Clinical Immunology 211 (2020) 108318

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Review Article

Emerging molecular biomarkers for predicting therapy response in psoriatic arthritis: A review of literature

Juliëtte Pouw[a,b,*], Emmerik Leijten[a,b], Timothy Radstake[a,b], Marianne Boes[b]

[a] Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, Heidelberglaan 100, 3584CX Utrecht, the Netherlands.
[b] Center for Translational Immunology, University Medical Center Utrecht, Lundlaan 6, 3584 EA Utrecht, the Netherlands.

A B S T R A C T

Psoriatic arthritis (PsA) is a heterogeneous, chronic inflammatory musculoskeletal disorder that affects ~0.1% of the population. PsA may severely impact quality-of-life and constitutes a significant economic burden on our health care system. While early effective treatment is deemed essential to prevent irreversible joint damage and functional impairment, not all patients respond to the same disease modifying anti-rheumatic drugs (DMARDs). DMARD options for PsA are rapidly evolving, yet only 50–60% of patients show a satisfactory response to their first-line DMARD therapy. Hence, there is an urgent medical need to predict which patients benefit from a particular treatment. To this end, molecular biomarkers capable of predicting therapeutic response are currently being scrutinized in clinical studies, that together should build a framework for clinical guidelines that improve personalized targeted treatment. In this review new developments within the field of biomarker discovery for predicting therapeutic response to DMARDs in PsA are examined.

1. Introduction

The identification of predictors of treatment response in psoriatic arthritis (PsA) is one of the candidate flagship research areas to "*permit personalized and stratified medicine approaches*", stated at the 2017 Collaborative Research Network Meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) [1]. This perspective from an international consortium of rheumatologists and dermatologists highlights the importance of identifying predictors to disease modifying anti-rheumatic drugs (DMARDs) before treatment initiation [2]. Furthermore, the European League Against Rheumatism (EULAR) - an organization representing European health care professionals, patients and scientific societies of rheumatology - addressed this matter in their 2015 research agenda [3].

PsA is a chronic inflammatory musculoskeletal disorder that affects ~0.1% of the global population [4]. It can severely impact quality of life and it contributes to a significant economic burden on our health care system [5,6]. Characterized by a heterogeneous disease presentation [7], PsA patients may suffer from diverse musculoskeletal and extra-articular manifestations including peripheral arthritis, axial spondyloarthritis, enthesitis, dactylitis, psoriasis and nail disease [5,8]. Therapies include non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular glucocorticoids and DMARDs [9], which have significantly improved quality-of-life of many patients [10]. The repertoire of DMARDs approved for PsA treatment consist of 15 options and is still expanding (see Table 1) [11,12]. Still, up to 40–50% of patients fail to show a partial or complete response [8,12]. This response deficit can have major implications. Firstly, early effective treatment is essential to prevent irreversible joint damage and functional impairment [7,13]. Secondly, DMARDs can be accompanied by serious adverse effects that should be avoided, particularly if there is no (expected) treatment benefit [14]. Lastly, the medications place tremendous strain on the healthcare system due to increasing costs [13]. All these factors underscore potential benefits of treating patients directly with the right drug of choice.

Thus far, no evidence-based strategies are available for rheumatologists that guide the decision as to which DMARD best suits the individual PsA patient [11]. The presence of certain disease phenotype or adverse prognostic factors – being polyarthritis, extra-articular manifestations, elevated acute phase reactants and radiographic damage – may somewhat guide clinicians in their therapeutic decision-making, as based on the international PsA management recommendations [9,13]. However, selection of a specific treatment based on an accurate prediction of the disease course is not possible [8], and it is unknown if and how the differential response to the available DMARDs could be predicted [8,9,13].

This calls for accurate predictors of a favorable drug response to identify patients who will benefit from particular DMARDs. The perfect predictor would be an objective, quantifiable, accurate and reproducible measurable indicator: a biomarker [15]. Biomarkers are an important clinical need to improve personalized medicine in care for patients with PsA [7,16–19]. Currently there is much progress in

* Corresponding author at: University Medical Center Utrecht, Room number KC02.084.2, P.O. Box 85500, 3508 GA Utrecht, the Netherlands.
E-mail addresses: J.N.Pouw-3@umcutrecht.nl (J. Pouw), M.L.Boes@umcutrecht.nl (M. Boes).

https://doi.org/10.1016/j.clim.2019.108318
Received 30 October 2019; Received in revised form 25 November 2019; Accepted 25 November 2019
Available online 27 November 2019

Table 1
DMARDs approved for treatment of psoriatic arthritis.

DMARD group	Generic name		Mechanism of action
Conventional synthetic	Methotrexate	MTX	Induce adenosine accumulation, alter pro-inflammatory cytokine production & modulate humoral / cellular immunity
	Cyclosporin	CSA	Reduces proliferation of activated T cells
	Leflunomide	LEF	Inhibits T cell activation and proliferation
	Sulfasalazine	SSZ	Inhibits NFκB, inhibits osteoclast formation & reduces secretion of pro-inflammatory cytokines
Biologic	Adalimumab	ADA	Anti-TNF-α monoclonal antibody
	Certolizumab pegol	CZP	Anti-TNF-α Fab fragment of monoclonal antibody
	Etanercept	ETN	Anti-TNF-α dimeric TNF receptor p75-IgG I fusion protein
	Golimumab	GOL	Anti-TNF-α monoclonal antibody
	Infliximab	IFX	Anti-TNF-α chimeric monoclonal antibody
	Ustekinumab	UST	Anti-IL-12 and − 23 monoclonal antibody to shared p40 subunit
	Ixekizumab	IXE	Anti-IL-17 monoclonal antibody
	Secukinumab	SEC	Anti-IL-17 monoclonal antibody
	Abatacept	ABT	Selectively inhibits T cell co-stimulation
Targeted synthetic	Tofacitinib	TOF	JAK1, −2 and 3 inhibitor
	Apremilast	APR	Intracellular PDE-4 inhibitor

Abbreviations: DMARD: disease modifying anti-rheumatic drug; IL: interleukin; JAK: janus kinase; NFκB: nuclear factor kappa B; PDE: phosphodiesterase; TNF: tumor necrosis factor;

biomarkers discovery on this topic, which we will summarize here [16–18,20,21]. Moreover, we will highlight their practical clinical use, review ongoing research, discuss future perspectives, and suggest recommendations for future research. Of note, the identification of biomarkers for other purposes, including diagnosis, disease onset and disease activity, are discussed elsewhere [5,17,21–23]. The scope of this review concerns predictive molecular biomarkers of drug response.

