Biomarkers of systemic treatment response in people with psoriasis: a scoping review

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The remaining authors declare that they have no relevant conflicts of interest.

**Key messages:**

What’s already known about this topic?

* Responses to the systemic treatments commonly used to treat psoriasis vary.
* Biomarkers that accurately predict effectiveness and safety would enable targeted treatment selection, improved patient outcomes and more cost-effective healthcare.

What does this study add?

* This review provides a comprehensive catalogue of investigated biomarkers of systemic treatment response in psoriasis.
* A diverse range of biomarker types and outcomes were found in the included studies, serving as a key resource for the translational research community.

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# Summary

**Background:**

Responses to the systemic treatments commonly used to treat psoriasis vary. Biomarkers that accurately predict effectiveness and safety would enable targeted treatment selection, improved patient outcomes and more cost-effective healthcare.

**Objectives:**

To perform a scoping review to identify and catalogue candidate biomarkers of systemic treatment response in psoriasis for the translational research community.

**Methods:**

A systematic search of CENTRAL, Embase, LILACS, and MEDLINE was performed for relevant articles published between 1990 and December 2021. Eligibility criteria were studies involving the psoriasis population (any age, n≥50) reporting biomarkers associated with systemic treatment response. The main outcomes were any measure of systemic treatment efficacy or safety. Data was extracted by one reviewer and checked by a second; studies meeting minimal quality criteria (use of methods to control for confounding) were formally assessed for bias. Candidate biomarkers were identified by an expert multi-stakeholder group using a majority voting consensus exercise and mapped to relevant cellular and molecular pathways.

**Results:**

Of 71 included studies (n=64 effectiveness outcomes and n=8 safety outcomes), most reported genomic or proteomic biomarkers associated with response to biologics (n=48 studies). Methodological or reporting limitations frequently compromised the interpretation of findings, including inadequate control for key prognostic factors, lack of adjustment for multiple testing and selective outcome reporting. We identified candidate biomarkers of efficacy to TNF inhibitors (variation in *CARD14*, *CDKAL1*, *IL1B*, *IL12B*, *IL17RA* loci and LPS-induced phosphorylation of NF-kB in Type 2 dendritic cells) and ustekinumab (*HLA-C\*06:02* and variation in an *IL1B* locus). None were supported by sufficient evidence for clinical use without further validation studies. Candidate biomarkers were found to be involved in the immune cellular crosstalk implicated in psoriasis pathogenesis, most notably antigen presentation, Th17 cell differentiation, positive regulation of NF-kB and Th17 cell activation.

**Conclusions:**

This comprehensive catalogue provides a key resource for researchers and reveals a diverse range of biomarker types and outcomes in the included studies. Candidate biomarkers identified require further evaluation in methodologically robust studies to establish potential clinical utility. Future studies should aim to address common methodological limitations highlighted in this review to expedite discovery and validation of biomarkers for clinical use.

# Introduction

Psoriasis is a common chronic inflammatory disease estimated to affect at least 60 million individuals globally1,2 and causes major impact on quality of life. Disease severity, particularly with respect to body surface area involvement, often dictates the therapeutic approach. Topical agents are generally used for localised disease, and phototherapy or systemic agents for extensive disease and/or where there is significant involvement of high need sites or associated psoriatic arthritis. The advent of (now increasingly) powerful biologic therapies means that moderate to severe disease can be very effectively controlled in many.3 However, variation is response, loss of benefit over time, toxicity, practical issues and high drug costs are all important barriers to effective management of the population as a whole.4

Pre-emptive identification of individuals with a higher likelihood of a safe and effective response to any selected treatment would enable targeted therapeutic selection, improved patient outcomes and more cost-effective healthcare. Biomarkers are critical to enabling this ‘personalised medicine’ agenda (not just in psoriasis), and have been defined (broadly) by the FDA-NIH as a characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.5

Across medicine, including psoriasis, advances in omics technologies and bioinformatic approaches have unravelled biomarkers from different molecular levels that have been shown to associate with clinically relevant outcomes in several disease settings6 and driven a radical paradigm shift from analysis of single biomarkers, to high-throughput screens profiling assays in heterogenous datasets. Efforts in psoriasis have been underpinned by major investment and collaboration. 7,8 In this context, collating up to date, accessible information on the status of biomarker discovery and validation is essential to avoid research waste and redundancy, and crucially, expedite translation of the biomarker discovery pipeline into clinical practice.

