randomised Controlled Trails (RCT) and  
672 observational studies of PsA.<sup>145</sup> Instruments for measuring QoL may be generic, applicable across  
673 diseases or the general population; or disease specific, attributing to the particular disease under  
674 consideration. Disease-specific QoL instruments cover concerns that are specific and relevant to  
675 the group of patients with the condition. Generic measures of QoL commonly used in PsA include  
676 the Medical Outcome Study Short Form 36 Item (SF36)<sup>146</sup> and the EuroQoL-5D<sup>147</sup>. The SF36  
677 scores in eight subdomains and aggregates into two summary domains of physical and mental  
678 health and has data supporting its validity in PsA.<sup>96</sup> The EQ5D is available as an index (with  
679 country specific adjustments) or Visual Analogue Scale (VAS). Disease specific instruments  
680 include the Psoriatic Arthritis Quality of Life Index (PsAQoL)<sup>148</sup> and more recently the Psoriatic  
681 Arthritis Impact of Disease score (PSAID).<sup>141</sup> The PSAID has been provisionally recommended  
682 by Outcome Measures in Rheumatology (OMERACT) for RCT's and observational studies in  
683 PsA.<sup>149</sup> The PSAID can be used in the 9 or 12 item versions and captures information in 0-10  
684 numeric rating scales of pain, fatigue, skin, work, function, discomfort, sleep, coping, anxiety,  
685 embarrassment, social participation and depression individually and in a summary score.

#### 686 ***Impact of PsA on Personal and Professional life***

687 With the development of improved patient reported measures of QoL such as the PSAID it has  
688 recently been possible to undertake large observational studies to quantify impact of disease on  
689 QoL. A global study of 1286 patients from eight countries identified high levels of residual disease  
690 impact despite being on treatment including; moderate/major impacts of PsA on physical activity  
691 (78%), ability to perform certain activities (76%), work productivity (62%), and career path  
692 (57%).<sup>150</sup> Skin/nail symptoms occurred in 80% of patients. Overall, 69% of patients reported that  
693 PsA had a moderate/major impact on emotional/mental wellbeing, 56% on romantic  
694 relationships/intimacy, and 44% on relationships with family and friends. Social impacts included  
695 emotional distress (58%), social shame or disapproval (32%), and ceased participation in social

696 activities (45%).<sup>150</sup> The relative impact of each domain of disease is uncertain. Evidence suggests  
697 that joints and pain are most strongly associated with reduced QoL in people living with PsA but  
698 that resolution of skin disease is required for optimal QoL. Pain from joint disease is often ranked  
699 as this highest priority to patients and was the highest ranked outcome in the PSAID development  
700 studies and a UK multicentre study.<sup>141,142</sup> However improving skin and joint disease symptoms are  
701 important to achieve optimal improvement in QoL.<sup>151,152</sup>

#### 702 ***Financial burden on individual and society***

703 Patients' experience of the disease vary considerably. One of the concerns of patients is the  
704 financial impact of the disease.<sup>145,153</sup> Even psoriasis alone has a significant impact on  
705 socioeconomic status.<sup>154</sup> The impact of PsA on finances may be through lost work  
706 productivity<sup>155,156</sup>, direct medical costs, insurance and pension costs, and broader financial impact  
707 on the family. Up to 50% of people with PsA become unemployed and those able to attend work  
708 report reduced effectiveness (presenteeism).<sup>157</sup> A study of work disability observed treatment of  
709 active PsA was associated with a 40% improvement in work disability after six months treatment  
710 with biologic therapy.<sup>158</sup> In a Danish study of healthcare and public transfer (allowance) costs in  
711 patients with PsA reported the relative risk (RR) for being on disability pension five years prior to  
712 PsA diagnosis was 1.36 (95% CI 1.24 to 1.49) compared with the general population rising to 1.60  
713 (95% CI 1.49 to 1.72) at the time of diagnosis and 2.69 (95% CI 2.40 to 3.02) 10 years after  
714 diagnosis, where 21.8% of the patients with PsA received disability pension.<sup>159</sup>

#### 715 ***Psychological impact of PsA***

716 People living with PsA suffer from a range of psychological impacts including disturbed sleep,  
717 fatigue, low-level stress, depression and mood/behavioural changes and poor body image/. Each  
718 individual respond to pain differently, depending on a variety of psychological factors including  
719 personality structure, cognition, and attention to pain.<sup>155</sup> Fatigue is now recognized as one of the  
720 core domains to be measured in RCTs for PsA, and have recognised to negatively impact to  
721 patients' QoL and work.<sup>160-162</sup> Anxiety and depression are known to be prevalent amongst people  
722 living with PsA. A recent systematic literature review of 24 studies and 31,227 people with PsA  
723 reported a pooled estimate of 33% (95%CI 17 to 53%) living with anxiety and up to 51% living  
724 with depression.<sup>163</sup>

#### 725 ***Management of PsA beyond musculoskeletal domains.***

726 The burden of PsA beyond musculoskeletal manifestation has been increasingly recognized. This  
727 highlighted the importance of a patient-centred holistic approach in the care of patients living with  
728 PsA. Different models of multi-disciplinary care lead by rheumatologist or dermatologist, together  
729 with specialized nurses, psychologists, and various therapists have been explored.<sup>164</sup> The evidence  
730 showing favourable outcomes are preliminary,<sup>165</sup> and further studies to better understand  
731 sustainable outcomes are required. Nonetheless, the awareness of the multi-dimensional needs of  
732 these patients remain the key to improving the care of these patients.

733

#### 734 **Box: patient experience**

The advent of effective DMARDs has changed the perspective of people with 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 $\alpha$  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 ~~advices~~ advice and still feeling isolated and losing 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 MTX 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 haven't found the holy grail of curing the disease, I am optimistic about the perspective for newly diagnosed people that is promising.

*Anon*

735

736

## Outlook

737 While the field of PsA has continued to evolve substantially over the last two decades, a number  
738 of outstanding gaps in basic, translational and clinical research remain unmet. There are several  
739 knowledge-based needs for further basic/translational advancement in the field. First, is the need  
740 for more detailed characterization of genetic and environmental factors that determine disease  
741 initiation.<sup>42</sup> Although several genome-wide association studies have contributed to the study of  
742 disease pathogenesis, multiple questions are yet to be answered, such as why the concordance rate  
743 for PsA is under 20% in monozygotic twins and what is the precise role of epigenetic  
744 modifications, environmental exposures, biomechanical stress and infections (including gut and  
745 skin dysbiosis) in the triggering of synovio-entheseal disease. Further, the cellular and molecular  
746 drivers of disease perpetuation remain to be fully elucidated. This is of high relevance because  
747 most of the latest advances in therapeutics derived from the discovery of a handful of unique,  
748 disease-specific targets, most notably IL-17 and IL-23 cytokines and/or their receptors. A more  
749 expansive and detailed characterization of T resident memory cells<sup>52</sup>, innate cells (i.e., gamma  
750 delta, ILCs, NKs)<sup>166</sup> and newly discovered players should include not only their molecular and  
751 functional capacity, but also their spatial interactions, homing features and migratory patterns so  
752 that their presence in various compartments can be studied and therapeutically addressed.