2. Methods

A literature search was conducted to identify articles discussing molecular biomarkers predictive of therapeutic response in PsA. PubMed and Embase were searched in September 2019 for combinations of synonyms, MeSH and Emtree terms for 'biomarkers' and 'psoriatic arthritis' (see Appendix Table A-C). In total 1119 articles were identified. Duplicates were removed and 849 articles were screened on title and abstract, based on pre-defined eligibility criteria (appendix Table D). Consequently, 74 selected articles were screened full-text on relevancy to include in the analysis. The search was supplemented by related citations in PubMed and reference citations of the identified articles in the initial search.

3. Results

3.1. Search

Nine studies identified molecular biomarkers that predict therapy response in PsA (see Fig. 1 and Table 2). All studies included patients using a tumor necrosis factor-α inhibitor (TNFi): adalimumab, certolizumab pegol, etanercept, golimumab and/or infliximab. Only one study included patients that were administered a non-TNFi [24]. The results are discussed below, subdivided by genetic, circulating and tissue biomarkers.

3.1.1. Genetic biomarkers

PsA is known to harbor a strong genetic inheritable component [25]. The risk ratio for first-degree relatives is up to 40, mainly explained by genetic variants within the human leukocyte antigen (HLA) region [22,25]. MicroRNAs, long non-coding RNAs, gene expression levels, human leukocyte antigen (HLA) variants and single nucleotide polymorphisms (SNPs) have been studied extensively in the search for biomarkers associated with the onset of PsA, its severity and its comorbidities [22]. Considering predicting therapeutic response, two polymorphisms (s6920220 and rs610604 (TNFAIP3)) were associated with improved quality-of-life at 3 and 6 months after initiation of TNFi based on the European Quality Of Life (EQ) – Visual Analogue Scale (VAS) [26]. However, no associations with other outcomes were observed (Psoriasis Area and Severity Index (PASI) and Numeric Rating Scale (NRS) for pain).

3.1.2. Circulating biomarkers

Throughout the years several potential circulating biomarkers have been studied, using peripheral blood measurements [18]. Examples include acute phase reactants like C-reactive protein (CRP), auto-antibodies, cytokines and peripheral blood mononuclear cell subsets. Already by 2007, CRP was suggested as a biomarker predictive of treatment response in refractory PsA [27]. Elevated baseline levels of CRP were associated with good therapeutic response to infliximab with multivariate regression analysis. Response was defined using the American College of Rheumatology (ACR)50 response criterion. CRP is a mediator of the innate immune mechanism of complement activation, and considering that high CRP levels associates with disease progression, CRP levels are widely used to monitor infection, inflammation, chronic disease and tissue injuries [28].

Lowered baseline levels of the complement component C3 was found to associate with response to adalimumab and etanercept after 22 weeks of treatment [29], based on the EULAR response criteria [30]. C3 is part of the complement cascade of the innate immune system and disturbances in complement activation might contribute to tissue damage [31]. However, in this study, no significant associations were found with CRP, erythrocyte sedimentation rate or other (activation-induced) complement cleavage products and therapy response.

As potential biomarkers for joint destruction and inflammation, increased baseline levels of matrix metalloproteinase (MMP)-3 were found to associate with response to TNFi therapy defined as PASI < 4, tender joint count (TJC) < 3 and swollen joint count (SJC) < 1 [32]. No associations were found for TNF superfamily member 14, receptor activator of NFκB ligand, osteoprotegerin, cartilage oligomeric matrix protein, c-propeptide of type II collagen, type II collagen neoepitopes Col2–3/4$C_{long\ mono}$ and C1−2C, aggrecan 846 epitope or CRP. MMP-3 is implicated in cartilage destruction in rheumatic inflammatory diseases [33], and has shown to be predictive of structural progression in ankylosing spondylitis [34].

Two protein panels predictive of response to the TNFi golimumab have been published [35]. Both panels revealed adiponectin, which is known to reduce inflammation in various cell types [36], and factor VII, a blood coagulation factor and antibacterial zymogen [37], as being predictive for response rate. Response was based upon the ACR20 response criterion and Disease Activity Score (DAS)28 for the first and second panel, respectively.

Finally, low-molecular mass hyaluronan (LMHA) was found predictive: normal serum levels are associated with better response to

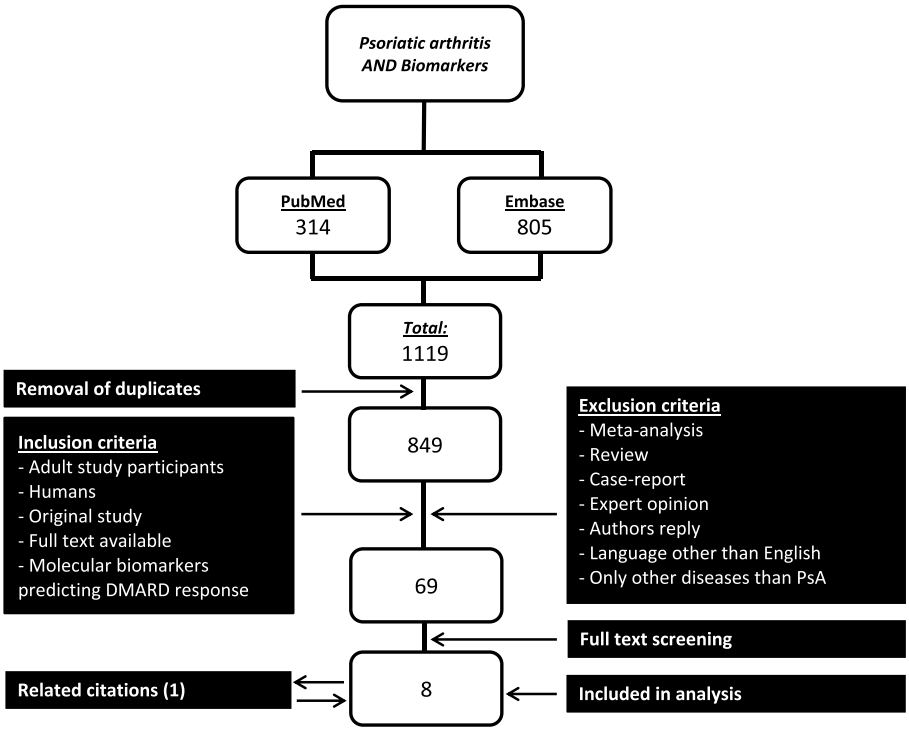

Fig. 1. Flowchart.
Legend: The search yielded 314 articles in PubMed and 805 in Embase. After removal of duplicates 849 articles remained for screening on title and abstract. 69 Articles were screened full-text for relevancy, of which 7 articles were included in the final analysis. One relevant articles was retrieved by assessing reference citations of the selected articles and related citations in PubMed.
Abbreviations: DMARD: disease modifying anti-rheumatic drug; PsA: psoriatic arthritis.

adalimumab [38]. Response was evaluated with ACR response criteria. LMHA is a polysaccharide present on the surface of epithelial cells and a known regulator of inflammation and tissue repair by recruiting immune cells and initiating secretion of cytokines [39]. For example, LMHA fragments can activate Toll Like Receptors [40].