The overall aim of this review is therefore to scope, review, and collate research investigating biomarkers of systemic treatment response in psoriasis. The specific aims are to (i) identify and catalogue studies relating to biomarkers of systemic treatment response in psoriasis as defined by efficacy, and/or safety outcomes (ii) select and functionally map biomarkers for which there is some evidence for potential prognostic value (iii) evaluate study quality and highlight limitations to inform future biomarker research.

# Materials and Methods

This scoping review was performed by a multi-stakeholder group of ten dermatologists, a patient representative, seven cutaneous immunology scientists, two bioinformaticians, two systematic reviewers and one information specialist from the International Psoriasis Council (IPC) and Biomarkers in Atopic dermatitis and Psoriasis (BIOMAP) - a large European-wide consortium whose strategic aims include biomarker discovery for atopic dermatitis and psoriasis.8,9

**Identification and cataloguing of studies of systemic treatment response biomarkers (stage 1)**

Literature searches

A single strategy (Appendix S1, section 6) was used to search for both studies of biomarkers of disease progression (reported separately, see XX) and biomarkers of treatment response. Electronic searches were performed in the Cochrane Central Register of Controlled Trials (CENTRAL), Embase, LILACS, and MEDLINE on 7th December 2021 for studies in the English language, published between 1990 (chosen since this heralded Human Genome Project start date) and December 2021 (KW).

Study selection

Criteria for study inclusion were established prior to study selection (Table 1). Titles and abstracts were single screened by one reviewer, with an independent second screening where requested (e.g. for abstracts where there was uncertainty regarding eligibility) (MC, RR, IAB, JS, MV, SH, SR). To assess the accuracy of our screening approach, every 10th excluded abstract was independently checked (500 in total) by a second screener (RR). From this list, full-texts were screened by one reviewer, with decisions (inclusion/exclusion) checked by a second; any disagreements were resolved by consensus or through discussion with a senior member of the team (MC, DM, RR).

Data extraction and cataloguing

A minimal dataset (design, population characteristics, biomarkers, outcome measures and basic result details) was defined by the multi-stakeholder group following review of pilot data extraction from a pilot sample of studies. Data were extracted (RR, MC), cross-checked by another researcher, and discrepancies resolved by discussion (MC, DM, RR). For each biomarker type (genomic, transcriptomic, proteomic, metabolomic, cellular and mixed), study details were presented in structured tables subdivided by biomarker function (MC, DM) using an informal classification. Studies meeting minimal study design quality criteria (studies with methods to control for confounding) underwent detailed review (stage 2).

**Subset of studies undergoing additional data extraction and quality assessment of studies (stage 2)**

Additional data were extracted on psoriasis clinical subtype, treatment history, study design and detailed results (including size and variance of effect estimates) (MC, DM, RR).

Quality assessment data were extracted by one researcher and checked by another (MC, DM, RR) with reference to domains within BIOCROSS10 and QUIPS, quality assessment tools specifically designed for evaluation of biomarker/ prognostic studies, to quality assess studies in stage 2.11 Studies that adjusted for both sex and age of disease onset (or age)12 (considered by the group to be the two most important prognostic factors to control for to avoid a high risk of confounder bias) were considered to be at *‘low or moderate risk of bias’*; all other studies were classified as *‘high risk of bias’*. Other potential prognostic factors adjusted or controlled for in individual studies were detailed in the summary tables in Appendix S1 (section 3).

Other study quality assessment criteria evaluated included: levels of attrition (losses to follow up) and adequacy of imputation of missing data, evidence of selective outcome reporting and adjustment for multiple statistical testing.13 Further details on quality assessment strategy is described in Appendix S1 (section 4).

