Diagnosis, prognosis and classification of early arthritis: results of a systematic literature informing the 2016 update of the EULAR recommendations for the management of early arthritis.

SUPPLEMENTARY MATERIALS

S1: Research questions

Question 1:

a) Can the recognition of arthritis by general practitioners (GPs) be trained, and if yes: how?
b) Which diagnostics should a GP perform in a patient with early arthritis?
c) How to recognize early arthritis (by the GP)?
d) Should all patients with early arthritis be referred to a medical specialist for further diagnosis and treatment? Or only patients with specific features (> 1 joint, rheumatoid factor positive)
e) How early should patients with arthritis be referred to a medical specialist? Or how early a patient with arthritis needs to be seen by the specialist?

Question 2:

a) Which is the place of laboratory tests such as RF, anti-CCP, ANA, new diagnostic tests (multibiomarker test..), etc in the diagnosis of early arthritis?
b) Which is the place of imaging such as plain X-rays, MRI, US, or other imaging modalities (Scintigraphy, PET scan, optical imaging methods: Xeralite Rheumascan; Hemics Handscan…) etc. in the diagnosis of early arthritis? Has US and MRI detected inflammation the same weight as clinical evaluation for the detection of synovitis at disease presentation?
c) Is there a minimum set of diagnostic procedures that need to be performed in a patient with early arthritis?

Question 3:

a) Which is the place of laboratory tests such as RF, anti-CCP, ANA, new diagnostic tests (multibiomarker test..), etc in the prognosis of early arthritis?
b) Which is the place of imaging such as plain X-rays, MRI, US, or other imaging modalities (Scintigraphy, PET scan, optical imaging methods: Xeralite Rheumascan; Hemics Handscan…) etc. in the prognosis of early arthritis? Has US and MRI detected inflammation the same weight as clinical evaluation for the detection of synovitis at disease presentation?

Question 4:

a) Which are relevant differential diagnostic considerations in patients referred with early undifferentiated arthritis in light of the epidemiology?

Question 5:

a) Is it still relevant to the individual patient to classify the disease according to recognised classification criteria?

S2: PICOTs

Question 1 :

a) What is the sensitivity/specificity of any tools applied by a GP for patients with suspected early arthritis to distinguish those with confirmed early arthritis from those with no early arthritis confirmed?

Population: patients suspected to have early arthritis, with confirmed EA according to an external standard (eg. rheumatologist's opinion)

Intervention: any tool applied by a GP to help diagnosing EA (questionnaires, algorithm, imaging, lab test, physical examination, etc.)

Control: patients suspected to have early arthritis in whom EA was not confirmed by an external standard (eg. rheumatologist's opinion)

Outcomes: Sensitivity and specificity/ PPV and NPV (and 2-by-2 table with crude numbers)/ OR or RR

Type of study: diagnostic experiment

b) What is the RR (OR) of patients with (a suspicion of) arthritis referred by the GP to a specialist in comparison to those not referred by the GP with respect of final diagnosis of any inflammatory rheumatic disease and with respect to radiographic progression?

Population: patients with i) suspicion of arthritis by the GP or ii) arthritis diagnosed by the GP; that have been referred to the rheumatologist

Intervention: Any tool applied by a GP to distinguish between referral and non-referral (imaging, ACPA, RF, more than 1 joint affected, family history, etc.)/ GP's clinical judgement/ No intervention defined

Control: patients with i) suspicion of arthritis by the GP or ii) arthritis diagnosed by the GP; that have not been referred to the rheumatologist

Outcomes: percentage of patients per group (or OR/RR) with i) diagnosis/classification of RA after x years; ii) a diagnosis/classification of any inflammatory rheumatic disease after x years; iii) radiographic progression after x years

Type of study: prognostic study with prospective follow-up

c) What is the RR (OR) of patients meeting remission or with non-radiographic progression when referred to specialist within x weeks compared to those referred beyond x weeks?

Population: patients with early arthritis that have been referred to specialist within x months after onset of arthritis

Intervention: Random allocation of early referral vs late referral/ The GP's judgement (early vs late referral)/ Any test result that guides early or late referral (eg. ACPA)/ No intervention

Control: patients with early arthritis that have been referred to specialist beyond x months after onset of arthritis

Outcomes: percentage of patients per group or as OR/RR with:/ clinical remission after x years/ non radiographic progression after x years.

Type of study: RCT or prognostic study with prospective follow-up

Question 2:

What is the PPV/NPV of ACPA/RF/ANA... when tested in a population with patients with arthralgia or early arthritis with respect to a classification of RA or other inflammatory rheumatic disease after x years?

Population: Patients with i) early arthritis or with ii) arthralgia who will develop RA or any other inflammatory rheumatic disease according to classification criteria
Intervention: Any laboratory tool applied to help diagnosing RA or any inflammatory rheumatic disease (ACPA, RF, ANA., ANCA)
Control: Patients with i) early arthritis or with ii) arthralgia who will NOT develop a RA or any other inflammatory rheumatic disease according to classification criteria
Outcomes: Sensitivity and specificity of the tool to predict RA/other diagnosis/ PPV and NPV (and 2-by-2 table with crude numbers)/ OR or RR
Type of study: i) case control studies and ii) Prognostic studies with prospective follow up

b) What is the PPV/NPV of imaging exams when tested in a population with arthralgia or early arthritis with respect to a classification of RA or other inflammatory rheumatic disease after x years?
Population: Patients with i) early arthritis or with ii) arthralgia who will develop a confirmed RA or any other inflammatory rheumatic disease according to classification criteria

Intervention: Any imaging exam (plain X-rays, MRI, US, Scintigraphy, PET scan, optical imaging methods) applied to help diagnosing RA or any inflammatory rheumatic disease

Control: Patients with i) early arthritis or with ii) arthralgia who will NOT develop a confirmed RA or any other inflammatory rheumatic disease according to classification criteria

Outcomes: Sensitivity and specificity of the tool to predict a classification of RA/other inflammatory disease/ PPV and NPV (and 2-by-2 table with crude numbers)/ OR or RR

Type of study: i) case control studies and ii) Prognostic studies with prospective follow up.
c) What is the PPV/NPV of a sequence of diagnostic procedures for diagnosing a rheumatic disease in patients with early arthritis?