753 Concomitantly, there are multiple challenges to be elucidated in the clinical realm. Those include  
754 the need for further characterization of factors associated with the development of PsA; the  
755 common definition of states that precede clinically overt synovio-enthesitis (i.e., what constitutes  
756 pre-clinical PsA); the meaning of imaging abnormalities present in patients with psoriasis without  
757 musculoskeletal symptoms<sup>167,168</sup>; the timing for potential immunomodulatory interventions and  
758 even preventive strategies<sup>15</sup>; and the distinction between various phenotypes of PsA from other  
759 forms of inflammatory arthritis (e.g., axial PsA from axial SpA).<sup>169</sup> Critically, and despite the  
760 achievement of remarkable outcomes in clearance of the skin with the newer generation of  
761 biologics (i.e., IL-23 and IL-17 blockers), the use of the same molecular strategies has not proven  
762 superior to TNF blockade when it comes to ameliorating peripheral arthritis or axial disease<sup>170</sup>.  
763 To overcome these challenges, multiple complementary and potentially synergistic priorities are  
764 envisioned. First, incorporating digital biomarkers into the clinical journey of patients with  
765 psoriatic disease should help address progression from psoriasis to PsA, flares and treatment  
766 response. Second, an in-depth study of cells and associated inflammatory mediators that modulate  
767 disease in the synovial, enthesal and axial tissues is gradually materializing. Several platforms  
768 promise to aid in this endeavour, including spatial transcriptomics<sup>171</sup>, ECCITE-seq<sup>172</sup> and other  
769 variations of single cell resolution sequencing technologies. In turn, these can aid in precision  
770 medicine approaches and treatment strategies based on synovial biopsy and/or synovial fluid  
771 cellular/molecular pathways. Critically, big data analytics that incorporate clinical, genetics,  
772 environmental, and immunologic variables into predictive algorithms for diagnostics and  
773 therapeutics are emerging and should serve as examples for bringing precision medicine initiatives  
774 into PsA.  
775 As these tools become available, it will be of the essence to apply the knowledge generated into  
776 avenues for new therapeutic paradigms. As discussed, the current approach of monotherapy  
777 strategies to improve the outcomes of a multi-domain, multi-cytokine condition such as PsA may  
778 be inadequate. Altering the strategies to psoriatic therapeutics by implementing multi-target  
779 approaches may prove more efficacious.<sup>173</sup> This has been done with multiple neoplastic syndromes  
780 and is currently being tested in related conditions, such as IBD. A concrete example is the VEGA  
781 trial, which is testing the hypothesis that biologic combination of a TNF inhibitor and an IL-23  
782 inhibitor will be superior to monotherapy.<sup>174</sup>  
783 Ultimately, the success of these endeavours will be dependent on innovative work performed by  
784 clinical and translational researchers and industry partners most likely through team science  
785 approach. Multiple recent programs have been launched that incorporate private-public  
786 partnerships to advance the field through collaborative efforts, using novel multi-disciplinary  
787 strategies. These include the National Psoriasis Foundation's psoriasis preventive initiative (PPI);  
788 the European Union's Innovative Medicines Initiative (IMI)<sup>175</sup> [a partnership between the  
789 European Commission and the European Federation of Pharmaceutical Industries and  
790 Associations (EFPIA)]; and the Accelerating Medicines Partnership (AMP)<sup>176</sup>, an NIH-led pre-  
791 competitive effort between government, industry, academia and non-profit organizations to  
792 harness collective capabilities, scale and resources toward the development of new therapies for

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793 complex, heterogeneous diseases. All three programs have funded (or propose to fund) large  
794 consortia of investigators in the field which, combined with individual efforts, will be fundamental  
795 to enhance the understanding of PsA pathogenesis, diagnostics, and new targets for better  
796 treatments and even preventive strategies.



797 **Tables**

798 **Table1:**

799 Clinical, laboratory and radiographic features which help to distinguish early, active PsA from  
 800 Rheumatoid Arthritis (RA), Osteoarthritis (OA) or Ankylosing Spondylitis (AS).

	<b>PsA</b>	<b>RA</b>	<b>OA</b>	<b>AS</b>
Polyarticular	Common	Very common	Common	Rare
Oligoarticular	Common	Occasional	Common	Occasional
DIP 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
RF ++	Occasional	Very common	Rare	Rare
aCCP +	<del>Occasional</del> Rare	Very Common	Rare	Rare
Elevated ESR/CRP	Common	Very common	Rare	Common
HLA-B27 positivity	Occasional	Rare	Rare	Very common
Joint erosion*	Common	Very common	Occasional	Occasional
Osteoproliferation*	Common	Rare	Common	Very common**
Sacroiliitis on radiographs*	Occasional	No	No	Nearly always

801 No = not found; Rare = <10%; Occasional = 10-30%; Common = 30-60%; Very common = 60-  
 802 90%; Nearly always = >90%

803 \*in disease >2 years duration

804 \*\* very common in spine or sacroiliacs; occasional in peripheral skeleton

805

806



810 **Table 3:**  
811 **Outcome Measures in PsA Clinical Trials<sup>82-84</sup>**

Domains	Instruments
<del>Joints</del> <u>Arthritis</u>	68/66 T/S joint count, ACR20/50/70 response, DAS28, PsARC, PsAJAI, DAPSA, cDAPSA
<u>Enthesitis</u>	<u>Leeds Enthesitis Index, SPARCC, MASES, 4-point*</u>
<u>Dactylitis</u>	<u>Leeds Dactylitis Index, Dactylitis Count, Dactylitis Severity Score</u>
Axial <u>Spondyloarthritis</u>	BASDAI, BASFI, BASMI
Skin, nails	PASI, target lesion, physician global, PSI, PSD, NAPSI, mNAPSI, nail VAS
Composite – multi-domain	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
<u>Physical Function</u>	HAQ, HAQ-S, <del>PSAID</del> , SF-36 PF, <u>PROMIS-PF</u>
HRQoL	SF-36, PSAID, PsAQoL, DLQI, <u>EQ-5D, PROMIS-Profiles</u>
Fatigue	FACIT- <u>Fatigue</u> , VAS, <u>PROMIS-Fatigue</u>
<u>Participation</u>	<u>PROMIS-Social Roles and participation</u>
<u>Enthesitis</u>	<u>Leeds, SPARCC, MASES, 4 point</u>
<u>Dactylitis</u>	<u>Leeds Dactylitis Index, Dactylitis Count, Dactylitis Severity Score</u>
Acute phase reactant	ESR, CRP
<del>Imaging</del> <u>Structural damage</u>	X-ray (modified Sharp or van der Heijde–Sharp), MRI, US
Work/home productivity	WPAI, WPS

812 HRQoL, Health-Related Quality of Life; ACR, American College of Rheumatology; DAS,  
813 Disease Activity Score; PsARC, Psoriatic Arthritis Response Criteria; PsAJAI, Psoriatic Arthritis  
814 Joint Activity Index; DAPSA, Disease Activity in Psoriatic Arthritis; cDAPSA, clinical Disease  
815 Activity in Psoriatic Arthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index;  
816 BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis  
817 Metrology Index; PASI, Psoriasis Area and Severity Index; PSI, Psoriasis Symptom Inventory;  
818 PSD, Psoriasis Symptom Diary; NAPSI, Nail Psoriasis Severity Index; mNAPSI, Modified Nail  
819 Psoriasis Severity Index; VAS, visual analogue scale; MDA, Minimal Disease Activity; VLDA,  
820 very low disease activity; PASDAS, Psoriatic Arthritis Disease Activity Score; CPDAI,  
821 Composite Psoriatic Disease Activity Index; GRAPPA, Group for Research and Assessment of  
822 Psoriasis and Psoriatic Arthritis; GRACE, GRAPPA Composite Exercise; NRS, numeric rating  
823 scale; HAQ, Health Assessment Questionnaire; HAQ-S, Health Assessment Questionnaire-

824 Spondyloarthritis; PSAID, Psoriatic Arthritis Impact of Disease; SF-36, Short Form 36; PsAQoL,  
825 Psoriatic Arthritis Quality of Life Index; DLQI, Dermatology Life Quality Index; FACIT,  
826 Functional Assessment of Chronic Illness Therapy; SPARCC, Spondyloarthritis Research  
827 Consortium of Canada; MASES, Maastricht Ankylosing Spondylitis Enthesis Score; ESR,  
828 erythrocyte sedimentation rate; CRP, C-reactive protein; MRI, Magnetic resonance imaging; US,  
829 Ultrasound; WPAI, Work Productivity and Activity Index; WPS, Work Productivity Survey.

830 \* Used in the impact study

834 **Table 4:**  
835 **PsA Therapeutic Groups<sup>5</sup>**

- Adjunctive therapies
    - NSAIDs, glucocorticosteroids [po, ia, topical]
  - Conventional synthetic DMARDs (cs-DMARDs)
    - Methotrexate, sulfasalazine, leflunomide, Cyclosporine
  - **bdDMARDs**
    - ◆○ TNF inhibitors (TNFi)
      - ⇒■ Etanercept\*, infliximab\*, adalimumab\*, golimumab, certolizumab
    - ◆○ IL12/23i
      - ⇒■ Ustekinumab
    - ◆○ IL17i
      - ⇒■ Secukinumab, ixekizumab, brodalumab ^, bimekizumab#
    - ◆○ IL23i
      - ⇒■ Guselkumab, risankizumab^, tildrakizumab^
    - ◆○ T cell modulator
      - ⇒■ Abatacept
  - Targeted synthetic DMARDs (ts-DMARDs)
    - PDE4i (apremilast)
    - JAKi (tofacitinib, upadacitinib; baricitinib#, , filgotinib#)
- (\*biosimilars available in 2021; ^approved for psoriasis, not PsA, in 2021; #in development)

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857 **Figure legends**

858  
859 **Figure 1:** Stages in the evolution of Pso to PsA. These stages include: ① patients with skin and/or  
860 nail psoriasis only but with risk factors, at present indeterminate, for subsequent development of  
861 PsA; ② MSK immune activation phase when there is evidence of cytokine (e.g. IL-23/IL-17  
862 and/or TNF) over-production at a cellular or tissue level; ③ a stage where there is asymptomatic  
863 evidence of synovio-enthesal inflammation on imaging: MRI or ultrasound; ④ a “prodromal  
864 stage” where psoriasis patients may have MSK symptoms such as arthralgia and/or stiffness but  
865 without sufficient signs to make a diagnosis of PsA; and ⑤ PsA meeting CASPAR criteria. The  
866 bidirectional arrows in Figure 1 reflect the important possibility that some of these stages may be  
867 reversible. At present, treatment is focused on those patients who receive a PsA diagnosis (stage  
868 ⑤ in Figure 1) and have ongoing inflammatory disease and evidence of radiographic damage.  
869 Future treatment intervention strategies may target patients at an earlier disease stage (1-4).

