Supplemental Online Content

Der Sarkissian S, Hessam S, Kirby JS, et al. Identification of biomarkers and critical evaluation of biomarker validation in hidradenitis suppurativa: a systematic review. *JAMA Dermatol*. Published online January 19, 2022. doi:10.1001/jamadermatol.2021.4926

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

1) Protocol and Registration:

This Study was registered with PROSPERO (Registration 230830) and conducted in line with the PRISMA checklist.

2) Eligibility Criteria:

Eligibility criteria for this review included randomized controlled trials, uncontrolled clinical trials, cohort studies, case-control studies and other observational studies with no restrictions of patient age, sex, ethnicity or language of publication. Abstracts/conference presentations were included and are identified as such in the reference section.

Eligible studies included:

- Studies reporting the identification and/or evaluation of biomarkers in Hidradenitis Suppurativa / Acne Inversa.
- Studies may include identification and/or evaluation of clinical/phenotypic; imaging-based; tissue and/or blood/serum biomarkers.

Studies deemed not eligible for inclusion included:

- Studies not pertaining to Hidradenitis Suppurativa/ Acne Inversa
- Studies regarding patient reported outcomes such as pain or quality of life.
- Case Reports
- In-vitro or molecular studies with no correlated clinical data

3) Information Sources:

1) Medline (1946-January 1 2021),
2) Embase (1980- January 1 2021)
3) Published Abstracts
5) Contact with Authors for abstracts without full text for clarification of data and methodology

4) Search Strategy:

((Hidradenitis Suppurativa OR Acne Inversa) AND (Biomarker OR subtype OR phenotype OR genotype OR endotype OR risk OR susceptibility OR diagnosis OR diagnostic OR monitoring OR activity OR severity OR prognosis OR progression OR predictive OR therapy OR therapeutic OR response OR safety OR pharmacodynamic))

5) Study Selection:

Period of the search was up to December 31, 2020. Data collection was performed independently by 2 authors (SDS and JWF) with any disagreements regarding inclusion of citations being referred to a third author for mediation. All results in the search strategy underwent title and abstract screening for relevance. Articles not meeting eligibility criteria were excluded. Full text screening of the remaining articles were undertaken by the same two independent authors. The information was collated using narrative synthesis classified by potential therapeutic target of interest.

6) Definitions of Biomarker types

Categorization of manuscripts into biomarker type was performed independently by 2 authors (SDS and JWF) with any disagreements regarding inclusion of citations being referred to a third author for mediation. Biomarkers were defined using the FDA FDA Biomarkers, EndpointS and other Tools (BEST) glossary (https://www.ncbi.nlm.nih.gov/books/NBK338448/).

SUSCEPTIBILITY/RISK BIOMARKERS: A biomarker that indicates the potential for developing a disease or medical condition in an individual who does not currently have clinically apparent disease or the medical condition.

DIAGNOSTIC BIOMARKERS: A biomarker used to detect or confirm presence of a disease or condition of interest or to identify individuals with a subtype of the disease.

MONITORING BIOMARKERS: A biomarker measured repeatedly for assessing status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent.

PREDICTIVE BIOMARKERS: A biomarker used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a medical product or an environmental agent.

PROGNOSTIC BIOMARKERS: A biomarker used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest.

PHARMACODYNAMIC/RESPONSE BIOMARKER: A biomarker used to show that a biological response has occurred in an individual who has been exposed to a medical product or an environmental agent.

SAFETY BIOMARKERS: A biomarker measured before or after an exposure to a medical product or an environmental agent to indicate the likelihood, presence, or extent of toxicity as an adverse effect.