3.1.3. Tissue biomarkers

Inflammation in PsA prototypically occurs at the site of both skin and joint. Some biomarker-finding research has therefore been focused on the discovery of tissue biomarkers in the synovium, the synovial lining of joints [41]. In a landmark study on synovial biomarkers in PsA, a panel of 57 proteins was shown to predict response to biologicals assessed by DAS28 [24]. Here, an unbiased high throughput approach was used to identify proteins with multiple reaction monitoring mass-spectrometry assays. This was the only study to also include a T cell inhibitor next to TNFi as therapy of interest. The most predictive protein was S100-A8, a known damage-associated molecular pattern and regulator of inflammatory processes and immune response. [42] S100-A8 does so via stimulation of leukocyte recruitment and induction of cytokine secretion [43]. Many of the other proteins of the panel are also known to be implicated in inflammation [24].

In another proteomics study using synovial tissue, two panels in two separate cohorts of 7 and 14 proteins were found predictive of TNFi response measured with ACR70, DAS28 and EULAR response criteria [44]. Proteins that changed in both cohorts were haptoglobin, actin, serum albumin, annexin A2, serum amyloid P, Collagen α3 and fibrinogen. These are involved in various pro- and anti-inflammatory processes [44]. However, not all the proteins overlapped and validation of these panels was not performed.

Of note, extensive research on synovial fluid in PsA has resulted in various new insights into the molecular basis of the disease, next to identification of both diagnostic as prognostic soluble biomarkers [45]. Yet our search revealed no studies on synovial fluid biomarkers predictive for therapy response. In addition, there have been no studies examining the skin of PsA patients as predictor of therapy response, whereas this is currently being explored for predicting PASI response in psoriasis patients [46,47].

4. Discussion

4.1. Challenges of implementation

Altogether the abovementioned studies provide experimental support for the predictive value of biomarkers for therapeutic response. However, none are currently implemented in routine practical clinical care [8,22,48,49]. Here we discuss possible explanations for the obstruction between biomarker discovery and the following steps of validation, clinical implementation and evaluation [50].

To find a predictor of therapy response, the definition of response should be unequivocal. However, in PsA this is not straightforward. Firstly because PsA - although now known as a clinical entity characterized by a distinct pathogenesis, phenotype and course - [7,16,51] has long been considered a relatively mild form of rheumatoid arthritis (RA) [7]. This led to initially copying outcome measures like DAS28 [7,30,51–53], which do not include PsA-specific manifestations [5,52]. This reduces the clinical applicability of some previously published work. Secondly, the heterogeneous disease manifestations of PsA make it difficult to define response [5,7,51,52]. For example, ACR response criteria are useful to assess peripheral arthritis. However, for disease activity of skin, dactylitis, axial spondyloarthritis and enthesitis other outcome measures are required. Since patients exhibit different disease phenotypes, treatment goals vary based upon their individual needs and complaints. It might thus be relevant to identify predictive biomarkers for specific clinical manifestations, next to pooling response to all disease manifestations as a whole.

Furthermore, the hypothesis that differences in immune pathogenesis underlie the heterogeneous disease manifestations [54], raises the question which tissue site should be studied for biomarker discovery: skin, synovium, synovial fluid or peripheral blood? For example, skin biomarkers may predict psoriasis remission, but not reduction in dactylitis or enthesitis. In this respect it is further important to acknowledge that even the same broad type of “tissue” (e.g. skin) shows site-specific differences in steady state across the human body [55,56]. The ideal biomarker is also practical and safe to obtain and this should be taken into account [24].

Finally, there are overarching challenges with respect to biomarker implementation in clinical practice [50]. Analysis methods used for

Table 2
Molecular biomarkers predictive of treatment response in psoriatic arthritis.

Article	Origin cohort	N	Previous treatment	Therapy (No. patients)	Assessment response (timing)	Material	Biomarker	Analysis	Statistics	Result
Ademowo (2014) *Ann Rheum Dis*	NL (discover) NL (confirm) IE (validate)	10 18 7	n/a n/a n/a	ADA (10) ADA (18) ABT (7)	DAS28-CRP ≤3.2 and improved > 1.2 (12 wk)	Synovium	107 proteins Panel 57 proteins Panel 57 proteins	MS MRM-MS assay MRM-MS assay	ANOVA (DEPs) Random forest Random forest	Panel of 57 proteins predictive of response (AUROC 0.76) (including: S100-A8, S100-A10, Ig κ chain C fibrinogen-α and -γ, haptoglobin, annexin A1 and A2, collagen α-2, vitronectin, α-1 acid glycoprotein)
Chandran (2013) *J Rheumatol*	CA	40	csDMARD NR	ADA (6), ETN (28), GOL (4), IFX (2) + csDMARD (26)	TJC < 3, SJC < 1, PASI < 4 (11 mo)	Serum	MMP-3	ELISA	Multivariate logistic regression	Higher MMP-3 (36.3 ± 23.8 vs 19.8 ± 6.6 ng/ml) associated with response (OR 1.07, $p = .045$)
Chimenti (2012) *Clin Exp Rheumatol*	IT	55	csDMARD NR or contra-indicated	ADA (28), ETN (27) +csDMARD (44)	EULAR response criteria [1] (22 wk)	Plasma	Complement C3	Nephelometry	Multivariate logistic regression	Lower C3 (116.1 ± 25.2 vs 135.5 ± 19.6 mg/dl) associated with response ($p = .011$)
Collins (2016) *Proteomics Clin Appl*	IE (pilot 1)	12	csDMARD NR or naïve	ETN (12)	ACR70 and good response EULAR criteria [1] (12 wk)	Synovium	7 proteins	MS	ANOVA (DEPs)	Single proteins associated with response: serum albumin, collagen α 3, annexin A1/2, Ig κ chain C, BTB/POZ domain-containing protein, tryptase
	NL (pilot 2)	10	csDMARD NR or naïve	ADA (10) +MTX (6)	DAS28-CRP ≤3.2 & improved > 1.2, and good response EULAR criteria [1] (12 wk)	Synovium	14 proteins	MS	ANOVA (DEPs)	Single proteins associated with response: annexin A1/2, serum albumin, haptoglobin, ApoA1, collagen α3, actin, ρ-GDP-dissociation inhibitor 2, α-1B-glycoprotein, 78 kDa glucose-related protein, replication protein A, PK-M1/2, HSP 70/71 kDa, vimentin, lamin-B2
Gratacós (2007) *Ann Rheum Dis*	ES	69	MTX NR or contra-indicated	IFX (69)	ACR50 (38 wk)	Serum	CRP	n/a	Multivariate logistic regression	Higher CRP (> 10 mg/L) associated with response (OR 18.7, 95% CI 1.8–181.6, p = .011)
Hellman (2019) *Scand J Rheumatol*	SE	18	TNFi-naïve	ADA (10)	ACR criteria (12 wk)	Serum	Hyaluronan	ELISA	Independent-samples Kruskal Wallis test	Hyaluronan serum levels within reference range (healthy controls 21.7 ± 11.4 ng/mL) associated with better response
Ovejero – Benito (2019) *J Eur Acad Derm Ven*	ES	20	n/a	TNFi (20)	EQ-VAS, NRS-pain50, PASI75 (3 and 6 mo)	Peripheral blood	rs6920220 rs610604	Genotyping	Multivariate logistic regression	SNPs rs6920220 and − 610,604 associated with improved quality of life at 3 (both) and 6 months (only rs610604) based upon EQ-VAS
Wagner (2013) *Ann Rheum Dis*	US	74	n/a	GOL (74) + csDMARD (26)	ACR20, good or moderate DAS28 response, PASI75 (14 wk)	Serum	2 panels consisting of 4 and 5 proteins	ELISA LUMINEX	Multivariate logistic regression	Two panels predictive: panel A (pyridinoline, adiponectin, PAP, factor VII) for ACR20 (specificity 65%, sensitivity 85%); and panel B (adiponectin, factor VII, SGOT, IgA, leptin) for DAS28 (specificity 71%, sensitivity 90%).

