SUPPLEMENTARY MATERIAL

Supplementary Text 1: Research questions (PICO framework)

Research questions	***Population***	***Intervention (Exposure)***	***Comparison***	***Outcome***
What is the evidence that interferon measurement is useful in the diagnosis of RMDs?				
	People presenting with any RMD Control population	IFN pathway assay measurement	RMD vs control population	Association between measurement of IFN pathway activation and RMD diagnosis
What is the evidence that interferon measurement reflects disease activity in RMDs?				
	People presenting with any RMD	IFN pathway assay measurement	Disease activity measurement	Association between measurement of IFN pathway activation and disease activity (difference between groups, association, correlation)
What is the evidence that interferon measurement is useful for the prognosis (natural history) of clinical status in RMDs?				
	People presenting with any RMD, 'at-risk' of RMDs or in preclinical	IFN pathway assay measurement	Disease exacerbation / flare vs no disease exacerbation / no flare	Association between measurement of IFN pathway activation and disease exacerbation,

	stages		Progression to clinical RMD (fulfillment of classification criteria) Severity of the clinical course (occurrence of comorbidity or organ involvement or damage)	progression to clinical RMD or severity
What is the evidence that interferon measurement is useful for the prognosis (response to treatment) in RMDs?				
	People presenting with any RMD starting a new therapy	IFN pathway assay measurement	Clinical response to treatment	Association between measurement of IFN pathway activation and clinical response
What is the evidence that interferon measurement is responsive (i.e. changes with changing disease status or treatment)?				
	People presenting with any RMD	IFN pathway assay measurement	Change in serial IFN measurements	Responsiveness (change) of serial measurements of IFN pathway activation

Supplementary Text 2: Search strategy for Ovid MEDLINE

1 interferon/ (21958)

2 (interferon* adj2 (biomarker* or sign*)).ti. (992)

3 (interferon* adj2 (biomarker* or sign*)).ab. /freq=2 (246)

4 exp interferon type i/ (48691)

5 "type 1 IFN".ti. (41)

6 "type 1 IFN".ab. /freq=2 (90)

7 (type 1 adj3 interferon*).ti. (205)

8 (type 1 adj3 interferon*).ab. /freq=2 (98)

9 (interferon* adj1 (alpha or alfa)).ti. (12678)

10 (interferon* adj1 (alpha or alfa)).ab. /freq=2 (5014)

11 (interferon* adj1 beta).ti. (4226)

12 (interferon* adj1 beta).ab. /freq=2 (1557)

13 or/1-12 [inteferons] (71976)

14 Lupus Erythematosus, Systemic/ (53310)

15 (systemic adj2 lupus).ti. (28721)

16 (systemic adj2 lupus).ab. /freq=2 (4269)

17 exp Arthritis, Rheumatoid/ (110425)

18 ((reumat* or rheumat* or psoriatic or juvenile or inflammatory or idiopathic) adj3 (arthrit* or artrit*)).ti. (71763)

19 ((reumat* or rheumat* or psoriatic or juvenile or inflammatory or idiopathic) adj3 (arthrit* or artrit*)).ab. /freq=2 (21982)

20 Arthralgia/ (7938)

21 arthralgia.ti. (631)

22 arthralgia.ab. /freq=2 (888)

23 Connective Tissue Diseases/ (6410)

24 connective tissue disease*.ti. (3395)

25 connective tissue disease*.ab. /freq=2 (1408)

26 exp Scleroderma, Systemic/ (20043)

27 (scleroderma or systemic sclerosis).ti. (17190)

28 (scleroderma or systemic sclerosis).ab. /freq=2 (6774)

29 Sjogren's Syndrome/ (12463)

30 ((sjogren* or sjoegren or sicca) adj2 syndrome).ti. (9830)

31 ((sjogren* or sjoegren or sicca) adj2 syndrome).ab. /freq=2 (3362)

32 (spondyloarthropath* or spondylarthropath*).ti. (1514)

33 (spondyloarthropath* or spondylarthropath*).ab. /freq=2 (748)

34 Spondylitis, Ankylosing/ (14342)

35 ankylosing spondylitis.ti. (8361)

36 ankylosing spondylitis.ab. /freq=2 (2758)

37 Vasculitis/ (12667)

38 vasculitis.ti. (11783)

39 vasculitis.ab. /freq=2 (9137)

40 Antiphospholipid Syndrome/ (7889)

41 (antiphospholipid syndrome or APS or APLS).ti. (5112)

42 (antiphospholipid syndrome or APS or APLS).ab. /freq=2 (9483)

43 Still's Disease, Adult-Onset/ (1280)

44 Still's Disease.ti. (1536)

45 Still's Disease.ab. /freq=2 (311)

46 exp Myositis/ (19181)

47 myositis.ti. (4738)

48 myostitis.ab. /freq=2 (0)

49 (Behcet* adj (disease or syndrome)).ti. (7844)

50 (Behcet* adj (disease or syndrome)).ab. /freq=2 (2829)

51 ((IgG4* or Immunoglobulin G4*) adj2 (syndrome or disease)).ti. (1246)

52 ((IgG4* or Immunoglobulin G4*) adj2 (syndrome or disease)).ab. /freq=2 (1188)

53 or/14-52 [RMD] (291413)

54 13 and 53 (1855)

55 exp animals/ not humans.sh. (4641021)

56 54 not 55 (1754)

57 remove duplicates from 56 (1744)

58 limit 57 to english language (1563)

Supplementary Text 3: Search strategy for Embase

1 interferon/ (78376)

2 (interferon* adj2 (biomarker* or sign*)).ti. (1447)

3 (interferon* adj2 (biomarker* or sign*)).ab. /freq=2 (518)

4 alpha interferon/ (54088)

5 alpha interferon A/ (289)

6 beta interferon/ (24399)

7 (interferon* adj1 (alpha or alfa)).ti. (15287)

8 (interferon* adj1 (alpha or alfa)).ab. /freq=2 (6077)

9 (interferon* adj1 beta).ti. (5808)

10 (interferon* adj1 beta).ab. /freq=2 (2295)

11 (type 1 adj3 interferon*).ti. (350)

12 "type 1 INF*".ab. /freq=2 (86)

13 or/1-12 [type 1 interferon] (151212)

14 systemic lupus erythematosus/ (96577)

15 (systemic adj2 lupus).ti. (40830)

16 (systemic adj2 lupus).ab. /freq=2 (6638)

17 exp Arthritis, Rheumatoid/ (219451)

18 ((reumat* or rheumat* or psoriatic or juvenile or inflammatory or idiopathic) adj3 (arthrit* or artrit*)).ti. (114993)

19 ((reumat* or rheumat* or psoriatic or juvenile or inflammatory or idiopathic) adj3 (arthrit* or artrit*)).ab. /freq=2 (41573)

20 Arthralgia/ (60181)

21 arthralgia.ti. (911)

22 arthralgia.ab. /freq=2 (1866)

23 Connective Tissue Diseases/ (11630)

24 connective tissue disease*.ti. (4727)

25 connective tissue disease*.ab. /freq=2 (2429)

26 Scleroderma, Systemic/ (17314)

27 (scleroderma or systemic sclerosis).ti. (26554)

28 (scleroderma or systemic sclerosis).ab. /freq=2 (12470)

29 Sjogren's Syndrome/ (12089)

30 ((sjogren* or sjoegren or sicca) adj2 syndrome).ti. (13295)

31 (spondyloarthropath* or spondylarthropath*).ab. /freq=2 (1029)

32 Spondylitis, Ankylosing/ (15590)

33 ankylosing spondylitis.ti. (13053)

34 ankylosing spondylitis.ab. /freq=2 (5036)

35 Vasculitis/ (40212)

36 vasculitis.ti. (16629)

37 vasculitis.ab. /freq=2 (15699)

38 Antiphospholipid Syndrome/ (16255)

39 (antiphospholipid syndrome or APS or APLS).ti. (7161)

40 (antiphospholipid syndrome or APS or APLS).ab. /freq=2 (14445)

41 Still's Disease, Adult-Onset/ (1317)

42 still's disease.ti. (2021)

43 still's disease.ab. /freq=2 (519)

44 Myositis/ (16388)

45 myositis.ti. (77)

46 myositis.ab. /freq=2 (37)

47 Behcet Syndrome/ (8519)

48 (Behcet* adj2 (syndrome or disease)).ti. (11087)

49 (Behcet* adj2 (syndrome or disease)).ab. /freq=2 (4765)

50 ((IgG4* or "Immunoglobulin G") adj2 (sydrome or disease)).ti. (1569)

51 ((IgG4* or "Immunoglobulin G") adj2 (sydrome or disease)).ab. /freq=2 (1713)

52 or/14-51 [RMD] (523688)

53 13 and 52 [interferon type 1 and RMD] (9125)

54 (exp animal/ or nonhuman/) not exp human/ (7037850)

55 53 not 54 (8634)

Supplementary Text 4: Search strategy for Web of Science

Indexes=SCI-EXPANDED, CPCI-S, ESCI Timespan=1900-2019

1 (TS=((interferon* Near/1 (alpha or alfa)))) AND LANGUAGE: (English)

2 (TS=((interferon* Near/1 beta))) AND LANGUAGE: (English)

3 (TS=((type 1 Near/3 interferon*))) AND LANGUAGE: (English)

4 TS=("type 1 INF*") or TS=(interferon* Near/2 biomarker*) or TS=(interferon* Near/2 sign*)

5 #4 OR #3 OR #2 OR #1

6 TS=((systemic Near/2 lupus))

7 TS=(((reumat* or rheumat* or psoriatic or juvenile or inflammatory or idiopathic) Near/3 (arthrit* or artrit*)))

8 TS=(Arthralgia)

9 TS=("connective tissue disease*")

10 TS=((scleroderma or "systemic sclerosis"))

11 TS=(((sjogren* or sjoegren or Sjogren's or sicca) Near/2 syndrome))

12 TS=((spondyloarthropath* or spondylarthropath*))

13 TS=("ankylosing spondylitis")

14 TS=(vasculitis)

15 TS=(("antiphospholipid syndrome" or APS or APLS))

16 TS=("still's disease")

17 TS=(Myositis)

18 TS=((Behcet* Near/2 (syndrome or disease)))

19 TS=(((IgG4* or "Immunoglobulin G") Near/2 (sydrome or disease)))

20 #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6

21 (#20 AND #5) AND LANGUAGE: (English)

22 (TS=("type 1 INF*") or TS=(interferon* Near/2 biomarker*) or TS=(interferon* Near/2 sign*)) AND LANGUAGE: (English)

24 (#23 AND #20) AND LANGUAGE: (English)

23 #22 OR #3 OR #2 OR #1

Supplementary Text 5: Inclusion and exclusion criteria (first step)

Inclusion criteria
• Subjects: human patients with RMDs • RMDs: systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), arthritis, juvenile idiopathic arthritis (JIA), arthralgia, Sjögren's syndrome (pSS), Sicca syndrome, dermatomyositis (DM), polymyositis (PM), myositis, connective tissue disease (CTD), scleroderma, systemic sclerosis (SSc), psoriatic arthritis (PsA), ankylosing spondylitis (AS), spondyloarthropathies (SpA), vasculitis, NCA-associated vasculitis (AAV), giant cell arteritis (GCA), antiphospholipid syndrome (APS), Still disease, adult-onset Still disease (AOSD), Behçet disease (BD), IgG4-related disease (IGRD) • Language: English only • Study design: longitudinal studies, cross-sectional studies, randomized controlled trials, case-control studies, cohort studies, non-controlled trials, intervention studies • Samples: blood, serum, plasma studies
Exclusion criteria
• Subjects: animal studies, pre-clinical studies, genetic studies • Study design: case studies, letters, non-original articles (reviews, editorials, opinion pieces, etc) • Samples: peripheral tissues or fluids other than blood, serum or plasma • Papers that do not specify the type of interferon that the assay measures

Supplementary Text 6: Eligibility criteria for clinical research questions

RQ1: What is the evidence that interferon measurement is useful in the diagnosis of RMDs?

- Clinical outcome: RMD diagnosis (validated classification criteria or diagnosis confirmed by a physician)
- Control population
- Study type: cross-sectional studies, diagnostic accuracy studies, case-control studies, cohort studies

RQ2: What is the evidence that interferon measurement reflects disease activity in RMDs?

- Clinical outcome: any disease activity measured by a validated instrument, including CRP or ESR levels, expressed as continuous or dichotomous variable
- Study type: longitudinal studies, randomized control trials, non-controlled trials, cross-sectional studies, case-control studies, cohort studies

RQ3: What is the evidence that interferon measurement is useful for the prognosis (natural history) of clinical status in RMDs?

- Clinical outcomes:
    - Disease exacerbation (pre-defined increase in disease activity)
    - Flare occurrence (by validated flare instruments)
    - Progression to clinical RMD (fulfillment of classification criteria)
    - Severity of the clinical course (occurrence of comorbidity or organ involvement or damage)
- Study type: longitudinal studies, randomized control trials, non-controlled trials, cohort studies

RQ4: What is the evidence that interferon measurement is useful for the prognosis (response to treatment) in RMDs?

- Clinical outcome: clinical response (validated response criteria or pre-defined change in disease active instrument) upon new treatment
- Study type: longitudinal studies, randomized control trials, non-controlled trials

RQ5: What is the evidence that interferon measurement is responsive (i.e. changes with changing disease status or treatment)?

- Clinical outcomes:
    - Change in measurements of IFN pathway activation before and after any treatment
    - Change in measurements of IFN pathway activation before and after disease exacerbation or flare
- Study type: longitudinal studies, randomized control trials, non-controlled trials, cohort studies

Supplementary Text 7: Risk of bias instruments

Research question	Instrument
RQ1	QUADAS-2 [1]
RQ2	JBI analytical cross sectional studies critical appraisal tool [2]
RQ3	QUIPS [3]
RQ4	Cochrane RoB2 [4] QUIPS [3]
RQ5	Cochrane RoB2 [4] JBI case series critical appraisal tool [5]

Supplementary Text 8: Summary and characteristics of assays measuring IFN pathway activation.