6) Critical Evaluation of Biomarker Validation

Assessment of each identified biomarker was undertaken in line with the FDA and EMA guidelines for the validation of proposed biomarkers. Any biomarker able to answer 'Yes' to the questions under each section below was said to have met the referenced criterion. These criteria consisted of:

1) Univariate Correlation
    a. Has the biomarker been studied in a single cohort or at a single site using univariate association with clinical outcomes (HISCR, Sartorius) and PROs (Pain, DLQI) compared to healthy control participants?
2) External Dataset Validation ("External Validation")
    a. Has the biomarker been identified as statistically significant in an independent study?
3) Analytical Validity Assessment ("Analytical Validation") (Only 2 of the 3 questions below need to be answered in the positive in order to meet the criteria)
    a. Pre-Analytical Validity- were the samples from disease and control consistent? Were they age and BMI matched?
    b. Analytical Validity – Has the test for measuring biomarker levels undergone technical validation?
    c. Post-Analytical Validity- Evaluation of dichotomous cutoffs for data interpretation
4) Clinical Validity Assessment ("Clinical Validation")
    a. Has the biomarker been used in the setting of a prospective clinical trial?
5) Clinical Utility Assessment ("Clinical Utility")
    a. Has the biomarker been shown to be clinical useful/meaningful in directing patient management?

Evaluation was undertaken independently by 2 authors (SDS and JWF) with any disagreements discussed between the authors and/or referred to a third author for mediation until consensus achieved. Across the 128 biomarkers identified, consensus was achieved between the two initial raters in 124/128 biomarkers (96.9%). Clarification of the criteria needed to achieve Analytical validity (achieving two out of three analytic criteria) increased the consensus rate to 100%. A roundtable discussion involving all authors was undertaken to ensure that consensus was achieved across the ratings of all identified biomarkers.