- Legend: [1] Van Gestel, A. M. et al. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Arthritis Rheum. 39, 34–40 (1996).
- Abbreviations: ACPA: Anti-Citrullinated Peptide Antibodies; ACR(x): (x% improvement of) ACR response criterion: American College of Rheumatology response criterion based on x% improvement of swollen and tender joints, quality of life questionnaires and three visual analogue scales scoring pain, patients and physicians global assessment of disease activity; ADA: adalimumab; ANOVA: analysis of variance; Apo: apolipoprotein; AUROC: area under the receiver operating characteristic curve; CI: confidence interval; CRP: c-reactive protein; csDMARD: conventional synthetic disease modifying anti-rheumatic drug (e.g. MTX, LEF, SSZ); DAS28: disease activity score, including joint count, visual analogue scale scoring patient's global assessment of disease activity, and acute phase reactants; DEP: differentially expressed protein; ELISA: enzyme-linked immunosorbent assay; EQ-VAS: European quality of life visual analog scale; ESR: erythrocyte sedimentation rate; ETN: etanercept; EULAR: European League Against Rheumatism; GOL: golimumab; GPA: patients global assessment of disease activity; HSP: heat shock protein; IFX: infliximab; IL: interleukin; MMP: matrix metalloproteinase; MRM: multiple reaction monitoring; MS: mass spectrometry; N: number of PsA patients included in the biomarker analysis; NR: non-responder to previous therapy; NRS-pain50: 50% improvement of numeric rating scale for pain; OPG: osteoprotegerin; OR: odds ratio; PASI(75): (75% improvement of) psoriasis area and severity index; PK: pyruvate kinase; PsA: psoriatic arthritis; RA: rheumatoid arthritis; SJC: swollen joint count; SNP: single nucleotide polymorphism; TJC: tender joint count; TNFi: tumor necrosis factor alpha inhibitor (ADA, CZP, ETN, GOL, IFZ); VAS: visual analogue scale.

discovery are frequently costly, technically difficult and labor-intensive [17,50]. Importantly, external validation is often lacking in studies that report on discovery of a new biomarker [50] and thus validation of candidate biomarkers has been difficult [18,57]. For example, a predictive value of CRP for TNFi responders [27] was validated by a single study [58], but not confirmed by three others [29,32,35]. Generally speaking, a biomarker for clinical use needs to demonstrate excellent sensitivity and specificity, thus a single biomarkers (e.g. protein) may lack the ability to singularly predict a certain outcome or definitive diagnosis [18,59].

Taking all these challenges into account, it might not be surprising that no biomarkers predictive of treatment response are implemented yet. It has becomes increasingly evident that it is a challenge to develop robust, reproducible, cheap and fast assays that are validated in representative PsA patient cohorts [60].

4.2. Emerging tools & approaches for biomarker research

In the past decade, advances in research have led to improved understanding of PsA etiology [8,22]. The current consensus is that the pathogenesis is multifactorial [8], and this awareness has resulted in expanding the field of biomarker discovery to include (*epi*)genetics, proteins, metabolites, microbioma and environmental factors [20]. In the few years technical advances have made it possible to extensively study all these 'multi-omics' with unbiased approaches, using various next-generation, high-throughput technologies [61]. For example in the field of epigenomics, multiple players in disease pathogenesis – including DNA methylation sites, histone modifications and microRNAs - were discovered with pan-genomic microarrays [62,63]. Also in other omics field – like proteomics, transcriptomics, exposomics, metabolomics and microbiomics - next-generation techniques are increasingly applied for biomarker discovery [18,44,45,63–66]. These evolving technologies result in large amounts of data, requiring computational modeling for advanced analyses and integration of multiple omics datasets to produce composite panels of biomarkers [18,64,67]. These advances may help drive future biomarker research, with a critical role for bioinformatics to analyze and integrate large omics datasets [16,68].

4.3. Future perspectives

Currently, biomarkers make up a notable part of the research agenda in rheumatology in the search for tools to improve personalized medicine [21]. Also within the PsA field researchers have made great strides. Recently, a trial was conducted that evaluated treatment efficacy of different drugs based on standard care versus strategically selected bDMARD choice, the latter guided by phenotypes of peripheral T helper cell characteristics [69]. They found significantly higher low disease activity after six months in the patients that received strategically selected drugs, showing the potential benefits of personalized medicine. Further trials to explore this concept are mandatory [70]. Furthermore, Table 3 highlights some promising research on the topic of biomarkers predictive of therapy response in PsA [58,71–75]. Our own group has initiated the TOFA-PREDICT study (EudraCT number 2017–003900-28), which is a multicenter randomized clinical trial in the Netherlands, integrating multiple data layers to predict treatment response to cs-, b- and tsDMARDs. Moreover, important data are expected from the OUTPASS study, a United Kingdom prospective observational cohort of 300 patients to investigate serological, clinical, genetic and psychological factors influencing PsA response to biologics (UKCRN number 13910) [76].