Population: Patients with undifferentiated early arthritis that will develop a rheumatic disease according to classification criteria after x years

Intervention: application of a pre-set sequence of diagnosis procedures

Control: Patients with undifferentiated early arthritis that have not developed a rheumatic disease according to classification criteria after x years

Outcomes: Sensitivity and specificity to diagnose RA or other rheumatological disease after x years/ PPV and NPV (and 2-by-2 table with crude numbers)/ OR or RR

Type of study: studies with prospective follow-up

Question 3:

a) What is the PPV/NPV of ACPA/RF/ANA... when tested in a population with arthralgia or early arthritis with respect to radiological outcome or functional outcome or remission outcome after x years?
Population: Patients with i) early arthritis or with ii) arthralgia who will develop a severe inflammatory rheumatic disease, in terms of functional outcome or radiological outcome or remission outcome
Intervention: Any laboratory tool (ACPA, RF, ANA., ANCA) applied to help diagnosing severe RA or any inflammatory rheumatic disease
Control: Patients with i) early arthritis or with ii) arthralgia who will NOT develop a severe inflammatory rheumatic disease, in terms of functional outcome or radiological outcome or remission outcome
Outcomes: Sensitivity and specificity of the tool to predict radiographic progression/functional disability/ PPV and NPV (and 2-by-2 table with crude numbers)/ OR or RR
Type of study: i) case control studies and ii) Prognostic studies with prospective follow up

b) What is the PPV/NPV of imaging exam when tested in a population with arthralgia or early arthritis with respect to radiological outcome or functional outcome after x years?
Population: Patients with i) early arthritis or with ii) arthralgia who will develop a severe inflammatory rheumatic disease, in terms of functional outcome or radiological outcome
Intervention: Any imaging exam (plain X-rays, MRI, US, Scintigraphy, PET scan, optical imaging methods) applied to help diagnosing severe RA or any inflammatory rheumatic disease
Control: Patients with i) early arthritis or with ii) arthralgia who will NOT develop a severe inflammatory rheumatic disease, in terms of functional outcome or radiological outcome
Outcomes: Sensitivity and specificity of the tool to predict radiographic progression/functional disability/ PPV and NPV (and 2-by-2 table with crude numbers)/ OR or RR
Type of study: i) case control studies and ii) Prognostic studies with prospective follow up

Question 4:

What is the frequency of rheumatic diseases toward which early arthritis evolve after x years?
Population: Patients presenting with undifferentiated early arthritis

Intervention: Follow-up during x years

Control: None

Outcome: Diagnosis of a specific rheumatic disease according to classification criteria

Type of study: Studies with prospective follow-up (inception cohorts)

Question 5:

a) Is the prognosis (in terms of radiographic progression or functionnal disability or persistent disease) of early RA responding to ACR/EULAR 2010 criteria better than the prognosis of early RA that are ACR/EULAR criteria negative?

Population: Patients with early rheumatoid arthritis diagnosed by the rheumatologist that are also ACR/EULAR 2010 criteria positive

Intervention: Application of the ACR/EULAR 2010 criteria

Control: Patients with early rheumatoid arthritis diagnosed by the rheumatologist that are (still) ACR/EULAR 2010 criteria negative

Outcomes: Percentage of patients (per group or os OR/RR) with persistent disease according to the rheumatologist:/ persistent synovitis/ persistent DMARDs treatment/ erosion

Type of study: Prognostic studies

b) Is the prognosis (in terms of radiographic progression or functionnal disability or persistent disease) of early PsA responding to CASPAR criteria better than the prognosis of early PsA that are CASPAR criteria negative?

Population: Patients with early psoriatic arthritis diagnosed by the rheumatologist that are also CASPAR criteria positive

Intervention: Application of the CASPAR criteria

Control: Patients with early psoriatic arthritis diagnosed by the rheumatologist that are (still) CASPAR criteria negative

Outcomes: Percentage of patients (per group or as OR/RR) with persistent PsA according to the rheumatologist:/ persistent synovitis/ persistent DMARD treatment/ radiographic abnormalities

Type of study : Prognostic studies

c) Is the prognosis (in terms of radiographic progression or functionnal disability or persistent disease) of early peripheral spondyloarthritis responding to ASAS 2009 criteria better than the prognosis of early peripheral spondyloarthritis that are ASAS2009 criteria negative?