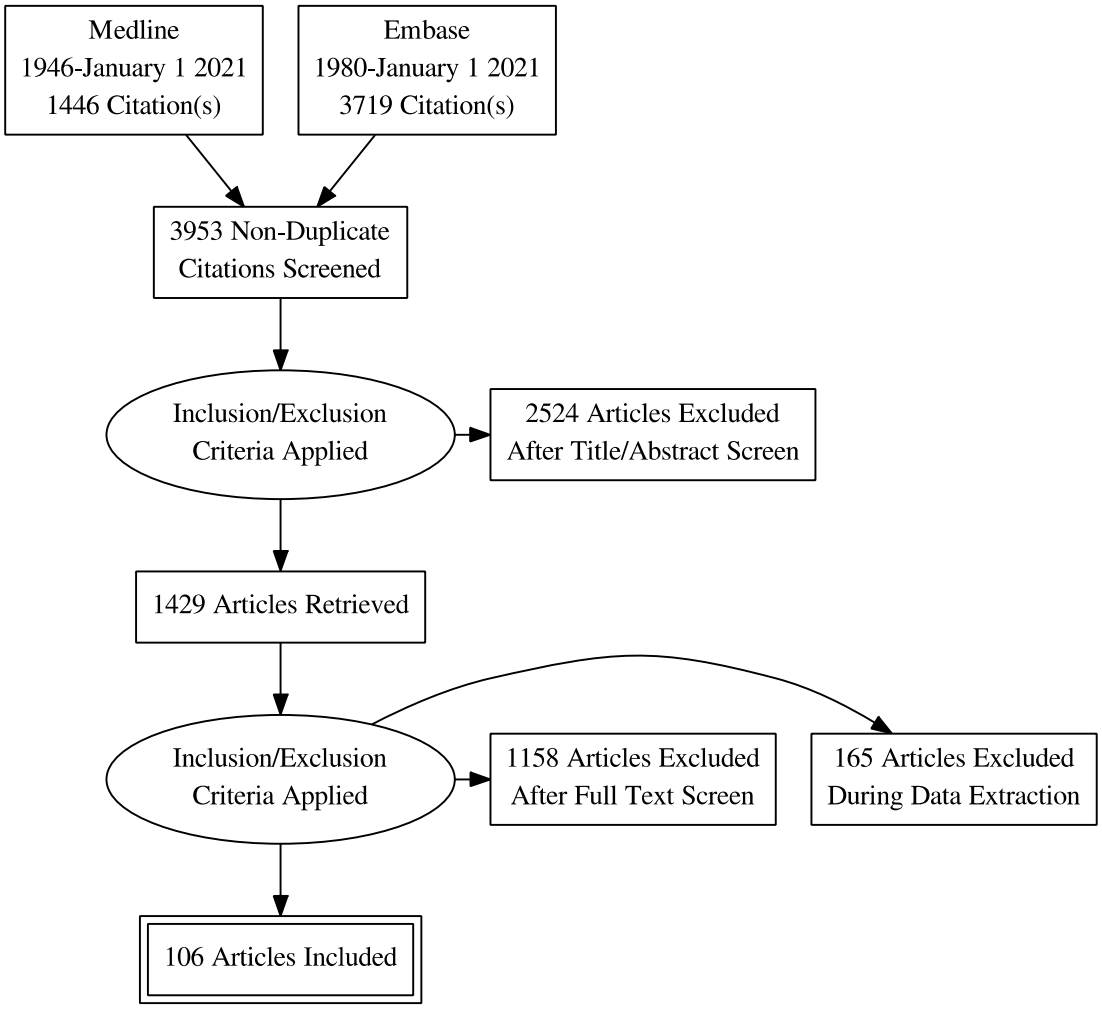
7) GRADE Assessment

The GRADE approach offers a system for rating quality of evidence, with a structured process for developing and presenting evidence summary and grading the strength of the overall published data. We included any identified biomarkers with one or more statistically significant

finding in individuals with HS. The following process was used to develop the GRADE ratings of identified biomarkers:

1) Data from observational studies were commenced at a “low” default rating, whilst data from randomized trials begin with a “high” default rating as per GRADE recommendations.
2) The decision to upgrade or downgrade an assessment level was made independently by 2 authors (SDS and JWF) with any disagreements regarding inclusion of citations being referred to a third author for mediation until consensus achieved. Reasons for upgrading or downgrading a rating include:
    a. Reason for Upgrade:
        i. Achieving ‘External Validation’
        ii. Achieving ‘Analytical Validation’
        iii. Achieving ‘Clinical Utility’

    NB: Achieving ‘Clinical Validation’ was not considered a reason to upgrade GRADE rating as studies achieving this criterion begin at a default ‘high’ GRADE rating
    b. Reasons for Downgrade:
        i. Broad ranges in effect size not explainable by inconsistent methodology or techniques
        ii. Within-study bias (eg Abstract or Case Report)



eFigure: PRISMA Diagram of Search Strategy. Figure describes the search search strategy and articles included and excluded.

eTable 1: Interpretation of the four levels of evidence used in the GRADE profile

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

eTable 2: Susceptibility/ Risk Biomarkers

Biomarker	Biomarker Level		Type of Study	Interpretation	Critical Evaluation				GRADE	References
	HS	OR			External Validation	Analytical Validation	Clinical Validation	Clinical Utility		
Serum Epigenetic Markers	Differentially Expressed	NR	Case-Control Study	Association but no analysis of predictive power or potential	N	N	N	N	Low	Ref 10
Tissue Epigenetic Markers	Differentially Expressed	NR	Case-Control Study	Association but no analysis of predictive power or potential	N	N	N	N	Low	Ref 11
Serum RBP4	Increased	OR = 3.86 (P < 0.001)	Case-Control Regression Modelling	High serum RBP4 and levels were associated with an increased risk for HS	N	N	N	N	Low	Ref 22
Serum Ghrelin	Decreased	OR = 3.86 (P < 0.001)	Case-Control Regression Modelling	Low ghrelin levels were associated with an increased risk for HS	N	N	N	N	Low	Ref 22
Serum Visfatin	Increased	OR = 1.56 (P = 0.003)	Case Control Regression Modelling	Increased serum visfatin increases the risk of HS	N	N	N	N	Low	Ref 12
BMI (Newborn)	increased	HR = 1.36 (lightest) - 1.39 (heaveiest) babies (p = 0.04)	Regression modelling	Both babies with lightest and heaviest weight are at increased risk of developing HS	N	N	N	N	Low	Ref 24
	Decreased	HR = 1.36 (p = 0.04)			N	N	N	N	Low	
BMI (Children)	Increased	HR = 1.32 at 7 years to 1.50 at 13 years	Regression modelling	Increasing BMI in childhood is associated with a greater risk of developing HS	N	N	N	N	Low	Ref 24
Depression, Type 1 diabetes, asthma, disease of vagina/vulva	Increased	NR	Retrospective cohort	The high preceding prevalence noted in this study suggests predictive potential	N	N	N	N	Low	Ref 25
TLR 10 single nucleotide polymorphisms	Not given	NR	Case control	Association	N	N	N	N	Low	Ref 23