**Selection of candidate biomarkers for cellular and molecular pathway mapping (stage 3)**

Given the breadth and heterogeneity of studies reviewed in stage 2, we then selected biomarkers for cellular and molecular pathway mapping to aid interpretation of findings and to direct future research (candidate biomarkers) based on consensus majority of the multi-stakeholder group (see Appendix S1, section 5 for details).

A biomarker-based ‘disease map’ was built to represent mechanistic and associative links of the candidate biomarkers to psoriasis pathogenesis (methodology detailed in section 6 of Appendix S1) and significantly enriched biological processes were highlighted.

# Results

**Overview of all included studies (stage 1)**

Following title and abstract screening, the full texts of 145 studies were sought, of which 71 met the review eligibility criteria (Figure 1 and see Appendix S1 for included/ excluded studies). On checking every 10th excluded abstract, none were considered incorrectly excluded, adding validity to the accuracy of the chosen screening approach. Study designs used included cohort studies (86%), registry studies (6%) and randomised controlled studies (6%). Investigated biomarkers covered a broad range of biological functions (Figure 2), although the majority related to immune processes.

Consistent with the explosion of effort around biomarker discovery over the last decade, nearly all studies were published after 2010 (64 studies). As anticipated, the evidence-base is largely dominated by studies of genomic (52%) and proteomic (21%) biomarkers (Table 2). In general, genomic biomarker studies evaluated more biomarkers per study than the proteomic biomarker studies, although the number of patients recruited were similar. No studies examining microbiomic biomarkers met the eligibility criteria. A full description of study characteristics, categorised by biomarker type, is reported in Appendix S1 (sections 2.1-2.6).

Across all included studies 17 different systemic treatments were evaluated, the most common being: TNF-inhibitors (etanercept- 34 studies, adalimumab- 31 studies, infliximab- 24 studies), ustekinumab (27 studies) and methotrexate (11 studies); 36 studies evaluated more than one treatment. Conversely, few studies examined IL17 inhibitors (secukinumab- eight studies, ixekizumab- three studies), IL23 inhibitors (risankizumab- one study) or small molecule inhibitors (apremilast- two studies, tofacitinib- two studies, baracitinib- one study).

**Characteristics of studies that underwent detailed data extraction and quality assessment (stage 2)**

38 studies fulfilled the criteria for further evaluation and quality assessment (Appendix S1, sections 3.1-3.4), which revealed important similarities in cohort characteristics between studies. These studies had a narrow mean age range (42-50 years), mean PASI (15-23) and mean durations of psoriasis (16-24 years). Most studies were conducted in Europe or North America (68%), although the ethnicity of study participants was infrequently reported. Most studies did not report participants’ psoriasis subtype; where reported all included studies investigated plaque psoriasis. Details on past treatment use and the proportion of cohorts with PsA were generally not well reported, or not reported at all.

All studies - except one of methotrexate only14- evaluated responses to a biologic therapy: usually one or more of adalimumab, etanercept, infliximab and ustekinumab. The biomarker examined in the highest number of studies was *HLA-C\*06:02* (14 studies).

Most studies evaluated treatment efficacy outcomes, reporting changes in PASI. Studies most frequently used dichotomous treatment response outcomes: usually one or more of PASI 50, PASI 75 and PASI 90. Only two studies reported on associations with adverse events.15,16 Other outcomes included drug survival and loss of response to treatment.

**Quality assessment (stage 2)**

Quality assessment of studies revealed at least one type of bias in nearly all studies (Appendix S1, sections 3 & 4 and Table 10). All studies that underwent further evaluation adjusted for confounding via their methods of analysis. Some studies also controlled for certain confounding by recruitment methods (e.g. controlling for ethnicity by recruiting a Caucasian cohort and controlling for previous exposure to a biologic therapy by recruiting a biologic-naïve cohort). Both pre-specified key prognostic factors were controlled for in ten of the 38 studies, so the possibility of results being affected by bias arising from confounding could not be ruled out for most studies.