Population: Patients with early peripheral spondyloarthritis diagnosed by the rheumatologist that are also ASAS 2009 criteria positive

Intervention: Application of rhe ASAS 2009 criteria

Control: Patients with early peripheral spondyloarthritis diagnosed by the rheumatologist that are (still) ASAS 2009 criteria negative

Outcomes: Percentage of patients (per group or as OR/RR) with persistent peripheral spondyloarthritis according to the rheumatologist

Type of study: Prognostic studies

S3: Search strategy

Question 1 - Recognition of arthritis and referral to a medical specialist

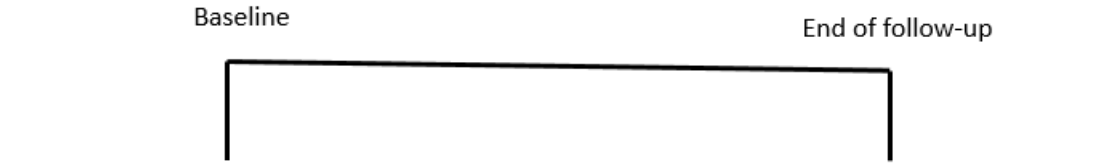
MEDLINE	**1**. exp Arthritis, Rheumatoid/; **2.** exp early diagnosis/; **3**. 1 and 2; **4**. exp Arthritis, Rheumatoid/ and (early or recent).tw.; **5**. ((early or recent$ or undifferentiated or persistent or unclassified) adj3 arthritis).tw.; **6**. or/3-5; **7**. exp "Referral and Consultation"/; **8.** exp Mass Screening/; **9**. Physicians, Primary Care/; **10**. exp Primary Health Care/; **11**. General Practitioners/; **12**. Triage/; **13**. Population Surveillance/mt [Methods]; **14**. exp "Predictive Value of Tests"/; **15**. Primary Care.tw.; **16**. General Practitioner$.tw.; **17**. screen$.tw.; **18**. refer$.tw.; **19**. case finding.tw.; **20**. consult$.tw.; **21**. or/7-20; **22**. 6 and 21; **23**. (sensitiv: or diagnos:).mp. or di.fs.; **24**. 6 and 23; **25**. 22 or 24; **26**. exp animals/ not humans.sh.; **27**. 25 not 26; **28**. limit 27 to "all adult (19 plus years)"; **29**. limit 28 to yr="2010 -Current"
The Cochrane Library	**#1** MeSH descriptor: [Arthritis, Rheumatoid] explode all trees; **#2** MeSH descriptor: [Early Diagnosis] explode all trees; **#3** #1 and #2 ; **#4** (early or recent):ti,ab ; **#5** #1 and #4 ; **#6** ((early or recent* or undifferentiated or persistent or unclassified) near/3 arthritis):ti,ab ; **#7** #3 or #5 or #6 ; **#8** MeSH descriptor: [Referral and Consultation] explode all trees; **#9** MeSH descriptor: [Mass Screening] explode all trees; **#10** MeSH descriptor: [Physicians, Primary Care] this term only; **#11** MeSH descriptor: [Primary Health Care] explode all trees; #12 MeSH descriptor: [General Practitioners] this term only; **#13** MeSH descriptor: [Triage] this term only; **#14** MeSH descriptor : [Population Surveillance] this term only and with qualifier(s): [Methods - MT]; **#15** MeSH descriptor: [Predictive Value of Tests] explode all trees; **#16** "Primary Care":ti,ab; **#17** "General Practitioner*":ti,ab ; **#18** screen*:ti,ab ; #19 refer*:ti,ab ; **#20** "case finding":ti,ab ; **#21** consult*:ti,ab ; **#22** #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 ; **#23** #7 and #22 ; **#24** (sensitiv* or diagnos*) ; **#25** Any MeSH descriptor with qualifier(s): [Diagnosis - DI]; **#26** #24 or #25 ; **#27** #7 and #26 ; **#28** #23 or #27 Publication Year from 2010 to 2015
EMBASE	**#24**. #23 AND [humans]/lim AND [embase]/lim AND ([adult]/lim OR [aged]/lim OR [middle aged]/lim OR [very elderly]/lim OR [young adult]/lim) AND (2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py); **#23.** #20 OR #22; **#22**. #6 AND #21; **#21.** 'diagnosis'/lnk OR predict*:ab,ti OR specificity:ab,ti; **#20**. #6 AND #19; **#19**. #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 ; **#18**. consult*:ab,ti ; **#17.** 'case finding':ab,ti; **#16.** refer*:ab,ti ; **#15.** screen*:ab,ti ; **#14.** 'general practitioner':ab,ti OR 'general practitioners':ab,ti; **#13.** 'primary care':ab,ti ; **#12.** 'predictive value'/de; **#11**. 'health survey'/exp; #10. 'primary health care'/exp; **#9.** 'general practitioner'/de; **#8**. 'mass screening'/exp; **#7**. 'patient referral'/de; **#6** #3 OR #4 OR #5 ; **#5**. ((early OR recent* OR undifferentiated OR persistent OR unclassified) NEAR/3 arthritis):ab,ti; **#4**. 'rheumatoid arthritis'/exp AND (early:ab,ti OR recent:ab,ti); **#3**. #1 AND #2; **#2**. 'early diagnosis'/de; **#1**. 'rheumatoid arthritis'/exp