5. Recommendations

Research initiatives in the field of biomarker discovery towards prediction of PsA therapy response are ongoing, and the discovery and validation of these biomarkers is internationally considered an important and urgent clinical need and therefore a recurring topic on international research agendas [1,16]. Since no biomarkers have been implemented in clinical care, we formulate specific points of consideration to improve the clinical utility of future biomarker research results.

Firstly, it is important to include DMARDs other than only TNFi [3]. Data on biomarkers predictive of response to targeted synthetic DMARDs, IL-17 inhibitors and IL-12/23 inhibitors are lacking to date. Since these treatment options are currently recommended in international guidelines and increasingly selected by clinicians [9], research on predictive biomarkers for these therapies is warranted (Table 4).

Secondly, future research needs accurate and robust composite responder indices, that take into account the core domains of this heterogeneous disease. To answer to this need, the Outcome Measures in Rheumatology (OMERACT) group published in 2017 an updated core outcome set for research [77]. Since one scoring system might not be attainable for all patients [53], outcome measures should be carefully selected dependent on both the treatment goals, as well as the research goals.

Thirdly, it is critical for researchers to not only discover, but also confirm and validate their findings in independent external cohorts of patients, since false-positive biomarker leads are unfortunately quite common in large datasets [48]. Preferably, after validation the assays would be translated and adapted into non-invasive, affordable and technically simple assays.

Fourthly, it is plausible that single biomarker might not exceed the thresholds for accurate and robust prediction of clinical outcomes [18]. Rather, we recommend first computationally exploring a broad range of biomarkers (based on different -omics approaches) in large cohorts of PsA patients followed throughout time, before and after treatment. In doing so, it may be possible to develop panels of biomarkers that reflect changes in clinical manifestations and response (or lack thereof) to treatment [16,18].

This brings us to our last recommendation: the sharing of data. Considering that PsA is a relatively uncommon disease, the sharing of patient data - clinical characteristics, demographics, imaging and omics – would enable higher patient numbers to discover and validate new

Table 3
Promising research on molecular biomarkers predictive of treatment response in PsA.

Abstract	N	Drug	Definition response	Biomarker	Result
Conti Ceccarelli (2019) *Ann Rheum Dis*	17	APR	EULAR criteria	Treg	Higher proportion of Tregs within CD4+ T cell population associated with response
David (2019) *Rheumatology*	50	Biologics	EULAR criteria, DAS28	HLA-B27	No association of HLA-B27 with response
Mascia (2019) *J Psoriasis PsA*	70	TNFi	PsARC, ACR20	SNP TNF-α genomic region	Significant association of SNP-29 with response
Scrivo (2019) *Clin Exp Rheumatol*	151	GOL	MDA	hsCRP	Higher hsCRP predictive of response

Abbreviations: ACR response: American College of Rheumatology response criterion; APR: apremilast; DAS28: disease activity score; GOL: golimumab; HLA: human leukocyte antigen; hsCRP: high sensitive C-reactive protein; MDA: minimal disease activity score; PsA: psoriatic arthritis; PsARC: Psoriatic Arthritis Response Criteria; SNP: single nucleotide polymorphism; TNF: tumor necrosis factor; TNFi: tumor necrosis factor alpha inhibitor (ADA, CZP, ETN, GOL, IFZ); Treg: T regulatory cell.

Table 4
Recommendations for research on biomarkers predicting therapy response in PsA.

Difficulty	Recommendation
o Large repertoire of available DMARDs o Defining therapy response o High false-positive rates in biomarker discovery o Invasive procedure for obtaining tissue material, followed by costly, labor-intense and technically difficult analyses methods o Relatively low disease prevalence	• Include other therapies than TNF-α inhibitors • Careful selection of the most appropriate outcome measure based on treatment and research goals • Validation in independent external cohorts of patients • Exploring not single, but combinations of biomarkers • Translation and adaption of discovery assays into less-invasive, affordable and technically simple assays for clinical implementation • Sharing of clinical, imaging, molecular data • International collaborations of patient representatives, health care professionals, non-profit organizations and pharmaceutical companies

- Abbreviations: DMARD: disease modifying anti-rheumatic drug; PsA: psoriatic arthritis; TNF: tumor necrosis factor.

findings. Improved collaboration with computational biologists will be critical for success [78]. The fruitful result of such a collaboration has already been described by Ademowo and collegues [24]. They used not only Irish patients for their biomarkers discovery, but also included a cohort of Dutch patients for validation of their findings. Another illustration of this line of thinking is the 'ArthroMark' project [79]. These German researchers created a cooperation between several national institutions that share their resources in a consortium for biomarker analysis in rheumatic diseases. Patient data is expected to be of more value if clinicians would accurately record clinical characteristics and collaborate with fundamental researchers and experts in genetics [22]. Another example in the field of collaborative projects is the Accelerating Medicines Partnership (AMP), an American partnership between the National Institutes of Health, Food and Drug Administration, pharmaceutical companies and non-profit organizations. They have already conducted some interesting research in the field of RA [80,81]. Projects like these are likely to optimize the process of discovery and validation of not only molecular biomarkers in this field, but also clinical and imaging biomarkers [79].

6. Conclusion

PsA is a potentially aggressive inflammatory musculoskeletal disorder, which may severely impact physical function and quality-of-life. Currently it is not possible to predict which patients respond to which particular treatment, which underlines the urgent clinical need for biomarkers predictive of drug response to optimize personalized medicine. Biomarker discovery has shown to be a time-consuming and difficult process, in which discovery has to be followed by confirmation, validation, clinical implement and evaluation. Promising new tools and approaches are emerging to identify new molecular biomarkers in omics datasets with computational modeling analyses. As several research groups are working on identification and validation of such markers in PsA, we anticipate that this urgent clinical need will be answered in the future to reduce health care costs and improve patient care.

7. Limitations

We are aware that our review has limitations. One important limitation is the reporting bias that is inherent to literature reviews [82], through which we might have missed research that studied biomarkers and did not find any predictive capacities of the biomarkers listed here. Moreover, given that we only included articles with (synonyms of) 'psoriatic arthritis' in their title or abstract we might have missed articles primarily describing biomarkers in the context of psoriasis or spondylarthropathies.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

JNP and MB were responsible for conception and writing of the manuscript. All authors contributed to substantial discussion of content, reviewing and revising the manuscript before submission.

Declaration of Competing Interest

The authors state no conflict of interest and have no disclosures.

Appendix A. Appendix

Appendix Table A
Literature search.