870  
871 **Figure 2.**

872 Distinct clinical phenotypes of psoriatic disease (PsD) occur as a consequence of genetic  
873 predisposition, environmental triggers (such as biomechanical or metabolic stress, infections and  
874 obesity) and local factors according to disease site (joints, skin, spine or entheses). Amplification  
875 of the IL-23–IL-17 axis is initiated via activation of innate cells in the skin, entheses and  
876 gastrointestinal tract, ultimately resulting in the expansion of CD4+ and CD8+ T helper 1 (TH1)  
877 and TH17 cells, which are expanded by IL-23 and IL-12 and produce TNF and IL-17. Different  
878 HLA alleles and/or haplotypes, T cell subsets and treatment response profiles are associated with  
879 different PsD phenotypes. Synovial-predominant PsD is associated with HLA-B\*08:01:01, HLA-  
880 C\*07:01:01 and haplotype HLA-B\*08:01:01–HLA-C\*07:01:01, CD8+ engagement with TH1  
881 cells and responsiveness to TNF inhibition. Cutaneous-predominant PsD is associated with HLA-  
882 B\*57:01 and HLA-C\*06:02, TH1 cell-driven and responsive to IL-17 and IL-23 inhibition.  
883 Enthesal-predominant with or without axial disease, which is associated with the HLA-  
884 B\*27:05:02 allele, involves engagement of both TH1 and TH17 cells that produce both TNF and  
885 IL-17, and is responsive to TNF and IL-17 inhibition. Psoriatic arthritis mutilans (PAM) likely  
886 represents a combination of these host genetic factors and T cell interactions. CXCR3, CXC-  
887 chemokine receptor 3; CCR, CC-chemokine receptor; IL-12R, IL-12 receptor; IL-23R, IL-23  
888 receptor. (From ref 42, with permission)

889  
890 **Figure 3. The complex model of quality of life for patients with PSA.**

893 **References**

- 894 1. Bowes, J. *et al.* Confirmation of TNIP1 and IL23A as susceptibility loci for psoriatic  
895 arthritis. *Ann. Rheum. Dis.* **70**, 1641–1644 (2011).
- 896 2. Hüffmeier, U. *et al.* Common variants at TRAF3IP2 are associated with susceptibility to  
897 psoriatic arthritis and psoriasis. *Nat. Genet.* **42**, 996–999 (2010).
- 898 3. Menon, B. *et al.* Interleukin-17+CD8+ T cells are enriched in the joints of patients with  
899 psoriatic arthritis and correlate with disease activity and joint damage progression.  
900 *Arthritis Rheumatol* **66**, 1272–81 (2014).
- 901 4. Alinaghi, F. *et al.* Prevalence of psoriatic arthritis in patients with psoriasis: A systematic  
902 review and meta-analysis of observational and clinical studies. *Journal of the American*  
903 *Academy of Dermatology* vol. 80 251–265 (2019).
- 904 5. Scotti, L., Franchi, M., Marchesoni, A. & Corrao, G. Prevalence and incidence of psoriatic  
905 arthritis: A systematic review and meta-analysis. doi:10.1016/j.semarthrit.2018.01.003.
- 906 6. Ogdie, A. *et al.* Prevalence and treatment patterns of psoriatic arthritis in the UK.  
907 *Rheumatol.* **52**, (2013).
- 908 7. Kaufman BP, A. A. *Epidemiology, Clinical Presentation, Genetics, Quality-of-Life Impact,*  
909 *and Treatment of Psoriasis in Non-White Racial/Ethnic Groups.* *Am J Clin Dermatol.*  
910 (2018). doi:10.1007/978-0-387-84929-4.
- 911 8. Weiss PF, R. J. Juvenile-Versus Adult-Onset Spondyloarthritis: Similar, but Different.  
912 *Rheum Dis Clin North Am* **46**, 241-257. (2020).
- 913 9. International League of Associations for Rheumatology. International League of  
914 Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis : Second  
915 Revision , Edmonton , 2001. *J. Rheumatol.* **31**, 390–392 (2001).
- 916 10. Stoll ML, Lio P, Sundel RP, N. P. Comparison of Vancouver and International League of  
917 Associations for rheumatology classification criteria for juvenile psoriatic arthritis.  
918 *Arthritis Rheum.* **59**, 51–8 (2008).
- 919 11. Southwood, T.R., Petty, R.E., Malleon, P.N., Delgado, E.A., Hunt, D.W., Wood, B.,  
920 Schroeder, M.L.  
921 Psoriatic arthritis in children. *Arthritis Rheum.* **8**,  
922 1007–13 (1989).
- 923 12. Brandon, T. G., Manos, C. K., Xiao, R., Ogdie, A. & Weiss, P. F. Pediatric Psoriatic Arthritis:  
924 A Population-Based Cohort Study of Risk Factors for Onset and Subsequent Risk of  
925 Inflammatory Comorbidities. *J. Psoriasis Psoriatic Arthritis* **3**, 131–136 (2018).
- 926 13. Ringold S, Angeles-Han ST, Beukelman T, Lovell D, Cuello CA, Becker ML, Colbert RA,  
927 Feldman BM, Ferguson PJ, Gewanter H, Guzman J, Horonjeff J, Nigrovic PA, Ombrello MJ,  
928 Passo MH, Stoll ML, Rabinovich CE, Schneider R, Halyabar O, Hays K, Shah AA, Sullivan, R.  
929 J. No Title2019 American College of Rheumatology/Arthritis Foundation Guideline for the  
930 Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic  
931 Polyarthritis, Sacroiliitis, and Enthesitis. *Arthritis Rheumatol* **71**, 846–863 (2019).
- 932 14. O’Rielly DD, Jani M, Rahman P, E. J. The Genetics of Psoriasis and Psoriatic Arthritis. *J*  
933 *Rheumatol Suppl* **95**, 46–50 (2019).