Question 2-5: Diagnosis, Prognosis, Classification

MEDLINE	**1**. exp Arthritis, Rheumatoid/; **2**. exp early diagnosis/; **3.** 1 and 2; **4.** exp Arthritis, Rheumatoid/ and (early or recent).tw.; **5**. ((early or recent$ or undifferentiated or persistent or unclassified) adj3 arthritis).tw.; **6.** exp Arthralgia/; **7.** arthralgi$.tw.; **8.** or/3-7; **9.** (sensitiv: or diagnos:).mp. or di.fs.; **10**. incidence.sh. or exp mortality/; **11.** follow-up studies.sh.; **12.** prognos:.tw.; **13.** predict:.tw.; **14.** course:.tw.; **15**. exp Classification/; **16.** classif$.tw.; **17.** Classification.fs.; **18.** or/9-18; **19**. 8 and 19; **20**. exp animals/ not humans.sh.; **21.** 19 not 20; **22.** limit 21 to "all adult (19 plus years)"; **23.** limit 22 to yr="2005 -Current"; **24.** limit 23 to english language
The Cochrane Library	**#1** MeSH descriptor: [Arthritis, Rheumatoid] explode all trees; **#2** MeSH descriptor: [Early Diagnosis] explode all trees; **#3** #1 and #2 ; **#4** (early or recent):ti,ab ; **#5** #1 and #4 ; **#6** ((early or recent* or undifferentiated or persistent or unclassified) near/3 arthritis):ti,ab ; **#7** MeSH descriptor: [Arthralgia] explode all trees; **#8** arthralgi*:ti,ab ; **#9** #3 or #5 or #6 or #7 or #8 ; **#10** (sensitiv* or diagnos*) ; **#11** Any MeSH descriptor with qualifier(s): [Diagnosis - DI]; **#12** MeSH descriptor: [Incidence] this term only; **#13** MeSH descriptor: [Mortality] explode all trees; **#14** MeSH descriptor: [Follow-Up Studies] this term only; **#15** prognos*:ti,ab ; **#16** predict*:ti,ab ; **#17** course*:ti,ab ; **#18** MeSH descriptor: [Classification] explode all trees; **#19** classif*:ti,ab ; **#20** Any MeSH descriptor with qualifier(s): [Classification - CL]; **#21** #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 ; **#22** #9 and #21 Publication Year from 2005 to 2015
EMBASE	**#17.** #16 AND [embase]/lim AND [humans]/lim AND [english]/lim AND ([adult]/lim OR [aged]/lim OR [middle aged]/lim OR [very elderly]/lim OR [young adult]/lim) AND (2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py) AND ('article'/it OR 'article in press'/it); **#16**. #8 AND #15; **#15.** #9 OR #10 OR #11 OR #12 OR #13 OR #14; **#14.** classif*:ab,ti ; **#13.** 'classification'/exp ; **#12.** prognos*:ab,ti ; **#11.** epidemiology/lnk ; **#10.** 'follow up'; **#9.** 'diagnosis'/lnk OR predict*:ab,ti OR specificity:ab,ti; **#8.** #3 OR #4 OR #5 OR #6 OR #7; **#7.** arthralgi*:ab,ti ; **#6.** 'arthralgia'/de ; **#5.** ((early OR recent* OR undifferentiated OR persistent OR unclassified) NEAR/3 arthritis):ab,ti; **#4.** 'rheumatoid arthritis'/exp AND (early:ab,ti OR recent:ab,ti); **#3.** #1 AND #2; **#2.** 'early diagnosis'/de; **#1.** 'rheumatoid arthritis'/exp

S4: Studies design. (A) For the diagnosis part and (B) for the prognosis part.

A.

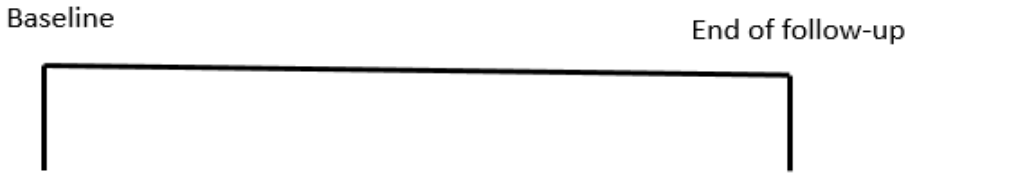


Undifferenciated arthritis:
- RF +/-
- Anti-CCP +/-

Rheumatoid arthritis or other rheumatic disease:
- ACR 87 criteria
- Experienced rheumatologist
- Persitent MTX use

	RA	**Not RA**	
RF/Anti-CCP +	True Positive	False Positive	**Sensitivity= TP/TP+FN Specificity= TN/TN+FP**
RF/Anti-CCP -	False negative	True Negative	
OR, Multivariate			

B.



Early Rheumatoid arthritis (ERA):
- RF +/-
- Anti-CCP +/-

Severe Rheumatoid arthritis:
- Radiographic progression
- No remission
- High HAQ score

	ERA	**Severe RA**	
RF/Anti-CCP +	True Positive	False Positive	**Sensitivity= TP/TP+FN Specificity= TN/TN+FP**
RF/Anti-CCP -	False negative	True Negative	
OR, Multivariate			

S5: (A) Value of laboratory tests in EA diagnosis and (B) Value of imaging tests in EA diagnosis.

A.

