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**Article:**

Zabotti, A, De Marco, G [orcid.org/0000-0003-2406-161X](https://orcid.org/0000-0003-2406-161X), Gossec, L et al. (26 more authors) (2023) *EULAR points to consider for the definition of clinical and imaging features suspicious for progression from psoriasis to psoriatic arthritis*. *Annals of the Rheumatic Diseases*. ISSN 0003-4967

<https://doi.org/10.1136/ard-2023-224148>

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# **EULAR Points to consider for the definition of clinical and imaging features suspicious for progression from Psoriasis to Psoriatic Arthritis**

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## **Abstract**

### **Background.**

The transition from psoriasis (PsO) to psoriatic arthritis (PsA) and the early diagnosis of PsA is of considerable scientific and clinical interest for the prevention and interception of PsA.

### **Objective**

To formulate EULAR points to consider (PtC) for the development of data-driven guidance and consensus for clinical trials and clinical practice in the field of prevention or interception of PsA and for clinical management of people with PsO at risk for PsA development.

### **Methods**

A multidisciplinary EULAR task force of 30 members from 13 European countries was established, and the EULAR standardized operating procedures for development for PtC were followed. Two systematic literature reviews (SLRs) were conducted to support the task force in formulating the PtC. Furthermore, the task force proposed nomenclature for the stages before PsA, through a nominal group process to be used in clinical trials.

### **Results**

Nomenclature for the stages preceding PsA onset, 5 overarching principles and 10 PtC were formulated. Nomenclature was proposed for three stages towards PsA development, namely people with PsO at higher risk of PsA, subclinical PsA and clinical PsA. The latter stage was defined as PsO and associated synovitis and it could be used as an outcome measure for clinical trials evaluating the transition from PsO to PsA. The overarching principles address the nature of PsA at its onset and underline the importance of collaboration of rheumatologists and dermatologists for strategies for prevention/interception of PsA. The 10 PtC highlight arthralgia and imaging abnormalities as key elements of subclinical PsA that can be used as potential short-term predictors of PsA development and useful items to design clinical trials for PsA interception. Traditional risk factors for PsA development (i.e., psoriasis severity, obesity and nail involvement) may represent more long-term disease predictors and be less robust for short-term trials concerning the transition from PsO to PsA.

**Conclusion.** These PtC are helpful to define the clinical and imaging features of people with PsO suspicious to progress to PsA. This information will be helpful for identification of those who could benefit from a therapeutic intervention to attenuate, delay, or prevent PsA development.

## Key messages

What is already known on this topic

- Given that psoriasis typically predates PsA by a decade or more, then skin involvement offers the opportunity to investigate risk factors and predictors of PsA development and to study PsA pre-clinical phases.

What this study adds

- Three distinct stages were relevant to the prevention of PsA: A) people with PsO at higher risk of PsA; B) subclinical PsA; C) clinical PsA.
- The presence of psoriasis and clinical synovitis not explained by other diagnoses was considered as diagnostic for new onset PsA in the setting of clinical trials focusing on prevention and/or interception of PsA.
- Five overarching principles and ten points to consider were developed in order to cover the key areas for conducting clinical research in people with psoriasis at higher risk for PsA development.

How this study might affect research, practice or policy

- This study will facilitate research investigating the stages preceding clinical PsA and the opportunity to prevent PsA development by modifying lifestyle habits or using systemic treatment that could act both on the skin and the joint to prevent PsA development.

## Introduction

The clinical onset of inflammatory rheumatic musculoskeletal diseases, including rheumatoid arthritis (RA), is usually preceded by a preclinical phase encompassing immunological abnormalities, arthralgia and imaging abnormalities prior to formal diagnosis (1–4). The major advantage for healthcare professionals assessing the preclinical stage of RA is that many ‘at-risk’ individuals have well-defined autoantibodies that antedate symptoms. In addition, the formal recognition and diagnosis of early RA is well defined (5). Indeed, such is the state of advancement of the RA field that experience in clinical prevention trials has already been gathered, with several conducted or in progress (1). Psoriatic arthritis (PsA) affects up to a third of people with psoriasis (PsO) and, similarly to RA, there is emergent evidence on the occurrence of arthralgia and imaging abnormalities preceding the diagnosis of PsA (6–10). However, data in this space is limited with the field being controversial with a lack of established serological markers and a standardised working definition for early phase PsA for PsA prevention studies (11). A specific practical advantage of undertaking prevention trials for PsA, unlike RA, is that many patients would qualify for therapy aimed at controlling the existing cutaneous manifestations of their disease, thus avoiding both added costs and/or toxicity (12–16). The environmental, genetic, clinical, and immunological predictors for PsA development remain poorly understood, although such factors are crucial for standardised and cost-effective trials in PsA prevention. Recently, expert consensus emerged on strategies for setting up/conducting prevention trials in PsA, initially proposing the distinction of three clinically quiet stages preceding PsA onset (i.e., preclinical PsA, subclinical PsA and prodromal PsA) (10). Subsequently, a Delphi exercise evaluating evidence pertaining to people with PsO at increased risk for PsA identified factors such as synovio-entheseal imaging abnormalities as well as musculoskeletal complaints not explained by other diagnoses occurring in people with PsO (11). In contrast to RA, where revised classification criteria (ACR/EULAR 2010) allow for classification of patients with early disease (5), this is not the case for PsA which thus hampers definitions of the evolution to early PsA as an outcome measure for prevention trials. Therefore, an unmet need exists to further explore and characterize the transition of PsO to PsA. To this extent, EULAR convened a task force with the goal of providing data-driven guidance and consensus for use in trials aimed at the prevention/interception of PsA and at the management of PsO people at risk for PsA development.