Category	Sub-category	Target	Sample source	Readout
Immunoassays	*Immunoassay*	Soluble protein(s) (IFNa/b proteins, IFN-stimulated proteins, chemokines, etc)	Serum, plasma, or whole blood lysates	Protein(s) concentration (individual or grouped as protein scores)
	DELFIA	Soluble protein(s) (IFNa/b proteins, IFN-stimulated proteins, chemokines, etc)	Serum or plasma	Protein(s) concentration (individual or grouped as protein scores)
	Simoa	Soluble protein(s) (IFNa/b proteins, IFN-stimulated proteins, chemokines, etc)	Serum or plasma	Protein(s) concentration (individual or grouped as protein scores)
	Acid-precipitation immunoassay	Soluble protein(s) (IFNa/b proteins, IFN-stimulated proteins, chemokines, etc)	Serum or plasma	Protein(s) concentration (individual or grouped as protein scores)
	Radioinmmunoassay	Soluble protein(s) (IFNa/b proteins, IFN-stimulated proteins, chemokines, etc)	Serum or plasma	Protein(s) concentration (individual or grouped as protein scores)
Flow cytometry	*Flow cytometry to detect IFN-induced proteins*	Membrane-bound IFN-stimulated proteins	Whole blood or isolated peripheral blood mononuclear cells (PBMCs)	Protein expression levels
Microarrays	*Microarray modules*	RNA from subsets of IFN-stimulated genes (usually pre-defined and sharing expression patterns)	RNA isolated from whole blood or PBMCs	Quantitative gene expression (fold enrichment/change) or categorical (number of genes up- and down-regulated, modular expression of gene

				signatures)
	Microarray scores and clustering	RNA from subsets of IFN-stimulated genes (usually pre-defined and sharing expression patterns)	RNA isolated from whole blood or PBMCs	Quantitative gene expression (gene scores)
qPCR	*qPCR*	RNA levels (IFN-a/b gene(s), IFN-stimulated gene(s), IFN-induced chemokine(s), etc)	RNA isolated from whole blood or PBMCs	Quantitative gene expression (fold enrichment/changes) either individual or composite scores (set of genes)
RNA Seq	*RNA Seq*	RNA from IFN-gene expression in whole transcriptome expression analysis	RNA isolated from whole blood or PBMCs	Quantitative gene expression or categorical (transcriptomic signature)
Nanostring	*Nanostring*	RNA from IFN-stimulated genes (pre-defined)	RNA isolated from whole blood or PBMCs	Quantitative gene expression (gene scores)
DNA methylation	*DNA methylation arrays*	Analysis of DNA methylation of IFN-stimulated genes in whole genome arrays	DNA from whole blood, isolated PBMCs or tissues	Number of genes with differential methylation, either individually or in gene sets
	Bisulfite sequencing	Analysis of DNA methylation in pre-defined IFN-stimulated genes sets	DNA from whole blood, isolated PBMCs or tissues	Number of genes with differential methylation, either individually or in pre-defined sets)
Reporter cell assays	*Reporter cell assays by qPCR*	IFN-stimulated gene(s) expression by qPCR in an experimental system upon stimulation with biological samples	Serum or plasma	Quantitative gene expression (fold

				enrichment/changes)
	Reporter cell assays (other)	IFN-stimulated gene(s) expression by luminometric or colorimetric in an experimental system upon stimulation with biological samples	Serum or plasma	Quantitative gene expression (fold enrichment/changes)
Cytopathic effect assay	*Cytopathic effect assay*	Functional (antiviral) effects of IFN in protecting cells from viral infections by analyzing cytopathic features	Serum or plasma	Antiviral activity measured in titres, arbitrary units, etc (quantitative)
Plaque-reducing assay	*Plaque-reducing assay*	Functional (antiviral) effects of IFN in protecting cells from viral infections by analyzing plaques of cultured cells	Serum or plasma	Measure of plaques of cultured cells (semi-quantitative)
Immunohistochemistry (IHQ)	*Immunohistochemistry (IHQ)*	IFN-stimulated proteins expression in tissues	Whole blood or other tissues	Protein levels (semi-quantitative)

Supplementary Table 1: Summary of the studies reporting assays to evaluate the potential use of IFN assays in the diagnosis of SLE.

Category	Sub-category	n assays	Results	Diagnostic statistics	Risk of bias	References
Immunoassays	*Immunoassays detecting IFNa protein*	21	17/21 studies found higher IFNa levels in SLE vs control populations 4 studies reported frequency of positive patients (from 40 to 72%) using different cut-offs	1 (Zecevic, 2018) AUC 0.517 (0.382-0.653), p=0.807; S: 7.3%, Sp: 96.0%, PPV: 80.0%, NPV: 32.0%	High	[6–26]
	Immunoassays detecting IFNb protein	1	4 SLE patients exhibited high IFNb serum levels, whereas 2 exhibited similar levels to controls	0	High	[9]
	Immunoassays detecting IFN-induced proteins	6	***Targets:*** Mx1 (2), Galectin 3 – binding protein (1), galectin 9 (1), MIP1a (2) ***Main findings:*** Increased Mx1 levels in whole blood (lysed) in SLE (2) Increased Galectin 3 serum levels in SLE (1) Increased Galectin 9 – binding protein serum levels in SLE (1) Increased MIP1a serum levels in SLE (1)	0	High	[27–32]
	DELFIA for IFNa	2	***Main findings:*** 2/2 reported IFNa was detected more often in SLE (9/20 and 6/11) samples than controls (0 and 0 HC)	0	High	[33,34]

	DELFIA for IFN-induced proteins	1	***Targets*** sSIGLEC-1 (1) ***Main findings:*** sSIGLEC-1 serum levels increased in SLE vs HC	0	High	[28]
	Simoa for IFNa	2	***Main findings:*** 2/2 reported IFNa serum levels higher in SLE than controls	0	High	[35,36]
	Other assays (Acid-precipitation immunoassay (1), RIA (2))	3		0	Unclear/high	[34,37,38]
Flow cytometry	*Flow cytometry to detect IFN-induced proteins*	6	***Targets:*** SIGLEC1 (3), CD64 (1), ITIM1 (1), Mx1 (1) ***Main findings:*** SIGLEC1 expression was higher in monocytes (2) and pDC (1) in SLE vs controls Increased expression of CD64 (1) and Mx1 (1) in monocytes and ITIM1 in platelets (1) in SLE vs controls	0	High	[20,28,31,39–41]
Microarrays	*Microarray modules*	5	***Sources:*** WB (3), PBMC (1), sorted cell populations (CD4+ and CD8+ T cells, monocytes and neutrophils) (1) ***Main findings:*** 5/5 reported IFN-related modules among the most upregulated genes in SLE vs HC M1.2, M3.4, and M5.12 reported in 3/5 Modular IFN signature observed in SLE ranging from 83% to 100% of the patients	0	High	[42–46]

	Microarray scores and clustering	20	***Sources:*** WB (10), PBMC (4), sorted cell populations (CD4+, T-cells, B-cells, monocytes or platelets) (6) ***Main findings:*** 15/20 reported IFN score and/or ISG expression significantly higher in SLE vs controls IFN signature positive/high patients ranged from 50 to 81% (reported in 5/20) 1/20 reported IFN score follow a bimodal distribution (1)	0	High	[20,39,41,47–63]
qPCR	*qPCR on individual ISG*	4	***Sources:*** WB (2), PBMC (2) ***Targets:*** IFNA (1), Mx1 (2) or ISG15 (1) ***Main findings:*** Increased expression of IFNA (1), Mx1 (2) or ISG15 (1) in SLE vs controls	1 (Yuan, 2018): ISG15: AUC 0.826 (0.715–0.937, p=0.000015), S: 89.3%, Sp: 68.8%	High	[6,64–66]
	qPCR on several ISG	38	***Sources:*** WB (19), leukocytes (3), PBMC (11), sorted cell populations (monocytes or platelets) (5) ***Targets:*** ISG scores calculated from 2 (1), 3 (7), 4 (5), 5 (9), 6 (3), 8 (1), 9 (2), 10 (1) or 23 (1) genes; 4 studies computed 2 scores (GC-A/B, score A/B, type I/II) ***Main findings:*** 38/38 reported IFN score and/or ISG expression significantly higher in SLE vs controls Differences across ISGs reported in	1 (Feng, 2015): IFN score: AUC 0.805, $p=1.4 \cdot 10^{-5}$	Unclear/high	[18,20,29,31,47,56,62,67–96]

			4/38 IFN positive patients ranged from 57 to 64%			
	qPCR on chemokines	1	***Sources:*** Leukocytes (1) ***Targets:*** CCL2 and IP-10 (1) ***Main findings:*** Increased expression of CCL2 and IP-10 in SLE vs controls	0	High	[72]
Nanostring		1	***Sources:*** WB ***Targets:*** 5 ISG ***Main findings:*** IFN score higher in SLE vs controls	0	High	[97]
DNA methylation	*DNA methylation arrays*	9	***Sources:*** WB (2), PBMC (2), sorted cell populations (CD4+ T-cells, CD19+ B-cells, CD14+ monocytes, neutrophils and low density granulocytes) (5) ***Main findings:*** 9/9 reported SLE-specific differentially methylated genes (mostly hypomethylated) related to ISG 6/9 reported ISG-related DMG among those with the largest size effect	1 (Imgenberg-Kreuz, 2019) Hypomethylation (DMG): AUC 0.940	High	[98–106]
	Bisulfite sequencing	3	***Sources:*** WB (2), sorted cell populations (neutrophils) (1) ***Main findings:*** 3/3 confirmed SLE-specific hypomethylated sites	1 (Zhao, 2016) Hypomethylation IFI44L: Site 1: AUC 0.968 (0.954-0.981), S: 93.6%; Sp: 96.8%. Site 2: AUC 0.982 (0.972-0.992), S: 94.1%; Sp:	High	[100,102,107]

				98.2%		
Reporter cell assays	*Reporter cell assays by qPCR*	8	***Main findings:*** 7/8 reported high IFN activity in SLE vs controls 1/8 reported no differences 1/8 reported important differences across genes	0	High	[86,108–114]
	Reporter cell assays (other)	4	***Main findings:*** 4/4 reported higher IFN bioactivity in SLE vs controls 1 reported high IFN activity in 42% of SLE patients	0	High	[115–117]
Cytopathic effect assay		3	***Main findings:*** 3/3 reported higher IFN activity in SLE vs controls	0	High	[118–120]
Plaque-reducing assay		4	***Main findings:*** 4/4 reported higher IFN activity in SLE compared to controls	0	High	[121–124]
IHQ		1	***Target:*** MxA ***Main findings:*** Granulocytes and monocytes from SLE patients also stained positively for MxA protein	0	High	[32]

Supplementary Table 2: Summary of the studies reporting assays to evaluate the potential use of IFN assays in the diagnosis of RA.

Category	Sub-category	n assays	Results	Diagnostic statistics	Risk of bias	References
Immunoassays	*Immunoassays detecting IFNa protein*	2	2/2 studies found higher IFNa levels in RA vs control populations	0	High	[125,126]
	Immunoassays detecting IFNb protein	2	1/2 reported IFNb marginally detected in juvenile chronic arthritis patients 1/2 reported IFNb serum levels higher in juvenile chronic arthritis patients compared to controls	0	High	[125,127]
	DELFIA for IFNa	1	***Main findings:*** IFNa was detected more often in RA (5/19) samples than in controls (0)	0	High	[128]
	Other assays (RIA (2))	2	***Main findings:*** 2/2 reported no differences in IFNa serum levels in RA patients vs controls	0	High	[129,130]
Microarrays	*Microarray scores and clustering*	7	***Sources:*** WB (5), PBMC (1), sorted cell populations (monocytes) (1) ***Targets:*** ISG scores ranging from 5 to 43 ISG ***Main findings:*** 7/7 reported IFN score and/or ISG expression significantly higher in RA vs HC IFN signature positive/high patients ranged from 22% to 45% (reported in 2/7) IFN signature qualitatively differs between RA and SLE (reported in 2/7)	0	High	[52,57,61,131–134]
qPCR	*qPCR on individual ISG*	3	***Sources:*** WB (3) ***Targets:*** IFIT1, IFIT2, IFI44L, ISG15, MXA, MXB, EPSTRLI1, RSAD, HERC5, Ly6E, IFI6, IFI35 (1), IFI44, IFI44L, IFI6, and MX1 (2) or IFI35,	0	High	[84,125,135]

			IFIT3, IFI44, IFI44L, OAS1, SIGLEC1 (1) ***Main findings:*** 1 reported MX1, MXB, IFIT1 and IFIT2, HERC5, ISG15, LY6E, RSAD2, IFI25 increased in established RA but not in early RA vs controls. No differences for IFI44, IFI6 1 reported IFI44L, IFI6, MX1 and IRF4 increased in RA. No differences in IFI44 1 reported IFI35 increased in RA. No differences in IFI44 (1)			
	qPCR on several ISG	6	***Sources:*** WB (5), PBMC (1) ***Targets:*** ISG scores calculated from 3 (1), 4 (1), 5 (2), 7 (1) or 23 (1) genes; 1 study computed 2 scores (GC-A/B) ***Main findings:*** 6/6 studies reported IFN score increased in RA (any subgroup) vs controls 1/6 reported IFN score higher in early RA but not in established 1/6 reported IFN score higher in established vs very early IFN positive patients ranged from 13% to 40% (reported in 3/6)	0	Unclear/high	[70,77,109,136–138]
	qPCR on chemokines	1	***Sources:*** WB ***Targets:*** RANTES, MCP-1, CCL19, MIG, IP-10, CXCL11, and IL-8 (1) ***Main findings:*** Increased expression of IFN-induced chemokine score in RA vs controls	0	High	[77]
RNA-seq		1	***Sources:*** sorted cell populations (neutrophils) ***Main findings:*** Most differently regulated signaling pathway in RA neutrophils was IFN signaling	0	High	[139]

Reporter cell assays	*Reporter cell assays by qPCR*	2	***Main findings:*** 1/2 reported high IFN activity in 29.7% of RA patients vs 6.3% of controls	0	High	[109,140]
	Reporter cell assays (other)	1	***Main findings:*** 1/1 detected decreased IFN-like substance in RA vs controls (below sensitivity in 39/49 of RA patients)	0	High	[130]
Cytopathic effect assay		1	***Main findings:*** Higher OAS activity in RA inactive vs active patients and vs controls	0	Unclear/high	[141]
Plaque-reducing assay		3	***Main findings:*** 3/3 reported higher IFN activity in RA vs controls	0	High	[121,122,142]

Supplementary Table 3: Summary of the studies reporting assays to evaluate the potential use of IFN assays in the diagnosis of pSS.

Category	Sub-category	n assays	Results	Diagnostic statistics	Risk of bias	References
Immunoassays	*Immunoassays detecting IFNa protein*	4	4/4 reported higher IFNa serum levels in pSS vs controls	0	High	[97,143–145]
	Immunoassays detecting IFNb protein	1	IFNb detected in most samples, increased in pSS but not significant	0	High	[146]
	Immunoassays detecting IFN-induced proteins	4	***Targets:*** MCP-1, MIP-1α, MIP-1β, MIG and IP-10 (1), Mx1 (1), IFI16 (1), IP-10 (1) ***Main findings:*** 4/4 increased IFN-induced protein serum levels in pSS vs controls	0	Unclear/high	[143,147–149]
	DELFIA for IFNa	1	IFNa was detected more often in pSS (3/38) samples than HC (0 and 0 HC), but low levels in all three patients	0	High	[128]
	Other assays (RIA (1))	1	Circulating IFNa lower in pSS vs controls	0	High	[150]
Flow cytometry	*Flow cytometry to detect IFN-induced proteins*	2	***Targets:*** SIGLEC1 (1), Mx1 (1) ***Main findings:*** SIGLEC1 (1/1) and Mx1 (1/1) expression were higher in monocytes in pSS vs controls Mx1 expression was correlated to IFN score (1/1)	0	High	[148,149]
Microarrays	*Microarray scores and clustering*	3	***Sources:*** WB (1), PBMC (1), sorted cell populations (CD14+/low monocyte subsets) (1) ***Targets:*** ISG scores ranging from 9 to 128 ISG ***Main findings:*** 3/3 found IFN-related genes among the most differentially expressed genes	0	High	[146,151,152]

qPCR	*qPCR on individual ISG*	3	***Sources:*** WB (2), sorted cell populations (monocytes) (1) ***Targets:*** IFNA (2) or IFI27 (1) ***Main findings:*** Increased expression of IFNA (2/3) or IFI27 (1/3) in pSS vs controls Increased expression of IFNA in a fraction of pSS patients (5/23 patients)		High	[144,146,152]
	qPCR on several ISG	7	***Sources:*** WB (4), PBMC (2), sorted cell populations (monocytes) (1) ***Targets:*** ISG scores calculated from 3 (1), 5 (5), 6 (1); 1 study computed 2 scores (type I/II) ***Main findings:*** 7/7 reported IFN score significantly higher in pSS vs controls IFN positive patients ranged from 51 to 70% (reported in 5/8)	0	High	[67,89,148,153–156]
RNA-seq		2	***Sources:*** WB (1), sorted cell populations (CD19+ B-cells) ***Main findings:*** 2/2 reported several IFN-related genes among those differentially expressed between pSS and controls		High	[83,145]
Nanostring		3	***Sources:*** WB (2), sorted cell populations (CD19+ B-cells) ***Targets:*** several ISG ***Main findings:*** 2/3 confirmed IFN-related genes increased in pSS vs controls 1/3 reported IFN score (5 genes) did not	0	High	[83,97,145]

			differ between pSS and controls			
DNA methylation	*DNA methylation arrays*	2	***Sources:*** WB (1), sorted cell populations (CD4+ T-cells) ***Main findings:*** 1/2 differentially methylated sites related to IFN pathway 1/2 extensive hypomethylation in IFN-related genes (STAT1, IFI44L, IFITM1 and USP18)	1 (Imgenberg-Kreuz, 2018) AUC=0.910	High	[103,157]
Reporter cell assays	*Reporter cell assays by qPCR*	3	***Main findings:*** 3/3 reported high IFN activity in pSS patients vs controls	0	High	[111,146,158]
	Reporter cell assays (other)	1	***Main findings:*** 1/1 increased IFN activity in pSS vs controls	0	High	[117]
Plaque-reducing assay		2	***Main findings:*** 2/2 reported higher IFN activity in pSS vs controls	0	Unclear/high	[121,122]

Supplementary Table 4: Summary of the studies reporting assays to evaluate the potential use of IFN assays in the diagnosis of SSc.