eTable 3: Diagnostic Biomarkers

Biomarker	Statistical Association		Type of Study	Interpretation	Critical Evaluation of Biomarkers				GRADE	References
	Population of Comparison	Significance			External Validation	Analytical Validation	Clinical Validation	Clinical Utility		
Tissue / Serum Lipocalin-2	HC	P < 0.001	Observational Case Control	Elevation associated with HS and severity of HS	N	N Matched only for gender	N	N	Low	Ref 98
Plasma Grehlin	HC	OR = 3.86 P = 0.013	Observational Case Control	Decreased levels associated with HS	N	N	N	N	Low	Ref 22
Plasma RBP4	HC	OR = 14.5 P < 0.0001		Elevation associated with HS	N	N	N	N	Low	
Serum Ferritin	HC	P < 0.001	Observational Case Control	Decreased levels associated with HS	N	N Insufficient info on controls in Ref 34.	N	N	Low	Ref 34
Serum Transferrin saturation	HC	P < 0.001	Observational Case Control	Decreased levels associated with HS	N	N Insufficient info on controls in Ref 34.	N	N	Low	Ref 34
Serum Iron	HC	P<0.001	Observational Case Control	Decreased levels associated with HS	N	N Insufficient info on controls in Ref 34.	N	N	Low	Ref 34
Tissue S100A4	HC	P = 0.02	Observational Case Control	Elevation associated with HS	N	N	N	N	Low	Ref 39
Serum sTNF-R1	HC	P < 0.01	Observational Case Control	Elevation associated with HS	N	N	N	N	Low	Ref 37
Serum Visfatin	HC	P =0.02	Observational Case Control	Elevation associated with HS	N	N	N	N	Low	Ref 12
Serum ASCA (IgG and IgA)	HC	P <0.001	Observational Case Control	Elevation associated with HS	N	N	N	N	Low	Ref 100
Serum MMP8	HC	P < 0.01	Observational Case Control	Elevation associated with HS	N	N	N	N	Low	Ref 101
Tissue MMP8	HC	P < 0.01			N	N	N	N	Low	Ref 101
Salivary Infrared Signatures	HC	P=0.00014	Observational Case Control	Observational Study	N	N	N	N	Low	Ref 102
Fat percentage	HC	P <0.0001	Univariate and Regression Modelling	High fat percentage, low muscle percentage and higher basal metabolic rate are associated with HS	N	N	N	N	Low	Ref 103
Muscle percentage	HC	P < 0.0001			N	N	N	N	Low	
Bone mass percentage	HC	P < 0.0001			N	N	N	N	Low	
Waist circumference	HC	P < 0.0001			N	N	N	N	Low	
Waist/ hip ratio	HC	P < 0.0001			N	N	N	N	Low	
BMR	HC	P < 0.0001			N	N	N	N	Low	
Serum natural T-regs	HC	P = 0.0012	Observational Case Control	Decreased levels associated with HS	N	N	N	N	Low	Ref 104
Serum T-cells	HC	Naïve T-cells (P = 0.0347) Memory T-cells (P = 0.0264)	Observational Case Control	Decreased levels associated with HS	N	N	N	N	Low	Ref 104
Tissue CCL-26	HC	P = 0.004	Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 106
Leukotriene B4	HC	P <0.001	Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 107
	Acinetobacter / Moraxella (HC)	P = 0.1			Y	N	N	N	Moderate	
	Staph Epidermis	Not given			Y	N	N	N	Moderate	
	Porphyromonas Peptoniphilus (HC)	P = 0.02			Y	N	N	N	Moderate	
	Propionibacterium acnes (NLT)	P < 0.001			Y	N	N	N	Moderate	
Tissue IL-1RA	Non-Lesional Tissue	1.5 fold increase P=0.0112	Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 55
Tissue IL-1B	HC	31 fold increase P=0.0028	Observational Case Control	Elevation Associated with HS	Y	N	N	N	Moderate	Ref 31
	Non-Lesional Tissue	P<0.001								Ref 30
		P<0.001								Ref 55
Tissue IL-6	Non-Lesional Tissue	P=0.05	Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 38
Serum IL-6R	HC	3.7 fold increase P=0.0028	Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 48
Serum IL-10	Non-Lesional Tissue	34 fold increase P=0.05	Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 38
Tissue IL-11	Non-Lesional Tissue	11 fold increase P=0.0056	Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 113
Tissue IL-16	Non-Lesional Tissue	5.3 fold increase P=0.0028	Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 113
Tissue IL-17C	Non-Lesional Tissue	P<0.01	Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 56
Serum IL-32	HC	P=0.01	Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 114