## Methods

This study was conducted using the updated EULAR standardized operating procedures for developing points to consider (PtC)/recommendations (17). After approval from the EULAR Council (March 2021), the convenor (DMG) and the co-convenor (JSS) formed the Steering Committee (SC) and set up a task force, inviting members representing 13 European countries. The SC included the conveners, one methodologist (LG) and one co-methodologist (XB), two fellows (AZ, GDM), two rheumatologists (AI, DA) and one dermatologist (PG). The task force comprised the SC members plus 21 additional researchers, including 14 rheumatologists (with two Emerging EULAR Network representatives and 7/14 rheumatologists were also experts of imaging in the field of PsA), four dermatologists, two patient research partners and one non-MD healthcare professional.

Due to COVID-19 pandemic restrictions, the task force meetings took place via virtual online platforms, with the first meeting in June 2021 and four subsequent online meetings between April and June 2022. At the time of the first meeting, the task force discussed the background and agreed on three key objectives:

- i) To define the major features (i.e. musculoskeletal symptoms and imaging features) of individuals transitioning from PsO to PsA;
- ii) To characterize the phenotype of PsO people at risk for development of PsA;
- iii) To develop definitions of pre-clinical and *very early* PsA.

To address these objectives, the task force performed a systematic review of the literature (*see accompanying SLR*).

During the virtual meetings held in 2022, task force members appraised the evidence from the literature and then formulated the overarching principles (OAP), the PtC and the nomenclature for the stages preceding PsA onset, through a nominal group process. As per EULAR methodology, consensus was accepted in the first-round of discussion if  $\geq 75\%$  of the members voted in favor of a statement, and in the second-round if  $>$  two thirds voted in favour. Within one month of the end of the virtual meetings each member –online and anonymously- indicated their level of agreement (LoA) to each OAP or PtC statement using RedCap (LoA, 0–10 numeric rating scale ranging from 0 = ‘completely disagree’ to 10 = ‘completely agree’). The mean and standard deviation of the LoA, alongside the percentage

of members with an agreement  $\geq 8$ , are presented. The Level of Evidence (LoE) was defined based on the Oxford system (18).



## Results

The task force developed and agreed on 5 OAP and 10 PtC (*Table 1*). When formulating OAP, task force discussions focused on the involvement of dermatologists in at-risk population identification and recruitment, and the key role of rheumatologists in diagnosing PsA at early stage. Mirroring the scenario of early RA (1), the members agreed that three distinct stages were relevant to the prevention of PsA. Namely, people with PsO at higher risk of PsA; subclinical PsA; and finally, the clinical PsA. Informed by the SLR, the task force also proposed a definition of PsA as an outcome measure for clinical trials in PsA prevention.

### **Proposed Nomenclature for research trials in PsO Subjects at Risk of PsA**

#### ***People with PsO at higher risk of PsA***

Although at least 70% of PsO cases do not develop PsA (19,20), theoretically all PsO people remain at risk due to the incomplete understanding of the immunogenetic and other factors linked to disease evolution (*see accompanying SLR*) (10,11,20,21).

Among risk factors, some are associated with a short-term risk and others with a risk in the medium/long term (*Table 2*). Risk factors, including nail disease, obesity, and PsO severity, may be more associated with a risk of PsA in the medium/long-term period and these clinical features characterized the stage here defined as “people with PsO at higher risk of PsA”. These risk factors are less relevant for trials that enrich for subjects “at risk” of imminent PsA development, since their mere presence is not indicative of imminent PsA. The familial predisposition, mainly having a first-degree relative with PsA, can also be considered a risk factor for PsA development (22,23). Future studies on genetics (24) and prediction models for PsA development (25) may overcome the use of single risk factors and offer new clinical tools including different risk factors estimating the real risk of PsA development in PsO people.

Due to the paucity of evidence available, it is not possible at present to provide any clear definition of the timings pertaining to “short term” or “medium to long term” risk of PsA onset. Limited evidence suggests an approximate cut-off of two years to define “short term risk of PsA onset” (26).

### ***Subclinical PsA***

Joint symptomatology, mainly arthralgia, and imaging abnormalities or their combination were considered for the definition of subclinical PsA and these, particularly when combined, can be considered as short-term risk factors for PsA development. The term subclinical refers to the absence of clinical arthritis, not to the absence of clinical symptoms as such. Therefore, similarly to RA, the presence of arthralgia in PsO is considered a subclinical sign of PsA, as it has been shown to be associated with increased risk of subsequent development of clinical PsA (6,7,27). Further, and again akin to the pre-clinical phases of RA, arthralgia (not specifically defined) in PsO has been associated with increased imaging detected synovitis and enthesitis (7,27,28). In turn, these imaging features were linked to PsA development (*see accompanying SLR*) (7,27–29). Some task force members supported the view that arthralgia associated with imaging evidence of inflammation would be tantamount to the presence of actual PsA and would be inclined to treat such patients as PsA in the real-world setting.