Category	Sub-category	n assays	Results	Diagnostic statistics	Risk of bias	References
Immunoassays	*Immunoassays detecting IFN-induced proteins*	4	***Targets:*** 93 proteins (1), CXCL10, CXCL11, CCL10 and CCL8 (1), IP-10 and I-TAC (1), IP-10, MCP-1, MIP1a and RANTES (1) ***Main findings:*** 1/4 reported increased IP10 and I-TAC in SSc vs controls 1/4 reported CXCL10 and CXCL11 increased in SSc vs controls 1/4 reported increased IP-10, MCP-1 and MIP1a in SSc vs controls 1/4 reported 37 proteins higher in SSc vs controls (including MCP1, MIP1b, RANTES, MIP3b, MIG, IP10, I-TAC, and MIF) IFN chemokine score: higher in SSc vs controls (39.2% SSc positive in IFN inducible score)	0	High	[159–162]
	DELFIA for IFNa	1	***Main findings:*** 33 and 23 out of 79 SSc sera induced IFNa when combined with necrotic or apoptotic material, higher compared to controls	0	High	[159]
Flow cytometry	*Flow cytometry to detect IFN-induced proteins*	1	***Targets:*** SIGLEC1 (1) ***Main findings:*** SIGLEC1 expression was higher in monocytes from SSc vs controls (almost absent) SIGLEC1 was highly expressed in SSc patients with high IFN score	0	High	[163]

Microarrays	*Microarray modules*	1	***Sources:*** WB ***Main findings:*** IFN-related (M1.2 and M3.4) and one neutrophil module (M5.15) were the only statistically significant upregulated modules in SSc vs controls	0	High	[164]
	Microarray scores and clustering	9	***Sources:*** WB (6), PBMC (2), sorted cell populations (monocytes) (1) ***Targets:*** ISG scores ranging from 9 to 129 ISG ***Main findings:*** 4/9 reported a variable number of IFN-related genes among those genes differentially expressed between SSc vs controls 4/9 reported higher IFN scores in SSc vs controls 1/9 reported some IFN-related genes among those genes differentially expressed between lcSSc vs controls 67% IFN positive patients in SSc (reported in 1/10) IFN positive prevalence varied across disease phenotypes (RP/nc/lc/dc) from 33.3% to 100% (reported in 1/9)	1 (Brkic, 2015) IFN score AUC: 0.823, S: 0.667, Sp: 0.881	Unclear/high	[41,47,52,57,160,163,165–167]
qPCR	*qPCR on individual ISG*	5	***Sources:*** WB (2), PBMC (3) ***Targets:*** MxA (1), SIGLEC (2), IRF7, G1P3 and S100A8 (1), or IFNA, IFNB, IRF7 OAS, MxA and 6-16 (1) ***Main findings:*** 1/5 reported increased expression of MxA in 9/50 SSc vs controls	0	High	[163,166–169]

			2/5 reported increased expression of SIGLEC1 in SSc vs controls 1/5 reported increased expression of IRF7, G1P3 and S100A8 in SSc vs controls 1/5 reported increased expression of IFNA, IFNb and OAS in SSc vs controls			
	qPCR on several ISG	7	***Sources:*** WB (6), sorted cell populations (monocytes) (1) ***Targets:*** ISG scores calculated from 3 (1), 5 (4), 6 (1), or 11 (1) ISGs ***Main findings:*** 6/7 reported IFN score significantly higher in SSc vs controls 1/7 reported IFN score elevated in 2/13 SSc patients	0	High	[47,83,89,165,170,171]
Nanostring		2	***Sources:*** WB (2) ***Main findings:*** 1/2 IFN score in 2/13 SSc patients 1/2 IFN score (5 genes) did not exhibit differences between SSc and controls	0	High	[83,97]
RNA-seq		1	***Sources:*** sorted cell populations (monocytes) (1) ***Main findings:*** 4/99 IFN-related lnRNA were upregulated in SSc vs controls		High	[161]
DNA methylation	*DNA methylation arrays*	1	***Sources:*** Sorted cell populations (CD4+ and CD8+ T-cells) (1) ***Main findings:*** Two IFN pathways were the most significantly enriched among	0	High	[172]

			hypomethylated regions			
Reporter cell assays	*Reporter cell assays by qPCR*	1	***Main findings:*** High IFN score in SSc (9/13) vs controls (0/13)	0	High	[173]
	Reporter cell assays (other)	2	***Main findings:*** 2/2 IFN bioactivity did not differ between SSc vs controls	0	High	[117]
Plaque-reducing assay		3	***Main findings:*** 2/3 IFN bioactivity increased in SSc vs controls 1/3 IFN bioactivity did not differ in SSc vs controls	0	Unclear/high	[121,122,169]

Supplementary Table 5: Summary of the studies reporting assays to evaluate the potential use of IFN assays in the diagnosis of PM/DM.

Category	Sub-category	n assays	Results	Diagnostic statistics	Risk of bias	References
Immunoassays	*Immunoassays detecting IFNa protein*	4	***Main findings:*** 2/4 reported higher IFNa serum levels in PM/DM vs controls 1/4 reported higher IFNa serum levels in a subset of patients (anti-MDA5 positive) 1/4 IFNa serum levels did not differ between PM/DM vs controls	0	High	[97,174–176]
	Immunoassays detecting IFNb protein	3	***Main findings:*** 2/3 IFNb serum levels elevated in PM/DM vs controls 1/3 IFNb serum levels did not differ between PM/DM and controls	0	High	[175,176]
	Simoa for IFNa	1	***Main findings:*** IFNa was increased in PM/DM vs controls	0	High	[36]
Microarrays	*Microarray scores and clustering*	6	***Sources:*** WB (5), PBMCs (1) ***Targets:*** ISG scores ranging from 5 to 43 ISGs ***Main findings:*** 6/6 reported IFN-related genes among the most differentially expressed genes / largest fold change 1/6 reported signature in 10/12 PM/DM patients	0	High	[48,52,57,175,177,178]
qPCR	*qPCR on individual ISG*	3	***Sources:*** WB (2), PBMCs (1) ***Targets:*** MXA (1), IRF7, ISG15 and MXA (1) or IFIT1 and MXA (1) ***Main findings:***	0	High	[174,178,179]

			1/3 reported increased MXA expression in PM/DM 1/3 reported increased expression of IRF7, ISG15, MXA in PM/DM 1/3 reported increased expression of IFIT1 and MXA in PM/DM vs controls			
	qPCR on several ISG	7	***Sources:*** WB (6), PBMC (1) ***Targets:*** ISG scores calculated from 3 (1), 6 (2), 8 (1), 13 (1), 23 (1); 1 study computed 2 scores (GC-A/B) ***Main findings:*** 6/7 reported IFN score elevated in PM/DM vs controls 1/7 reported IFN positive patients in 2/8 PM/DM patients 1/7 IFN score in PM/DM is predominant GC-A (SLE-like)	1 (Feng, 2015): IFN score: AUC 0.805, $p=1.4\cdot10^{-5}$	High	[36,73,83,136,177,180]
RNA-seq		2	***Sources:*** WB (1), sorted cell populations (B-cells) ***Main findings:*** 1/2 reported IFN-related genes among the most significantly expressed genes between PM/DM vs controls 1/2 validated microarrays results	0	High	[83,181]
Nanostring		2	***Sources:*** WB (2) ***Main findings:*** 1/2 IFN score increased in PM/DM patients (100%) vs controls 1/2 IFN score in 2/8 PM/DM patients	0	High	[83,97]
Reporter cell assays	*Reporter cell assays by qPCR*	3	***Main findings:*** 1/3 reported high IFN activity in PM/DM patients 1/3 reported no increased IFN activity in	0	Unclear/high	[182–184]

			PM/DM (most did not induce up-regulation of the ISG, 2 induced high IFNa activity, and 5 induced low activity (+)) vs controls 1/3 high IFN bioactivity was dependent on IFN score status in PM/DM patients			
	Reporter cell assays (other)	1	***Main findings:*** Increased IFN activity present in 54% (13/24) of DM, 67% (8/12) of PM and 5% (1/22) of myositis samples	0	Unclear/high	[175]

Supplementary Table 6: Summary of the studies reporting assays analyzing associations between IFN assays and disease activity in SLE.

Category	Sub-category	Reference	n	Disease activity measure	Results	Risk of bias
Immunoassays	*Immunoassays detecting IFNa protein*	Abdel Galil, 2018 [6]	126	SLEDAI-2K	Positive correlation (r=0.640, p<0.001)	High
		Baechler, 2003 [49]	48	Number of SLE disease criteria	Positive correlation (p<0.0002)	High
		Becker-Merok, 2013 [7]	87	SLEDAI	No association (p=0.070)	High
		Bengtsson, 2000 [185]	30	SLEDAI	Positive correlation (r=0.479, p=0.007)	High
		Fernández-Matilla, 2000 [19]	142	SELENA-SLEDAI CRP ESR	No association	Unclear
		Fragoso-Loyo, 2012 [8]	34	SLEDAI-2K	Positive correlation (r=0.330, p=0.050)	High
		Jonsen, 2003 [186]	57	SLEDAI	No association	High
		Kim, 1987 [38]	30	Clinical activity score	Positive correlation (r=0.600, p<0.010)	High
		Mathian, 2019 [187]	68	SELENA-SLEDAI	Positive association (high SELENA-SLEDAI score: AUC 0.830; Sensitivity: 68.7 (57.6–78.4); specificity: 85.1 (74.3–92.6); PPV: 85.1; NPV 68.7)	High
		Mathian, 2019b [35]	254	Remission (SELENA-SLEDAI)	Positive association (abnormal IFN levels associated with no remission (OR 11.4, p<0.0001))	High
		Oke, 2017 [11]	261	SLEDAI	No association	Unclear

		Postal, 2012 [12]	57	SLEDAI	Positive correlation (r=0.430, p=0.012)	High
		Rodero, 2017 [36]	72	SLEDAI ESR CRP	SLEDAI: positive association (higher SLEDAI in patients with high IFN (p<0.001) ESR: positive association (higher ESR in patients with high IFN (p<0.010) CRP: no association (ns)	Low
		Rose, 2013 [188]	79	mSLEDAI BILAG-2004	mSLEDAI: positive correlation (r=0.4359, p<0.0001) BILAG-2004: positive correlation (r=0.4476, p<0.0001)	Low
		Rose, 2017 [189]	26	BILAG-2004	Positive correlation (r=0.420, p=0.0022)	High
		Schneider, 2015 [190]	172	SLEDAI SLICC	SLEDAI: positive correlation (r=0.219, p=0.004) SLICC: no association (r=0.063, p=ns)	Low
		Shi, 1987 [37]	47	Disease activity stages	Positive association (81% samples of patients with high disease activity were positive compared to 10% samples positive during quiescent stages; p<0.005)	High
		Willis, 2012 [14]	35	SLAM-R	Positive correlation (r=0.314, p=0.054)	High
		Yin, 2014 [16]	79	SLEDAI CRP	SLEDAI: no correlation (r=0.129, p=0.264) CRP: no correlation (r=0.183, p=0.126)	Unclear
		Hashad, 2012 [21]	52	SLEDAI	Positive correlation (p=0.030)	High
		Ma, 2012 [23]	37	SLEDAI	No association (active SLE vs inactive SLE: p=0.690; active SLE vs HC: p=0.098; inactive SLE vs HC: p=0.077)	High
		Mandal, 2014 [24]	129	SLEDAI	Positive correlation (r=0.260, p=0.002)	High
		Robak, 2004 [26]	36	SLAM	No association	High
		Oke, 2019 [191]	497	SLEDAI SDI SLAM	SLEDAI: no association (high IFNa: OR 0.9 (0.5-1.9), p=ns) SDI: no association (high IFNa: OR 0.8 (0.4-1.6), p=ns) SLAM: no association (high IFNa: OR 0.8 (0.4-1.6), p=ns)	Unclear
	Immunoassays detecting IFNb protein	Munroe, 2017 [192]	13	SELENA-SLEDAI	Positive correlation (p<0.0001)	High

	Immunoassays detecting IFN-induced proteins	Oliveira, 2018 [28]	34	SLEDAI	Positive correlation (sSIGLEC: r=0.100, p=0.070)	High
		Zhuang, 2005 [18]	66	SLEDAI	No association (Mx1: ns)	High
		Bauer, 2006 [193]	30	SLEDAI SLAM-R ESR	SLEDAI: positive correlation (MCP-2: r=0.520, p<0.010; MCP-1: r=0.350, p<0.050; I-TAC: r=0.420, p<0.050; IP-10: r=0.370, p<0.050; MIP-3B: p<0.001; MIP-1A: r=0.590, p<0.010); no association (MIG: p=ns) SLAM-R: positive correlation (MCP-2; r=0.600, p<0.010; MCP-1: r=0.390, p<0.050; MIG: r=0.480, p<0.010; I-TAC: r=0.670, p<0.0001; IP-10: r=0.500, p<0.010; MIP-3B: r=0.57, p<0.001; MIP-1A: r=0.680, p<0.001) ESR: positive correlation (MCP-2: r=0.620, p<0.010; MCP-1: r=0.540, p<0.050; MIG: r=0.560, p<0.010; I-TAC r=0.700, p<0.0001; IP-10: r=0.560, p<0.001; MIP-3B: r=0.330, p<0.050; MIP-1A: r=0.600, p<0.001)	Unclear
		Bauer, 2009 [194]	267	SLEDAI	Positive association (chemokine score: SLEDAI was elevated in chemokine-high patients compared to chemokine-intermediate ($p=3.8\times10^{-5}$) and chemokine-low patients ($p=1.0\times10^{-7}$).	High
		Casey, 2018 [90]	304	SLEDAI-2K CLASI	SLEDAI-2K: positive correlation (27 proteins were significantly correlated with SLEDAI-2K and significantly higher in high SLEDAI-2K vs low SLEDAI-2K) CLASI: positive correlation (7 proteins were significantly correlated with CLASI and showed higher concentrations in patients with high CLASI)	Unclear
		Connelly, 2016 [195]	151	Adjusted mean SLEDAI	Positive association (high IFN chemokine score scores were significantly associated with high disease activity (OR [95% CI]: 2.56 [1.03, 6.37]; p=0.040)	High
		Connelly, 2018 [196]	109	SLEDAI-2K	Positive correlation (IFN chemokine score: r=0.730, (95% CI: 0.12, 1.43), p=0.020)	High
		Lee, 2016 [197]	30	SLEDAI	Positive association (IFN chemokine score high patients exhibited higher SLEDAI compared to IFN low group, p=0.0006)	High