Tissue IL-32a Tissue IL-32 B Tissue IL32g	Non-Lesional Tissue	P=0.01 P=0.0001 P=0.0161	Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 114
Serum IL-36a Serum IL-36B Serum IL-36 g Serum IL-36RA	HC		Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 115
Tissue IL-36a Tissue IL-36B Tissue IL36g Tissue IL36RA	HC	P = 0.0174 P = 0.0001 P = 0.0161 P = 0.0001	Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 116
Tissue IL37	HC	P = 0.0001	Observational Case Control	Elevation associated with HS Tissue	N	N	N	N	Low	Ref 116
Tissue IL38	HC	P = 0.0069	Observational Case Control	Elevation associated with HS Tissue	N	N	N	N	Low	Ref 116
Serum TNF-a	Non-Lesional Tissue	P=0.02	Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 47
Serum total monocytes (absolute count)	HC	HC vs. Hurley Stage III P = 0.004	Observational Case Control	Elevation associated with HS Tissue	N	N	N	N	Low	Ref 47
Serum $CD14^{bright}/CD16^{dim}$ (absolute count)	HC	HC vs. Hurley Stage III: P = 0.001	Observational Case Control	Elevation associated with HS Tissue	N	N	N	N	Low	Ref 47
Serum patrolling monocytes (absolute count)	HC	HC vs. Hurley Stage III: P = 0.037	Observational Case Control	Elevation associated with HS Tissue	N	N	N	N	Low	Ref 47
Tissue TNF-a	Non-Lesional Tissue	P=0.01 P<0.01 P<0.001 P<0.05 NS	Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 31 Ref 32 Ref 33 Ref 55 Ref 40
Serum TNFR2	HC	P=0.0028	Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 32
Tissue hBD3	HC	P = 0.004	Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 31
Tissue hBD1	HC	P = 0.014	Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 31
Tissue hBD2	HC	P < 0.001	Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 31
Serum s100A7	HC	P<0.001	Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 41
Tissue LL37	Non-Lesional Tissue	P<0.05	Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 41
Tissue a-MSH	Non-Lesional Tissue	P<0.01	Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 41
Tissue CCL3	Non-Lesional Tissue	P=0.0196	Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 32
Tissue CCL5	Non-Lesional Tissue	P =0.0112	Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 32
Tissue CCl20	Non-Lesional Tissue	P<0.05	Observational Case Control	Elevation Associated with HS	Y	N	N	N	Low	Ref 31 Ref 40
Tissue CCL27	Non-Lesional Tissue	P<0.05	Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 40
Serum ESR	HC	P<0.001 P<0.01	Observational Case Control Multivariate Logistic Regression	Elevation Associated with HS	N	N	N	N	Low	Ref 37 Ref 45
Serum IFNg	HC	P=0.027 p-=NS	Observational Case Control	Elevation Associated with HS	Y	N	N	N	Low	Ref 31 Ref 40
Serum MMP2	HC	P<0.05	Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 31
Tissue BLC	Non-Lesional Tissue	10.5 fold increase P=0.0056	Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 30
Tissue ICAM1	Non-Lesional Tissue	3.1 fold increase P=0.0028	Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 115
Tissue CXCL9	Non-Lesional Tissue	16 fold increase P=0.0028	Observational Case Control	Elevation Associated with HS	N	N	N	N	Low	Ref 30