The included studies had several additional methodological limitations. Many analyses were limited by the lack of adjustment for multiple hypothesis testing; of the 21 studies which evaluated more than one biomarker, only five reported using such adjustments. Another source of bias were imputation methods used for dealing with data for patients lost to follow up. Additionally, there was evidence suggesting bias arising from selective outcome (or result) reporting in several studies. Overall, the quality assessment findings indicated that the results of all included studies should be interpreted with some caution: all studies except three were judged to be at high risk of bias.

**Candidate biomarker associations (stage 3)**

Seven different biomarkers (eight biomarker-outcome associations) were selected as candidate biomarkers for systemic treatment efficacy, based on the evidence available (Table 3): five genomic biomarkers for TNF-inhibitor treatment (*CARD14, CDKAL1*, *IL1B*, *IL12B* and *IL17RA* loci), one cellular biomarker for adalimumab treatment (LPS-induced phosphorylation of NF-kB in Type 2 dendritic cells) and two genomic biomarkers for ustekinumab treatment (*HLA-C\*06:02* and variation in an *IL1B* locus).

All selected candidate biomarkers were at a single molecular level, although IL1B was also found to associate with etanercept efficacy at the genomic and proteomic level.17 Allele frequencies of genomic biomarkers were rarely reported, as well as justifications for thresholds of significance used for non-genomic biomarkers, often limiting the interpretation of findings.

**Pathway mapping of candidate biomarkers (stage 3)**

Most candidate biomarkers were found to be involved in signalling pathways implicated in psoriasis pathogenesis,18 including antigen processing and presentation (*HLA-C\*06:02*), Th17 cell differentiation (*IL1B*) and immune response (*IL12B*) and regulation of NF-kB activity (*CARD14*, *IL17RA*) (see interactive map of psoriasis biomarkers: <https://imi-biomap.elixir-luxembourg.org/minerva/index.xhtml?id=psobiomarkers_map>). The most enriched pathways amongst candidate TNF-inhibitor treatment response biomarkers were cytokine-mediated signalling pathway and granulocyte macrophage colony-formation factor production (Appendix S1, Figure 1).

# Discussion

**Summary of findings**

This scoping review has identified a comprehensive catalogue of studies reporting data on a diverse range of biomarker types associated with outcomes to systemic psoriasis therapies. Most of these related to biologics (TNF antagonists, ustekinumab) and methotrexate. These studies have focused on short term efficacy with only one study addressing loss of response (secondary failure) in psoriasis, and very few addressing toxicity. Of the biomarkesr reviewed in detail by the stakeholder group, 7 (6 genomic, and one cellular) were selected as candidates for future research, mapping to immune pathways strongly implicated in disease pathogenesis and/or drug mechanism, consistent with the principle that the ideal biomarker is on the causal pathway of interest.

Notably, *HLA-C\*06:02*, the primary susceptibility allele in psoriasis and most extensively studied biomarker, showed a consistent association with ustekinumab response, and potential utility as a stratification tool to select those more likely to respond to ustekinumab (positive status) compared to TNF antagonists.19,20 Of the remaining biomarkers selected, two (CDKAL1 and IL12B loci) also showed consistency of effect in two independent studies, positively associating with TNF antagonist efficacy. No biomarkers were identified as being suitable for clinical use, reflecting the acknowledged need for further validation and performance testing.

The fact that most studies investigated first generation biologics (TNF-inhibitors, ustekinumab) and methotrexate illustrates an important challenge for biomarker research: that is, the timeline for biomarker discovery and validation can outstrip the pace of change in therapeutics. Integration of co-diagnostics into drug development programmes is one solution. Developing biomarkers with utility across drug class and across diseases (for example TNF antagonists across immune-mediated diseases) also enhances the value of the biomarker development pipeline, although may miss disease- or drug -specific mechanistic differences.