		Munroe, 2017 [192]	13	SELENA-SLEDAI	Positive correlation (MCP1/CCL2: p=0.0203; MCP3/ccl7: p=0.0022; MIP1ab/CCL4: p=0.0388; CXCVL8/IL8: p=0.0034; MIG/CXCL: p=0.0159; IP10/CXCL10: p=0.0298)	High
		Nielsen, 2014 [27]	70 SLE-DK 68 SLE-SE 26 SLE-IFNa	SLEDAI SLICC	SLEDAI: positive association (Galectin 3–binding protein: SLE-DK: r=0.410 p=0.0004; SLE-IFNa: r=0.420 p=0.030); no association (Galectin 3–binding protein: SLE-SE: r=−0.0025 p=0.980) SLICC: no association (Galectin 3–binding protein: SLE-DK: r=−0.08 p=0.530; SLE-SE: r=0.036 p=0.770)	Low
		Rose, 2013 [188]	79	mSLEDAI-2K BILAG-2004	mSLEDAI-2K: positive correlation (IP-10: r=0.335, p=0.001; SIGLEC1: r=0.434, p<0.001) BILAG-2004: positive correlation (IP-10: r=0.385, p<0.001; SIGLEC1: r=0.540, p<0.001)	Low
		Rose, 2017 [189]	26	BILAG-2004	Positive correlation (IP-10: r=0.500, p=0.002)	High
		Van den Hoogen, 2018 [87]	50	SLEDAI	Positive correlation (Galectin-9: r=0.320, p=0.003)	High
		Wahadat, 2018 [31]	23	SELENA-SLEDAI	No association (MxA: ns)	High
Flow cytometry	*Flow cytometry to detect IFN-induced proteins*	Biesen, 2008 [41]	25	SLEDAI	***Target (source):*** Siglec1 (monocytes) ***Main findings:*** positive correlation: Siglec1–positive inflammatory monocytes and Siglec1–positive resident monocytes both correlated with SLEDAI (p=0.006 and p=0.005, respectively)	High
		Li, 2010 [39]	108	SLEDAI	***Target (source):*** CD64 (monocytes) ***Main findings:*** positive correlation (r=0.3023, p=0.0017)	High
		Oliveira, 2018 [28]	34	SLEDAI	***Target (source):*** Siglec1 (monocytes) ***Main findings:*** positive correlation (r=0.100, p=0.070)	High
		Rose, 2013 [188]	79	mSLEDAI-2K BILAG-2004	***Target (source):*** Siglec1 (monocytes) ***Main findings:*** mSLEDAI-2K: positive correlation (r=0.434, p<0.0001); BILAG-2004: positive correlation	Low

					(r=0.5409, p<0.0001)	
		Wilhem, 2016 [40]	22	SLEDAI	***Target (source):*** Siglec1 (pDCs), Siglec1 (monocytes) ***Main findings:*** positive correlation (Siglec1 (pDCs): r=0.550, p=0.008; Siglec1 (monocytes): r=0.620, p=0.003)	High
Microarrays	*Microarray modules*	Chiche, 2014 [46]	62	SELENA-SLEDAI	***Source:*** WB ***Main findings:*** significant correlation was observed between expression of M3.4 and M5.12 modules and the presence of a flare	High
		Mackay, 2016 [44]	43	SLEDAI	***Source:*** WB ***Main findings:*** no association between SLEDAI and IFN modules	High
	Microarray scores and clustering	Assassi, 2010 [47]	74	SLAM-R	***Source:*** WB ***Main findings:*** positive correlation (IFN score: p=0.010)	High
		Baechler, 2003 [49]	48	Number of SLE criteria	***Source:*** PBMC ***Main findings:*** positive association (IFN-high group showed higher number of SLE criteria compared to IFN-low group, p=0.004)	High
		Baechler, 2007 [48]	12	SLEDAI	***Source:*** WB ***Main findings:*** positive association (SLEDAI was higher in IFNhigh compared to IFNlow, p=0.050)	High
		Bauer, 2006 [193]	81	SLEDAI SLAM-R ESR	***Source:*** WB ***Main findings:*** SLEDAI: positive correlation (IFN score: r=0.430, p<0.050) SLAM-R: positive correlation (IFN score: r=0.680, p<0.0001) ESR: positive correlation (IFN score: r=0.520, p<0.010)	Low
		Higgs, 2011 [52]	261	SLEDAI BILAG-2004	***Source:*** WB ***Main findings:*** SLEDAI: positive association (IFN score higher in SLEDAI>8 compared to SLEDAI<8, p<0.0001) BILAG-2004: positive association (IFN score higher in BILAG>8 compared to BILAG<8, p=0.0006)	Unclear
		Kawasaki, 2011 [198]	12	SLEDAI (active vs inactive)	***Source:*** sorted cell populations (T-cells) ***Main findings:*** positive association (IFN-related genes were the most frequently annotated among genes differing	High

					between active and inactive SLE patients)	
		Kennedy, 2015 [63]	61 60 135 80 238	BILAG SELENA-SLEDAI CLASI	***Source:*** PBMC ***Main findings:*** BILAG, SELENA-SLEDAI: no associations (ns) CLASI damage score: positive association (IFN score high patients exhibited higher CLASI score compared to IFN score low patients, p=0.0209) CLASI activity score: no associations (ns)	High
		Lauwerys, 2013 [58]	27	SLEDAI-2K	***Source:*** WB ***Main findings:*** no associations (ns)	High
		Petri, 2009 [199]	66	SLEDAI	***Source:*** WB ***Main findings:*** positive association (high IFNr group patients exhibited greater SLEDAI scores, $p=2.3 \cdot 10^{-4}$)	High
		Becker, 2013 [50]	15	SLEDAI	***Source:*** sorted cell populations ***Main findings:*** positive associations (a number of IFN-related differentially expressed genes was observed between active or inactive disease in B, T and myeloid cells)	High
		Bennet, 2003 [131]	30	SLEDAI	***Source:*** WB ***Main findings:*** positive association (10 IFN-related genes correlated with SLEDAI, all p<0.050)	High
		Biessen, 2008 [41]	47	SLEDAI	***Source:*** sorted cell populations (monocytes) ***Main findings:*** positive association (IFN-positive patients had higher SLEDAI than IFN-negative patients, p<0.010)	High
		Nikpour, 2008 [200]	269	SLEDAI-2K	***Source:*** WB ***Main findings:*** positive association (IFN-positive patients had higher SLEDAI-2K than IFN-negative patients, p<0.001)	High
		Sharma, 2015 [201]	42	SLEDAI	***Source:*** sorted cell populations (CD4+ T-cells, CD8+ T-cells, CD14+ monocytes and CD20+ B-cells) ***Main findings:*** no association (ns)	High
qPCR	*qPCR on individual ISG*	Abdel Galil, 2018 [6]	126	SLEDAI	***Source:*** WB ***Number of ISG:*** 1 ***Main findings:*** IFNA expression higher in the highly active group than in the mild and moderately active groups	High
		Li, 2009	39	SLEDAI	***Source:*** PBMC	High

		[65]			***Number of ISG:*** 1 ***Main findings:*** positive correlation (MXA: r=0.4814, p=0.0019)	
		Yuan, 2018 [66]	28	SLEDAI	***Source:*** WB ***Number of ISG:*** 1 ***Main findings:*** positive correlation (ISG15: r=0.520, p=0.0059)	High
		Rodríguez-Carrio, 2019 [84]	75	SLEDAI	***Source:*** WB ***Number of ISG:*** 4 ***Main findings:*** no associations (any ISG)	High
		Tang, 2008 [85]	144	SLEDAI-2K	***Source:*** PBMC ***Number of ISG:*** 1 ***Main findings:*** positive correlation (LY6E: r=0.300, p<0.010)	High
		Zhuang, 2005 [18]	88	SLEDAI	***Source:*** WB ***Number of ISG:*** 1 ***Main findings:*** no association (Mx1)	High
		Kawasaki, 2011 [198]	12	SLEDAI	***Source:*** sorted cell populations (T-cells) ***Number of ISG:*** 6 ***Main findings:*** positive association (IFI35, JAK1, STAT1, IFITM1, JAK2, STAT2 expression was higher in active phase of SLE vs non active phase, all p<0.05)	High
	qPCR for IFN scores	Assassi, 2010 [47]	17	SLAM-R	***Source:*** WB ***Number of ISG:*** 3 ***Main findings:*** positive correlation (IFN score: p=0.010)	High
		Braunstein, 2012 [68]	30	CLASI	***Source:*** PBMC ***Number of ISG:*** 5 ***Main findings:*** positive correlation (IFN score: r=0.550, p=0.001)	Low
		Dominguez-Gutierrez, 2014 [71]	103	SLEDAI: active (SLEDAI >4) or inactive (SLEDAI ≤4)	***Source:*** leukocytes ***Number of ISG:*** 3 ***Main findings:*** no associations	High
		El-Sherbiny, 2018 [74]	114	BILAG Overall, BILAG Skin, BILAG MSK,	***Source:*** WB ***Number of ISG:*** 31 (2 scores) ***Main findings:*** positive associations depended on organ	Unclear

				BILAG Haem	involvement: IFN score A/IFN score B: OR (90% CI), p Mucocutaneous: 1.71 (1.02-2.86), p=0.042 / 1.41 (1.08-1.84), p=0.012 Musculoskeletal: 0.79 (0.46-1.34), p=0.381 / 0.82 (0.63-1.08), p=0.165 Haematological: 1.90 (1.11-3.24), p=0.020 / 1.44 (1.09-1.90), p=0.012	
		Feng, 2017 [75]	35	SLEDAI SLICC	***Source:*** WB ***Number of ISG:*** 5 ***Main findings:*** SLEDAI: positive correlation (IFN score: r=0.690, p=0.001) SLICC: no associations	Low
		Feng, 2015 [76]	69	SLEDAI	***Source:*** WB ***Number of ISG:*** 5 ***Main findings:*** positive correlation (IFN score: r=0.310, p=0.014)	Low
		Feng, 2006 [92]	48	SELENA-SLEDAI	***Source:*** WB ***Number of ISG:*** 5 ***Main findings:*** positive association (IFN score: higher in active disease (SLEDAI 5–12) or severe disease activity (SLEDAI >12) vs inactive or mild disease activity (SLEDAI 0-4): p=0.009 and p=0.002)	High
		Fu, 2008 [77]	68	SLEDAI	***Source:*** WB ***Number of ISG:*** 5 ***Main findings:*** positive correlation (IFN score: p=0.023)	High
		Kennedy, 2015 [63]		SELENA-SLEDAI CLASI	***Source:*** WB ***Number of ISG:*** 3 ***Main findings:*** SELENA-SLEDAI: no associations CLASI damage score: positive association (higher in IFNhigh vs IFNlow patients, p=0.020) CLASI activity score: no associations	Low
		Kirou, 2005 [93]	73	SLEDAI-2K score SLEDAI-2K	***Source:*** PBMC ***Number of ISG:*** 3 ***Main findings:***	Unclear

				truncated ESR Number of SLE criteria SDI	SLEDAI-2K: positive association (higher in IFNhigh vs IFNlow, p=0.003) SDI: positive association (higher in IFNhigh vs IFNlow, p=0.0009) ESR: positive association (higher in IFNhigh vs IFNlow, p=0.0105) Number of ACR criteria: positive association (higher in IFNhigh vs IFNlow, p=0.001)	
		Landolt-Maricortena, 2009 [80]	94	SLEDAI-2K	***Source:*** PBMC ***Number of ISG:*** 5 ***Main findings:*** positive correlation (r=0.253, p=0.0318)	High
		Liu, 2018 [81]	44	SLEDAI	***Source:*** PBMC ***Number of ISG:*** 4 ***Main findings:*** positive association (IFNhigh patients showed higher SLEDAI vs IFNlow, p<0.050)	High
		Wahadat, 2018 [31]	23	SELENA-SLEDAI	***Source:*** sorted populations (monocytes) ***Number of ISG:*** 6 ***Main findings:*** no association	High
		Merrill, 2017 [202]	98	SLEDAI BILAG	***Source:*** WB ***Number of ISG:*** 1 score ***Main findings:*** SLEDAI: positive association (IFNhigh patients showed higher SLEDAI vs IFNlow, p=0.009) BILAG: (IFNhigh patients showed higher SLEDAI vs IFNlow, p=0.040)	Unclear
		Sharma, 2015 [201]	42	SLEDAI	***Source:*** sorted populations (monocytes) ***Number of ISG:*** 46 ***Main findings:*** no association	High
	qPCR for IFN-induced chemokines	Fu, 2008 [77]	68	SLEDAI	***Source:*** WB ***Number of ISG:*** 12 ***Main findings:*** positive correlation (IFN chemokine score: r=0.340, p<0.005)	High
DNA methylation	*DNA methylation arrays*	Coit, 2013 [98]	18	SLEDAI	***Source:*** sorted populations (CD4+ T-cells) ***Main findings:*** no association	High
		Joseph, 2019 [99]	57	SLEDAI	***Source:*** PBMC ***Main findings:*** positive association (higher	High

					hypomethylation in several ISG in active SLE (SLEDAI>6) vs controls, but no differences between inactive SLE (SLEDAI<6) and controls	
		Absher, 2013 [101]	49	SLEDAI	***Source:*** sorted populations (CD4+ T-cells) ***Main findings:*** no association	High
	Pyrosequencing	Zhao, 2016 [107]	30	SLEDAI	***Source:*** WB ***Main findings:*** positive association (higher methylation in IFI44L promoter in remission vs patients with active disease, p<0.001 and p=0.036)	High
Reporter cell assays	*Reporter cell assays by qPCR*	Andrade, 2015 [108]	28	SLEDAI	***Assay:*** Mx1 expression ***Main findings:*** no association	High
		Nielsen, 2014 [27]	70 SLE-DK 68 SLE-SE 26 SLE-IFNa	SLEDAI SLICC	***Assay:*** Mx1 expression ***Main findings:*** no association	High
		Oke, 2019 [191]	497	SLEDAI SDI SLAM	***Assay:*** MX1, EIF2AK2 and IFIT1 expression ***Main findings:*** SLEDAI: positive correlation (r=0.3, p<0.0001) SDI: negative correlation (r=-0.13, p<0.0001) SLAM: positive correlation (r=0.3, p<0.0001)	Low
	Reporter cell assays (other)	Dall'era, 2005 [116]	64	SLEDAI ESR	***Assay:*** luciferase/ chemoluminiscence ***Main findings:*** SLEDAI: positive correlation (IFN activity: r=0.451, p<0.001) ESR: positive correlation (IFN activity: r=0.481, p<0.001)	Low
		Kato, 2018 [117]	54	SLEDAI	***Assay:*** luciferase/ chemoluminiscence ***Main findings:*** positive correlation (IFN bioactivity: r=0.3034, p=0.0185; ISG-inducing activity: r=0.407, p=0.0009)	High
Cytopathic effect assay		Hervier, 2011 [120]	54	SLEDAI	Positive association (increased IFN activity in patients with active SLE vs inactive, p=0.004)	High

		Mathian, 2019 [187]	96	SELENA-SLEDAI	Positive association (IFN bioassay identified high disease activity: AUC 0.790; Sensitivity: 62.7 (51.3–73.0); Specificity: 94.0 (85.4–98.4); PPV: 92.9; NPV: 67.0)	High
		Rich, 1986 [203]	11	Disease activity	Positive association (IFN activity positivity associated with disease activity)	High
		Preble, 1982 [119]	86	Flare/remission	Positive association (52.3% samples during flare contained IFN (8-128 IU/ml) vs 25% samples during remission)	High
Plaque-reducing assay		Hooks, 1982 [123]	14	Clinical disease activity grades	Positive association (IFN titre positively associated with high disease activity)	High
		Hooks, 1979 [121]	28	Active/inactive disease groups	Positive association (IFN was found in the serum of 71% patients with active disease but only in 21% of those with inactive disease)	High
		Ytterberg, 1982 [124]	23	Disease activity stages (absent, possible, definite mild, definite moderate, definite severe)	Positive correlation (IFN levels: $r=0.620$, $p<0.010$)	High

Supplementary Table 7: Summary of the studies reporting assays analyzing associations between IFN assays and disease activity in RA.