Legend: *Abstract Only

eTable 4: Monitoring Biomarkers

Biomarker	Disease Severity Association		Type of Study	Interpretation	Critical Evaluation				GRADE Evidence Profile	Reference
	Disease Severity Index	Significance			External Validation	Analytical Validation	Clinical Validation	Clinical Utility		
Serum Lipocalin 2	Sartorius Score	R= 0.65 P < 0.001	Observational Case Control	Correlation with Disease Severity	N	N	N	N	Low	Ref 98
Serum Retinol binding protein 4 (RBP4)	HS PGA	R = 0.639 P < 0.0001	Observational Case Control	Correlation with Disease Severity	N	N	N	N	Low	Ref 22
Serum IL-17 (Stimulated PBMCs)	Hurley Stage	Heat-killed Candida albicans (HKCA)-Stimulation: Hurley I and II vs. III: P = 0.008 Heat-killed Staphylococcus aureus (HKSA)-Stimulation: Hurley I and II vs. III: P = 0.026	Observational Case Control	Decreased with Disease Severity	N	N	N	N	Low	Ref 47**
Serum IL-10 (Stimulated PBMCs)	Hurley Stage	Heat-killed Staphylococcus aureus (HKSA)-Stimulation: Hurley I and II vs. III: P = 0.048	Observational Case Control	Decreased with Disease Severity	N	N	N	N	Low	Ref 47**
Serum total monocytes (absolute count)	Hurley Stage	Hurley Stage I vs. III: P = 0.026	Observational Case Control	Correlation with Disease Severity	N	N	N	N	Low	Ref 47
	Sartorius Score	R = 0.361 P = 0.003								
Serum CD14^{bright}/CD16^{dim} (absolute count)	Hurley Stage	Hurley Stage I vs. III: P = 0.012 Hurley II vs. III: P = 0.008	Observational Case Control	Correlation with Disease Severity	N	N	N	N	Low	Ref 47
Serum IL-1B	HS PGA	R = 0.28 P= 0.016	Observational Case Control	Correlation with Disease Severity	N	N	N	N	Low	Ref 37
Plasma YLK-40 /Chitinase 3	Hurley Stage	P < 0.001	Observational Case Control	Correlation with Disease Severity	N	N	N	N	Low	Ref 36
Serum Hepcidin	HS-PGA	P=0.03	Observational Case Control	Correlation with Disease Severity	N	N	N	N	Low	Ref 35
Serum IL-2R	Hurley Stage	Hurley I vs. II: P = 0.005 Hurley I vs. III: P < 0.0001 Hurley II vs. I: P = 0.005 Hurley II vs. III: P < 0.001 Hurley III vs. I: P < 0.0001 Hurley III vs. II: P < 0.001	Observational Case Control	Correlation with Disease Severity	N	N	N	N	Low	Ref 99
WBC	Hurley Stage	Hurley I vs. II: P = 0.03	Observational Case Control	Correlation with Disease Severity	N	N	N	N	Low	Ref 99
Serum IL-6	HS-PGA	R = 0.53 P<0.001	Observational Case Control	Correlation with Disease Severity	N	N	N	N	Low	Ref 37
	Hurley Stage	Kruskal-Wallis: P < 0.001								
Serum IL-10	HS-PGA	R = 0.34 P = 0.0034	Observational Case Control	Correlation with Disease Severity	N	N	N	N	Low	Ref 37
Serum IL-10 (Stimulated PBMCs)	Hurley Stage	Heat-killed Staphylococcus aureus (HKSA)-Stimulation: Hurley I and II vs. III: P = 0.026		Decreased with Disease Severity	N	N	N	N	Low	Ref 47
Serum IL12p70	HS-PGA	R = 0.30 P = 0.008	Observational Case Control	Correlation with Disease Severity	N	N	N	N	Low	Ref 37
Soluble TNF receptor II	HS-PGA	R = 0.4 P < 0.001	Observational Case Control	Correlation with Disease Severity	N	N	N	N	Low	Ref 37
	Hurley Stage	Kruskal-Wallis: P = 0.001								
Soluble TNF receptor I	Hurley Stage	Kruskal-Wallis: P < 0.001	Observational Case Control	Correlation with Disease Severity	N	N	N	N	Low	Ref 37
Serum TNF-a	HS-PGA	One-Unit increase in TNF-a level: 9.74 times (CI 1.1-107.8) higher risk of severe disease (HS-PGA 4 or 5) vs. (HS-PGA 1 or 2)	Observational Case Control and ordinal regression modelling	Correlation with Disease Severity	N	N	N	N	Low	Ref 108
Sonographic Hurley staging	Hurley Stage	Higher number of nodules found by clinical examination vs. sonographic: P < 0.01 Higher number of abscesses found by sonographic vs. clinical examination: P < 0.01	Observational Case Control	44.7% of patients with Hurley stage I as determined by clinical examination changed to a more severe stage after sonographic examination	N	N	N	N	Low	Ref 61
Sonographic Scoring of HS based on no. of fluid collections, no. of fistulous tracts and no. of affected localizations	Hurley Stage	Fleiss' kappa test: (K = 0.27; P = 0.02)	Observational Case Control	Correlation with Disease Severity	N	N	N	N	Low	Ref 60
MRI Dilatation of dermal tunnels	Hurley Stage	Descriptive	Descriptive	Correlation with Disease Severity	N	N	N	N	Low	Ref 109***
Medical infrared thermography	Skin inflammation	Descriptive	Observational Case Control	Correlation with skin inflammation	N	N	N	N	Low	Ref 110