Genomic or proteomic biomarkers appear to dominate the research landscape, and the assessment of multiple biomarkers simultaneously reflects advances in high-throughput biological assays and their application to larger scale cohorts. In this context, genomic biomarkers have an advantage given the clear causal direction between genomic biomarker and outcome. The identified candidate biomarkers of treatment efficacy mapped to immune pathways known to underpin psoriasis pathogenesis indicate the largely ‘hypothesis-driven’ approach to date, where biomarkers are selected for study based on established knowledge of the role of a gene/ molecule in disease pathogenesis. Very recently, studies have been performed using a less directed, ‘hypothesis free’ approach offering potential to uncover new mechanistic insight into drug response. This is exemplified in the study by Andres-Ejarque *et al*, which identified enhanced NF-kB signalling in type 2 dendritic cells as a biomarker of TNF antagonist nonresponse.21 Genome wide association studies, similarly ‘hypothesis’ free, have not to date revealed strongly significant associations due to the requirement of large sample sizes to offset the necessity for multiple testing adjustment.

Modest effect sizes observed in included studies mean that the clinical utility of many of the reported biomarkers is likely to be limited. Combining multiple biomarkers of small effect size, with established clinical ‘biomarkers’ (for example high BMI and presence of psoriatic arthritis),22,23 and indicators of drug exposure into risk prediction tools may better reflect the complexity of drug response, and hence ability to accurately predict treatment response.24,25

**Limitations of included studies**

This review highlights key methodological and reporting limitations which had the potential to compromise the interpretation of findings in the included studies. Lack of measuring and adjusting for key prognostic factors was a common limitation. Even studies which controlled for key prognostic factors were at additional risk of bias due to one or more of: absence of consideration of the impact of missing data, lack of adjustment for multiple testing, and selective outcome reporting. Future studies should also consider possible confounding by the presence of other biomarkers to help identify independent associations with outcomes.

Few studies adequately imputed data from patients who discontinued treatment early, whether due to lack of efficacy or adverse events. For a biomarker which is genuinely predictive of treatment efficacy, a difference in treatment discontinuation rates might be expected (between the biomarker present versus absent groups). Therefore, the omission of such imputed data could underestimate associations between biomarker and treatment efficacy, and lead to bias.

Only one study reported biomarker results for patients taking placebo.26 Data from placebo, standard care treatments or healthy volunteers (e.g., for mechanistic/functional biomarkers detected at baseline21) can be very informative in classifying and validating biomarker mechanisms. Such data are necessary to classify a biomarker as being predictive of a treatment response (only biomarker-positive patients under the test treatment are likely to benefit) rather than being a prognostic biomarker (biomarker-positive patients have better outcomes for both test treatment and placebo). Different randomised study designs have been proposed to address this issue. The most pragmatic approach may be to use data from regulatory efficacy trials, if available. Additionally, prospective randomised study designs specifically address the issue of validating a biomarker as being predictive. These include the ‘biomarker by treatment interaction’ and ‘biomarker-strategy’ designs, among several others.27,28

Heterogeneity of the outcome definition across studies also made the comparative assessment difficult for biomarker-outcome associations. There was variation in the timepoint for assessment of outcomes and in the dichotomous treatment response outcomes used. In future studies, analyses should be performed using both continuous and categorical data wherever possible, ideally using pre-defined categories and evaluation timepoints, to help reduce the risk of selective result reporting.

**Strengths and limitations of the review**

The main strength of the review is its breadth of scope – we believe this review to be the most comprehensive evaluation of biomarkers of systemic treatment response in psoriasis to date. The bibliographic database searches were extensive, allowing identification of nearly all relevant studies. However, there is a potential for the search strategy to have missed studies, such as trial reports, where keywords may not have been included in the abstract. This may bias towards some negative findings being missed. Eligibility criteria were designed to be as inclusive as was practicable, given that it was anticipated that a large number of studies would be included.

By excluding studies of 50 patients or less we may have missed important, early discovery studies particularly those deploying high resolution information platforms. Other limitations were the exclusion of papers not reported in English and the single-screening of some titles and abstracts, although we consider our strategies for mitigation means the risk of missing studies is low.

**Conclusion and next steps for future research**

The wide extent of research on biomarkers of systemic treatment response revealed in this scoping review reflects the key unmet clinical need in psoriasis. Candidate biomarkers and pitfalls in reporting identified in this review can help focus future research effort to expedite the validation of biomarkers for clinical use.