Study [LoE]	Population at baseline	Time for RA diagnosis (outcome)	% of pts achieving outcome	Laboratory test (+ vs -)	Sens	Spec	PPV	NPV	OR (95%CI)
Raza [2b] [22]	EA (n= 97)	1 year	25	Anti-CCP	63	94	79	88	NR
				RF	63	99	94	89	NR
				Anti-CCP and RF	58	100	100	88	NR
				Anti-CCP or RF	67	97	76	89	NR
van Gaalen [2b] [23][1]	EA (n= 467)	1 year	33	Anti-CCP	54	96	86	81	NR
Nell [2b] [24][2]	EA (n= 200)	1 year	51	Anti-CCP	41	98	96	62	NR
				RF	55	89	84	65	NR
				RF, high titer	41	98	92	63	NR
				Anti-RA33	28	90	74	55	NR
Boire [2b] [25]	EA (n= 149)	30 months	19	Anti-CCP	39	67	NR	NR	NR
				RF	57	63	NR	NR	NR
				Anti-cit-vim	39	73	NR	NR	NR
Fernandez-Suarez [2b] [26]	EA (n= 78)	1 year	68	Anti-CCP	53	100	100	58	NR
				RF	57	97	97	60	NR
				Anti-CCP or RF	68	97	97	67	NR
				Anti-CCP and RF	42	100	100	53	NR
Kudo-Tanaka [2b] [27]	EA (n= 146)	1 year	12	Anti-CCP	83	93	65	97	NR
				RF	78	68	30	98	NR
				Anti-CCP and RF	72	96	72	96	NR
				MMP-3	60	71	25	92	NR
Ateş [2b] [28]	EA (n= 64)	9 months	50	Anti-CCP	44	97	92	71	NR
				RF	41	95	85	69	NR
				Anti-CCP and RF	33	100	100	67	NR
				Anti-CCP or RF	52	92	82	72	NR

Kondo [2b] [29]	EA (n= 70)	1 year	31	Anti-CCP	64	96	88	85	NR
				RF	73	69	52	85	NR
Ursum [2b] [44]	EA (n= 162)	1 year	76	Anti-CCP	55	92	96	NR	NR
				Anti-MCV	59	92	96	NR	NR
Mjaavatten [2b] [30]	EA (n= 384)	1 year	18	Anti-CCP	NR	NR	NR	NR	19.3(6.8-54.4)
				RF	NR	NR	NR	NR	5.0 (1.5-17.1)
van der Linden [2b] [31][1]	EA (n= 625)	1 year	32	Anti-CCP	50	88	67	79	NR
				RF	48	86	62	78	NR
				Anti-MCV	57	78	56	79	NR
Funovits [2b] [32]	EA (n= 3115)	1 year	NR	RF or anti-CCP, low titers	NR	NR	NR	NR	2.2 (1.8-3.3)
				RF or Anti-CCP, high titers	NR	NR	NR	NR	3.9 (3.0-5.0)
Damjanovska [4] [46]	EA (n= 917)	NR	62	Anti-CCP	57	93	93	57	NR
				Anti-MCV	62	83	85	58	NR
Emad [2b] [33]	EA (n= 69)	1 year	26	Anti-CCP	57	38	65	39	NR
				RF	56	79	65	44	NR
				Anti-CCP and RF	36	65	57	44	NR
Gossec [2b] [34] [2]	EA (n= 731)	1 year	51	Anti-CCP	66	77	83	71	NR
				RF	69	77	75	71	NR
Duer-Jensen [2b] [35]	EA (n= 116)	12 to 23 months	23	Anti-CCP	33	91	53	82	NR
				RF	59	80	47	87	7.0 (2.3-22.9)
Pratt [2b] [36]	EA (n= 75)	Median of 28 months	39	Anti-CCP	48	98	93	75	NR
				Anti-cit-vim	14	98	80	64	NR
				RF	59	76	61	74	NR
Bizzaro [2b] [37]	EA (n= 192)	2 years	38	Anti-CCP	74	78	66	83	NR
				Anti-CCP, low titers	1	95	54	64	3.2 (1.3-8.1)

				Anti-CCP, high titers	64	83	69	79	4.3 (2.0-9.2)
				RF	63	72	57	76	NR
				RF, low titers	15	86	42	63	0.80 (0.20-2.5)
				RF, high titers	47	84	64	73	0.70 (0.20-2.4)
				Anti-CCP and RF	60	83	67	77	NR
Chen [2b] [38]	EA (n= 218)	2 years	20	Anti-CCP	34	94	56	85	1.1 (1.0-1.2)
				RF	41	79	33	84	NR
				Anti-CCP and RF	9	98	50	81	NR
				Anti-CCP or RF	41	81	35	84	NR
Hiura [2b] [39]	EA (n= 99)	1 year	44	Anti-CCP	75	98	97	83	NR
				RF	58	84	77	77	NR
				MMP-3	43	80	53	64	NR
Goëb [2b] [47]	EA (n= 250)	Approx. 5 years	43	Anti-CCP	35	94	NR	NR	NR
Moghimi [4] [40]	EA (n= 193)	NR	NR	Anti-CCP	47	93	84	70	NR
				RF	57	84	73	72	NR
				Anti-CCP and RF	39	97	89	68	NR
Nicaise-Roland [2b] [48] [2]	EA (n= 188)	2 years	51	Anti-CCP	30	93	80	56	NR
				Anti-MCV	31	88	73	55	NR
				Anti-CCP or anti-MCV	32	87	71	56	NR
				Anti-CCP and anti-MCV	28	94	82	56	NR
Regueiro [2b] [41]	EA (n= 552)	2 years	46	Anti-CarP	53	80	NR	NR	NR
				Anti-CCP and RF	NR	NR	92	80	NR
				Anti-CCP and RF and anti-CarP	NR	NR	92	82	NR

LoE, Level of Evidence; RA, rheumatoid arthritis; Pts, patients; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; These values are in percentages. OR, Odds-ratio; CI, confidence interval; NR, not reported; EA, early arthritis; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide antibodies; MMP-3, matrix metalloproteinase 3; anti-MCV, anti-mutated citrullinated vimentine antibodies; cit-vim, citrullinated vimentin; anti-CarP, anti-carbamylated protein antibodies;

[1]Studies with this footnote were conducted in the same cohort: the Leiden Early Arthritis cohort. [2]Studies with this footnote were conducted in the same cohort: the ESPOIR cohort

Due to limitation of space, we decided to present in this table only the studies for which either Sens, Spec, PPV, NPV or multivariate OR were available. Moreover, we decided to present only the studies evaluating a laboratory tools studied more than once. Details of non-presented studies are available on request.