Category	Biomarker	Psoriatic arthritis
MeSH term	Biomarkers	Arthritis, Psoriatic
Emtree term	Biological marker	Psoriatic arthritis
Synonyms	Biologic marker*	Arthritic psoriasis
	Biological marker*	Arthropathic psoriasis
	Biomarker*	Psoriasis arthropathica
	Laboratory marker*	Psoriatic arthritis
	Serum marker*	Psoriatic arthropathies
		Psoriatic arthropathy

- Abbreviations: Emtree: Embase subject headings; MeSH: medical subject headings.

Appendix Table B
Search syntax PubMed.

Search term	Syntax	Results [1]
1. Biomarker	(((((Biomarkers[MeSH Major Topic]) OR Biologic Marker*[Title/Abstract]) OR Biological Marker*[Title/Abstract]) OR Biomarker*[Title/Abstract]) OR Laboratory Marker*[Title/Abstract]) OR Serum Marker*[Title/Abstract]	449.854
2. Psoriatic arthritis	((((((Arthritis, Psoriatic[MeSH Major Topic]) OR Arthritic psoriasis[Title/Abstract]) OR Arthropathic psoriasis[Title/Abstract]) OR Psoriasis arthropathica[Title/Abstract]) OR Psoriatic arthritis[Title/Abstract]) OR Psoriatic arthropathies[Title/Abstract]) OR Psoriatic arthropathy[Title/Abstract]	9.163
1 AND 2	(((((((Biomarkers[MeSH Major Topic]) OR Biologic Marker*[Title/Abstract]) OR Biological Marker*[Title/Abstract]) OR Biomarker*[Title/Abstract]) OR Laboratory Marker*[Title/Abstract]) OR Serum Marker*[Title/Abstract])) AND (((((((Arthritis, Psoriatic[MeSH Major Topic]) OR Arthritic psoriasis[Title/Abstract]) OR Arthropathic psoriasis[Title/Abstract]) OR Psoriasis arthropathica[Title/Abstract]) OR Psoriatic arthritis[Title/Abstract]) OR Psoriatic arthropathies[Title/Abstract]) OR Psoriatic arthropathy[Title/Abstract])	314

- Legend: [1] Search conducted on the 3rd of September 2019.

Appendix Table C
Search syntax Embase.

Search term	Syntax	Results [1]
1. Biomarker	'biological marker'/de OR 'biologic marker*':ab,ti OR 'biological marker*':ab,ti OR biomarker*:ab,ti OR 'laboratory marker*':ab,ti OR 'serum marker*':ab,ti	464.737
2. Psoriatic arthritis	'psoriatic arthritis'/de OR 'arthritic psoriasis':ab,ti OR 'psoriasis arthropathica':ab,ti OR 'psoriatic arthritis':ab,ti OR 'psoriatic arthropathies':ab,ti OR 'psoriatic arthropathy':ab,ti	23.233
1 AND 2	('biological marker'/exp. OR 'biological marker' OR 'biologic marker*':ab,ti OR 'biological marker*':ab,ti OR biomarker*:ab,ti OR 'laboratory marker*':ab,ti OR 'serum marker*':ab,ti) AND ('psoriatic arthritis'/exp. OR 'psoriatic arthritis' OR 'arthritic psoriasis':ab,ti OR 'psoriasis arthropathica':ab,ti OR 'psoriatic arthritis':ab,ti OR 'psoriatic arthropathies':ab,ti OR 'psoriatic arthropathy':ab,ti)	805

- Legend: [1] Search conducted on the 4th of September 2019.

Appendix Table D
Eligibility criteria.

Inclusion	- Adult study participants
	- Humans
	- Original study
	- Full text available
	- Molecular biomarkers predicting DMARD response
Exclusion	- Meta-analysis
	- Review
	- Case-report
	- Expert opinion
	- Authors reply
	- Language other than English
	- Only other diseases than PsA

- Abbreviations: DMARD: disease modifying anti-rheumatic drug; PsA: psoriatic arthritis.

References

[1] D.R. Jadon, et al., Proceedings of the 2017 GRAPPA collaborative research network meeting, J. Rheumatol. Suppl. 94 (2018) 54–61.
[2] S. Menegatti, et al., Anti-TNF therapy in spondyloarthritis and related diseases, impact on the immune system and prediction of treatment responses, Front. Immunol. 10 (382) (2019).
[3] L. Gossec, et al., European league against rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update, Ann. Rheum. Dis. 75 (2016) 499–510.
[4] L. Scotti, M. Franchi, A. Marchesoni, G. Corrao, Prevalence and incidence of psoriatic arthritis: a systematic review and meta-analysis, Semin. Arthritis Rheum. 48 (2018) 28–34.
[5] C.T. Ritchlin, R.A. Colbert, D.D. Gladman, Psoriatic arthritis, NEJM 10 (2017).
[6] N. McHugh, et al., Evaluation of the economic burden of psoriatic arthritis and the relationship between functional status and healthcare costs, J. Rheumatol. (2019) [Epub ahead of print].
[7] M. Haroon, O. FitzGerald, Psoriatic arthritis: complexities, comorbidities and implications for the clinic, Expert. Rev. Clin. Immunol. 12 (2016) 405–416.
[8] D.J. Veale, U. Fearon, Psoriatic arthritis 1 the pathogenesis of psoriatic arthritis, Lancet 391 (2018) 2273–2284.
[9] L. Gossec, et al., Management of psoriatic arthritis in 2016: a comparison of EULAR and GRAPPA recommendations, Nat. Rev. Rheumatol. 12 (2016) 743–750.
[10] E.J. Kang, A. Kavanaugh, Psoriatic arthritis: latest treatments and their place in therapy, Ther. Adv. Chronic Dis. 6 (2015) 194–203.
[11] S. D'Angelo, G. Tramontano, M. Gilio, P. Leccese, I. Olivieri, Review of the treatment of psoriatic arthritis with biological agents: choice of drug for initial therapy and switch therapy for non-responders, Open. Access. Rheumatol. Res. Rev. 9 (2017) 21–28.
[12] O. FitzGerald, C. Ritchlin, Opportunities and challenges in the treatment of psoriatic arthritis, Best Pract. Res. Clin. Rheumatol. 32 (2018) 440–452.
[13] F. Van Den Bosch, L. Coates, Psoriatic Arthritis 2 Clinical Management of Psoriatic Arthritis, *www.thelancet.com* 391 (2018).
[14] J.A. Singh, et al., American college of Rheumatology/National Psoriasis foundation guideline for the treatment of psoriatic arthritis, Arthritis Care Res. 71 (2019) (2018) 2–29.
[15] K. Strimbu, J.A. Tavel, What are biomarkers? Curr. Opin. HIV AIDS 5 (2010) 463.
[16] F. Villanova, P. Di Meglio, F.O. Nestle, Biomarkers in psoriasis and psoriatic arthritis, Ann. Rheum. Dis. 72 (2013) ii104–ii110.
[17] A. Berekmeri, F. Mahmood, M. Wittmann, P. Helliwell, Expert review of clinical immunology Tofacitinib for the treatment of psoriasis and psoriatic arthritis, Expert. Rev. Clin. Immunol. 0 (2018).
[18] M.K. Verheul, U. Fearon, L.A. Trouw, D.J. Veale, Biomarkers for rheumatoid and psoriatic arthritis, Clin. Immunol. 161 (2015) 2–10.
[19] S.Y. Paek, et al., Emerging biomarkers in psoriatic arthritis, IUBMB Life 67 (2015) 923–927.
[20] E. Generali, C.A. Scirè, E.G. Favalli, C. Selmi, Expert review of clinical immunology