Synergised efforts, through interdisciplinary collaborations such as the BIOMAP project,8 offer great opportunity for efficient and effective biomarker research, and also drive incorporation of biomarker discovery into drug development programmes. This has the potential to bring clinically useful biomarkers into psoriasis therapeutics, and enable rationalised early stratification of patients undergoing systemic treatment.29

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# Supporting information

**Appendix S1-** Preliminary work and study design, overview of results, summary of quality assessment, candidate biomarker selection methodology, molecular and cellular pathway mapping, literature searches, list of excluded studies.

# Figure legends

Figure 1: PRISMA Flow chart showing the number of studies identified and eligible for inclusion

**Figure 2:** **Primary functions of biomarkers in all included studies.** Categories of biomarker function were devised using an informal classification, designed to capture the breadth of biomarker function in included studies. Segments represent the number of biomarker studies examining biomarkers with a given primary function (n). Studies examining multiple biomarkers which have more than one function or single biomarkers with multiple key functions may be represented in more than one segment of the ring chart.

# Tables

**Table 1: Eligibility criteria for the scoping review**

|  |  |
| --- | --- |
| **Review component** | **Criteria** |
| Population | People with psoriasis, with or without PsA, already taking, or commencing, a systemic treatment for psoriasis were eligible. Systemic treatments include methotrexate, ciclosporin, acitretin, dimethylfumarate, etanercept, adalimumab, infliximab, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, certolizumab pegol, tildrakizumab, risankizumab, apremilast, tofacitinib, ruxolitinib, baricitinib, and peficitinib, at any dose. |
| Interventions | Genomic, epigenomic, transcriptomic, proteomic, cellular, microbiomic and metabolomic biomarkers were included  Physiologic or radiographic biomarkers were excluded |
| Comparators | Studies could be of one or more biomarkers |
| Outcomes | *Treatment response outcomes* :  • Clinical responses using objectively validated outcome measures were the main outcomes of interest: for example, PGA, PASI or BSA. Outcomes could be reported as binary results (e.g. PASI 75) or continuous results (e.g. change in PASI).  • Other binary outcome measures which were pre-specified in studies, such as clear/nearly clear, were also eligible.  • Loss of response  • Quality of life outcomes  • PsA response outcomes  *Adverse event outcomes:* Adverse events leading to treatment withdrawal, serious adverse events, serious infection resulting in hospitalisation, intravenous antibiotics or death, immune mediated disease (including demyelination disorders, inflammatory bowel disease, autoimmune hepatitis, cutaneous immune mediated disease), liver disease (advanced fibrosis/cirrhosis), major adverse cardiac events, bone marrow suppression |
| Study designs | Reviews and studies including fewer than 50 participants (excluding healthy control participants or other non-psoriasis participants) were excluded.  Studies were included providing the duration of systemic treatment was at least the period recommended to evaluate treatment response in SmPCs (summary of product characteristics documents). In included studies, the populations had to have less than 50% of participants with PsA. |

Table 2: Summary characteristics of the included studies, overall and by type of biomarker

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Characteristic** | **Type of biomarker evaluated** | | | | | | **Totals** |
| **Genomic** | **Transcriptomic** | **Proteomic** | **Metabolomic** | **Cellular** | **Mixed** | **All biomarkers** |
| **No. of included studies (% of total)** | 37 (52%) | 4 (6%) | 15 (21%) | 2 (3%) | 3 (4%) | 10 (14%) | 71 |
| **Mean / median biomarkers per study** | 30 / 4 | 12 / 9 | 13 / 3 | 3 / 3 | 3 / 3 | 9 / 9 | 21 / 3 |
| **Mean / median no. of psoriasis patients** | 200 / 130 | 142 / 129 | 218 / 128 | 85 / 85 | 116 / 95 | 150 / 142 | 187 / 137 |
| **No. of studies evaluated further1 (% of studies in biomarker category)** | 24 (65%) | 2 (50%) | 7 (47%) | 0 | 0 | 5 (50%) | 38 (54%) |
| **Candidate biomarkers (% of total)** | 6 (86%) | 0 | 0 | 0 | 1 (14%) | 0 | 7 |