B.

Study [LoE]	Population at baseline	Time for RA diagnosis (outcome)	% of pts achieving outcome	Imaging test	Evaluated parameter	Topography	Sens	Spec	PPV	NPV	OR (95% CI)
de Rooy [2b] [52]	EA (n= 80)	1 year	44	DXR on hands XR	Elevated BMD loss[#] at 6 months	Hand	26	95	85	52	NR
Duer-Jensen [2b] [35]	EA (n= 116)	12 to 23 months	23	MRI	Bone edema, RAMRIS System	Wrist	33	82	36	80	NR
						MCP	0	94	0	76	NR
						PIP	0	100	1	77	NR
						MTP	15	97	57	79	NR
						Wrist + MTP	NR	NR	NR	NR	1.4 (1.0-2.0)*
					TS	Hand	30	89	44	81	NR
Nieuwenhuis [2b][49][1]	EA (n= 178)	1 year	39	MRI	TS	MCP 5 flexor	20	92	61	65	4.2 (1.4–12.9)[$]
						MCP 2 extensor	14	98	83	64	9.4 (2.0–45.8) [$]
						MCP 4 extensor	12	99	89	64	20.1 (2.2–186.0) [$]
						Compartment 1 wrist extensor	19	94	68	65	3.7 (1.3–10.4) [$]

						Compartment 2 wrist extensor	19	92	59	64	2.3 (0.90–6.0) [$]
						Compartment 4 wrist extensor	33	82	53	66	2.1 (1.0–4.5) [$]
Nieuwenhuis [2b] [50][1]	EA (n= 202)	1 year	14	MRI	Any MRI inflammation[$], RAMRIS system	MCP, wrist and MTP	NR	NR	NR	NR	5.6 (1.2-25.6) [$]
					TS	MCP, wrist and MTP	NR	NR	NR	NR	5.4 (1.9-15.2) [$]
Sahbudin [2b] [51]	EA (n= 107)	18 months	40	US	TS, OMERACT recommendations	Extensor carpi ulnaris	NR	NR	NR	NR	5.5 (2.3-13.4)[§]
						Hand extensor tendons	NR	NR	NR	NR	4.8 (1.8–13.1) [§]
					PD TS symmetry	Hand flexor or extensor tendons	NR	NR	NR	NR	6.3 (2.2-17.9) [§]
						Wrist extensor tendons	NR	NR	NR	NR	6.3 (2.1-19.1) [§]

LoE, Level of Evidence; RA, rheumatoid arthritis; Pts, patients; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; These values are in percentages. OR, Odds-ratio; CI, confidence interval; NR, not reported; MRI, Magnetic Resonance Imaging; RAMRIS, Rheumatoid Arthritis Magnetic Resonance Imagins Score; MCP; metacarpophalangeal joint; PIP, proximal interphalangeal joint: MTP, metatarsophalangeal joint; TS, tenosynovitis; DXR, digital x-ray radiogrammetry; XR, x-rays; BMD, bone marrow density ; US, ultrasonography; PD, power Doppler; OMERACT, Outcome Measures in Rheumatoid Arthritis Clinical Trials

[#]Elevated BMD loss means a change $\geq 2.5 mg/cm^2$/month.

[1]Studies with this footnote were conducted in the same cohort.
*The OR for MRI bone marrow edema of the wrist and MTP are for the per unit of change in the RAMRIS system. The scale of this score for wrist + MTP is 0-66.
[$]The OR for MRI Tenosynovitis or MRI inflammation (bone edema or synovitis or tenosynovitis) are for presence vs absence.
[§]The OR of US Tenosynovitis are for presence vs absence

S6: (A) Value of laboratory tests in EA prognosis and (B) Value of imaging tests in EA prognosis.

A.

Study [LoE]	Population at baseline	Outcome	Definition of outcome*	Time for outcome evaluation	% of pts achieving outcome	Laboratory test (+ vs -)	Sens	Spec	PPV	NPV	OR (95% CI)
Boire [1b] [25]	EA (n= 165)	Presence of severity criteria	M-HAQ ≥1 and/or total SvH > 15	30 months	38	Anti-CCP	43	71	NR	NR	0.90 (0.30-3.0)
						Anti-CCP high titers	NR	NR	NR	NR	1.7 (0.60-5.2)
						RF	55	63	NR	NR	1.8 (0.60-5.8)
						Anti-cit-vim	45	79	NR	NR	8.8 (2.1-36.4)
Goldbach-Mansky [1b] [53]	ERA (n= 98)	Structural damage	≥1 erosion	1 year	44	RF	NR	NR	NR	NR	1.4 (0.60-3.1)
						SE	NR	NR	NR	NR	2.4 (1.0-5.9)
Nell [1b] [24][1]	ERA (n= 66)	Structural damage	≥2 erosions	1 year	55	Anti-CCP	61	90	88	66	NR
						RF high titers	58	80	78	62	NR
						Anti-Ra33	31	77	61	48	NR
Young-Min [1b] [54]	ERA (n= 118)	XR progression	Change in Larsen score	2 years	42	RF	NR	NR	46	68	NR
						SE	NR	NR	52	67	NR