Category	Sub-category	Reference	n	Disease activity measure	Results	Risk of bias
Immunoassays	*Immunoassays detecting IFNa protein*	Rodríguez-Carrio, 2014 [126]	120	DAS28 CRP ESR	DAS28: positive association (higher in IFNhigh vs IFNlow patients, p<0.050) CRP: no association ESR: positive association (higher in IFNhigh vs IFNlow patients, p<0.050)	High
		Weix, 2013 [125]	7	DAS28-CRP	No association	High
	Immunoassays detecting IFNb protein	Weix, 2013 [125]	7	DAS28-CRP	No association	High
Microarrays	*Microarray scores and clustering*	Cantaert, 2010 [204]	21	DAS28 ESR CRP	***Source:*** WB ***Main findings:*** no association	Unclear
		Higgs, 2011 [52]	45	Moderate (n=29) vs severe (n=16) stages	***Source:*** WB ***Main findings:*** no association	High
		Reynier, 2011 [132]	81	DAS28	***Source:*** WB ***Main findings:*** no association	Unclear
qPCR	*qPCR on individual ISG*	Weix, 2013 [125]	10	DAS28-CRP	***Source:*** PBMC ***Number of ISG:*** 6 ***Main findings:*** no association (no differences in any of the genes between active or inactive disease)	High
	qPCR for IFN scores	Rodríguez-Carrio, 2019 [84]	98	DAS28 ESR	***Source:*** WB ***Number of ISG:*** 4 (cluster analysis) ***Main findings:*** DAS28: positive association (higher DAS28 in cluster I, low	Unclear

					expression of ISG, p<0.001) ESR: positive association (higher ESR in cluster III, high expression of ISG, p=0.025)	
		Cooles, 2018 [138]	75	DAS28	***Source:*** WB ***Number of ISG:*** 6 ***Main findings:*** positive correlation in early RA (IFN score: r=0.193, p=0.014) and established RA (IFN score: r=0.554, p=0.036)	Unclear
		De Jong, 2016 [70]	182	DAS28 ESR CRP	***Source:*** WB ***Number of ISG:*** 19 ***Main findings:*** no associations	Unclear
		Rodríguez-Carrio, 2017 [137]	98	DAS28	***Source:*** WB ***Number of ISG:*** 4 ***Main findings:*** no association in very early RA (IFN score: r=-0.055, p=0.014), or bDMARD-naïve RA (IFN score: p=ns), and negative association in bDMARD patients (IFN score: r=-0.358, p=0.032)	High
		Thurlings, 2010 [205]	20 31	DAS28 ESR CRP	***Source:*** PBMC ***Number of ISG:*** 3 ***Main findings:*** no association	Unclear
Reporter cell assays	*Reporter cell assays (other)*	Shiozawa, 1986 [130]	40	Disease activity groups (active if arthritis w/pain and/or swelling in >4 joints by physician assessment + fatigue and >11 morning stiffness + increased	***Assay:*** luciferase/ chemoluminiscence ***Main findings:*** no association	High

				ESR and/or CRP; inactive if criteria for clinical remission)		
Cytopathic effect assay		Hertzog, 1988 [141]	12	Disease activity groups: inactive (MS<15min, no fatigue, no joint pain, no joint tenderness, no joint/tendon swelling, ESR<20) or active (no inactive criteria)	Negative association (OAS activity: higher in inactive RA vs controls, p<0.001)	High
Plaque-reducing assay		Arvin, 1984 [142]	65	Active vs inactive disease	Positive association (IFN activity: present in 10% inactive samples vs 47% active samples)	High

Supplementary Table 8: Summary of the studies reporting assays analyzing associations between IFN assays and disease activity in pSS.

Category	Sub-category	Reference	n	Disease activity measure	Results	Risk of bias
Immunoassays	*Immunoassays detecting IFN-induced proteins*	James, 2019 [206]	47	ESSDAI	Positive association (IFN-induced protein clusters positively associated with ESSDAI)	High
		Maria, 2014 [148]	24	ESSDAI	Positive correlation (MxA: r=0.650, p<0.010)	High
		Rose, 2016 [149]	25	ESSDAI	No association (IP-10: p=0.580)	High
Flow cytometry	*Flow cytometry to detect IFN-induced proteins*	Maria, 2014 [148]	28	ESSDAI	***Target (source):*** MxA (monocytes) ***Main findings:*** positive correlation (MxA: r=0.450, p=0.020)	High
		Rose, 2016 [149]	25	ESSDAI	***Target (source):*** Siglec1 (monocytes) ***Main findings:*** positive correlation (Siglec1: r=0.540, p=0.005)	High
Microarrays	*Microarray scores and clustering*	James, 2019 [206]	47	ESSDAI	***Source:*** WB ***Main findings:*** no associations between clusters and ESSDAI (p=0.190)	High
qPCR	*qPCR on individual ISG*	Kimoto, 2011 [152]	37	ESR Schirmer test (mm/5 min)	***Source:*** WB ***Number of ISG:*** 1 ***Main findings:*** ESR: positive correlation (IFI27: r=0.333, p<0.050) Schirmer R: no association (IFI27: r=0.076, p=0.709) Schirmer L: no association (IFI27: r=-0.085, p=0.677)	Low
	qPCR for IFN scores	Bodewes, 2018 [89]	86	ESSDAI ClinESSDAI CRP ESR Schirmer test Saliva flow	***Source:*** WB ***Number of ISG:*** 3 scores ***Main findings:*** ESSDAI: no association (p=0.472) ClinESSDAI: no association (p=0.929) CRP: no association (p=0.567) ESR: positive association (higher ESR in IFN-I/II high patients, p<0.001)	Low

					Schirmer test: negative association (decreased in IFN-I/II high patients, p=0.028) Saliva flow: no association (p=0.274)	
		Bodewes, 2019 [153]	77	ESSPRI	***Source:*** WB ***Number of ISG:*** 7 ***Main findings:*** negative association (IFN signature associated with reduced scores of the pain and fatigue domain of the ESSPRI)	Unclear
		Brkic, 2013 [154]	38	ESSDAI ESSPRI	***Source:*** monocytes ***Number of ISG:*** 5 ***Main findings:*** positive correlation (IFN signature: r=0.458, p=0.003)	Low
		Maria, 2014 [148]	114	ESSDAI	***Source:*** monocytes ***Number of ISG:*** 5 ***Main findings:*** positive association (IFNhigh patients showed higher ESSDAI than IFNlow patients, p<0.050)	Unclear
		Olsson, 2019 [207]	90	ESSDAI ESSPRI	***Source:*** WB ***Number of ISG:*** 5 ***Main findings:*** ESSDAI articular domain: positive association (p<0.010) ESSPRI total score: positive association (p=0.040) ESSPRI sicca score: positive association (p=0.030) ESSPRI pain score: positive association (p=0.020)	Low

Supplementary Table 9: Summary of the studies reporting assays analyzing associations between IFN assays and disease activity in SSc.

Category	Sub-category	Reference	n	Disease activity measure	Results	Risk of bias
Immunoassays	*Immunoassays detecting IFNa protein*	Eloranta, 2010 [159]	70	ESR Digital ulcers	ESR: positive correlation (r=0.390, p<0.001) Digital ulcers: positive association (p=0.029)	High
	Immunoassays detecting IFN-induced proteins	Eloranta, 2010 [159]	70	ESR	Positive correlation (IP-10 r=0.380, p=0.002; MCP-1: r=0.250, p=0.045; MIP-1A: r=0.460, p<0.001)	High
		Liu, 2013 [162]	266	mRSS DLC FVC	mRSS: positive association (chemokine score: r=0.210, p=0.002), no association (IP-10: r=0.16, p=0.014; I-TAC: r=0.04, p=0.205) DLC: negative association (chemokine score: r=-0.18, p=0.008; I-TAC: r=-0.21, p=0.002), no association (IP-10: r=-0.10, p=0.160) FVC: negative association (chemokine score: r=-0.17, p=0.012; I-TAC: r=-0.21, p=0.003), no association (IP-10: r=-0.08, p=0.272)	Low
Microarrays	*Microarray scores and clustering*	Assassi, 2010 [47]	74	mRSS FVC DLCO	***Source:*** WB ***Main findings:*** no association	Unclear
		Higgs, 2011 [52]	45	mRSS	***Source:*** WB ***Main findings:*** positive association (mRSS higher in gene signature positive vs negative groups, p=0.030)	High
		Bos, 2009 [165]	43	Digital ulcers	***Source:*** WB ***Main findings:*** positive association (greater number of digital ulcers in IFNhigh patients, p=0.050)	High
		Tan, 2006 [166]	18	mRSS	***Source:*** WB ***Main findings:*** no association	High
qPCR	*qPCR on individual ISG*	Airo, 2008 [168]	50	FVC DLCO Skin score	***Source:*** WB ***Number of ISG:*** 1 ***Main findings:***	Unclear

				Digital ulcers	FVC: negative association (lower FVC in patients with high MxA levels, p=0.020) DLCO: no association (p=0.070) Skin score: no association (p=0.140) Digital ulcers: positive association (higher number of digital ulcers in patients with high MxA levels, p=0.002)	
Reporter cell assays	*Reporter cell assays (other)*	Eloranta, 2010 [159]	70	ESR Digital ulcers	***Assay:*** IFNa-inducing capacity of sera ***Main findings:*** ESR: positive association (higher ESR in patients with high IFNa-inducing capacity, p=0.022) Digital ulcers: positive association (higher ESR in patients with high IFNa-inducing capacity, p=0.025)	Unclear

Supplementary Table 10: Summary of the studies reporting assays analyzing associations between IFN assays and disease activity in PM/DM.

Category	Sub-category	Reference	n	Disease activity measure	Results	Risk of bias
Immunoassays	*Immunoassays detecting IFNa protein*	Krol, 2011 [208]	19	MYOACT MRI-VAS	MYOACT: no association MRI-VAS: negative correlation (r=-0.580, p=0.0095)	High
		Sun, 2012 [174]	16	Skin lesion activity score ESR	Skin lesion activity score: positive correlation (r=0.600, p=0.0147) ESR: positive correlation (r=0.530, p=0.0329)	High
		Huard, 2017 [209]	42	CDASI	CDASI: no association (r=0.290, p=0.090)	Low
	Immunoassays detecting IFNb protein	Huard, 2017 [209]	42	CDASI	CDASI: positive correlation (r=0.540, p=0.0003)	Low
	Immunoassays detecting IFN-induced proteins	Huard, 2017 [209]	42	CDASI	Positive correlation (CXCL10: r=0.630, p<0.0001)	Low
		Baechler, 2007 [48]	12	Disease activity score (muscle strength testing, muscle enzyme elevation, ulcerative skin disease and patient's report of functional assessment)	Positive association (IP-10: elevated in active patients (no statistical analyses reported; MCP-1: r=0.550, p<0.050; MCP-2: r=0.600, p<0.010)	High
Microarrays	*Microarray scores and*	Baechler, 2007 [49]	12	Disease activity score	***Source:*** WB ***Main findings:*** positive correlation (IFN score: r=0.440,	High

	clustering			(muscle strength testing, muscle enzyme elevation, ulcerative skin disease and patient's report of functional assessment)	p=0.060; higher in active disease vs inactive disease, p=0.050)	
		Greenberg, 2012 [177]	21	MITAX	***Source:*** WB ***Main findings:*** positive association (IFN score higher in patients with high disease activity vs low or moderate disease activity, p<0.010)	High
		Higgs, 2011 [52]	45	Low / high disease activity	***Source:*** WB ***Main findings:*** positive association (IFN score higher in high disease activity vs low, p=0.004)	Unclear
		Walsh, 2007 [178]	36	Active disease / improving disease	***Source:*** WB ***Main findings:*** positive association (genes most upregulated in patients vs controls were highly down-regulated in improving disease group: IFI27, IFI44L, RSAD2, IFI44, OAS1, BIRC4BP)	Unclear
qPCR	*qPCR on individual ISG*	O'Connor, 2006 [179]	14	DAS muscle DAS skin	***Source:*** PBMC ***Number of ISG:*** 1 ***Main findings:*** DAS muscle: positive correlation (MxA: r=0.800, p<0.001) DAS skin: no association (MxA: r=-0.208, p=0.476)	Low
	qPCR for IFN scores	Bilgic, 2009 [180]	37	Physician global VAS MMT8 score	***Source:*** WB ***Number of ISG:*** 3 ***Main findings:*** Physician global VAS: positive correlation (IFN signature: r=0.410, p=0.007) MMT8 score: negative correlation (IFN signature: r=-0.48, p=0.002)	Unclear

		Ekholm, 2016 [184]	92	Physician global disease activity assessment Patient global disease activity assessment MMT8	***Source:*** WB ***Number of ISG:*** 8 ***Main findings:*** Physician global disease activity assessment: no association (p=0.442) Patient global disease activity assessment: no association (p=0.443) MMT8: no association (p=0.250)	Unclear
		Huard, 2017 [209]	42	CDASI	***Source:*** WB ***Number of ISG:*** 10 ***Main findings:*** positive correlation (IFN signature: r=0.610, p<0.001)	Low
	qPCR for IFN-induced chemokines	Bilgic, 2009 [180]	37	Physician global VAS Muscle VAS score MMT8 score	***Source:*** WB ***Number of ISG:*** 3 ***Main findings:*** VAS score: positive correlation (r=0.61, p<0.0001) Muscle VAS score: positive correlation (r=0.470, p<0.001) MTT8 score: negative correlation (r=-0.440, p=0.002)	Low
RNA-seq	*RNA-seq*	Huard, 2017 [209]	42	CDASI	***Source:*** WB ***Main findings:*** positive association (K-means: optimal grouping of patients with a CDASI=12 (accuracy=0.952); cluster analysis: type I IFN-induced genes correlated with CDASI, patients with mild CDASI similar to controls)	Unclear
Reporter cell assays	*Reporter cell assays by qPCR*	Ekholm, 2016 [184]	40	Physician global disease activity assessment Patient global disease activity assessment	***Assay:*** RSAD2, IFI44L and MX1 expression ***Main findings:*** no association	Unclear

				MMT8		
		Niewold, 2009 [182]	30	Muscle enzymes DAS skin	***Assay:*** IFIT1, MX1, PRKR expression ***Main findings:*** Active patients: positive correlation (serum CPK: r=0.525, p=0.025, AST: r=0.705, p=0.002, and aldolase: r=0.447, p=0.036) Inactive patients: negative correlation (DAS skin: r=-0.781, p=0.002)	Unclear

Supplementary Table 11: Summary of the studies reporting assays analyzing associations between IFN assays and prognosis (natural history) in SLE.