Echocardiography (epicardial fat thickness)	Hurley Stage	R = 0.432 P = 0.001 For EFT ≥ 5.9 mm: Hurley III vs. I and II: OR = 1.876 P = 0.018	Multivariate analysis and regression modelling	Correlation with Disease Severity	N	N	N	N	Low	Ref 111
Serum MMP8	mHSS	R = 0.454 P = 0.039	Observational Case Control	Correlation with Disease Severity	N	N	N	N	Low	Ref 101
	Number of affected areas with inflammatory nodes	R = 0.514 P = 0.017								
	Number of areas with fistulas	R = 0.486 P = 0.026								
Serum ASCA (IgG and IgA)	Hurley Stage	P < 0.001 For Hurley III: OR = 3.54 P = 0.003	Univariate and Multivariate analysis	Correlation with Disease Severity	N	N	N	N	Low	Ref 100
Serum Neutrophil Count	Hurley Stage	Kruskal-Wallis: P = 0.002	Multivariate analysis and regression modelling	Correlation with Disease Severity	N	N	N	N	Low	Ref 67
	mHSS	R = 0.33 P = 0.0009								
Smoking pack-years	Hurley Stage	Hurley III and II vs. I: OR = 1.02 P = 0.001	Multivariate analysis and regression modelling	Correlation with Disease Severity	N	N	N	N	Low	Ref 16
Disease duration	Hurley Stage	Hurley III and II vs. I: OR = 1.03 P < 0.001	Multivariate analysis and regression modelling	Correlation with Disease Severity	N	N	N	N	Low	Ref 16
Localization	Hurley Stage	Hurley III and II vs. I: Axillary OR = 2.24 P < 0.001 perianal OR = 1.92 P < 0.001 Mammary OR = 1.48 P = 0.03								
Tissue Citrullinated H3 Protein	Hurley Stage	R = 0.75 P < 0.0001	Observational Case Control	Correlation with Disease Severity	N	N	N	N	Low	Ref 64