biomarkers in psoriatic arthritis: a systematic literature review biomarkers in psoriatic arthritis: a systematic literature review, Expert. Rev. Clin. Immunol. 12 (2016) 651–660.
[21] V. Chandran, J.U. Scher, Biomarkers in psoriatic arthritis: recent progress, Curr. Rheumatol. Rep. 16 (2014) 453.
[22] D.E. Furst, J. Belasco, J.S. Louie, Genetic and inflammatory factors associated with psoriatic arthritis: relevance to diagnosis and management, Clin. Immunol. 202 (2019) 59–75.
[23] N. Iragorri, G. Hazlewood, B. Manns, V. Danthurebandara, E. Spackman, Psoriatic arthritis screening: a systematic review and meta-analysis, Rheumatology (Oxford) 58 (2019) 692–707.
[24] O.S. Ademowo, et al., Discovery and confirmation of a protein biomarker panel with potential to predict response to biological therapy in psoriatic arthritis, Ann. Rheum. Dis. 75 (2016) 234–241.
[25] A. Karason, T.J. Love, B. Gudbjornsson, A strong heritability of psoriatic arthritis over four generations–the Reykjavik psoriatic arthritis study, Rheumatology 48 (2009) 1424–1428.
[26] M.C. Ovejero-Benito, et al., Polymorphisms associated with anti-TNF drugs response in patients with psoriasis and psoriatic arthritis, J. Eur. Acad. Dermatol. Venereol. 33 (2019) e175–e177.
[27] J. Gratacós, E. Casado, J. Real, J.C. Torre-Alonso, Prediction of major clinical response (ACR50) to infliximab in psoriatic arthritis refractory to methotrexate, Ann. Rheum. Dis. 66 (2007) 493–497.
[28] Y. Wu, L.A. Potempa, D. El Kebir, J.G. Filep, C-reactive protein and inflammation: conformational changes affect function, Biol. Chem. 396 (2015) 1181–1197.
[29] M. Chimenti, et al., Complement system in psoriatic arthritis: a useful marker in response prediction and monitoring of anti-TNF treatment, Clin. Exp. Rheumatol. 30 (2012).
[30] A.M. van Gestel, et al., Development and validation of the european league against rheumatism response criteria for rheumatoid arthritis: comparison with the preliminary american college of rheumatology and the world health organization/international league against rheumatism criteria, Arthritis Rheum. 39 (1996) 34–40.
[31] M.J. Walport, Complement, N. Engl. J. Med. 344 (2001) 1058–1066.
[32] V. Chandran, et al., Soluble biomarkers associated with response to treatment with tumor necrosis factor inhibitors in Psoriatic arthritis, J. Rheumatol. 40 (2013) 866–871.
[33] C. Ribbens, et al., Increased matrix metalloproteinase-3 serum levels in rheumatic diseases: relationship with synovitis and steroid treatment, Ann. Rheum. Dis. 61 (2002) 161–166.
[34] W.P. Maksymowych, et al., Serum matrix metalloproteinase 3 is an independent predictor of structural damage progression in patients with ankylosing spondylitis, Arthritis Rheum. 56 (2007) 1846–1853.
[35] C.L. Wagner, et al., Markers of inflammation and bone remodelling associated with improvement in clinical response measures in psoriatic arthritis patients treated with golimumab, Ann. Rheum. Dis. 72 (2013) 83–88.
[36] Z.V. Wang, P.E. Adiponectin Scherer, The past two decades, J. Mol. Cell Biol. 8 (2016) 93–100.
[37] J. Chen, et al., Coagulation factors VII, IX and X are effective antibacterial proteins against drug-resistant gram-negative bacteria, Cell Res. 29 (2019) 711–724.
[38] U. Hellman, A. Engström-Laurent, A. Larsson, U. Lindqvist, Hyaluronan concentration and molecular mass in psoriatic arthritis: biomarkers of disease severity, resistance to treatment, and outcome, Scand. J. Rheumatol. (2019), https://doi.org/10.1080/03009742.2019.1577490.
[39] D. Jiang, J. Liang, P.W. Noble, Hyaluronan as an immune regulator in human diseases, Physiol. Rev. 91 (2011) 221–264.
[40] A. Marshak-Rothstein, Toll-like receptors in systemic autoimmune disease, Nat. Rev. Immunol. 6 (2006) 823–835.
[41] A.W.R. van Kuijk, et al., A prospective, randomised, placebo-controlled study to identify biomarkers associated with active treatment in psoriatic arthritis: effects of adalimumab treatment on synovial tissue, Ann. Rheum. Dis. 68 (2009) 1303–1309.
[42] A. Cesaro, et al., An inflammation loop orchestrated by S100A9 and calprotectin is critical for development of Arthritis, PLoS One 7 (2012) e45478.
[43] S. Wang, et al., S100A8/A9 in inflammation, Front. Immunol. 9 (2018) 1298.
[44] E.S. Collins, et al., A clinically based protein discovery strategy to identify potential biomarkers of response to anti-TNF-α treatment of psoriatic arthritis, Proteomics Clin. Appl. 10 (2016) 645–662.
[45] S.M. Mahendran, V. Chandran, Exploring the Psoriatic Arthritis proteome in search of novel biomarkers, Proteomes 6 (2018).
[46] J.G. Krueger, et al., IL-17A inhibition by secukinumab induces early clinical, histopathologic, and molecular resolution of psoriasis, J. Allergy Clin. Immunol. (2019) 750–763, https://doi.org/10.1016/j.jaci.2019.04.029.
[47] S. Visvanathan, et al., Psoriatic skin molecular and histopathologic profiles after treatment with risankizumab versus ustekinumab, J. Allergy Clin. Immunol. 143 (2019) 2158–2169.
[48] D.S. Gibson, et al., Biomarkers in rheumatology now and in the future, Rheumatology 51 (2012) 423–433.
[49] K.L. Winthrop, et al., Unmet need in rheumatology: reports from the targeted therapies meeting 2018, Ann. Rheum. Dis. 78 (2019) 872–878.
[50] J.P.A. Ioannidis, P.M.M. Bossuyt, Waste, leaks, and failures in the biomarker pipeline, Clin. Chem. 63 (2017) 963–972.
[51] T. Lancet, Psoriatic arthritis: classification and holistic management, Lancet 391 (2018) 2185.