However, isolated imaging abnormalities, that is, in absence of joint symptoms, were also associated with subsequent PsA development in some publications appraised by the task force (28,29). Yet, given the high prevalence of imaging abnormalities, in the range of 40-50% in completely asymptomatic PsO people, but even in the healthy population (8,30,31), it was considered that isolated imaging abnormalities can be considered a less strong predictor of imminent PsA development. Hence, the task force considered that the combination of arthralgia and imaging abnormalities were both part of the subclinical phase of PsA, representing a subset group at particularly high risk for PsA development in the short term (*see accompanying SLR*). Furthermore, the members considered that regression of arthralgia in people with PsO, coupled with resolution of subclinical joint inflammation, could be considered as a potential outcome measure for clinical trials representing surrogates for PsA interception.

### ***Clinical PsA***

For randomized controlled trials in PsA prevention, the development of clinical PsA or its prevention is an obvious outcome, so the task force suggested a definition for new onset PsA to be used within the context of clinical trials focused on PsA prevention. Such definition is not intended for the clinical diagnosis of new onset PsA in the standard real-world clinical

setting. The limited data available (*see accompanying SLR*) describing PsO people followed-up longitudinally and until the clinical development of PsA illustrated that the majority of subjects presented with clinical synovitis (i.e. the presence of swollen joints), with enthesitis, or axial disease being uncommon (6,7,32–34) in the early clinical stage. Therefore, the presence of PsO and clinical synovitis was considered the clinical hallmark of new onset PsA. Since dactylitis is associated with both synovitis and tenosynovitis and is a characteristic feature of PsA it can be included in the joint swelling that is linked to PsA presentation.

Hence the presence of PsO and clinical synovitis, including synovitis and swelling that accompanies dactylitis, not explained by other diagnoses was considered as diagnostic for new onset PsA.

The limited data suggested a mean low swollen joint count (ranged from 1.5 to 3.2) at diagnosis, which could be used as an outcome measure for the trials on prevention or interception of PsA (6,7,21,33,34). Furthermore, this could also provide a starting point for studies of therapy initiation in the earliest phases of PsA. It is important to underscore that the task force members recognized that the definition proposed may occasionally miss instances of purely enthesitic presentation of PsA, or that it would not capture isolated axial disease development/evolution. However, these recognizable clinical patterns of presentations are uncommon at this stage of the disease.

The task force acknowledged that synovitis, once diagnosed, could be transient, but for a trial for prevention new unexplained synovitis could represent an endpoint. The usual cut-off for chronicity in RA is 6 weeks of synovitis duration (5,35). Once other possible causes of synovitis in people with PsO are excluded, acute onset of arthritis (i.e. usually defined as a sudden onset of mono-oligoarthritis) should be considered as possible PsA. Indeed, after triggering infections or after an acute musculoskeletal injury PsA can present as an acute onset of mono- or oligoarthritis (15,36). This led the task force to not specify a minimum duration of synovitis and leave the differential diagnosis of a new onset synovitis to the clinical expertise of rheumatologists.

## **Overarching principles**

### **A. People with PsO may develop PsA at different time-points**

This principle emphasizes that arthritis usually develops in a setting of an established diagnosis of PsO, in approximately 70% of cases (19,37). Some individuals may develop PsO or have a diagnosis of PsO (particularly in the case of minimal skin involvement) at the time of, or subsequent to, PsA clinical onset.

When rheumatological manifestations antedate the onset of the cutaneous lesions, often in combination with family history of PsO, such patients tend to be diagnosed as PsA “sine psoriasis” (38). Furthermore, the task force members highlighted that, at the time of onset of PsA, arthritis severity may range from mild to severe disease, or it can change over time, and different therapeutic approaches may be needed.

**B. Close collaboration between dermatologists and rheumatologists is important to understand and optimize PsA prevention, interception and early diagnosis**

Since PsO precedes PsA in about 70% of cases and it represents an easily identifiable clinical biomarker on clinical examination there is a potentially identifiable at-risk pool of people that could benefit from prevention, interception of PsA and/or from an early diagnosis of PsA (12,39).

The task force agreed that prevention and interception are not interchangeable terms, since the former should be applied to PsO people with risk factors for PsA (e.g., severe skin involvement, nail involvement, obesity) but no features or symptoms of PsA, while the latter to subclinical PsA or new onset of PsA.

In this scenario, this OAP highlights the importance of close collaboration between dermatologists and rheumatologists, in clinical and research settings, aimed at improving knowledge of the transition from PsO to PsA and timely referral of new-onset PsA cases.

The early diagnosis of PsA is an important cornerstone in the management of PsA, since even a diagnostic delay as short as 6 months can lead to significantly more severe radiographic joint damage, worse physical function and decrease the chances of therapeutic success (40,41).

Therefore, developing the concept of transition from PsO to PsA, early PsA detection and management within the dermatology clinic should be prioritized, in order to improve the clinical outcomes of patients and facilitate early combined intervention in cooperation with rheumatologists (13). Furthermore, a substantial number of people with limited PsO (that is,

not requiring systemic therapy in dermatology settings) remain under the care of their primary care practitioners, suggesting the importance of involving general practitioners (GPs) in the diagnostic pathways for the early referral of PsO people affected by musculoskeletal symptoms.

### **C. The identification of risk factors for PsA development in people with PsO may influence therapy choices for PsO**

Research in the field of the transition from PsO to PsA is rapidly evolving, but we are still unable to precisely identify PsO people who ultimately develop PsA. The presence of defined risk factors for PsA development or the presence of subclinical arthritis could influence therapy for PsO in real world settings; for example, a higher risk for PsA may modify the PsO treatment choice towards a compound that has proven efficacy in skin PsO and PsA. This OAP is particularly relevant to real world dermatological practice where physician suspects the early stages of PsA but is keen to rapidly initiate therapy for PsO without further investigations.