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Check spelling and grammar

- 934 15. Scher, J. U., Ogdie, A., Merola, J. F. & Ritchlin, C. Preventing psoriatic arthritis: focusing  
935 on patients with psoriasis at increased risk of transition. *Nat. Rev. Rheumatol.* **15**, 153–  
936 166 (2019).
- 937 16. Taylor, W. *et al.* Classification criteria for psoriatic arthritis: Development of new criteria  
938 from a large international study. *Arthritis Rheum.* **54**, 2665–2673 (2006).
- 939 17. Villani, A. P. *et al.* Prevalence of undiagnosed psoriatic arthritis among psoriasis patients:  
940 systematic review and meta-analysis. *J Am Acad Dermatol* **73**, 242–8 (2015).
- 941 18. Ogdie, A. The preclinical phase of PsA: a challenge for the epidemiologist. *Ann Rheum Dis*  
942 **76**, 1481–1483 (2017).
- 943 19. Gupta, S., Syrimi, Z., Hughes, D. M. & Zhao, S. S. Comorbidities in psoriatic arthritis: a  
944 systematic review and meta-analysis. *Rheumatol. Int.* **41**, 275–284 (2021).
- 945 20. Karmacharya P, Chakradhar R, O. A. The epidemiology of psoriatic arthritis: A literature  
946 review. *Best Pr. Res Clin Rheumatol.* (2021).
- 947 21. Kumthekar, A. & Ogdie, A. Obesity and Psoriatic Arthritis: A Narrative Review.  
948 *Rheumatol. Ther.* **7**, 447–456 (2020).
- 949 22. Ogdie, A. & Weiss, P. The Epidemiology of Psoriatic Arthritis. *Rheumatic Disease Clinics of*  
950 *North America* vol. 41 545–568 (2015).
- 951 23. Dubreuil, M. *et al.* Diabetes incidence in psoriatic arthritis, psoriasis and rheumatoid  
952 arthritis: A UK population-based cohort study. *Rheumatol. (United Kingdom)* **53**, 346–352  
953 (2014).
- 954 24. Ogdie A, Grewal SK, Noe MH, Shin DB, Takeshita J, Chiesa Fuxench ZC, Carr RM, G. J. Risk  
955 of incident liver disease in patients with psoriasis, psoriatic arthritis, and rheumatoid  
956 arthritis: a population-based study. *Physiol. Behav.* **176**, 139–148 (2019).
- 957 25. Lukmanji A, Basmadjian RB, Vallerand IA, Patten SB, T. K. Risk of Depression in Patients  
958 With Psoriatic Disease: A Systematic Review and Meta-Analysis. *J Cutan Med Surg* **2**, On  
959 line ahead of print (2020).
- 960 26. Mease, P. J. Fibromyalgia, a missed comorbidity in spondyloarthritis: prevalence and  
961 impact on assessment and treatment. *Curr. Opin. Rheumatol.* **29**, 304–310 (2017).
- 962 27. Lubrano E, Scryfallano S, Morelli R, P. F. Assessment of widespread and extra-articular  
963 pain in psoriatic arthritis: a case-control study. *J Rheumatol* (2021)  
964 doi:10.3899/jrheum.201163.
- 965 28. Michelsen, B. *et al.* Do depression and anxiety reduce the likelihood of remission in  
966 rheumatoid arthritis and psoriatic arthritis? Data from the prospective multicentre NOR-  
967 DMARD study. *Ann Rheum Dis* **76**, 1906–1910 (2017).
- 968 29. Elsayy NA, Helal AH, Abd ElHamid HA, A.-F. Y. Fibromyalgia in patients with psoriatic  
969 arthritis: Impact on disease activity indices, fatigue and health-related quality of life. *Int J*  
970 *Rheum Dis* **24**, 189–196 (2021).
- 971 30. Bengtsson, K. *et al.* Incidence of extra-articular manifestations in ankylosing spondylitis,  
972 psoriatic arthritis and undifferentiated spondyloarthritis: results from a national register-  
973 based cohort study. *Rheumatology* 1–10 (2020) doi:10.1093/rheumatology/keaa692.
- 974 31. Bradley Pittam, Sonal Gupta, Nicholas L Harrison, Selina Robertson, David M Hughes, S. S.  
975 Z. Prevalence of extra-articular manifestations in psoriatic arthritis: a systematic review  
976 and meta-analysis. *Rheumatology* **59**, 2199–2206 (2020).
- 977 32. O’Rielly DD, R. P. Genetic, Epigenetic and Pharmacogenetic Aspects of Psoriasis and

- 978 Psoriatic Arthritis. *Rheum Dis Clin North Am.* **41**, 623–42 (2015).
- 979 33. Li, Q. *et al.* Quantifying Differences in Heritability among Psoriatic Arthritis (PsA),  
980 Cutaneous Psoriasis (PsC) and Psoriasis vulgaris (PsV). *Sci. Rep.* **10**, 1–6 (2020).
- 981 34. Winchester, R. *et al.* HLA associations reveal genetic heterogeneity in psoriatic arthritis  
982 and in the psoriasis phenotype. *Arthritis Rheum* **64**, 1134–44 (2012).
- 983 35. Okada Y, Han B, Tsoi LC, Stuart PE, Ellinghaus E, Tejasvi T, Chandran V, Pellett F, Pollock R,  
984 Bowcock AM, Krueger GG, Weichenthal M, Voorhees JJ, Rahman P, Gregersen PK, Franke  
985 A, Nair RP, Abecasis GR, Gladman DD, Elder JT, de Bakker PI, R. S. Fine mapping major  
986 histocompatibility complex associations in psoriasis and its clinical subtypes. *Am J Hum*  
987 *Genet* **95**, 162–72 (2014).
- 988 36. Bowes, J. *et al.* Cross-phenotype association mapping of the MHC identifies genetic  
989 variants that differentiate psoriatic arthritis from psoriasis. *Ann. Rheum. Dis.* **76**, 1774–  
990 1779 (2017).
- 991 37. Winchester, R. & FitzGerald, O. The many faces of psoriatic arthritis: their genetic  
992 determinism. *Rheumatology (Oxford)*. **59**, i4–i9 (2020).
- 993 38. Haroon, M., Winchester, R., Giles, J. T., Heffernan, E. & FitzGerald, O. Certain class I HLA  
994 alleles and haplotypes implicated in susceptibility play a role in determining specific  
995 features of the psoriatic arthritis phenotype. *Ann. Rheum. Dis.* **75**, 155–62 (2016).
- 996 39. Haroon, M., Winchester, R., Giles, J. T., Heffernan, E. & FitzGerald, O. Certain class I HLA  
997 alleles and haplotypes implicated in susceptibility play a role in determining specific  
998 features of the psoriatic arthritis phenotype. *Ann Rheum Dis* **75**, 155–62 (2016).
- 999 40. Bowes, J. *et al.* Dense genotyping of immune-related susceptibility loci reveals new  
1000 insights into the genetics of psoriatic arthritis. *Nat. Commun.* **6**, 7741 (2015).
- 1001 41. Apel, M. *et al.* Variants in RUNX3 contribute to susceptibility to psoriatic arthritis,  
1002 exhibiting further common ground with ankylosing spondylitis. *Arthritis Rheum.* **65**,  
1003 1224–1231 (2013).
- 1004 42. Ritchlin, C. T., Colbert, R. A. & Gladman, D. D. Psoriatic Arthritis. *N. Engl. J. Med.* **376**,  
1005 2095–6 (2017).
- 1006 43. Thorarensen, S. M. *et al.* Physical trauma recorded in primary care is associated with the  
1007 onset of psoriatic arthritis among patients with psoriasis. *Ann. Rheum. Dis.* **76**, 521–525  
1008 (2017).
- 1009 44. Schett G, Lories RJ, D’Agostino MA, Elewaut D, Kirkham B, Soriano ER, M. D. Enthesitis:  
1010 from pathophysiology to treatment. *Nat Rev Rheumatol* **13**, 731–741 (2017).
- 1011 45. Green, A. *et al.* Modifiable risk factors and the development of psoriatic arthritis in  
1012 people with psoriasis. *Br. J. Dermatol.* **182**, 714–720 (2020).
- 1013 46. Gilis E, Mortier C, Venken K, Debusschere K, Vereecke L, E. D. The Role of the  
1014 Microbiome in Gut and Joint Inflammation in Psoriatic Arthritis and Spondyloarthritis. *J*  
1015 *Rheumatol Suppl* **94**, 36–39 (2018).
- 1016 47. Abusleme L, M. N. IL-17: overview and role in oral immunity and microbiome. *Oral Dis*  
1017 **23**, 854–865 (2017).
- 1018 48. Schluter, J. *et al.* The gut microbiota is associated with immune cell dynamics in humans.  
1019 *Nature* **588**, 303–307 (2020).
- 1020 49. Jadon, D. R., Stober, C., Pennington, S. R. & FitzGerald, O. Applying precision medicine to  
1021 unmet clinical needs in psoriatic disease. *Nat Rev Rheumatol* **16**, 609–627 (2020).