Category	Sub-category	Reference	n	Endpoint	Results	Risk of bias
Immunoassays	*Immunoassays detecting IFNa protein*	Rose, 2013 [188]	31	Flare (new BILAG A or B score at 180 days)	Positive association (High IFN serum levels (>20 pg/ml) predicted flare, p=0.0004)	Unclear
	Simoa for IFNa	Mathian, 2019 [187]	74	SELENA-SLEDAI flare instrument	Positive association (IFNa serum levels detect flare: AUC 0.840, sensitivity: 73.0 (61.4–82.7), specificity: 82.9 (72.5–90.6); PPV: 80.6; NPV 75.9)	Low
		Mathian, 2019b [35]	254	SELENA-SLEDAI flare instrument (1 year)	Positive association (elevated IFNa levels at baseline predicted higher risk of relapse, HR 5.5 (2.4-2.5), p<0.0001; isolated elevated IFNa levels predicted flare, HR 5.5 (1.7-18.1), p=0.005)	Low
	DELFIA for IFNa	Rose, 2017 [189]	26	Change in mSLEDAI-2K Change in BILAG-2004 Flare (new BILAG A or B score at 180 days) Remitting disease (improving of A or B in BILAG)	Change in mSLEDAI-2K: positive correlation (change in IFNa serum levels: r=0.447, p=0.001) Change in BILAG-2004: positive correlation (change in IFNa serum levels: r=0.420, p=0.002) Flare: positive association (AUC 0.56 (0.31-0.81), p=0.600, sensitivity: 41.67, specificity: 100, PPV: 100) Remitting disease: positive association (AUC 0.84 (0.52-0.97), p=0.005, sensitivity: 62.50 specificity: 90.48, PPV: 76.00)	High
	Immunoassays detecting IFNb protein	Munroe, 2017 [192]	26	SELENA-SLEDAI flare instrument (6-12 weeks) SELENA-SLEDAI at follow-up	SELENA-SLEDAI flare instrument: positive association (IFNb serum levels lower at baseline in patients without flare vs those with flare, p<0.010) SELENA-SLEDAI at follow-up: positive correlation (IFNb: r=0.426, p=0.0691)	High
	Immunoassays detecting IFN-induced proteins	Rose, 2017 [189]	26	Change in mSLEDAI-2K Change in BILAG-2004 Flare (new BILAG A or B score at 180	Change in mSLEDAI-2K: positive correlation (r=0.759, p<0.0001) Change in BILAG-2004: positive correlation (r=0.504, p=0.0002) Flare: positive association (AUC 0.75 (0.55-0.91), p=0.017, sensitivity: 50.00, specificity: 95.24, PPV:	High

				days) Remitting disease (improving of A or B in BILAG)	75.00) Remitting disease: positive association (AUC 0.75 (0.49-0.97), p=0.040, sensitivity: 62.50, specificity: 95.24, PPV: 71.43)	
		Munroe, 2017 [192]	26	SELENA-SLEDAI flare instrument (6-12 weeks) SELENA-SLEDAI at follow-up	SELENA-SLEDAI flare instrument: MCP1: positive association (lower at baseline in patients non-flare vs those with flare, p<0.001) MCP3: positive association (lower at baseline in patients non-flare vs those with flare, p<0.001) MIG: positive association (MIG lower at baseline in patients non-flare vs those with flare, p<0.001) IP10: positive association (lower at baseline in patients non-flare vs those with flare, p<0.001) MIP-1b: positive association (lower at baseline in patients non-flare vs those with flare, p<0.001) SELENA-SLEDAI at follow-up MCP1: positive correlation (r=0.452, p=0.0547) MCP3: positive correlation (r=0.573, p=0.0178) MIG: positive correlation (r=0.468, p=0.0468) IP10: no association (r=0.426, p=0.0691) MIP-1b: no association (r=0.407, p=0.0697)	High
		Bauer, 2009 [210]	267	Flare (1 year)	Positive association (IFN-chemokine score rise at the time of flare (p<0.001) and decreased as disease remitted (p<0.001); IFN-chemokine score predicted flare in patients with SLEDAI<4 at baseline, HR 2.52 (1.63-4.09), p<0.0001)	Low
Flow cytometry	*Flow cytometry to detect IFN-induced proteins*	Rose, 2017 [189]	26	Change in mSLEDAI-2K Change in BILAG-2004 Flare (new BILAG A or B score at 180 days) Remitting disease (improving of A or B	***Target (source):*** Siglec1 (monocytes) ***Main findings:*** Change in mSLEDAI-2K: positive correlation (r=0.463, p<0.001) Change in BILAG-2004: positive correlation (r=0.448, p<0.001) Flare: positive association (AUC 0.78 (0.57-0.96), p=0.008, sensitivity: 83.33, specificity: 90.48, PPV: 71.43)	High

				in BILAG)	Remitting disease: positive association (AUC 0.75 (0.42-1.00), p=0.040, sensitivity: 75.00, specificity: 95.24, PPV: 85.71)	
Microarrays	*Microarray scores and clustering*	Hoffman, 2017 [53]	1760	SELENA-SLEDAI flare instrument, 1 year	***Source:*** WB ***Number of ISG:*** 34 ***Main findings:*** positive association (IFN score: RR 5.6, p=0.0015 (ILLUMINATE1 cohort); RR 5.9, p=0.0002 (ILLUMINATE2 cohort))	Low
		Mackay, 2016 [44]	27	SELENA-SLEDAI flare instrument (1 year)	***Source:*** WB ***Number of ISG:*** 2 IFN scores (A/B) ***Main findings:*** positive association (IFN score higher at baseline in patients with flare, p=0.006)	Unclear
qPCR	*qPCR for IFN scores*	El-Sherbiny, 2018 [74]	60	Flare occurrence Organ involvement	***Source:*** PBMC ***Number of ISG:*** 1 ***Main findings:*** Flare occurrence: positive association (high IFN score A, p=0.042), no association (IFN score B, p=0.343) Organ involvement: no association (IFN score A, p=0.124), positive association (high IFN score B, p=0.037)	High
		Feng, 2006 [92]	48	SELENA-SLEDAI flare instrument	***Source:*** WB ***Number of ISG:*** 6 ***Main findings:*** IFN score: positive association (higher in patients with severe flare vs those mild/moderate (p=0.020) or stable (p=0.020)) LY6E: positive association (higher in patients with severe flare vs stable, p=0.020)	High
		Landolt-Maricortena, 2009 [80]	27	Change in disease activity (1 year)	***Source:*** WB ***Number of ISG:*** 5 ***Main findings:*** no association (IFN score: r=-0.022, p=0.910)	Unclear
		Md Yusof, 2018 [82]	105	CTD development (1 year)	***Source:*** PBMC ***Number of ISG:*** 2 IFN scores (A/B) ***Main findings:*** positive association (IFN scores higher in at-risk progressors vs non-progressors, p=0.018 and	Low

					p<0.001)	
		Steiman, 2015 [211]	102	Clinical quiescence: SACQ (2-year without clinical activity but persistent serologic activity), SQCQ (inactive controls, 2-year without clinical or serologic activity) and SACA (clinical activity requiring use of GC and/or immunosuppressive agents)	***Source:*** WB ***Number of ISG:*** 5 ***Main findings:*** positive association (IFIT1, ISG15, LY6E, MX1 and OAS1 expression were higher in SACA vs SACQ, p=0.0034, p=0.044, p=0.0014, p=0.027 and p=0.0047; IFN score was higher in SACA vs SACQ, p=0.0025)	Unclear
Nanostring	*Nanostring*	Wither, 2017 [97]	23 UCTD 19 ANA+	SARD development (1 year)	***Source:*** WB ***Number of ISG:*** 5 ***Main findings:*** no association	High
DNA methylation	*DNA methylation arrays*	Ulf-Moller, 2018 [104]	15 twin pairs	Flare (2 years)	***Source:*** sorted populations (CD4+ T-cells, monocytes, granulocytes, B cells) ***Main findings:*** positive association (Several ISG exhibit differential methylation, mostly hypomethylation, in twins with flare vs those in remission in CD4+ T-cells (8), monocytes (8), granulocytes (9), and B-cells (8))	High
Reporter cell assays	*Reporter cell assays by qPCR*	Andrade, 2015 [108]	28	Poor outcomes of pregnancy	***Assay:*** Mx1 expression ***Main findings:*** positive association (MX1 expression was higher in patients who developed preeclampsia vs those with other (p<0.006) or without outcomes (p<0.040))	High
Cytopathic effect assay		Mathian, 2019 [187]	74	SELENA-SLEDAI flare instrument	Positive association (increased IFN bioactivity predicted flare: AUC 0.780, sensitivity: 63.5 (51.5–74.4), specificity: 88.2 (78.7–94.4), PPV: 83.9, NPV: 71.3)	Low

Supplementary Table 12: Summary of the studies reporting assays analyzing associations between IFN assays and prognosis (natural history) in RA.

Category	Sub-category	Reference	n	Endpoint	Results	Risk of bias
Microarrays	*Microarray scores and clustering*	van Baarsen, 2010 [212]	109	RA development (1 year)	***Source:*** WB ***Number of ISG:*** 52 gene sets (cluster analysis) ***Main findings:*** positive association (IFN signature associated with RA development, OR 21 (95% CI: 2.8–156.1), p=0.003)	High
qPCR	*qPCR for IFN scores*	Cooles, 2018 [138]	632	Disease activity (DAS28) at 6 months	***Source:*** WB ***Number of ISG:*** 5 ***Main findings:*** positive correlation (r=0.319, p=0.002)	High
		Lubbers, 2013 [213]	115 73	RA development	***Source:*** WB ***Number of ISG:*** 7 ***Main findings:*** positive association (cohort 1: 15/25 IFNhigh patients developed RA vs 29/90 IFNlow, p=0.001, AUC 0.602 (95% CI 0.491-0.714, p=0.066; cohort 2: IFN score higher in presymptomatic individuals who developed RA vs controls, p=0.002; IFNhigh status: 14/23 RA, 15/25 presymptomatic, 10/45 HC, p=0.004)	High

Supplementary Table 13: Summary of the studies reporting assays analyzing associations between IFN assays and prognosis (natural history) in SSc.

Category	Sub-category	Reference	n	Endpoint	Results	Risk of bias
Microarrays	*Microarray modules*	Assassi, 2019 [164]	62	Increase in FVC%, 26 months Change in mRSS, 26 months	***Source:*** WB ***Main findings:*** Increase in FVC%: negative correlation (M1.2: r=-0.430, p=0.009; M3.4: r=-0.450, p=0.007) Change in mRSS: no associations	High

Supplementary Table 14: Summary of the studies reporting assays analyzing associations between IFN assays and prognosis (response to treatments) in SLE.

Category	Sub-category	Reference	n	Treatment [target]	Endpoint	Results	Risk of bias
Microarrays	*Microarray scores and clustering*	Hoffman, 2017 [53]	1760	Tabalumab [B cell activating factor]	SRI (52 weeks)	***Source:*** WB ***Number of ISG:*** 34 ***Main findings:*** no association	Unclear
qPCR	*qPCR for IFN scores*	Furie, 2017 [214]	304	Anifrolumab (300 mg, n=99 and 1000 mg, n=103) [IFN alpha receptor subunit 1]	SRI(4) including GC taper (52 weeks) SRI(4) excluding GC taper (52 weeks) SRI(7) (52 weeks) BICLA (52 weeks)	***Source:*** WB ***Number of ISG:*** 4 ***Main findings:*** positive association (greater effect size in IFNhigh patients) Anifrolumab 300 mg SRI(4) including GC taper: IFNhigh OR 4.30 (2.34-7.91), p<0.001; IFNlow 1.47 (0.55-3.93), p=0.514 SRI(4) excluding GC taper: IFNhigh OR 2.98 (1.69-5.24), p<0.001; IFNlow 2.07 (0.77-5.53), p=0.225 SRI(7): IFNhigh OR 4.59 (2.26-9.33), p<0.001; IFNlow 0.94 (0.29-3.04), p=0.930 BICLA: IFNhigh OR 3.65 (2.02-6.60), p<0.001; IFNlow 3.19 (1.16-8.73), p=0.059 Anifrolumab 1000 mg SRI(4) including GC taper: IFNhigh OR 2.52 (1.37-4.64), p=0.013; IFNlow 0.89 (0.34-2.35), p=0.849 SRI(4) excluding GC taper: IFNhigh OR 2.33 (1.34-4.04), p=0.012; IFNlow 0.85 (0.34-2.12), p=0.763 SRI(7): IFNhigh OR 2.65 (1.29-5.34), p=0.26; IFNlow 0.81 (0.25-2.61), p=0.763 BICLA: IFNhigh OR 2.41 (1.34-4.35), p=0.014; IFNlow 1.38 (0.51-3.70), p=0.596	Low
		Kalunian, 2016 [215]	238	Rontalizumab [IFN alpha protein]	BILAG index response (24 weeks) SRI4 (24	***Source:*** WB ***Number of ISG:*** 3 ***Main findings:*** positive association (SRI response was higher and steroid use was lower in the IFNlow	Unclear

					weeks)	rontalizumab treated patients) BILAG response index: IFNhigh: placebo 21/55 (38.2%) vs rontalizumab 53/123 (43.1%), 5.2% (−7.6 - 18.1%), p=0.510 IFNlow: placebo 12/24 (50%) vs rontalizumab 18/33 (54.5%), 4.5% (−17.7 - 26.5%), p=0.790 SRI4: IFNhigh: placebo 26/55 (47.3%) vs rontalizumab 55/123 (44.7%), −2.3% (−15.5 - 10.9%), p=0.780 IFNlow: placebo 10/24 (41.7%) vs rontalizumab 24/33 (72.7%), 31.1% (8.9 - 51.0%) p=0.030	
		Merrill, 2018 [216]	201	Anifrolumab 300 mg [IFNA receptor subunit 1]	SLEDAI-2K-defined resolution of rash BILAG-defined improvement in rash Improvement in CLASI Resolution in SLEDAI-2K-defined arthritis Improvement in BILAG-defined arthritis Mean change in swollen and tender joint counts	***Source:*** WB ***Number of ISG:*** 4 ***Main findings:*** positive association (greater effect in IFNhigh patients) SLEDAI-2K-defined resolution of rash: IFNhigh: placebo 7/65 (10.8) vs anifrolumab 33/67 (49.3), OR 8.08 (3.72-17.52), p<0.001 IFNlow: placebo 6/23 (26.1) vs anifrolumab 6/21 (28.6), OR 1.40 (0.43-4.53), p=0.639 BILAG-defined improvement in rash: IFNhigh: placebo 17/64 (26.6) vs anifrolumab 35/61 (57.4), OR 3.78 (2.00-7.14), p<0.001 IFNlow: placebo 7/21 (33.3) vs anifrolumab 13/21 (61.9), OR 3.93 (1.28-12.04), p=0.044 Improvement in CLASI: IFNhigh: placebo 21/67 (31.3) vs anifrolumab 43/70 (61.4), OR 3.67 (2.01-6.71), p<0.001 IFNlow: placebo 9/22 (40.9) vs anifrolumab 14/22 (63.3), OR 2.70 (0.94-7.80), p=0.123 Resolution in SLEDAI-2K-defined arthritis: IFNhigh: placebo 29/73 (39.7) vs anifrolumab 41/73 (56.2), OR 2.11 (1.20-3.71), p=0.030 IFNlow: placebo 13/26 (50.5) vs anifrolumab 14/24 (58.3), OR 1.41 (0.55-3.64), p=0.547	Unclear

						Improvement in BILAG-defined arthritis: IFNhigh: placebo 34/72 (47.2) vs anifrolumab 47/71 (66.2), OR 2.39 (1.34-4.27), p=0.013 IFNlow: placebo 13/23 (56.5) vs anifrolumab 18/23 (78.3), OR (2.91 (0.97-8.72), p=0.110 Mean change in swollen and tender joint counts: IFNhigh: placebo -3.0(5.8) vs anifrolumab -4.9(6.1), mean difference (SE) –1.9(0.8), p=0.014 IFNlow: placebo -4.5(6.1) vs anifrolumab -7.4(6.3), mean difference (SE), –2.1(1.4), p=0.140	
		Petri, 2013 [217]	213	Sifalimumab (0.3-10 mg) [IFN alpha protein]	Mean reduction in SELENA-SLEDAI	***Source:*** WB ***Number of ISG:*** 21 ***Main findings:*** no association (greater but non-significant SELENA-SLEDAI reduction vs placebo: mean change: -2.6 vs -2.4)	Unclear

Supplementary Table 15: Summary of the studies reporting assays analyzing associations between IFN assays and prognosis (response to treatments) in RA.