### **D. Certain systemic treatments of PsO may reduce the risk of transition to PsA**

Preliminary evidence, albeit from retrospective cohorts, suggests that PsO without defined risk factors for PsA that are treated with biological agents had a significantly lower risk of PsA development compared with those treated with phototherapy (33), topical/no treatment (42) or no biological treatment (43). In contrast, *Meer et al* (44), using a retrospective electronic health record database, found a higher incidence of PsA among individuals treated with biologics for PsO than people on oral or phototherapy. However, the results of this last study appear inconsistent with clinical experience and may be biased by “confounding by indication” and “protopathic bias”(12). Longitudinal prospective studies are needed to establish the potential impact of therapies given for the skin or nail in attenuating, delaying or intercepting PsA. In this scenario of PsA prevention and interception, the task force members emphasized the importance of close collaboration between dermatologists and rheumatologists at the time of subclinical PsA stage, to facilitate the early recognition of

clinical PsA or to evaluate a potential musculoskeletal domain response in PsO people that started systemic therapy for the skin/nail domains.

#### **E. The rheumatologist has a key role in the diagnosis and management of PsA**

In its simplest and commonest form, PsA is clinically recognised by clinical synovitis occurring in an individual affected by PsO. Nevertheless, PsA may present –or clinically evolve- in heterogeneous ways, affecting other musculoskeletal domains, simultaneously or not. Moreover, mimics of PsA (e.g. osteoarthritis, fibromyalgia, gout) could complicate the diagnostic process (45–48). In the absence of serum biomarkers, the diagnosis of PsA ultimately relies on the rheumatologists' clinical expertise that might entail a combination of clinical and imaging findings (*see accompanying SLR*).

#### **Points to Consider**

***PtC 1: Arthralgia in people with PsO should be considered as a risk factor for PsA development, taking into account alternative diagnoses such as osteoarthritis and fibromyalgia.***

Arthralgia of otherwise unexplained origin should be considered the hallmark symptom preceding the onset of clinical PsA, and a risk factor for development of PsA in the short term (6,7,27). The incidence rate of PsA development in PsO people with arthralgia is significantly higher compared to PsO without such symptom, ranging from 10.9 (6) to 34.3 (19) per 100 patient-years (26). However, any precise definition of arthralgia specifically predictive of progression to PsA is still lacking. The characterization of arthralgia in terms of type of pain (e.g., non-specific musculoskeletal pain vs inflammatory pain), sites involved (e.g., Achilles tendon) and duration of symptoms will certainly be a matter of future studies focussing on the field of transition from PsO to PsA.

Fibromyalgia and osteoarthritis are relevant PsA-mimickers, particularly at the early stages of PsA, when signs of articular inflammation less easily detectable by clinicians (45,47).

***PtC 2: In people with PsO, joint and enthesal pain and functional limitation should be enquired about regularly and, if present, referral to a rheumatologist should be considered.***

This is the only PtC for which task force members needed a second round of voting. The members agreed that these three key clinical elements (i.e., joint and enthesal pain and functional limitation) summarize the clinical musculoskeletal symptoms before PsA onset in PsO people, nevertheless the evidence from SLRs was limited (*see accompanying SLR*).

In prospective studies, PsO people who later developed PsA had significantly higher baseline pain scores (6,7,27), HAQ, and joint tenderness (7,27). *Eder et al.*(6) reported that arthralgia affecting women, morning joint and spine stiffness, fatigue, and impaired physical function were associated with the development of PsA in PsO. The authors also observed that the intensity and number of musculoskeletal symptoms increased in the period prior to the diagnosis of PsA.

Furthermore, *Green et al.* (49) reported that over one-fifth of the PsO subjects who went on to develop PsA consulted their GPs with musculoskeletal-related symptoms during the 5 years prior to their diagnosis of PsA. This proportion gradually increased and reached over 57% in the 6 months immediately preceding the diagnosis of PsA. In this scenario, task force members felt it was appropriate to underline the important role of dermatologists, GPs and PsO people themselves in monitoring the onset, severity and evolution of musculoskeletal symptoms – in particular joint and enthesal pain, especially if associated with functional limitation – in order to facilitate early referral to rheumatology.

***PtC 3: Imaging (including ultrasound and MRI) in people with PsO could be used to help identify those at risk of PsA; in particular to detect synovio-enthesal involvement/abnormality***

Imaging may be more sensitive than clinical examination for the detection of musculoskeletal inflammation (30). Up to 40% of PsO people, even if not affected by joint pain, show subclinical synovio-enthesal inflammation on imaging (31,50). The role of subclinical inflammation detected by imaging as a predictor of later PsA development is a matter of ongoing research, mainly investigating peripheral involvement. Notably, the lack of bespoke studies in axial disease represents an unmet research need (51). Imaging-determined subclinical enthesal involvement seems to be a promising predictive tool, however,

contradictory results are reported for subclinical synovitis and tenosynovitis (*see accompanying SLR*).

Subclinical enthesitis detected by ultrasonography and structural enthesal lesions detected by high-resolution peripheral quantitative computed tomography (HR-pQCT) seem to be a predictor of PsA development in a few recently published studies (7,28,29). Overall, the evidence for the use of imaging to predict PsA development is limited, and further studies are needed to identify the best imaging predictors and potential “sentinel sites” where imaging should better be performed. The task force concluded that this PtC should be applied only to research settings and not to the clinical management of PsO people.