- 1022 50. Queiro R, Gonzalez S, López-Larrea C, Alperi M, Sarasqueta C, Riestra JL, B. J. HLA-C locus  
1023 alleles may modulate the clinical expression of psoriatic arthritis. *Arthritis Res. Ther.* **8**,  
1024 R185 (2006).
- 1025 51. Leijten EF, van Kempen TS, Olde Nordkamp MA, Pouw JN, Kleinrensink NJ, Vincken NL,  
1026 Mertens J, Balak DMW, Verhagen FH, Hartgring SA, Lubberts E, Tekstra J, Pandit A,  
1027 Radstake TR, B. M. Tissue-resident memory CD8+ T cells from skin differentiate psoriatic  
1028 arthritis from psoriasis. *Arthritis Rheumatol.* (2021) doi:10.1002/art.41652. Epub ahead  
1029 of print.
- 1030 52. Steel, K. J. A. *et al.* Polyfunctional, Proinflammatory, Tissue-Resident Memory Phenotype  
1031 and Function of Synovial Interleukin-17A+CD8+ T Cells in Psoriatic Arthritis. *Arthritis*  
1032 *Rheumatol.* **72**, 435–447 (2020).
- 1033 53. Polachek A, Cook R, Chandran V, Abji F, Gladman D, E. L. The Association Between HLA  
1034 Genetic Susceptibility Markers and Sonographic Enthesitis in Psoriatic Arthritis. *Arthritis*  
1035 *Rheumatol.* **71**, 625 (2019).
- 1036 54. Costello, P. J. *et al.* Psoriatic arthritis joint fluids are characterized by CD8 and CD4 T cell  
1037 clonal expansions appear antigen driven. *J Immunol* **166**, 2878–86 (2001).
- 1038 55. Cañete, J. D. *et al.* Ectopic lymphoid neogenesis in psoriatic arthritis. *Ann. Rheum. Dis.* **66**,  
1039 720–726 (2007).
- 1040 56. Penkava F, Velasco-Herrera MDC, Young MD, Yager N, Nwosu LN, Pratt AG, Lara AL,  
1041 Guzzo C, Maroof A, Mamanova L, Cole S, Efremova M, Simone D, Filer A, Brown CC,  
1042 Croxford AL, Isaacs JD, Teichmann S, Bowness P, Behjati S, H. A.-M. M. Single-cell  
1043 sequencing reveals clonal expansions of pro-inflammatory synovial CD8 T cells expressing  
1044 tissue-homing receptors in psoriatic arthritis. *Nat. Commun.* **11**, 4767 (2020).
- 1045 57. Abji, F., Pollock, R. A., Liang, K., Chandran, V. & Gladman, D. D. Brief Report: CXCL10 Is a  
1046 Possible Biomarker for the Development of Psoriatic Arthritis Among Patients With  
1047 Psoriasis. *Arthritis Rheumatol. (Hoboken, N.J.)* **68**, 2911–2916 (2016).
- 1048 58. Holland, R. *et al.* Psoriatic arthritis is associated with diagnostic delay and worse outcome  
1049 at 3 months when compared to rheumatoid arthritis: Results from the UK National Audit  
1050 for Inflammatory Arthritis. *Ann. Rheum. Dis.* **76**, FRI0514 (2017).
- 1051 59. Tillett, W. *et al.* Smoking and delay to diagnosis are associated with poorer functional  
1052 outcome in psoriatic arthritis. *Ann. Rheum. Dis.* **72**, 1358–61 (2013).
- 1053 60. Haroon, M., Gallagher, P. & FitzGerald, O. Diagnostic delay of more than 6 months  
1054 contributes to poor radiographic and functional outcome in psoriatic arthritis. *Ann.*  
1055 *Rheum. Dis.* **74**, 1045–50 (2015).
- 1056 61. Mease, P. J., Garg, A., Helliwell, P. S., Park, J. J. & Gladman, D. D. Development of criteria  
1057 to distinguish inflammatory from noninflammatory arthritis, enthesitis, dactylitis, and  
1058 spondylitis: a report from the GRAPPA 2013 Annual Meeting. *J Rheumatol* **41**, 1249–1251  
1059 (2014).
- 1060 62. Bonifati, C. *et al.* The diagnosis of early psoriatic arthritis in an outpatient dermatological  
1061 centre for psoriasis. *J Eur Acad Dermatol Venereol* **26**, 627–633 (2012).
- 1062 63. Kane, D., Stafford, L., Bresnihan, B. & FitzGerald, O. A prospective, clinical and  
1063 radiological study of early psoriatic arthritis: an early synovitis clinic experience.  
1064 *Rheumatol.* **42**, 1460–8 (2003).
- 1065 64. Moghaddassi, M., Shahram, F., Chams-Davatchi, C., Najafizadeh, S. R. & Davatchi, F.

- 1066 Different aspects of psoriasis: analysis of 150 Iranian patients. *Arch Iran Med* **12**, 279–283  
1067 (2009).
- 1068 65. Coates, L. C. *et al.* Sensitivity and specificity of the classification of psoriatic arthritis  
1069 criteria in early psoriatic arthritis. *Arthritis Rheum* **64**, 3150–5 (2012).
- 1070 66. Niccoli, L. *et al.* Frequency of iridocyclitis in patients with early psoriatic arthritis: a  
1071 prospective, follow up study. *Int J Rheum Dis* **15**, 414–418 (2012).
- 1072 67. Reich, K., Kruger, K., Mossner, R. & Augustin, M. Epidemiology and clinical pattern of  
1073 psoriatic arthritis in Germany: a prospective interdisciplinary epidemiological study of  
1074 1511 patients with plaque-type psoriasis. *Br J Dermatol* **160**, 1040–1047 (2009).
- 1075 68. Gladman, D. D., Ziouza, O., Thavaneswaran, A. & Chandran, V. Dactylitis in psoriatic  
1076 arthritis: Prevalence and response to therapy in the biologic ERA. *J. Rheumatol.* **40**,  
1077 1357–1359 (2013).
- 1078 69. Torre Alonso, J. C. *et al.* Psoriatic arthritis (PA): a clinical, immunological and radiological  
1079 study of 180 patients. *Br J Rheumatol* **30**, 245–250 (1991).
- 1080 70. Scarpa, R. *et al.* Early psoriatic arthritis: the clinical spectrum. *J Rheumatol* **35**, 137–141  
1081 (2008).
- 1082 71. Coates, L. C. *et al.* Effect of tight control of inflammation in early psoriatic arthritis  
1083 (TICOPA): a UK multicentre, open-label, randomised controlled trial. *Lancet* **386**, 2589–98  
1084 (2015).
- 1085 72. Chandran V, Barrett J, Schentag CT, Farewell VT, G. D. Axial psoriatic arthritis: update on  
1086 a longterm prospective study. *Arthritis Rheum* **64**, 1560–1563 (2012).
- 1087 73. Battistone, M. J., Manaster, B. J., Reda, D. J. & Clegg, D. O. The prevalence of sacroilitis in  
1088 psoriatic arthritis: new perspectives from a large, multicenter cohort. A Department of  
1089 Veterans Affairs Cooperative Study. *Skelet. Radiol* **28**, 196–201 (1999).
- 1090 74. Helliwell, P. S., Hickling, P. & Wright, V. Do the radiological changes of classic ankylosing  
1091 spondylitis differ from the changes found in the spondylitis associated with inflammatory  
1092 bowel disease, psoriasis, and reactive arthritis? *Ann. Rheum. Dis.* **57**, 135–140 (1998).
- 1093 75. Jadon, D. R. *et al.* Axial Disease in Psoriatic Arthritis study: Defining the clinical and  
1094 radiographic phenotype of psoriatic spondyloarthritis. *Ann. Rheum. Dis.* **76**, 701–707  
1095 (2017).
- 1096 76. Moll, J. M. H. & Wright, V. Psoriatic arthritis. *Semin. Arthritis Rheum.* **3**, 55–78 (1973).
- 1097 77. Gladman, D. D., Shuckett, R., Russell, M. L., Thorne, J. C. & Schachter, R. K. Psoriatic  
1098 arthritis (PSA)—an analysis of 220 patients. *Q J Med* **62**, 127–41 (1987).
- 1099 78. Congi, L. & Roussou, E. Clinical application of the CASPAR criteria for psoriatic arthritis  
1100 compared to other existing criteria. *Clin Exp Rheumatol* **28**, 304–310 (2010).
- 1101 79. Tillett, W. *et al.* The classification for psoriatic arthritis (CASPAR) criteria—a retrospective  
1102 feasibility, sensitivity, and specificity study. *J Rheumatol* **39**, 154–6 (2012).
- 1103 80. Chandran, V., Schentag, C. T. & Gladman, D. D. Sensitivity of the classification of psoriatic  
1104 arthritis criteria in early psoriatic arthritis. *Arthritis Rheum* **57**, 1560–1563 (2007).
- 1105 81. van den Berg, R., van Gaalen, F., van der Helm-van Mil, A., Huizinga, T. & van der Heijde,  
1106 D. Performance of classification criteria for peripheral spondyloarthritis and psoriatic  
1107 arthritis in the Leiden Early Arthritis cohort. *Ann Rheum Dis* **71**, 1366–1369 (2012).
- 1108 82. Jones, S. M. *et al.* Psoriatic arthritis: outcome of disease subsets and relationship of joint  
1109 disease to nail and skin disease. *Br. J. Rheumatol.* **33**, 834–839 (1994).