Category	Sub-category	Reference	n	Treatment [target]	Endpoint	Results	Risk of bias
Immunoassays	*Immunoassays detecting IFNa protein*	Rodríguez-Carrio, 2014 [126]	26	Anti-TNF (various agents) [TNF protein]	EULAR clinical response (12 weeks)	Positive association (lower effect in IFNhigh patients (0% good response, 41.6% moderate response, 58.3% no response) compared to IFNlow (35% good response, 35% moderate response, 0% no response).	High
Microarrays	*Microarray scores and clustering*	Cantaert, 2010 [204]	21	Infliximab [TNF protein]	EULAR clinical response (24 weeks)	***Source:*** WB ***Number of ISG:*** 43 ***Main findings:*** no association	High
		Reynier, 2011 [132]	22	Anti-TNF (various agents) [TNF protein]	EULAR clinical response (24 weeks)	***Source:*** WB ***Number of ISG:*** 35 ***Main findings:*** no association	High
		Sanayama, 2014 [218]	40 20	Tocilizumab [anti-IL-6R]	Clinical response by physician global assessment	***Source:*** PBMC ***Number of ISG:*** number of differentially expressed genes (DEG) ***Main findings:*** positive association (409 probes fulfilled criteria for DEG (>1.5 FC): IFI6 (higher in responders, 0.006, AUC 0.693), MX2 (higher in responders, p=0.004, AUC 0.920), OASL (higher in responders, p=0.024, AUC 0.627; IFI6, MX2 and OASL score: AUC 0.853, sensitivity 80.0, specificity 80.0, PPV 92.0, NPV 57.0)	High
		van Baarsen, 2010 [212]	15	Infliximab [TNF protein]	EULAR clinical response (24 weeks)	***Source:*** WB ***Number of ISG:*** 15 ***Main findings:*** positive association (increased IFN score at 4 weeks was associated with poor clinical response, p=0.022)	High
		Vosslamber,	13	Rituximab	Change in	***Source:*** WB	High

		2011 [219]		[CD20]	DAS: >1.2/<1.2 (24 weeks) EULAR clinical response (24 weeks)	***Number of ISG:*** number of differentially expressed genes, gene clusters ***Main findings:*** Change in DAS: positive association (increased IFN response during treatment was associated with good or moderate response, p=0.018) EULAR clinical response: positive association (equivalent results)	
qPCR	*qPCR for IFN scores*	Raterman, 2012 [220]	27	Rituximab [CD20]	Responders (dDAS>1.2) vs non-responders (dDAS<1.2) (24 weeks)	***Source:*** WB ***Number of ISG:*** 8 ***Main findings:*** positive association (IFN score at baseline was negatively correlated with dDAS<1.2, OR: 0.25 (0.09-0.70), p=0.008; IFN score at baseline was lower in responders vs non-responders, AUC 0.820, p=0.0074)	Low
		Cooles, 2018 [138]	32	MTX, HCQ	EULAR clinical response (24 weeks) Need of additional GC doses (24 weeks)	***Source:*** WB ***Number of ISG:*** 5 ***Main findings:*** EULAR clinical response: positive association (IFN score at baseline was negatively associated with good response, p=0.044) Need of additional GC doses: positive association (IFN score at baseline was negatively associated with additional GC administration, p=0.0003)	Low
		De Jong, 2015 [221]	40	Rituximab [CD20]	Change dDAS>1.2 (24 weeks)	***Source:*** WB ***Number of ISG:*** 8 ***Main findings:*** positive association (higher IFN score at baseline was associated with non-response, AUC 0.828 (0.699-0.957), p<0.001)	Unclear
		Rodríguez-Carrio, 2017 [137]	18 13	GC+MTX Anti-TNF (various agents) [TNF protein]	EULAR clinical response (12 and 24 weeks) DAS28 (24 and 52	***Source:*** WB ***Number of ISG:*** 4 ***Main findings:*** VERA cohort (n=18) EULAR clinical response: positive association (higher IFN score was associated with poor clinical response, p=0.006, AUC 0.917 (0.782 – 1.000),	Unclear

					weeks)	p=0.004) DAS28: positive correlation (24 weeks: r=0.620, p=0.008; 52 weeks: r=0.552, p=0.041) Anti-TNF (n=13) DAS28: positive association (IFN score at baseline predicted higher DAS28 at 12 weeks after adjusting for confounders, B (95% CI): 0.577 (0.052-1.102), p=0.035)	
		Thurlings, 2010 [205]	20 31	Rituximab [CD20]	EULAR clinical response, (12 and 24 weeks) DAS28 decrease (12 and 24 weeks)	***Source:*** PBMC ***Number of ISG:*** 3 ***Main findings:*** Cohort 1 (n=20) EULAR clinical response: no association DAS28 decrease: no association Cohort 2 (n=31) EULAR clinical response: positive association (IFNhigh patients less likely to achieve a good response, 12 weeks p=0.043, 24 weeks: p=0.059) DAS28 decrease: positive association (lower reduction in IFNhigh patients, 12 weeks: p=0.008, 24 weeks: p=0.027) Pooled analysis: positive association (high IFN signature associated with poor clinical response and DAS28 decrease)	Unclear
RNA-seq	*RNA-seq*	Wright, 2015 [139]	30	Anti-TNF (various agents) [TNF protein]	EULAR clinical response (12 weeks) Change DAS28>1.2 (12 weeks) Change in DAS28 (12	***Source:*** neutrophils ***Number of ISG:*** 128 ***Main findings:*** EULAR clinical response: positive association (high IFN score at baseline predicted good clinical response, AUC 0.760) Change DAS28>1.2: positive association (high IFN score more likely to have a change DAS28<1.2, AUC 0.640)	High

					weeks)	Change in DAS28: positive correlation (r=0.210, p=0.020)	
Reporter cell assays	*Reporter cell assays by qPCR*	Thurlings, 2010 [205]	2031	Rituximab [CD20]	EULAR clinical response (12 and 24 weeks) DAS28 decrease (12 and 24 weeks)	***Assay:*** serum IFN bioactivity ***Main findings:*** EULAR clinical response: no association DAS28 decrease: no association	High
		Mavragani, 2010 [140]	47	Anti-TNF (various agents) [TNF protein]	EULAR clinical response (14 weeks)	***Assay:*** serum IFN bioactivity ***Main findings:*** positive association (high IFN bioactivity associated with a good clinical response, OR 1.36 (1.05-1.76), p=0.027)	High
		Muskardin, 2016 [222]	3292	Anti-TNF (various agents) [TNF protein]	EULAR clinical response (12 weeks)	***Assay:*** serum IFN bioactivity ***Main findings:*** Test cohort (n=32) EULAR clinical response: positive association (IFNb/a ratio >1.3 associated with a lack of EULAR clinical response, p=0.010) Validation cohort (n=92) EULAR clinical response: positive association (IFNb/a ratio >1.3 associated with no response at 12 weeks, OR 6.67 (1.37-32.55), p=0.018)	High

Supplementary Table 16: Summary of the studies reporting assays analyzing associations between IFN assays and prognosis (response to treatments) in PM/DM.

Category	Sub-category	Reference	n	Treatment [target]	Endpoint	Results	Risk of bias
Immunoassays	*Immunoassays detecting IFNa protein*	Reed, 2012 [223]	51	Immunomodulatory treatment (AZA, MTX, MMF, HCQ and GC)	Change in global VAS Change in muscle VAS Change in extra-skeletal VAS	Change in global VAS: no association (IFNa: r=-0.140, p=0.460) Change in muscle VAS: no association (IFNa: r=-0.17, p=0.380) Change in extra-skeletal VAS: no association (IFNa: r=-0.220, p=0.260)	High
	Immunoassays for IFN-induced proteins	Reed, 2012 [223]	51	Immunomodulatory treatment (AZA, MTX, MMF, HCQ and GC)	Change in global VAS Change in muscle VAS Change in extra-skeletal VAS	Change in global VAS: negative correlation (MIP1a: r=-0.190, p=0.320, IP-10: r=-0.610, p<0.001; IFN-chemokine score: r=-0.590, p<0.001) Change in muscle VAS: no association (MIP1a: r=-0.190, p=0.330); negative correlation (IP-10: r=-0.510, p<0.001; IFN-chemokine score: r=-0.500, p<0.0001) Change in extra-skeletal VAS: no association (MIP1a: r=-0.090, p=0.670), negative correlation (IP-10: r=-0.640, p<0.001; IFN-chemokine score: r=-0.620, p<0.001)	High
		Reed, 2015 [224]	177	Rituximab [CD20]	Changes in muscle VAS (16 weeks) Physician global VAS scores (16	Changes in muscle VAS: positive association (IFN-chemokine score at baseline predicted larger improvements in muscle VAS, depending on the autoantibody profile) Physician global VAS scores: no association (p=0.090)	High

					weeks)		
qPCR	*qPCR for IFN scores*	Reed, 2012 [223]	51	Immunomodulatory treatment (AZA, MTX, MMF, HCQ and GC)	Change in global VAS Change in muscle VAS Change in extra-skeletal VAS	***Source:*** WB ***Number of ISG:*** 3 ***Main findings:*** Change in global VAS: negative correlation (IFN score: r=-0.430, p=0.003) Change in muscle VAS: negative correlation (IFN score: r=-0.560, p<0.0001) Change in extra-skeletal VAS: negative correlation (IFN score: r=-0.300, p=0.048)	High

Supplementary Table 17: Summary of the studies reporting assays analyzing associations between IFN assays and prognosis (response to treatments) in pSS.

Category	Sub-category	Reference	n	Treatment	Endpoint	Results	Risk of bias
qPCR	*qPCR for IFN scores*	Bodewes, 2019 [153]	37	HCQ	Change in ESR (12, 24 and 48 weeks) Change in IgG and IgM levels (12, 24 and 48 weeks) Change in ESSDAI and ESSPRI (12, 24 and 48 weeks) Change in ocular or oral dryness (12, 24 and 48 weeks) Change in SF-36 or HAD scales (12, 24 and 48 weeks)	***Source:*** WB ***Number of ISG:*** 5 ***Main findings:*** Change in ESR: no association Change in IgG and IgM levels: no association Change in ESSDAI and ESSPRI: no association Change in ocular or oral dryness: no association Change in SF-36 or HAD scales: no association	High
		Quartuccio, 2017 [225]	12	Belimumab [B lymphocyte	Change in ESSDAI (28 and 52	***Source:*** PBMC ***Number of ISG:*** 3 ***Main findings:*** no association	High

				stimulator]	weeks)		

Supplementary Table 18: Summary of the studies reporting assays analyzing responsiveness to change of IFN assays in SLE.

Category	Sub-category	Reference	n	Treatment [target]	Timepoints	Results	Risk of bias
Immunoassays	*Immunoassays detecting IFNa protein*	Bengtsson, 2000 [185]	30	Usual care	Pre-flare / flare / post-flare visits Intervals: Pre-flare vs flare: median 4 months (1-21) Post-flare 1 vs flare: 2 months (0.5-9) Post-flare 2 vs post-flare 1: 2.5 months (1-5)	Changes observed: IFNa levels increased at flare vs pre-flare (p=0.005), post-flare 1 (p=0.0008) and post-flare 2 (p=0.002)	Unclear
		Fragoso-Loyo, 2012 [8]	20	Usual care	6 months	No change (IFNa: T0 52.4 (3.2–1074.4) vs T6 77.6 (3.2–2321.4), p=0.200)	High
		Willis, 2012 [14]	35	HCQ	Consecutive visits (not specified)	No change (IFNa decreased (non-significant) by 33.5%: 573.06 to 381.03, p=0.2507)	Low
	Immunoassays for IFN-induced proteins	Bauer, 2009 [210]	73	Usual care	Consecutive visits from patients who exhibited a reduction in disease	***Target:*** 3 chemokines (CXCL10, CCL19, CCL2) ***Main findings:*** changes observed (IFN-chemokine score drop at disease activity reduction, p<0.0010; Chemokine score increased at interim visits (42% increase) and at flare visits (53% increase))	Low

					activity (decrease in SLEDAI ≥3) along 1 year		
		Connelly, 2018 [196]	109	Usual care	Consecutive visits (median length follow up = 3.2 years, median clinical visits = 7)	***Target:*** 3 chemokines (CXCL10, CCL19, CCL2) ***Main findings:*** changes observed in association with disease activity (increase of one unit in IFN-CK score was significantly associated with an increase in SLEDAI-2K of 0.7 (RC = 0.73, (95% CI: 0.12, 1.43) p = 0.02))	Unclear
		Casey, 2018 [90]	304	Anifrolumab (3, 300 or 1000 mg) [IFNA receptor subunit 1]	1 year	***Target:*** 134 chemokines (CXCL10, CCL19, CCL2) ***Main findings:*** changes observed (Anifrolumab suppressed 11/27 proteins elevated in patients with SLEDAI-2K>10 and 5/7 proteins elevated in patients with CLASI>10)	Unclear
Flow cytometry		Alexander, 2015 [226]	12	Bortezomib (21-day cycles) [proteasome]	2 (mean) 21-day cycles	***Target (source):*** Siglec1 (monocytes) ***Main findings:*** changes observed (Siglec1 expression decreased upon treatment, baseline: 42.3 vs post-treatment: 18.8, p<0.001)	Low
		Li, 2010 [39]	4	High dose IV prednisolone (1 g/day)	3 days	***Target (source):*** CD64 (monocytes) ***Main findings:*** changes observed (CD64 decreased at day 3, p=0.006)	High
Microarrays	*Microarray modules*	Chiche, 2014 [46]	29	Usual care	At least three visits: median follow-up: 8.3 (2–28) months, median interval	***Source:*** WB ***Main findings:*** changes observed (module M1.2 very stable over time within individual patients (coefficient of variation=0.05); module M3.4: greater variation (CV=0.39); module M5.12: much greater variation (CV=0.91))	Low

					between visits:3.2 (0.5–19)		
		Petri, 2019 [227]	243	Usual care	2 or more clinical visits (not specified)	***Source:*** WB ***Main findings:*** no changes (IFN modules highly stable over time: M1.2 (ICC 0.88), M3.4 (ICC 0.79), M5.12 (ICC 0.75))	Unclear
	Microarray scores and clustering	Petri, 2009 [199]	11	Usual care	2-3 longitudinal visits (not specified)	***Source:*** WB ***Number of ISG:*** 4 ***Main findings:*** no changes (IFN scores remained constant, despite significant changes in disease activity)	Unclear
		Bennet, 2003 [131]	3	IV glucocorticoids 30 mg/kg/day	3 days	***Source:*** PBMC ***Number of ISG:*** several ISG ***Main findings:*** changes observed (significant downregulation of several ISG, overall p<0.001; interferon signature decreased, but granulocyte-related signature not affected)	High
		Hoffman, 2017 [53]	1760	Tabalumab [B cell activating factor]	1 year	***Source:*** WB ***Number of ISG:*** 34 ISG ***Main findings:*** no change (no change in IFN score over the 52-week duration in the placebo or tabalumab group; IFN signature was not down-modulated in patients who showed improvement in disease activity)	Unclear
		Kawasaki, 2011 [198]	12	Prednisolone initiation or increase in doses	Before (active phase) and after (inactive phase) of steroid treatment	***Source:*** CD3+ T-cells ***Number of ISG:*** signaling pathways and differentially expressed genes (DEG) ***Main findings:*** changes observed (711 DEG detected; interferon pathway ranked the top, with higher levels during the active phase)	Low
		Lauwerys, 2013 [58]	27	IFNa-kinoid	168 days	***Source:*** WB ***Number of ISG:*** 21	Unclear