***PtC 4. Imaging abnormalities in the absence of musculoskeletal symptoms should be considered carefully in order to avoid the risk of inappropriate treatment.***

The detection of subclinical synovio-enthesal inflammation (8,31,50) in PsO people is a common finding, even in patients without musculoskeletal complaints. The task force felt it was appropriate to underline that the identification, co-incidental or in a research setting, of subclinical musculoskeletal inflammation and/or damage needs to be interpreted carefully within the specific clinical context. Clinical examination and the symptoms reported by patients remain the cornerstones of PsA diagnosis and imaging remains an aid to the clinical diagnosis. Recently, IL-12/IL-23 inhibition for skin involvement demonstrated suppression of subclinical enthesopathy in PsO people without clinical arthritis (14). This study lays the foundation for further research studies on PsA interception and supports the hypothesis that inducing regression of subclinical enthesopathy with biological agents prescribed for skin involvement, but also efficacious in joint disease, could modify the expression of subclinical enthesopathy that may be a very early feature of PsA (14,16,52). Subclinical findings detected by imaging can be present in the subclinical PsA phase but there is no evidence that this should favor specific therapeutic choices in the management of PsO people without musculoskeletal symptoms or be sufficient for the diagnosis of PsA.

***PtC 5. The combination of musculoskeletal symptoms and imaging abnormalities in people with PsO without a diagnosis of PsA should be considered as an entry criterion for clinical trials to prevent the transition to PsA.***



The combination of musculoskeletal symptoms and imaging abnormalities emerged as predictor of PsA development in PsO people (27,28). Among musculoskeletal symptoms, arthralgia was the symptom most frequently reported in the literature and most often associated with later PsA development (7,27). As for the discussion in PtC 1, the clear identification of musculoskeletal features and imaging findings preceding PsA development are key topics for a research agenda. The combination of clinical symptoms and subclinical imaging abnormalities could improve the characterization of the subclinical PsA phase, allowing the identification of homogeneous cohorts of PsO people at very high risk for PsA transition that could facilitate trials of PsA interception. To summarise, whilst subclinical PsA was defined as either arthralgia or imaging abnormalities, it was felt that the combination of these was most suitable for PsA prevention trials.

***PtC 6. In the context of clinical trials, people with PsO and clinically evident synovitis should be considered to have PsA, when alternative diagnoses are excluded.***

The prevention, or interception, of PsA development in PsO people and the early recognition of PsA development are key topics in the research agenda (53). When investigating subclinical and newly diagnosed PsA, an attempt to define the clinical aspect of new onset PsA is crucial, since it is one of the outcomes of interest in clinical trials for prevention or interception of PsA development. The absence of serum biomarkers and the limited value of C-reactive protein (CRP) make the clinical examination as the cornerstone for the identification of new onset PsA. The SLR performed as part of this EULAR activity provided evidence that peripheral arthritis, mainly in form of oligoarthritis (*see accompanying SLR*), is the main pattern of presentation in individuals with new-onset PsA. Such findings led to the choice of the clinical evidence of synovitis, not explained by other possible diagnoses like gout, osteoarthritis, as the most likely specific clinical sign of new-onset PsA. In the literature, isolated enthesitis or isolated axial symptoms are uncommon patterns of PsA onset (7,21,33,34) and are currently difficult to clearly define, even with current advanced imaging methods. Accordingly, emphasis on clinical joint swelling, which is a simple and robust measure of articular inflammation, was agreed on.

**PtC 7. In PsO people that require systemic treatment, the risk of transition to PsA should be taken into account in the choice of treatment.**

The severity of psoriasis involvement is one of the main risk factors for PsA development in PsO people (10,11,26,54) and recently three retrospective studies (33,42,43) reported that systemic treatment, mainly biologics, prescribed to ameliorate skin severity of PsO, may reduce the occurrence of PsA in PsO people. On the contrary, *Meer et al.* (44) reported that use of biologic agents in PsO was actually associated with subsequent PsA development and not prevention. Recently, in a retrospective cohort of PsO patients, *Singla et al.* (55) identified that treatment with IL-23 inhibitors was associated with reduced risk of progression to PsA compared to TNF inhibitors. In the transition from PsO to PsA, retrospective studies should be considered as hypotheses-generating. The existing findings need to be validated in prospective randomized controlled trials (56). In the absence of definitive data on the role of systemic treatment for PsO in prevention, mitigation or delay of PsA onset, the task force members agreed that in PsO people requiring systemic treatment for their skin or nail involvement, the presence of risk factors for PsA development should favor the use of treatment that could ameliorate both skin and joint manifestations, particularly in the case of subclinical PsA.

**PtC 8. People with PsO with obesity, nail disease and/or extensive psoriasis should be considered at increased risk for PsA development over the longer term.**

The risk factors for PsA development could be categorized into those linked to subclinical PsA (i.e. imaging and arthralgia) and those usually not necessarily linked to subclinical PsA (i.e., nail involvement, high Psoriasis Area Severity Index (PASI) score, obesity) (Figure 1). As expected, the former predict increased PsA development in the short-term period (usually within two years), while the latter are considered traditional risk factors for PsA development in PsO people in the long-term, i.e. with an average time between the onset of PsO and arthritis of 8-12 years (57). Task force members agreed that among traditional risk factors for PsA development obesity, nail involvement and extensive psoriasis are those with the strongest evidence and PsO people with at least one of these factors should be considered at higher risk.