1 Studies which were eligible for detailed data extraction and quality assessment; N/A Not applicable (only one study)

**Table 3: Summary details of studies examining prioritised candidate biomarkers of treatment response**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study/ number of psoriasis patients** | **Biomarker/ biomarker type** | **Systemic therapy** | **Number of review pre-specified key prognostic factors adjusted for** | **Outcome/ timepoint** | **Results** |
| ***HLA-C\*06:02*** | | | | | |
| Burlando et al 202030  N=101 | *HLA-Cw6*  Genomic | Adalimumab, etanercept, infliximab, golimumab, certolizumab pegol, ixekizumab, ustekinumab, secukinumab | 2: Age/ disease duration, sex | PASI 90 at week 16 and 48 | No significant difference between *HLA-Cw6* positive and negative groups (OR 1.53, 95% CI 0.22 to 30.7) at week 16 or 48 |
| Chiu et al 201431  N=66 | *HLA-Cw6*  Genomic | Ustekinumab | 1: Sex | PASI 50, PASI 75, PASI 90.  Week 16 | No significant association for PASI 75 at week 18. Further result details not reported. |
| Costanzo et al 201832  N=434 | *HLA-Cw6*  Genomic | Secukinumab | No review-specified key prognostic factors controlled for | PASI 90, change in PASI, adverse events.  Week 16 | No significant difference for PASI 90 at week 16 (OR 0.75, 95% CI 0.44 to 1.28; p=0.29), nor for PASI change.  Treatment-emergent AEs: No significant difference (p=0.30) |
| Dand et al 201919  N=1326 | *HLA-C\*06:02*  Genomic | Adalimumab, ustekinumab | 1: Age at onset | PASI 75, PASI 90, PASI 100.  6 months | *HLA-C\*06:02* associated with a better response with ustekinumab (OR 1.72, p=0.02) and with a poorer response with adalimumab (OR 0.54, p=1.7x10-4) at 6 months. |
| Indhumathi et al 201714  N=189 | *HLA-Cw6*  Genomic | Methotrexate | 2: Sex, age at disease onset | PASI 50, PASI 75.  Timepoint unclear | Significant association for PASI 75, OR 2.74 (95% CI 1.39 to 5.43, p=0.0004) but timepoint for evaluation unclear. |
| Svedbom et al 202033  N=167 | *HLA-C\*06:02*  Genomic | Ustekinumab | No review-specified key prognostic factors controlled for | Drug survival, maintenance PASI.  2 years | No significant association (p=0.11). No significant difference for PASI during maintenance treatment. |
| Talamonti et al 201720  N=255 | *HLA-C\*06*  Genomic | Ustekinumab | 2: Sex, age at disease onset | PASI 50, PASI 75, PASI 90.  Week 12 | Significant association for PASI 75 at 12 weeks, OR 3.28 (95% CI 1.92 to 5.59; p< 0.0001).  Significant results also at weeks 28, 40 and 52, and for PASI 90 and PASI 100 from weeks 12 to 52. |
| Talamonti et al 201334  N=51 | *HLA-Cw6*  Genomic | Ustekinumab | 2: Sex, age at disease onset | PASI 50, PASI 75.  Week 12 | Significant association for PASI 75 at 12 weeks, OR 13.4 (95% CI 1.6 to 12.6, p<0.008). Also significant for PASI 75 at 28 weeks: OR 4.0 (95% CI 1.1 to 8.8), p = 0.016. |
| van den Reek et al 201735  N=234 | *HLA-C\*06*  Genomic | Etanercept, adalimumab, ustekinumab | No review-specified key prognostic factors controlled for | PASI 75, change in PASI.  3 months | Unadjusted analysis: No significant associations for all three biologics (p>0.3) for either outcome. |
| Zorlu et al 202036  N=180 | *HLA-Cw6*  Genomic | Adalimumab, etanercept, infliximab, ustekinumab | 1: Age at onset | Drug survival (PASI<50) | *HLA-Cw6* negativity significantly associated with treatment failure (HR 8.95, 95% CI 1.8 to 44.5). |