- 1110 83. Marsal, S. *et al.* Clinical, radiographic and HLA associations as markers for different  
1111 patterns of psoriatic arthritis. *Rheumatol.* **38**, 332–7 (1999).
- 1112 84. Chandran, V., Barrett, J., Schentag, C. T., Farewell, V. T. & Gladman, D. D. Axial psoriatic  
1113 arthritis: update on a longterm prospective study. *J. Rheumatol.* **36**, 2744–2750 (2009).
- 1114 85. Chandran, V., Tolusso, D. C., Cook, R. J. & Gladman, D. D. Risk factors for axial  
1115 inflammatory arthritis in patients with psoriatic arthritis. *J. Rheumatol.* **37**, 809–815  
1116 (2010).
- 1117 86. Gladman, D. D. & Farewell, V. T. Progression in psoriatic arthritis: role of time varying  
1118 clinical indicators. *J. Rheumatol.* **26**, 2409–2413 (1999).
- 1119 87. Brockbank, J. E., Stein, M., Schentag, C. T. & Gladman, D. D. Dactylitis in psoriatic  
1120 arthritis: a marker for disease severity? *Ann Rheum Dis* **64**, 188–190 (2005).
- 1121 88. Wervers, K. *et al.* Influence of Disease Manifestations on Health-related Quality of Life in  
1122 Early Psoriatic Arthritis. *J Rheumatol* **45**, 1526–1531 (2018).
- 1123 89. Coates, L. C. *et al.* Comparison of three screening tools to detect psoriatic arthritis in  
1124 patients with psoriasis (CONTEST study). *Br J Dermatol* **168**, 802–7 (2013).
- 1125 90. Haroon, M., Kirby, B. & Fitzgerald, O. High prevalence of psoriatic arthritis in patients  
1126 with severe psoriasis with suboptimal performance of screening questionnaires. *Ann.*  
1127 *Rheum. Dis.* (2012) doi:10.1136/annrheumdis-2012-201706.
- 1128 91. Coates LC, Savage LJ, Chinoy H, Laws PM, Lovell CR, Korendowych E, Mahmood F,  
1129 Mathieson HR, McGonagle D, Warren RB, Waxman R, H. P. Assessment of two screening  
1130 tools to identify psoriatic arthritis in patients with psoriasis. *J Eur Acad Dermatol*  
1131 *Venerol.* **32**, 1530–1534 (2018).
- 1132 92. National Institute for Clinical Excellence. Psoriasis - Management of psoriasis. (2012).
- 1133 93. Eder, L. *et al.* The Incidence and Risk Factors for Psoriatic Arthritis in Patients with  
1134 Psoriasis: A Prospective Cohort Study. *Arthritis Rheumatol.* **68**, 915–23 (2016).
- 1135 94. Orbai, A.-M. *et al.* Updating the Psoriatic Arthritis (PsA) Core Domain Set: A Report from  
1136 the PsA Workshop at OMERACT 2016. *J. Rheumatol.* **44**, 1522–1528 (2017).
- 1137 95. Ogdie A, Coates LC, M. P. Measuring Outcomes in Psoriatic Arthritis. *Arthritis Care Res* **72**  
1138 **Suppl 1**, 82–109 (2020).
- 1139 96. Mease, P. J. Measures of psoriatic arthritis: Tender and Swollen Joint Assessment,  
1140 Psoriasis Area and Severity Index (PASI), Nail Psoriasis Severity Index (NAPSI), Modified  
1141 Nail Psoriasis Severity Index (mNAPSI), Mander/Newcastle Enthesitis Index (MEI), Leeds  
1142 Enthesit. *Arthritis Care Res* **63 Suppl 1**, S64-85 (2011).
- 1143 97. Mease P, van der H. D. Joint damage in psoriatic arthritis: How is it assessed and can it  
1144 be prevented? *Int. J. Adv. Rheumatol.* **4**, 38–48 (2006).
- 1145 98. Kivitz AJ, Espinoza LR, Sherrer YR, et al. A comparison of the efficacy and safety of  
1146 celecoxib 200 mg and celecoxib 400 mg once daily in treating the signs and symptoms of  
1147 psoriatic arthritis. *Semin Arthritis Rheum.* **37**, 164–73 (2007).
- 1148 99. Mease PJ. Biologic Therapy for Psoriatic Arthritis. *Rheum Dis Clin North Am* **41**, 723–38  
1149 (2015).
- 1150 100. Ceponis A, K. A. Use of methotrexate in patients with psoriatic arthritis. *Clin Exp*  
1151 *Rheumatol.* **28(5 Suppl)**, S132-7 (2010).
- 1152 101. Mease PJ. Spondyloarthritis: Is methotrexate effective in psoriatic arthritis? *Nat. Rev.*  
1153 *Rheumatol.* **8**, 251–2 (2012).

- 1154 102. Kingsley GH, Kowalczyk A, Taylor H, et al. A randomized placebo-controlled trial of  
1155 methotrexate in psoriatic arthritis. *Rheumatol.* **51**, 1368–77 (2012).
- 1156 103. Mease, P. J. et al. Etanercept and Methotrexate as Monotherapy or in Combination for  
1157 Psoriatic Arthritis: Primary Results From a Randomized, Controlled Phase III Trial. *Arthritis*  
1158 *Rheumatol.* **71**, 1112–1124 (2019).
- 1159 104. Clegg, D. O. et al. Comparison of sulfasalazine and placebo in the treatment of psoriatic  
1160 arthritis. A Department of Veterans Affairs Cooperative Study. *Arthritis Rheum* **39**, 2013–  
1161 20 (1996).
- 1162 105. Kaltwasser JP, Nash P, Gladman D, et al. Efficacy and safety of leflunomide in the  
1163 treatment of psoriatic arthritis and psoriasis: a multinational, double-blind, randomized,  
1164 placebo-controlled clinical trial. *Arthritis Rheum* **50**, 1939–50 (2004).
- 1165 106. Mease, P. J. & Armstrong, A. W. Managing patients with psoriatic disease: The diagnosis  
1166 and pharmacologic treatment of psoriatic arthritis in patients with psoriasis. *Drugs* **74**,  
1167 423–441 (2014).
- 1168 107. Mease PJ, Goffe BS, Metz J, et al. Etanercept in the treatment of psoriatic arthritis and  
1169 psoriasis: a randomised trial. *Lancet* **356**, 985–90 (2000).
- 1170 108. Antoni CE, Kavanaugh A, Kirkham B, et al. Sustained benefits of infliximab therapy for  
1171 dermatologic and articular manifestations of psoriatic arthritis: results from the  
1172 infliximab multinational psoriatic arthritis controlled trial (IMPACT). *Arthritis Rheum* **52**,  
1173 1227–36 (2005).
- 1174 109. McInnes IB, Kavanaugh A, Gottlieb AB, et al. Efficacy and safety of ustekinumab in  
1175 patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-  
1176 blind, placebo-controlled PSUMMIT 1 trial. *Lancet* **382**, 780–9 (2013).
- 1177 110. Ritchlin C, Rahman P, Kavanaugh A, et al. Efficacy and safety of the anti-IL-12/23 p40  
1178 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite  
1179 conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month  
1180 and 1-year results of the phase 3, m. *Ann Rheum Dis* **73**, 990–9 (2014).
- 1181 111. Deodhar A, Gensler LS, Sieper J, et al. Three Multicenter, Randomized, Double-Blind,  
1182 Placebo-Controlled Studies Evaluating the Efficacy and Safety of Ustekinumab in Axial  
1183 Spondyloarthritis. *Arthritis Rheumatol. (Hoboken, N.J.)* **71**, 258–70 (2019).
- 1184 112. Kavanaugh A, Puig L, Gottlieb AB, et al. Efficacy and safety of ustekinumab in psoriatic  
1185 arthritis patients with peripheral arthritis and physician-reported spondylitis: post-hoc  
1186 analyses from two phase III, multicentre, double-blind, placebo-controlled studies  
1187 (PSUMMIT-1/PSUMMIT-2). *Ann Rheum Dis* **75**, 1984–8 (2016).
- 1188 113. Baraliakos, X. et al. Secukinumab in patients with psoriatic arthritis and axial  
1189 manifestations: Results from the double-blind, randomised, phase 3 MAXIMISE trial. *Ann.*  
1190 *Rheum. Dis.* **80**, 582–590 (2021).
- 1191 114. Mease, P. J. et al. A head-to-head comparison of the efficacy and safety of ixekizumab  
1192 and adalimumab in biological-naïve patients with active psoriatic arthritis: 24-week  
1193 results of a randomised, open-label, blinded-assessor trial. *Ann. Rheum. Dis.* **79**, 123–131  
1194 (2020).
- 1195 115. McInnes IB, Behrens F, Mease PJ, et al. Secukinumab versus adalimumab for treatment  
1196 of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-  
1197 controlled, phase 3b trial. *Lancet* **395**, 1496–505 (2020).