**PtC 9. People with PsO should be informed about the risk of developing PsA and prompted to report their symptoms to facilitate early PsA recognition**

The lifetime risk of PsA development in PsO people is up to 30% and the chance of achieving remission of PsA symptoms appears to have a significant negative association with a diagnostic delay of > 1 year, and a significant positive association with an early rheumatologist referral of < 6 months (40,41). People with PsO should be informed by dermatologists and primary care practitioners about this risk and about the importance of an early referral to rheumatologists when musculoskeletal symptoms develop. The education of PsO people regarding their risk of PsA and symptoms and signs suspicious for PsA is a cornerstone for early PsA diagnosis.

**PtC 10.—In people with PsO, risk factors for PsA development should be regularly assessed over time**

Recognizing and assessing risk factors can favour PsA prevention, since a modification of these may alter the progression from PsO to PsA or the severity of the PsA presentation. Recently, *Green et al.* reported on the association between reducing Body Mass Index (BMI) and reduction in the risk of developing PsA over a 10-year period (58). As discussed in the previous PtC, systemic treatment for nail involvement and severe PsO could reduce the risk of PsA development but there is no current clear evidence that a treat-to-remission strategy for PsO is superior to other strategies in reducing the risk of PsA development. Regarding short-term risk factors for PsA development, the onset of a musculoskeletal complaint should be assessed regularly (ideally every 6-12 months) in order to facilitate an early PsA diagnosis. Outside research studies, there is no evidence for the role of imaging to stratify the risk of PsA development among PsO people.

## Discussion

The EULAR task force evaluated PtC for the definition of clinical and imaging features suspicious for progression to PsA, proposed nomenclature for the stages before PsA onset and a definition for early PsA as an outcome measure to be used in clinical trials aimed at PsA prevention. Unlike RA prevention, data on the transition phase from PsO to PsA are scarce. The task force agreed that PsO people at higher risk for PsA should be defined for research purposes when predictors for PsA (e.g., nail involvement) are present; subclinical PsA when PsO people have arthralgia or imaging evidence of synovio-entheseal complex inflammation, or ideally both. Finally, clinical PsA is diagnosed when synovitis is present at the clinical examination. This proposed nomenclature reflects a temporal, albeit non-linear continuum of psoriatic disease: A) the “at higher risk” stage typically lasts on average 7-12 years before the PsA onset, B) the “subclinical stage”, including imaging features typically linked to more imminent progression to PsA (1-3 years) and C) the “clinical” stage defined by the presence of clinical synovitis in an individual with PsO that has been longitudinally evaluated for synovitis, which is tantamount to early PsA (Figure 1).

This nomenclature could be relevant for studies looking at PsA prevention or interception with two potential new outcomes in the field of transition: i) the regression of joint symptoms and imaging features in PsO people with subclinical PsA and ii) reduction of new clinical PsA cases. In RA, the identification of early (< 12 months) or very early (<3 months) disease is important, since this classification is linked to different chances of achieving remission(59–62). Starting a conventional disease modifying anti-rheumatic drug at early stages improves the rate of remission and drug-free remission. Preliminary data seem to confirm this point also in PsA (40,41). The definition of early PsA is recognized by the task force as an important unmet need both for research studies and clinical practice but the definition of this term was considered beyond this Task Force’s remit.

The five OAPs and ten PtC set out a broad framework, covering the key areas for conducting clinical research in PsO people at higher risk for PsA development and with subclinical PsA. This task force emphasizes the essential role of collaboration between rheumatologists and dermatologists to achieve the goals of prevention and early diagnosis of PsA. Furthermore, these points to consider provide to the dermatological community important insights that

could inform clinical practice. The importance of regularly assessing risk factors, including musculoskeletal complaints or functional limitation, are key points for early PsA diagnosis, as well as the need to inform PsO people about their risk of developing PsA, highlighting the importance of promptly reporting musculoskeletal symptoms.

The main limitation of these results lays in the limited evidence from prospective studies in the field of transition from PsO to PsA. This is not surprising, since the incidence rate of PsA development in PsO people ranges from 0.3 to 3 events per 100 patient-years (26,37,54,63,64). Therefore, prospective studies with many patients followed with a long follow-up (i.e., > 5 years) in unselected cases would be required. In the future, prospective studies (56) will be necessary to refine and update of these EULAR Points to Consider and the comprehensive involvement of other specialists (e.g. dermatologists, radiologists, dieticians) will require to produce new strategy of prevention and interception of PsA.

In conclusion, these PtC will facilitate research investigating the stages preceding clinical PsA and the opportunity to prevent PsA development by modifying lifestyle habits or using systemic treatment that could act both on the skin and the joint to prevent PsA development. These findings set the scene for both PsA as an outcome in prevention studies and the regression of arthralgia and imaging abnormalities as bespoke strategy relevant to PsA cases, many of whom require chronic therapy for cutaneous PsO.