Legend: **This study involved stimulation of PBMCs compared to other observational studies.
*** Case Report only

eTable 5: Predictive Biomarkers

Biomarker	Response to Therapy		Type of Study	Interpretation	Critical Evaluation				GRADE Evidence Profile	Reference
	Treatment	Outcome Measure (Significance)			External Validation	Analytical Validation	Clinical Validation	Clinical Utility		
Serum CRP	Infliximab	PGA (P=0.0112)	Multivariate analysis and regression modelling Prospective pilot	Higher levels of CRP correlate with lower response to infliximab	N	N	N	N	Low	Ref 75
	Adalimumab	mHSS (P=0.04								Ref 38
Serum IL-6	Infliximab	PGA (p=0.02064)	Multivariate analysis and regression modelling Prospective pilot	Higher IL-6 correlate to lower response to infliximab	N	N	N	N	Low	Ref 75
	Adalimumab	mHSS (p=0.003)								Ref 38
Serum IL-1B	Etanercept	mHSS (p=0.022)	Multivariate analysis and regression modelling Case Control	Clinical Improvement correlated with increased IL-1B	N	N	N	N	Low	Ref 47
Serum IL-17	Etanercept	mHSS (p=0.022)	Multivariate analysis and regression modelling Case Control	Clinical Improvement correlated with increased IL17	N	N	N	N	Low	Ref 47
Serum IL-8	Adalimumab	mHSS (R=0.52) (P=0.024)	Regression Analysis Case Control	Decreasing IL-8 correlated with treatment response	N	N	N	N	Low	Ref 38
sTNF-RI	Adalimumab	mHSS (R=0.55) (p=0.015)	Linear Correlations		N	N	N	N	Low	Ref 38
Serum Anti-Adalimumab antibody Level;	Adalimumab	HiSCR (P=0.0006)	Multivariate analysis and regression modelling Retrospective case series (no control arm)	Correlation between serum adalimumab levels, anti-adalimumab antibodies and clinical response.	N	N	N	N	Low	Ref 112
Tissue Cell Counts CXCL6	Adalimumab	R vs NR (P=0.046)	Multivariate analysis and regression modelling Observational Mechanistic Study	Higher tissue cell counts associated with non-responders to Adalimumab therapy	N	N	N	N	Low	Ref 65
Tissue Cell Counts CXCR1	Adalimumab	R vs NR (p=0.009)								
Tissue Cell Counts IL-1a	Adalimumab	R vs NR (p=0.0009)								
Tissue Cell Counts CCL 17	Adalimumab	R vs NR (p=0.027)								
Tissue Cell Counts CCR7	Adalimumab	R vs NR (p=0.004)								
Tissue Cell Counts CXCR4	Adalimumab	R vs NR (p=0.01)								
TISSUE Cell Counts CD19	Adalimumab	R vs NR (p=0.003)								
Tissue Cell Counts CXCR5	Adalimumab	R vs NR (p=0.008)								
Tissue Cell Counts BAFF	Adalimumab	R vs NR (p=0.005)								

eTable 6: Limitations and Proposed Future Directions of Biomarker Research in HS

Limitation(s)	Proposed Solution(s)
Lack of Independent Validation of HS Biomarkers	Biomarker-Specific, Multicentre, Independent Validation Studies
Biomarker Identification Based on Pre-selected targets only	Assumption-Free 'omics' biomarker feature selection studies and methodologies
Lack of co-linearity assessments in existing range of biomarkers	Directed assessment of co-linearity in currently identified biomarkers Identify HS-specific biomarkers in assumption-free datasets
Deficiencies in existing Clinical Outcomes for validation of monitoring and predictive biomarkers	Development of Validated, Reliable Clinical Outcome Measures Development of Treat-to-target outcome measures
Need for biomarker integration into clinical trials	Involvement of stakeholders in development in priorities and goals for biomarker development in HS
High variability in biopsy techniques and definitions	International Consensus Agreement on Biopsy sites and techniques

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