| ***IL12B*** | | | | | |
| Indhumathi et al 201714  N=189 | IL12B  Genomic | Methotrexate | 2: Sex, age at disease onset | PASI 50, PASI 75.  Timepoint unclear | No significant association (p-value NR for adjusted analysis) |
| Ovejero-Benito et al 201837  N=95 | *IL12B rs2546890*  Genomic | Adalimumab, infliximab | No review-specified key prognostic factors controlled for | PASI 75  3 months | Significant association, OR 0.12 (95% CI 0.01 to 0.95, p=0.04) |
| Prieto-Perez et al 201738  N=69 | *IL12B* rs2546890  Genomic | Ustekinumab | No review-specified key prognostic factors controlled for | PASI 75  4 months | No significant association (p=0.35) |
| Preito-Perez et al 201839  N=144 | *IL12B* rs2546890  Genomic | Etanercept, adalimumab, infliximab | No review-specified key prognostic factors controlled for | PASI 75  3 months | Significant association, OR 3.22 (95% CI 1.23 to 8.40, p=0.017) for TNF-antagonist treatment (3 treatments analysed in one grouping). |
| van den Reek et al 201735  N=234 | *IL12B* rs3213094  Genomic | Etanercept, adalimumab, ustekinumab | No review-specified key prognostic factors controlled for | PASI 75, change in PASI.  3 months | Unadjusted: No significant association.  PASI change, 3 months: Significant association for ustekinumab, n=66, p=0.02. |
| ***IL17RA*** | | | | | |
| Batalla et al 201840  N=238 | *IL17RA* rs4819554 and rs879577  Genomic | Adalimumab, etanercept, infliximab | No review-specified key prognostic factors controlled for | PASI 50, PASI 75.  12 weeks | Significant association for rs4819554 allele A (p=0.01) for PASI 75 at 12 and 24 weeks. No significant association for rs879577. |
| ***IL1B*** | | | | | |
| Loft et al 201841  N=478 | *IL1B rs1143623, rs1143627*  Genomic | Ustekinumab, adalimumab, infliximab, etanercept | 1: Sex | PASI change, drug survival.  3 months | Significant associations for PASI change with response to both ustekinumab and TNF-antagonists for both SNPs. No significant associations for drug survival. |
| ***CARD14*** | | | | | |
| Coto-Segura et al 201642  N=116 | 5 CARD14 SNPs  Genomic | Adalimumab, etanercept, infliximab | No review-specified key prognostic factors controlled for | PASI 75  Week 24 | Significant associations for rs11652075 (OR 3.71, 95% CI: 1.30 to 10.51, p=0.01) but not for the other SNPs. |
| ***CDKAL1*** | | | | | |
| Coto-Segura et al 201543  N=116 | 4 CDKAL1 SNPs  Genomic | Adalimumab, etanercept, or infliximab | 2: Sex, age at disease onset | PASI 75  Week 24 | Significant associations for rs6908425, OR 3.14 (95% CI: 1.40 to 7.05) but not for the other SNPs. |
| Preito-Perez et al 201839  N=144 | *CDKAL1* rs6908425  Genomic | Etanercept, adalimumab, infliximab | No review-specified key prognostic factors controlled for | PASI 75  6 months | Significant association OR 0.14 (95% CI 0.03 to 0.66, p=0.01) |
| **LPS-induced phosphorylation of NF-kB in Type 2 dendritic cells** | | | | | |
| Andres-Ejarque et al 202121  N=67 | LPS-induced phosphorylation of NF-kB in Type 2 dendritic cells  Cellular | Adalimumab | 2: Age, sex | PASI 75 at week 12 | Baseline NF-κB translocation in dendritic cells correlated with lack of PASI 75 response (p=0.01). |

FU follow up, LOCF Last observation carried forward, N Number of psoriasis patients, NR Not reported, only studies which underwent detailed data extraction and quality assessment included in table- for further study details see Appendix S1 Section 3.