- 1198 116. Mease PJ, Genovese MC, Greenwald MW, et al. Brodalumab, an anti-IL17RA monoclonal  
1199 antibody, in psoriatic arthritis. *N Engl J Med* **370**, 2295–306 (2014).
- 1200 117. Mease PJ, Helliwell PS, Hjuler KF, et al. Brodalumab in psoriatic arthritis: results from the  
1201 randomised phase III AMVISION-1 and AMVISION-2 trials. *Ann Rheum Dis* **80**, 185–93  
1202 (2021).
- 1203 118. Ritchlin CT, Kavanaugh A, Merola JF, et al. Bimekizumab in patients with active psoriatic  
1204 arthritis: results from a 48-week, randomised, double-blind, placebo-controlled, dose-  
1205 ranging phase 2b trial. *Lancet* **395**, 427–40 (2020).
- 1206 119. Deodhar A, Helliwell PS, Boehncke WH, et al. Guselkumab in patients with active  
1207 psoriatic arthritis who were biologic-naive or had previously received TNFalpha inhibitor  
1208 treatment (DISCOVER-1): a double-blind, randomised, placebo-controlled phase 3 trial.  
1209 *Lancet* **395**, 1115–25 (2020).
- 1210 120. Mease PJ, Rahman P, Gottlieb AB, et al. Guselkumab in biologic-naive patients with  
1211 active psoriatic arthritis (DISCOVER-2): a double-blind, randomised, placebo-controlled  
1212 phase 3 trial. *Lancet* **395**, 1126–36 (2020).
- 1213 121. Mease PJ, Helliwell P, Gladman DD, et al. Efficacy of Guselkumab, a Monoclonal  
1214 Antibody that Specifically Binds the p19 Subunit of IL-23, on Axial Involvement in Patients  
1215 with Active PsA with Sacroiliitis: Post-hoc Analyses Through Week 52 from the Phase 3,  
1216 Randomized, Double-blind, Placebo-contr. *Lancet Rheumatol*.
- 1217 122. Mease, P. Ustekinumab Fails to Show Efficacy in a Phase III Axial Spondyloarthritis  
1218 Program: The Importance of Negative Results. *Arthritis Rheumatol. (Hoboken, N.J.)* **71**,  
1219 179–81 (2019).
- 1220 123. Mease P. Efficacy and safety of risankizumab, a selective il-23p19 inhibitor, in patients  
1221 with active psoriatic arthritis over 24 weeks: results from a phase 2 trial. *Ann Rheum Dis*  
1222 **77**, 200–1 (2018).
- 1223 124. Mease, P. J. et al. Efficacy and safety of tildrakizumab in patients with active psoriatic  
1224 arthritis : results of a randomised , week phase IIb study. 1–11 (2021)  
1225 doi:10.1136/annrheumdis-2020-219014.
- 1226 125. Mease PJ, Gottlieb AB, van der Heijde D, et al. Efficacy and safety of abatacept, a T-cell  
1227 modulator, in a randomised, double-blind, placebo-controlled, phase III study in psoriatic  
1228 arthritis. *Ann Rheum Dis* **76**, 1550–8 (2017).
- 1229 126. Kavanaugh A, Mease PJ, Gomez-Reino JJ, et al. Treatment of psoriatic arthritis in a phase  
1230 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4  
1231 inhibitor. *Ann Rheum Dis* **73**, 1020–6 (2014).
- 1232 127. Cutolo M, Myerson GE, Fleischmann RM, et al. A Phase III, Randomized, Controlled Trial  
1233 of Apremilast in Patients with Psoriatic Arthritis: Results of the PALACE 2 Trial. *J*  
1234 *Rheumatol* **43**, 1724–34 (2016).
- 1235 128. Edwards CJ, Blanco FJ, Crowley J, et al. Apremilast, an oral phosphodiesterase 4  
1236 inhibitor, in patients with psoriatic arthritis and current skin involvement: a phase III,  
1237 randomised, controlled trial (PALACE 3). *Ann Rheum Dis* **75**, 1065–73 (2016).
- 1238 129. Mease, P. et al. Tofacitinib or Adalimumab versus Placebo for Psoriatic Arthritis. *N. Engl.*  
1239 *J. Med.* **377**, 1537–1550 (2017).
- 1240 130. Gladman D, Rigby W, Azevedo VF, et al. Tofacitinib for Psoriatic Arthritis in Patients with  
1241 an Inadequate Response to TNF Inhibitors. *N Engl J Med* **377**, 1525–36 (2017).

- 1242 131. Mease P, Charles-Schoeman C, Cohen S, et al. Incidence of venous and arterial  
1243 thromboembolic events reported in the tofacitinib rheumatoid arthritis, psoriasis and  
1244 psoriatic arthritis development programmes and from real-world data. *Ann Rheum Dis*  
1245 **79**, 1400–13 (2020).
- 1246 132. Mease PJ, Lertratanakul A, Anderson JK, et al. Upadacitinib for psoriatic arthritis  
1247 refractory to biologics: SELECT-PsA 2. *Ann Rheum Dis* **10**, (2020).
- 1248 133. Mease P, Coates LC, Helliwell PS, et al. Efficacy and safety of filgotinib, a selective Janus  
1249 kinase 1 inhibitor, in patients with active psoriatic arthritis (EQUATOR): results from a  
1250 randomised, placebo-controlled, phase 2 trial. *Lancet* **392**, 2367–77 (2018).
- 1251 134. Papp K, Gordon K, Thaci D, et al. Phase 2 Trial of Selective Tyrosine Kinase 2 Inhibition in  
1252 Psoriasis. *N Engl J Med* **379**, 1313–21 (2018).
- 1253 135. Mease PJ, Deodhar A, van der Heidje D, et al. Efficacy and Safety of Deucravacitinib  
1254 (BMS-986165), an Oral, Selective Tyrosine Kinase 2 Inhibitor, in Patients with Active  
1255 Psoriatic Arthritis: Results from a Phase 2, Randomized, Double-Blind, Placebo-Controlled  
1256 Trial. *ACR Conver. Abstr. LB03*. (2020).
- 1257 136. Coates, L. C. et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis  
1258 2015 Treatment Recommendations for Psoriatic Arthritis. *Arthritis Rheumatol.*  
1259 *(Hoboken, N.J.)* **68**, 1060–1071 (2016).
- 1260 137. Gossec L, Baraliakos X, Kerschbaumer A, et al. EULAR recommendations for the  
1261 management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann*  
1262 *Rheum Dis* **79**, 700–12 (2020).
- 1263 138. Singh JA, Guyatt G, Ogdie A, et al. Special Article: 2018 American College of  
1264 Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic  
1265 Arthritis. *Arthritis Rheumatol. (Hoboken, N.J.)* **71**, 5–32 (2019).
- 1266 139. Husted, J. A., Gladman, D. D., Farewell, V. T. & Cook, R. J. Health-related quality of life of  
1267 patients with psoriatic arthritis: a comparison with patients with rheumatoid arthritis.  
1268 *Arthritis Rheum* **45**, (2001).
- 1269 140. Moverley, A. R., Vinall-Collier, K. A. & Helliwell, P. S. It's not just the joints, it's the whole  
1270 thing: qualitative analysis of patients' experience of flare in psoriatic arthritis.  
1271 *Rheumatology* **54**, 1448–1453 (2015).
- 1272 141. Gossec, L. et al. A patient-derived and patient-reported outcome measure for assessing  
1273 psoriatic arthritis: elaboration and preliminary validation of the psoriatic arthritis impact  
1274 of disease (PsAID) questionnaire, a 13-country EULAR initiative. *Ann Rheum Dis* **73**, 1012–  
1275 9 (2014).
- 1276 142. Tillett, W. et al. A multicentre nominal group study to rank outcomes important to  
1277 patients and their representation in existing composite outcome measures for psoriatic  
1278 arthritis. *J. Rheumatol.* **44**, 1445–52 (2017).
- 1279 143. Geijer, M. et al. Health-related quality of life in early psoriatic arthritis compared with  
1280 early rheumatoid arthritis and a general population. *Semin. Arthritis Rheum.* **51**, 246–252  
1281 (2021).
- 1282 144. Haroon, M., Gallagher, P. & FitzGerald, O. Diagnostic delay of more than 6 months  
1283 contributes to poor radiographic and functional outcome in psoriatic arthritis. *Ann*  
1284 *Rheum Dis* **74**, 1045–50 (2015).
- 1285 145. Orbai, A.-M. et al. International patient and physician consensus on a psoriatic arthritis