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| <b>2022 EULAR Points to consider for the definition of clinical and imaging features suspicious for progression to Psoriatic Arthritis</b>                                                                               |                  |                          |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|--------------------------|
| <b>Overarching Principle</b>                                                                                                                                                                                             | LoE <sup>ψ</sup> | LoA <sup>*</sup>         |
| A. People with PsO may develop PsA at different time-points.                                                                                                                                                             | n.a.             | 9.7 (± 0.7)<br>95.8% > 8 |
| B. Close collaboration between dermatologists and rheumatologists is important to understand and optimize PsA prevention, interception and early diagnosis.                                                              | n.a.             | 9.7 (± 0.6)<br>91.6% > 8 |
| C. The identification of risk factors for PsA development in people with PsO may influence therapy choices for PsO.                                                                                                      | n.a.             | 8.9 (± 1.3)<br>75.0% > 8 |
| D. The rheumatologist has a key role in the diagnosis and management of PsA.                                                                                                                                             | n.a.             | 9.7 (± 0.6)<br>91.6% > 8 |
| E. Certain systemic treatments of PsO may reduce the risk of transition to PsA.                                                                                                                                          | n.a.             | 8.4 (± 1.8)<br>56.0% > 8 |
| <b>Specific Points to Consider</b>                                                                                                                                                                                       |                  |                          |
| 1. Arthralgia in people with PsO should be considered as a risk factor for PsA development, taking into account alternative diagnoses such as osteoarthritis and fibromyalgia.                                           | 3a               | 9.2 (± 1.3)<br>75.0% > 8 |
| 2. In people with PsO, joint and enthesal pain and functional limitation should be enquired about regularly and, if present, referral to a rheumatologist should be considered                                           | 3b               | 9.3 (± 0.9)<br>83.3% > 8 |
| 3. Imaging (including ultrasound and MRI) in people with PsO could be used to help identify those at risk for PsA; in particular to detect synovio-enthesal involvement/abnormalities                                    | 3b               | 9.1 (± 1.2)<br>75.0% > 8 |
| 4. Imaging abnormalities in the absence of musculoskeletal symptoms should be considered carefully in order to avoid the risk of inappropriate treatment <sup>†</sup>                                                    | 3b               | 9.5 (± 0.9)<br>83.3% > 8 |
| 5. The combination of musculoskeletal symptoms and imaging abnormalities in people with PsO, without a diagnosis of PsA, should be considered as an entry criterion for clinical trials to prevent the transition to PsA | 5                | 8.8 (± 1.2)<br>58.3% > 8 |
| 6. In the context of clinical trials, people with PsO and clinically evident synovitis should be considered to have PsA, when alternative diagnoses have been excluded                                                   | 5                | 9.3 (± 0.8)<br>83.3% > 8 |
| 7. In PsO people that require systemic treatment, the risk of transition to PsA should be taken into account in the choice of treatment                                                                                  | 5                | 9.1 (± 1.3)<br>75.0% > 8 |
| 8. PsO people with obesity, nail disease and/or extensive psoriasis should be considered at increased risk for PsA development over the longer term                                                                      | 3a               | 9.3 (± 0.9)<br>83.3% > 8 |
| 9. People with PsO should be informed about the risk of developing PsA and prompted to report their symptoms to facilitate early PsA recognition                                                                         | 5                | 9.5 (± 0.8)<br>83.3% > 8 |
| 10. In people with PsO, risk factors for PsA development should be regularly assessed over time                                                                                                                          | 5                | 9.5 (± 0.8)<br>87.5% > 8 |

**Table 1. Overarching principle and points to consider for the definition of clinical and imaging features suspicious for progression to Psoriatic Arthritis.** <sup>‡</sup> LoE: Level of Evidence. \* LoA: Level of Agreement. <sup>†</sup> In the event that physicians incidentally perform musculoskeletal imaging (e.g., ultrasound and MRI) in PsO people without joint symptoms and the imaging is abnormal, then this in itself is not an impetus to consider therapy as such abnormalities are not uncommon in healthy individuals and consequently also psoriasis (30,31,50). The task force agreed that musculoskeletal imaging should be performed in people with PsO without joint symptoms only in research setting and not in clinical practice.

| Risk Factors for PsA development |                                                                                     |
|----------------------------------|-------------------------------------------------------------------------------------|
| Medium to long term              | Short term                                                                          |
| <i>Nail Involvement</i>          | <i>Arthralgia</i>                                                                   |
| <i>Obesity</i>                   | <i>Subclinical imaging-determined disease (e.g., sonographic enthesial changes)</i> |
| <i>Psoriasis severity</i>        |                                                                                     |
| <i>Familial history of PsA *</i> |                                                                                     |

**Table 2. Risk Factors for PsA development.** \*"mainly having a first-degree relative with PsA" citing PtC 8.

**Figure 1. Proposed nomenclature for the transition from PsO to PsA for clinical trials of PsA Prevention.** A simple three stage scheme for progression from at risk of PsA to frank PsA. It is acknowledged that onset may be variable and could occur quickly in some subjects e.g., after trauma or following infection with a reactive arthritis type onset. Although arrows imply directionality and inevitable progression, it is acknowledged that some subjects may have spontaneous resolution of PsA and that subjects with arthralgia may regress and that strategies in at risk people e.g., weight loss in obesity may lead to reduction of risk. This scheme recognizes the importance of enthesitis in pathophysiology but for trials of interception suggest the use of synovitis development as an outcome measure since this was by far the commonest manifestation of early disease from the accompanying SLR. †Role of Immunogenetics awaits definition.

## **Funding**

Funded by EULAR grant QoC 002

## **Ethical approval information**

Not applicable

## **Contributors:**

All authors have contributed to this work and approved the final version.