[52] D. Solmaz, L. Eder, S.Z. Aydin, Update on the epidemiology, risk factors, and disease outcomes of psoriatic arthritis, Best Pract. Res. Clin. Rheumatol. 32 (2018) 295–311.
[53] A.-M. Orbai, Content validity of psoriatic arthritis composite indices: anchoring with the patient perspective and the core domain set, Rheumatology (2019), https://doi.org/10.1093/rheumatology/kez372.
[54] O. FitzGerald, M. Haroon, J.T. Giles, R. Winchester, Concepts of pathogenesis in psoriatic arthritis: genotype determines clinical phenotype, Arthritis. Res. Ther. 17 (2015) 115.
[55] C. Ospelt, M. Frank-Bertoncelj, Why location matters-site-specific factors in rheumatic diseases, Nat. Rev. Rheumatol. 13 (2017) 433–442.
[56] E. Del Duca, et al., Major differences in expression of inflammatory pathways in skin from different body sites of healthy individuals, J. Invest. Dermatol. (2019) 139.
[57] V. Brower, Biomarkers: portents of malignancy, Nature 471 (2011) S19–S20.
[58] R. Scrivo, et al., An observational prospective study on predictors of clinical response at six months in patients with active psoriatic arthritis treated with golimumab, Clin. Exp. Rheumatol. (2019).
[59] A.G. Chambers, A.J. Percy, J. Yang, A.G. Camenzind, C.H. Borchers, Multiplexed quantitation of endogenous proteins in dried blood spots by multiple reaction monitoring-mass spectrometry, Mol. Cell. Proteomics 12 (2013) 781–791.
[60] A. Mc Ardle, et al., Early biomarkers of joint damage in rheumatoid and psoriatic arthritis, Arthritis Res. Ther. 17 (2015) 141.
[61] Y. Hasin, M. Seldin, A. Lusis, Multi-omics approaches to disease, Genome Biol. 18 (2017) 83.
[62] W.H. Robinson, R. Mao, Biomarkers to guide clinical therapeutics in rheumatology? Curr. Opin. Rheumatol. 28 (2016) 168–175.
[63] R. Celis, et al., Psoriatic synovitis: singularity and potential clinical implications, Front. Med. 6 (14) (2019).
[64] R. Lorenzon, et al., Clinical and multi-omics cross-phenotyping of patients with autoimmune and autoinflammatory diseases: the observational TRANSIMMUNOM protocol, BMJ Open 8 (2018) 1–8.
[65] S. Lambrecht, D. Deforce, D. Elewaut, Entering the era of proteomics in rheumatology, Expert Opin. Drug Discovery 1 (2006) 539–548.
[66] N. Nair, et al., Mass cytometry as a platform for the discovery of cellular biomarkers to guide effective rheumatic disease therapy, Arthritis. Res. Ther. 17 (2015) 127.
[67] S. Tasaki, et al., Multi-omics monitoring of drug response in rheumatoid arthritis in pursuit of molecular remission, Nat. Commun. 9 (2018).
[68] C. Ritchlin, Biomarker development in psoriatic arthritis, J. Rheumatol. Suppl. 89 (2012) 57–60.
[69] I. Miyagawa, et al., Precision medicine using different biological DMARDs based on characteristic phenotypes of peripheral T helper cells in psoriatic arthritis, Rheumatology 58 (2019) 336–344.
[70] I. Miyagawa, S. Nakayamada, Y. Tanaka, Optimal biologic selection for treatment of Psoriatic arthritis: the approach to precision medicine, Curr. Rheumatol. Rep. 21 (2019) 21.
[71] Fulvia Ceccarelli, et al., T regulatory cells as biomarker of disease activity and response in psoriatic Arthritis patients: results from apremilast-treated cohort, Ann. Rheum. Dis. 78 (2019) 864.
[72] Trixy David, Meghna Jani, John Bowes, Hector Chinoy, Is HLA-B27 a predictor of treatment response to biologics in psoriatic arthritis? Rheumatol. (United Kingdom) 58 (2019) iii128.
[73] E., M., S., O., A., M. & A., C, Genetic variants in the TNF-alpha region: a novel biomarker of clinical response to anti TNF-alpha drugs in psoriatic arthritis patients, J. Psoriasis. Psoriatic. Arthritis. 4 (2019) 99.
[74] P.M. Ridker, High-sensitivity C-reactive protein, Circulation 103 (2001) 1813–1818.
[75] K. Musunuru, et al., The use of high sensitivity c-reactive protein in clinical practice, Nat. Clin. Pract. Cardiovasc. Med. 5 (2008) 621.
[76] M. Jani, H. Chinoy, A. Barton, The journal of rheumatology treatment in Psoriatic Arthritis study syndicate of long-term disability in patients with psoriatic arthritis: results from the outcomes association of pharmacological biomarkers with treatment response and, J. Rheumatol. Rheumatol. J. Oct. 10 (2019).
[77] A.-M. Orbai, et al., International patient and physician consensus on a psoriatic arthritis core outcome set for clinical trials, Ann. Rheum. Dis. 76 (2017) 673–680.
[78] L. Gossec, et al., EULAR points to consider for the use of big data in rheumatic and musculoskeletal diseases, Ann. Rheum. Dis. (2019) annrheumdis-2019-215694, , https://doi.org/10.1136/annrheumdis-2019-215694.
[79] T. Häupl, et al., Biomarker und Bildgebung zur Diagnose und Stratifizierung der rheumatoiden Arthritis und Spondylarthritis im BMBF-Verbund ArthroMark, Z. Rheumatol. 77 (2018) 16–23.
[80] D.E. Orange, et al., Identification of three rheumatoid Arthritis disease subtypes by machine learning integration of synovial histologic features and RNA sequencing data, Arthritis Rheumatol. (HobokenN.J.) 70 (2018) 690–701.
[81] F. Zhang, et al., Defining inflammatory cell states in rheumatoid arthritis joint synovial tissues by integrating single-cell transcriptomics and mass cytometry, Nat. Immunol. 20 (2019) 928–942.
[82] B. Duyx, G.M.H. Swaen, M.J.E. Urlings, L.M. Bouter, M.P. Zeegers, The strong focus on positive results in abstracts may cause bias in systematic reviews: a case study on abstract reporting bias, Syst. Rev. 8 (2019) 174.