- 1286 core outcome set for clinical trials. *Ann. Rheum. Dis.* **76**, 673–680 (2017).
- 1287 146. Ware J. E., J. & Sherbourne, C. D. The MOS 36-item short-form health survey (SF-36). I.
- 1288 Conceptual framework and item selection. *Med Care* **30**, 473–483 (1992).
- 1289 147. Nord, E. EuroQol: health-related quality of life measurement. Valuations of health states
- 1290 by the general public in Norway. *Health Policy (New York)*. **18**, 25–36 (1991).
- 1291 148. McKenna, S. P. *et al.* Development of the PsAQoL: a quality of life instrument specific to
- 1292 psoriatic arthritis. *Ann Rheum Dis* **63**, 162–169 (2004).
- 1293 149. Holland, R. *et al.* Psoriatic Arthritis Impact of Disease (PsAID12) Was Provisionally
- 1294 Endorsed at Omeract 2018 As Core Instrument to Measure Psoriatic Arthritis-Specific
- 1295 Health-Related Quality of Life in Randomized Controlled Trials and Longitudinal
- 1296 Observational Studies. in *J Rheumatol* vol. 46 990–995 (WILEY 111 RIVER ST, HOBOKEN
- 1297 07030-5774, NJ USA, 2019).
- 1298 150. Coates, L. C. *et al.* Results of a global, patient-based survey assessing the impact of
- 1299 psoriatic arthritis discussed in the context of the Psoriatic Arthritis Impact of Disease
- 1300 (PsAID) questionnaire. *Health Qual. Life Outcomes* **18**, 173 (2020).
- 1301 151. Tillett, W. *et al.* Disease Characteristics and the Burden of Joint and Skin Involvement
- 1302 Amongst People With Psoriatic Arthritis: A Population Survey. *Rheumatol. Ther.* **7**, 617–
- 1303 637 (2020).
- 1304 152. Kavanaugh, A. *et al.* The contribution of joint and skin improvements to the health-
- 1305 related quality of life of patients with psoriatic arthritis: a post hoc analysis of two
- 1306 randomised controlled studies. *Ann. Rheum. Dis.* **78**, 1215–1219 (2019).
- 1307 153. McHugh N, Maguire Á, Handel I, Tillett W, Morris J, Hawkins N, Cavill C, Korendowych E,
- 1308 M. F. Evaluation of the Economic Burden of Psoriatic Arthritis and the Relationship
- 1309 Between Functional Status and Healthcare Costs. *J Rheumatol* **47**, 701–707 (2020).
- 1310 154. Thomsen SF, Skov L, Dodge R, Hedegaard MS, K. J. Socioeconomic Costs and Health
- 1311 Inequalities from Psoriasis: A Cohort Study. *Dermatology* **235**, 372–379 (2019).
- 1312 155. Husni, M. E., Merola, J. F. & Davin, S. The psychosocial burden of psoriatic arthritis.
- 1313 *Semin. Arthritis Rheum.* **47**, 351–360 (2017).
- 1314 156. Tillett, W. *et al.* Factors influencing work disability in psoriatic arthritis: first results from
- 1315 a large UK multicentre study. *Rheumatol.* **54**, 157–162 (2015).
- 1316 157. Tillett, W., de-Vries, C. & McHugh, N. J. Work disability in psoriatic arthritis: a systematic
- 1317 review. *Rheumatol.* **51**, 275–283 (2012).
- 1318 158. Tillett, W. *et al.* Effect of anti-TNF and conventional synthetic disease-modifying anti-
- 1319 rheumatic drug treatment on work disability and clinical outcome in a multicentre
- 1320 observational cohort study of psoriatic arthritis. *Rheumatol.* **56**, 603–612 (2017).
- 1321 159. Kristensen, L. E. *et al.* Societal costs and patients' experience of health inequities before
- 1322 and after diagnosis of psoriatic arthritis: a Danish cohort study. *Ann Rheum Dis* **76**, 1495–
- 1323 1501 (2017).
- 1324 160. Conaghan, P. G. *et al.* Relationship of pain and fatigue with health-related quality of life
- 1325 and work in patients with psoriatic arthritis on TNFi: results of a multi-national real-world
- 1326 study. *RMD Open* **6**, e001240 (2020).
- 1327 161. Walsh, J. A. *et al.* Work productivity loss and fatigue in psoriatic arthritis. *J Rheumatol* **41**,
- 1328 1670–1674 (2014).
- 1329 162. Tan, J. S. Q., Fong, W., Kwan, Y. H. & Leung, Y. Y. Prevalence and variables associated with

- 1330 fatigue in psoriatic arthritis: a cross-sectional study. *Rheumatol Int* **40**, 1825–1834 (2020).
- 1331 163. Zhao, S. S. *et al.* Systematic review of mental health comorbidities in psoriatic arthritis.
- 1332 *Clin. Rheumatol.* **39**, 217–225 (2020).
- 1333 164. Visalli, E., Crispino, N. & Foti, R. Multidisciplinary Management of Psoriatic Arthritis: The
- 1334 Benefits of a Comprehensive Approach. *Adv Ther* **36**, 806–816 (2019).
- 1335 165. Cobo-Ibanez, T. *et al.* Multidisciplinary dermatology-rheumatology management for
- 1336 patients with moderate-to-severe psoriasis and psoriatic arthritis: a systematic review.
- 1337 *Rheumatol Int* **36**, 221–229 (2016).
- 1338 166. Soare, A. *et al.* Cutting Edge: Homeostasis of Innate Lymphoid Cells Is Imbalanced in
- 1339 Psoriatic Arthritis. *J. Immunol.* **200**, 1249–1254 (2018).
- 1340 167. Kaeley, G. S., Bakewell, C. & D. The importance of ultrasound in identifying and
- 1341 differentiating patients with early inflammatory arthritis: a narrative review. *Arthritis*
- 1342 *Res. Ther.* **22**, 1–10 **22**, 1–10 (2020).
- 1343 168. Kampylafka, E. *et al.* Disease interception with interleukin-17 inhibition in high-risk
- 1344 psoriasis patients with subclinical joint inflammation - Data from the prospective IVEPSA
- 1345 study. *Arthritis Res. Ther.* **21**, 1–9 (2019).
- 1346 169. Feld, J. Is axial psoriatic arthritis distinct from ankylosing spondylitis with and without
- 1347 concomitant psoriasis? *Rheumatology* **59**, 1340–1346 (2019).
- 1348 170. Ritchlin, C. & Scher, J. U. Strategies to Improve Outcomes in Psoriatic Arthritis. *Curr*
- 1349 *Rheumatol Rep* **21**, 72 (2019).
- 1350 171. Moncada R, Barkley D, Wagner F, Chiodin M, Devlin JC, Baron M, Hajdu CH, Simeone DM,
- 1351 Y. I. Integrating microarray-based spatial transcriptomics and single-cell RNA-seq reveals
- 1352 tissue architecture in pancreatic ductal adenocarcinomas. *Nat. Biotechnol.* **38**, 333–342
- 1353 (2020).
- 1354 172. Mimitou EP, Cheng A, Montalbano A, Hao S, Stoeckius M, Legut M, Roush T, Herrera A,
- 1355 Papalex E, Ouyang Z, Satija R, Sanjana NE, Koralov SB, S. P. Multiplexed detection of
- 1356 proteins, transcriptomes, clonotypes and CRISPR perturbations in single cells. *Nat*
- 1357 *Methods* **16**, 409–412 (2019).
- 1358 173. Haberman, R. H., Castillo, R. & Scher, J. U. Induction of remission in biologic-naive, severe
- 1359 psoriasis and PsA with dual anti-cytokine combination. *Rheumatol.* (2020)
- 1360 doi:10.1093/rheumatology/keaa880.
- 1361 174. <https://clinicaltrials.gov/ct2/show/NCT03662542>. A Study of Efficacy and Safety of
- 1362 Combination Therapy With Guselkumab and Golimumab in Participants With Moderately
- 1363 to Severely Active Ulcerative Colitis (VEGA).
- 1364 175. Goldman M. The innovative medicines initiative: a European response to the innovation
- 1365 challenge. *Clin Pharmacol Ther* **91**, 418–425 (2012).
- 1366 176. Dolgin E. Massive NIH-industry project opens portals to target validation. *Nat Rev Drug*
- 1367 *Discov* (2019) doi:10.1038/d41573-019-00033-8.
- 1368
- 1369