			> 0			MMP-3	NR	NR	62	76	NR
Machold [1b] [55]	ERA (n= 55)	Structural damage	≥1 erosion	3 years	64	Anti-CCP	40	95	96	45	NR
						RF	40	90	92	44	NR
Hetland [1b] [71]	ERA (n= 139)	XR progression	Change in total SvH > 0	5 years	53	Anti-CCP	NR	NR	NR	NR	4.0 (1.7-9.8)
Nell-Duxneuner [1b] [56][1]	EA (n= 66)	Structural damage	≥2 erosions	5 years	55	Anti-CCP	61	90	88	66	NR
						RF	58	80	78	62	NR
						Anti-CCP and/or RF	78	73	78	73	NR
						Anti-Ra33	0	83	29	71	NR
Mouterde [1b] [72][2]	EA (n= 736)	XR progression	Change in total SvH ≥ 1	1 year	28	Anti-CCP	NR	NR	NR	NR	4.1 (2.6-6.5)
						SE	NR	NR	NR	NR	1.7 (1.0-2.7)
Burr [1b][57]	EA (n= 487)	Structural damage	≥1 erosion	5 years	43	Anti-CCP	53	90	NR	NR	3.8 (1.3-12),
						Anti-CCP, high titers	NR	NR	NR	NR	9.0 (4.4-18),
						RF	44	84	NR	NR	NR
			Larsen score > 15	5 years	31	Anti-CCP	61	86	NR	NR	5.3 (1.7-16)
						Anti-CCP, high titers	NR	NR	NR	NR	9.7 (4.7-20)
						RF	50	82	NR	NR	NR

van den Broek [1b] [58][3]	ERA (n= 465)	XR progression	Change in total SvH ≥ 5	1 year	22	Anti-CCP	77	43	28	87	NR
						RF	82	40	28	89	NR
van den Broek [1b] [73][3]	ERA (n= 484)	XR progression	Change in total SvH > 5	8 years	NR	Anti-CCP	NR	NR	NR	NR	3.8 (2.5-5.0)
Tobon [1b] [59][2]	EA (n= 500)	XR progression	Change in total SvH > 5	2-3 years	18	Anti-CCP	62	65	29	88	NR
						RF	65	60	27	88	NR
						Anti-CCP and/or RF	67	64	25	92	NR
Andersson [1b] [74][4]	ERA (n= 349)	XR progression	Change in total SvH ≥ 5.8	5 years	56	Anti-CCP	NR	NR	NR	NR	4.9 (2.5-9.7)
						COMP	NR	NR	NR	NR	3.1 (1.2-7.8)
Combe [1b][75][2]	EA (n= 813)	XR progression	Change in total SvH ≥ 1	3 years	79	Anti-CCP	NR	NR	NR	NR	2.2 (1.4-3.4)
Wevers-de Boer [1b] [60][5]	EA (n= 428)	XR progression	Change in total SvH ≥ 0.5	1 year	7	Anti-CCP	82	44	1	97	NR
						RF	64	44	1	95	NR
						Anti-CCP and RF	68	54	1	96	NR
Barra [1b] [61]	EA (n= 841)	XR progression	Apparition of ≥ 1 erosion	1 year	28	Anti-CCP	15	88	32	73	5.5 (1.4–21.2);
						RF	40	86	40	75	1.5 (0.40–5.5)
						Anti-CCP and RF	42	54	26	71	3.7 (1.1–12.1)

Hafstrom [1b] [62][4]	ERA (n= 117)	XR progression	Change in total SvH ≥ 5.8	2 years	39	Anti-CCP	67	61	53	74	9.4 (2.5-35.2)
						RF	72	58	52	76	8.7 (2.5-31.3)
Markusse [1b] [78][3]	ERA (n= 125)	XR progression	Change in total SvH > 0	1 year	42	MBDA (per unit of increase)	NR	NR	NR	NR	1.0 (1.0-1.1)
						Anti-CCP	NR	NR	NR	NR	3.2 (1.1-10.0)
Hambardzumyan [1b] [79]	ERA (n= 235)	XR progression	Change in total SvH ≥ 5	1 year	18	MBDA (> 44)	98	17	21	97	3.9 (1.0-14.3)
						MBDA (per unit of increase)	NR	NR	NR	NR	1.1 (1.0-1.1)
Degboé [1b] [63][2]	ERA (n= 566)	XR progression	Change in total SvH ≥ 5	1 year	26	Anti-CCP	60	59	33	81	2.1 (1.4-3.2)
						RF	68	51	32	82	2.1 (1.4-3.2)
						Anti-MCV, low titers	60	62	35	82	NR
						Anti-MCV, high titers	NR	NR	NR	NR	2.2 (1.5-3.2)
Fedele [1b] [76]	ERA (n= 386)	XR progression	Apparition of ≥ 1 erosion or change in	1 year	13	Anti-CCP	NR	NR	NR	NR	3.6 (1.4-9.5)

			erosion SvH > 0								
Akdemir [1b] [68][5]	EA (n=488)	XR progression	Change in total SvH ≥ 0.5	2 years	10	Anti-CCP	70	45	13	93	1.4 (0.60-3.5)
						RF	62	45	11	87	NR
						Anti-CarP	44	73	16	92	1.1 (0.10-9.7);
						Anti-CCP and anti-CarP	NR	NR	NR	NR	2.5 (1.2-5.6)