## **Acknowledgements**

None

## **Data sharing statement**

Not applicable

## **Patient and Public Involvement**

two patient research partners were involved in the study

## **Competing interests**

*Alen Zabotti Speakers bureau: AbbVie, Novartis, Janssen, Lilly, UCB, Amgen, Paid instructor for: AbbVie, Novartis, UCB, All support for the present manuscript: EULAR fellowship; Gabriele De Marco EULAR fellowship; Laure Gossec Consultant of: AbbVie, Amgen, BMS, Celltrion, Galapagos, Janssen, Lilly, MSD, Novartis, Pfizer, Sandoz, UCB, Grant/research support from: Sandoz, UCB;*

*Xenofon Baraliakos Speakers bureau: Abbvie, BMS, MSD, Sandoz, Novartis, Pfizer, Galapagos, UCB, Lilly, Paid instructor for: Abbvie, BMS, MSD, Sandoz, Novartis, Pfizer, Galapagos, UCB, Lilly, Consultant of: Abbvie, BMS, MSD, Sandoz, Novartis, Pfizer, Galapagos, UCB, Lilly, Grant/research support from: Abbvie, MSD, Novartis;*

*Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid : Editorial Board Member of Annals of Rheumatic Diseases, ASAS President Daniel Aletaha received grants, speaker fees, or consultancy fees from Abbvie, Gilead, Galapagos, Eli Lilly, Janssen, Merck, Novartis, Pfizer, Sandoz, and Sanofi; Editorial Board Member of Annals of Rheumatic Diseases*

*Annamaria Iagnocco* Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events AbbVie, Alfa-sigma, BMS, Celgene, Celltrion, Eli-Lilly, Galapagos, Gilead, Janssen, MSD, Novartis, Pfizer, Sanofi Genzyme, SOBI Grant/research support from: Pfizer, Abbvie, Novartis; Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid: EULAR President, Member of the EULAR Board, Member of EULAR Advocacy Committee; *Paolo Gisondi*: Payment or honoraria for lectures, presentations, speakers bureaus, Manuscript writing or educational events Abbvie, Almirall, Amgen, UCB, Sanofi, Pfizer, Novartis, Eli Lilly, Janssen, Leo pharma; *Peter Balint* None; *Heidi Bertheussen*: None declared, *Wolf-Henning Boehncke* Speakers bureau: Abbvie, Almirall, BMS, Janssen, Leo, Lilly, Novartis, and UCB, Consultant of: Abbvie, Almirall, BMS, Janssen, Leo, Lilly, Novartis, and UCB, *Nemanja Damjanov*: None declared, *Maarten de Wit*: Payment or honoraria for lectures, presentations, speakers bureaus, Manuscript writing or educational events: UCB;

*Enzo Errichetti* Consultant of: AbbVie, Janssen, Novartis, Amgen, *Helena Marzo-Ortega* Speakers bureau: AbbVie, Biogen, Eli Lilly, Janssen, Moonlake, Novartis, Pfizer, Takeda and UCB Pharma., Consultant of: AbbVie, Biogen, Eli Lilly, Janssen, Moonlake, Novartis, Pfizer, Takeda and UCB Pharma., Grant/research support from: Janssen, Novartis and UCB, *Mikhail Protopopov*: Support for attending meetings and/or travel: Pfizer, Abbvie, UCB; *Luis Puig* Speakers bureau: Janssen, Lilly, Novartis, UCB, Consultant of: Abbvie, Almirall, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Janssen, Leo-Pharma, Lilly, Novartis, Pfizer, Sandoz, Sanofi, UCB, Grant/research support from: Abbvie, Almirall, Amgen, Boehringer Ingelheim, Leo-Pharma, Lilly, Novartis, Pfizer, Sanofi, UCB;

*Rubén Queiró Silva*: Grants or contracts from any entity: Novartis, Janssen, Pfizer; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events: Amgen, Janssen, Eli Lilly, Novartis, UCB, Pfizer.

, *Piero Ruscitti*: None declared, *Laura Savage* Speakers bureau: AbbVie, Almirall, Amgen, Aspire Pharma, Biogen, Boehringer-Ingelheim, Bristol-Myers-Squibb, Celgene, Celltrion, Fresenius Kabi, Galderma, Janssen, Leo, Lilly, Novartis, Pfizer, MSD, Sanofi, Takeda, UCB, Consultant of: AbbVie, Boehringer-Ingelheim, Bristol-Myers-Squibb, Fresenius Kabi, Janssen, Lilly, Novartis, UCB, Grant/research support from: Janssen, Pfizer; *Georg Schett*: None declared, *Stefan Siebert* Speakers bureau: AbbVie, GSK, Janssen, UCB, Consultant of: AbbVie, Amgen, Eli Lilly,

*Janssen, UCB, Grant/research support from: Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, GSK, Janssen and UCB, Tanja Stamm Speakers bureau: AbbVie, Roche, Sanofi, Takeda and Novartis, Grant/research support from: AbbVie and Roche, Paul Studenic Speakers bureau: Astra Zeneca, Ilaria Tinazzi Speakers bureau: Janssen, Pfizer, Filip van den Bosch: None declared, Annette van der Helm – van Mil: None declared, Abdulla Watad: Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events: Janssen Neopharm, Eli Lilly Novartis, AbbVie; Consulting fees: Novartis, AbbVie, Janssen; Josef S. Smolen: Josef S. Smolen: Consulting fees: Abbvie, Galapagos/Gilead, Novartis-Sandoz, BMS, Samsung Sanofi, Chugai R-Pharma, Lilly; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events: Samsung, Lilly, R-Pharma, Chugai, MSD, Janssen Novartis-Sandoz; Editor in Chief of Annals of Rheumatic Diseases Dennis McGonagle Speakers bureau: AbbVie, Celgene, Janssen, Merck, Novartis, Pfizer, UCB, Consultant of: AbbVie, Celgene, Janssen, Merck, Novartis, Pfizer, UCB, Grant/research support from: AbbVie, Celgene, Janssen, Merck, Novartis, Pfizer*