						Main findings: changes observed (21 ISG changed from day 0 to day 122 and 168; IFNa-kinoid reduced the expression of ISG in IFNpositive patients)	
		Petri, 2013 [217]	161	Sifalimumab (0.3-10 mg/kg) every other 2 weeks [IFNa protein]	26 weeks under treatment + 24 weeks follow up	***Source:*** WB ***Number of ISG:*** 21 ***Main findings:*** changes observed (sustained inhibition with sifalimumab in IFNhigh patients, maximum average inhibition of 38.7% in the 1 mg/kg group)	Low
qPCR	*qPCR for IFN scores*	Kennedy, 2015 [63]	61	Rontalizumab [IFNa protein]	36 weeks	***Source:*** PBMC ***Number of ISG:*** 3 ***Main findings:*** changes observed (rontalizumab decreased IFN score over time vs placebo, IFNlow patients exhibited a greater effect but downregulation in IFNhigh did not reach IFNlow levels)	Unclear
		Dominguez-Gutierrez, 2014 [71]	60	Usual care	Follow-up of patients with at least 2 visits (not specified)	***Source:*** PBMC ***Number of ISG:*** 3 ***Main findings:*** changes observed (patients can be classified into increasing and decreasing IFN score groups)	High
		Liu, 2018 [81]	7	Not specified	Not specified	***Source:*** PBMC ***Number of ISG:*** 4 ***Main findings:*** changes observed (IFN-I score decrease ($p<0.050$) upon treatment or follow up (duration and treatment not disclosed))	High
		Aranow, 2015 [228]	48	Vitamin D (0, 2000 IU or 4000 IU)	12 weeks	***Source:*** WB ***Number of ISG:*** 3 ***Main findings:*** no change (IFN score was unchanged upon vitamin D treatment)	Low
		Fu, 2008 [77]	4	Treatment for active nephritis (various agents)	12 weeks	***Source:*** WB ***Number of ISG:*** 7 (IFN-induced chemokines) ***Main findings:*** changes observed (3/4 had their chemokine-induced score reduced and improved nephritis; 1/4 had their score	High

						increased and progressed to renal failure)	
		Furie, 2019 [79]	12	BIIB059 (20 mg/kg) [BDCA2]	1 day	***Source:*** WB ***Number of ISG:*** 9 ***Main findings:*** changes observed (a single BIIB059 dose lead to a rapid and partial neutralization of ISG expression compared to placebo)	Unclear
		Hasni, 2019 [229]	10	Omalizumab [IgE]	16 weeks	***Source:*** WB ***Number of ISG:*** 4 ***Main findings:*** no change (IFN score: all group p=0.110, IFNhigh p=0.052)	Unclear
		Kawasaki, 2011 [198]	12	Prednisolone initiation or increase in doses	Before (active phase) and after (inactive phase) of steroid treatment	***Source:*** CD3+ T-cells ***Number of ISG:*** 6 ***Main findings:*** changes observed (higher ISG expression in active vs non-active phase, all p<0.050)	Low
		Li, 2010 [39]	4	High dose IV prednisolone (1 g/day)	3 days	***Source:*** WB ***Number of ISG:*** 3 ***Main findings:*** changes observed (Mx1 expression decreased at day 3, p<0.050)	High
		McBride, 2012 [230]	32	Rontalizumab (single-dose or repeat dose) [IFN alpha protein]	6 months	***Source:*** WB ***Number of ISG:*** 7 ***Main findings:*** changes observed (rontalizumab induced a substantial decline (>50%) in relative gene expression at 3 mg/kg (31.3% of baseline) and 10 mg/kg (23.1% of baseline), different doses lead to different length of the sustained suppression)	Unclear
		Merrill, 2011 [231]	34	Sifalimumab (doses from 0 to 30 mg/kg) [IFN alpha protein]	84 days	***Source:*** WB ***Number of ISG:*** 21 ***Main findings:*** changes observed (doses 0, 3 and 10 led to changes in IFN score at day 14 (p<0.050, p=0.010 and p=0.010); no changes	Unclear

						with doses 1 or 3, p=0.090 and p=0.060)	
Reporter cell assays	*Reporter cell assays by qPCR*	Hua, 2006 [109]	2	Usual care	5 or 7 months	***Number of ISG:*** 5 ***Main findings:*** changes observed (IFN score varied over time, but fluctuations may be confounded by GC pulses or HCQ)	High
		Niewold, 2008 [111]	28	Usual care	Not specified	***Number of ISG:*** 3 ***Main findings:*** changes observed (patients could be classified into stable or unstable IFN signature)	High
Cytopathic cell assay		Lackovic, 1984 [118]	4	Usual care	Not specified	No change (no consistent pattern)	High
		von Wussow, 1988 [232]	61	Usual care	Not specified	No change (no consistent pattern)	High
Plaque assay		Ytterberg, 1982 [124]	14	Usual care	Not specified	Changes observed (IFN bioactivity patterns found in association with disease activity, p<0.050)	High

Supplementary Table 19: Summary of the studies reporting assays analyzing responsiveness to change of IFN assays in RA.

Category	Sub-category	Reference	n	Treatment [target]	Timepoints	Results	Risk of bias
Immunoassays	*Immunoassays for IFN-induced proteins*	Quartier, 2011 [233]	24	Anakinra [IL-1a]	6 months	***Target:*** 2 chemokines (IP-10 and TRAIL) ***Main findings:*** changes observed (IP-10 and TRAIL significantly increased in anakinra-treated patients at 6 months, p=0.0316 and p=0.0003)	Unclear
Microarrays	*Microarray modules*	Quartier, 2011 [233]	24	Anakinra [IL-1a]	6 months	***Source:*** WB ***Main findings:*** changes observed (coordinated upregulation of type I IFN-inducible transcripts (module M3.1) in the anakinra but not in the placebo-treated group, regardless of the clinical response)	Unclear
	Microarray scores and clustering	van Baarsen, 2010 [212]	15	Anti-TNF (infliximab) [TNF protein]	1 month	***Source:*** WB ***Number of ISG:*** 34 ***Main findings:*** no changes (no variation in ISG (mean 34 genes or mean 3 IFN genes) after 1 month upon anti-TNF)	Low
qPCR	*qPCR for IFN scores*	Bienkowska, 2014 [234]	340	Baminercept (700 or 200 mg) [lymphotoxin β]	14 weeks	***Source:*** WB ***Number of ISG:*** 15/3 ***Main findings:*** changes observed (IFN reduced in IFNhigh patients upon treatment in two cohorts)	Unclear
		Cantaert, 2010 [204]	18	Anti-TNF [TNF protein]	1 month	***Source:*** WB ***Number of ISG:*** 43 ***Main findings:*** no change (TNF blockade did not modulate the mean expression of ISG, increasing in 3 patients, decrease in 11 patients)	Low
		Cooles, 2018 [138]	11	Initiation of GC, MTX, HCQ	6 months	***Source:*** WB ***Number of ISG:*** 5 ***Main findings:*** changes observed (sustained decrease in IGS after 6 months of treatment, 1 month: p<0.010; 3 months: p<0.010 and 6 months: p<0.050)	Low

		Rodríguez-Carrio, 2017 [137]	13	Anti-TNF (various agents) [TNF protein]	3 months	***Source:*** WB ***Number of ISG:*** 4 ***Main findings:*** no change (no changes in ISG or IFN score upon TNF-blockade, all p>0.050)	Low
		Rodríguez-Carrio, 2019 [84]	13	Anti-TNF (various agents) [TNF protein]	3 months	***Source:*** WB ***Number of ISG:*** 5 ***Main findings:*** no change (no changes in ISG or IFN score upon TNF-blockade regardless of the response status, all p>0.050)	Low
		Vosslamber, 2011 [219]	22	Rituximab [CD20]	3 months	***Source:*** WB ***Number of ISG:*** 6 ***Main findings:*** changes observed (IFN score increased at 3 months compared to baseline in responders but not in non-responders, p=0.0040)	Low
		Weix, 2013 [125]	10	Not specified (pregnant RA patients)	Pre-pregnancy to postpartum	***Source:*** PBMC ***Number of ISG:*** 6 ***Main findings:*** changes observed (IFI35 and IFI44 expression changed along pregnancy and postpartum; no differences in IFI44L, IFIT3 and OAS1)	Unclear
Reporter cell assays	*Reporter cell assays by qPCR*	Muskardin, 2015 [222]	32 92	Anti-TNF (various agents) [TNF protein]	4-6 weeks	***Number of ISG:*** 5 ***Main findings:*** changes observed (decrease in total IFN activity, IFNb activity and IFNb/a ratio was associated with no response, all p<0.050)	Unclear

Supplementary Table 20: Summary of the studies reporting assays analyzing responsiveness to change of IFN assays in SSc.

Category	Sub-category	Reference	n	Treatment	Timepoints	Results	Risk of bias
Immunoassays	*Immunoassays for IFN-induced proteins*	Liu, 2013 [162]	63	Usual care	Consecutive visits (mean time in study: 3.1±1.2 years)	***Target:*** IP-10 and I-TAC ***Main findings:*** no changes observed (IP-10 p=0.977; I-TAC p=0.512; IFN-induced chemokine score p=0.621)	Unclear
		Assassi, 2019 [164]	62	Cyclophosphamide (n=35) Hematopoietic cell transplant (n=27)	6 and 12 months	***Target:*** 15 chemokines ***Main findings:*** changes observed (chemokine protein score significantly decreased in the hematopoietic cell transplant arm; no significant change in the cyclophosphamide group)	Unclear
Microarrays	*Microarray modules*	Assassi, 2019 [164]	62	Cyclophosphamide (n=35) Hematopoietic cell transplant (n=27)	6 and 12 months	***Source:*** WB ***Main findings:*** changes observed (decline in IFN modules (M1.2 and M3.4) post treatment, greater effect in the hematopoietic cell transplant group)	Unclear

Supplementary Table 21: Summary of the studies reporting assays analyzing responsiveness to change of IFN assays in pSS.

Category	Sub-category	Reference	n	Treatment [target]	Timepoints	Results	Risk of bias
Immunoassays	*Immunoassays detecting IFNa protein*	Pollard, 2013 [143]	28	Rituximab (1000 mg, day 1 and 15) [CD20]	Pre- and post-treatment (5, 12, 24, 36 and 48 weeks)	Changes observed (IFNa decreased levels after treatment at 5 and 12 weeks, p<0.050)	High
	Immunoassays for IFN-induced proteins	Pollard, 2013 [143]	28	Rituximab (1000 mg, day 1 and 15) [CD20]	Pre- and post-treatment (5, 12, 24, 36 and 48 weeks)	***Target:*** MIP-1b and MIG ***Main findings:*** changes observed (MIP1b decreased levels after treatment at 12 weeks, p<0.050; MIG decreased levels after treatment at 5, 12 and 36 weeks, all p<0.050)	High
Flow cytometry		Rose, 2016 [149]	11	GC (n=5) HCQ (n=6)	Pre- and post-treatment (GC: 5.5 months, HCQ: 5 months)	***Target (source):*** Siglec1 (monocytes) ***Main findings:*** changes observed (Siglec1 expression reduced upon GC and HCQ, p=0.028 and p=0.046)	Unclear
qPCR	*qPCR for IFN scores*	Brkic, 2013 [154]	69	Usual care	Two measurements (3.6±2.5 years)	***Source:*** sorted cell populations (monocytes) ***Number of ISG:*** 5 ***Main findings:*** no change	High
		Bodewes, 2019 [153]	77	HCQ	Pre- and post-treatment (24 weeks)	***Source:*** WB ***Number of ISG:*** 5 ***Main findings:*** changes observed (IFN-I score reduced upon HCQ treatment at 24 weeks, p<0.050)	Unclear
Reporter cell assays	*Reporter cell assays by qPCR*	Mavragani, 2007 [158]	10	Etanercept (25 mg, twice weekly) [TNF protein]	Pre- and post-treatment (12 weeks)	***Number of ISG:*** 2 ***Main findings:*** changes observed (IFN bioactivity increased upon treatment, baseline 4.12±1.77 vs post-treatment 7.46±5.34, p=0.040)	Unclear

Supplementary Table 22: Summary of the studies reporting assays analyzing responsiveness to change of IFN assays in PM/DM.

Category	Sub-category	Reference	n	Treatment [target]	Timepoints	Results	Risk of bias
Immunoassays	*Immunoassays for IFN-induced proteins*	Reed, 2015 [224]	177	Rituximab [CD20]	Pre- and post-treatment (16 weeks)	***Target:*** IP-10, I-TAC and MCP-1 ***Main findings:*** changes observed (IFN chemokine scores fluctuated upon treatment depending on autoantibody profiles)	Unclear
		Reed, 2012 [223]	51	Immunosuppressive regimens (various agents)	Two consecutive visits (interval not specified)	***Target:*** IP-10, I-TAC and MCP-1 ***Main findings:*** changes observed (IFN chemokine scores correlated with changes in global (r=0.530, p<0.001), muscle (r=0.500, p<0.001) and extra-skeletal VAS (r=0.550, p<0.001); changes in IP-10 correlated changes in global (r=0.530, p<0.001), muscle (r=0.440, p=0.002) and extra-skeletal VAS (r=0.520, p<0.001)	Low
		López de Padilla, 2015 [235]	200	Rituximab [CD20]	Pre- and post-treatment (8 and 16 weeks)	***Target:*** MCP1, IP10, I-TAC ***Main findings:*** no changes	Unclear
Microarrays	*Microarray scores and clustering*	Higgs, 2014 [236]	39	Sifalimumab [IFN alpha protein]	Pre- and post-treatment (28, 56 and 98 days)	***Source:*** WB ***Number of ISG:*** 13 ***Main findings:*** changes observed (IFN score neutralized (from 53% to 66%) across the three time points vs placebo, p=0.019)	Unclear
qPCR	*qPCR for IFN scores*	Greenberg, 2012 [177]	24	Usual care	Over 80 visits (at least 2/patient)	***Source:*** sorted cell populations (monocytes) ***Number of ISG:*** 13 ***Main findings:*** changes observed (21/24 patients exhibited an elevation of the type I IFN score IFN score, IFI44L and RSAD2 expression	Unclear

						changed in parallel to disease activity over time; 3/24 patients experienced no change in disease activity and exhibited no change in IFN score, IFI44L or RSAD2)	
		Huard, 2017 [209]	13	Usual care	2 or more longitudinal visits/patient	***Source:*** WB ***Number of ISG:*** 10 ***Main findings:*** changes observed (IFN score changed from baseline correlated changes in CDASI, r=0.280, p=0.060)	High
		Walsh, 2007 [178]	9	Usual care	2 paired samples (active vs improving disease)	***Source:*** WB ***Number of ISG:*** 25 ***Main findings:*** changes observed (MxA, RSAD2, IFI44L, HERC5, ISG15 and OASL expression decreased with disease improvement; little changes observed in all genes in refractory patients)	High
		O'Connor, 2006 [179]	14	Immunosuppressive therapy (>1 dose of IV methyprednisolone 30 mg/kg, parenteral MTX, folic acid and others)	1 year	***Source:*** WB ***Number of ISG:*** 1 ***Main findings:*** changes observed (change in MxA expression correlated change in DAS muscle (r=0.630, p=0.040) but not DAS skin (r=0.000, p>0.990))	High
		Reed, 2012 [223]	51	Immunosuppressive regimens (various agents)	Two consecutive visits (interval not specified)	***Source:*** WB ***Number of ISG:*** 3 ***Main findings:*** changes observed (changes in IFN gene score correlated changes in global (r=0.330, p=0.023) and muscle VAS (r=0.440, p=0.002)	Low
Reporter cell assays	*Reporter cell assays by qPCR*	Dastmalchi, 2008 [237]	10	Infliximab [TNF protein]	Not specified	***Number of ISG:*** 3 ***Main findings:*** changes observed (IFN bioactivity increased upon treatment, regardless of disease improvement, baseline: 1.54 (2.41) vs post-treatment: 3.88 (4.03), p=0.037)	Low

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