LoE, Level of Evidence; ERA, early rheumatoid arthritis; Pts, patients; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; These values are in percentages. OR, Odds-ratio; CI, confidence interval; NR, not reported; SvH, Sharp-van der Heijde score; HAQ, health assessment questionnaire; RF, rheumatoid factor; anti-CCP, anti-citrullinated antigen antibodies; SE, shared epitope; COMP, cartilage oligomeric matrix protein; anti-CarP, anti-CarP, anticarbamylated protein antibodies; MBDA, multi-biomarker disease activity; XR, x-rays; XR progression, radiographic progression

[1]Studies with this footnote were conducted in the same cohort: the Austrian Early Arthritis Action cohort. [2]Studies with this footnote were conducted in the same cohort: the ESPOIR cohort. [3]Studies with this footnote were conducted in the same cohort: the BeST cohort. [4]Studies with this footnote were conducted in patients from the same trial: the BARFOT study.[5]Studies with this footnote were conducted in patients from the same trial: the IMPROVED study.

* In all studies, radiographic outcomes were evaluated from hands and feet X-Rays

Due to limitation of space, we decided to present in this table only the studies for which either Sens, Spec, PPV, NPV or multivariate OR were available. Moreover, we decided to present only the studies evaluating a laboratory tools studied more than once and only studies using structural data as outcome. Details of non-presented studies are available on request.

B.

Study [LoE]	Population at baseline	Outcome	Definition of outcome*	Time for outcome evaluation	% of pts achieving outcome	Imaging test	Evaluated parameter	Sens	Spec	PPV	NPV	OR (95% CI)
Forslind [1b] [106]	ERA (n= 379)	XR progression	Change in total SvH ≥ 5.8	2 years	41	DXR on hands XR	BMD loss[#] at 1 year	67	60	49	76	NR
Wevers-de Boer [1b] [60]	EA (n= 428)	XR progression	Change in total SvH ≥ 0.5	1 year	7	DXR on hands XR	BMD loss[§] at 4 months	NR	NR	NR	NR	1.4 (1.1-1.7)
						XR[¤]	Erosions at baseline	39	87	18	95	3.9 (1.6-9.5)
van den Broek [1b] [73]	ERA (n= 465)	XR progression	Change in total SvH ≥ 5	Years 1-8	22	XR[¤]	Change in total SvH ≥ 5 at 1 year	NR	NR	NR	NR	2.0 (1.0-4.2)
Combe [2b] [75][1]	EA (n= 813)	XR progression	Change in total SvH ≥ 1	3 years	79	XR[¤]	Erosion SvH > 0 at baseline	NR	NR	NR	NR	2.3 (1.4-3.8)
Tobon [2b] [59][1]	EA (n= 500)	XR progression	Change in total SvH > 5	2-3 years	18	XR[¤]	Erosion SvH at baseline	54	71	30	87	NR
							Change in total SvH > 5 at 1 year	53	25	32	88	NR
Funck-Brentano [2b] [81][1]	EA (n= 127)	XR progression	Change in Erosion SvH ≥ 5	1 year	9	US on MCP/ MTP	PD score at baseline	NR	NR	NR	NR	1.2 (1.0-1.4)[£]
		Structural damage	Presence of erosions	2 years	39		Presence of erosions at baseline	NR	NR	NR	NR	1.4 (1.0-2.0)

El Miedany [2b] [82]	EPsA (n= 126)	XR progression	Apparition of JSN and/or erosions	1 year	NR	US of hands and feet	PD score ≥ 2 at baseline	NR	NR	NR	NR	2.7 (1.1-2.8)
							GS score ≥ 2 at baseline	NR	NR	NR	NR	2.6 (1.3–2.9)
Yoshikazu [2b] [80]	ERA (n= 76)	XR progression	Change in total SG > 3	1 year	16	MRI of wrist and fingers	Bone edema, RAMRIS system	NR	NR	NR	NR	1.1 (1.0-1.2)*

LoE, Level of Evidence; RA, rheumatoid arthritis; Pts, patients; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; These values are in percentages. NR, not reported; XR, x-rays; XR progression, radiographic progression; SvH, Sharp-van der Heijde score; SG, Genant modified Sharp score; US, ultrasound; MRI, magnetic resonance imaging; ERA, early rheumatoid arthritis; EPsA, early psoriatic arthritis; JSN, joint space narrowing. GS, gray scale

[1]Studies with this footnote were conducted in the same cohort: the ESPOIR cohort.

[¤] In all studies evaluating x-rays parameters, x-rays were performed on hands and feet

[#] BMD loss means a change ≥ 2.5mg/cm^2 at 1 year

[§] BMD loss means a change ≥ 1.5 mg/cm^2 at 4 months

[£]The ORs for US PD score of MCP and MTP are for the per unit of change in the OMERACT PD score. The scale of this score is 0-3 for each joint.

* The ORs for MRI bone marrow edema of the wrist and fingers are for 5 units of change in the RAMRIS system. The scale of this score for wrist + MCP + PIP is 0-90.

Due to limitation of space, we decided to present in this table only the studies for which either Sens, Spec, PPV, NPV or multivariate OR were available. Moreover, we present only studies using structural data as outcome Details of non-presented studies are available on request.