“Early Rheumatoid Arthritis: Is it too late?”

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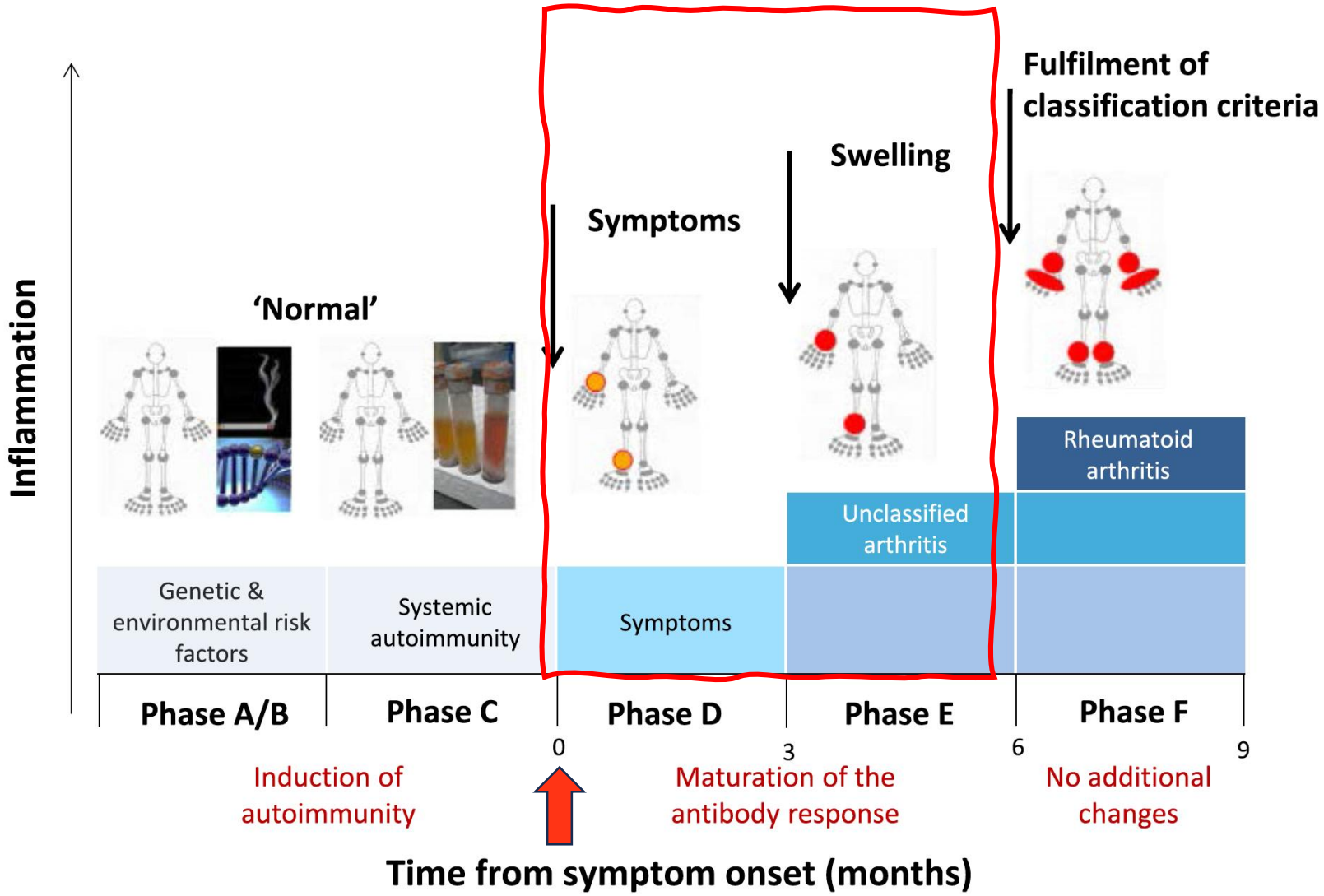
ΙΑΤΡΙΚΗ ΣΧΟΛΗ

Menu

Early arthritis cohorts data on:

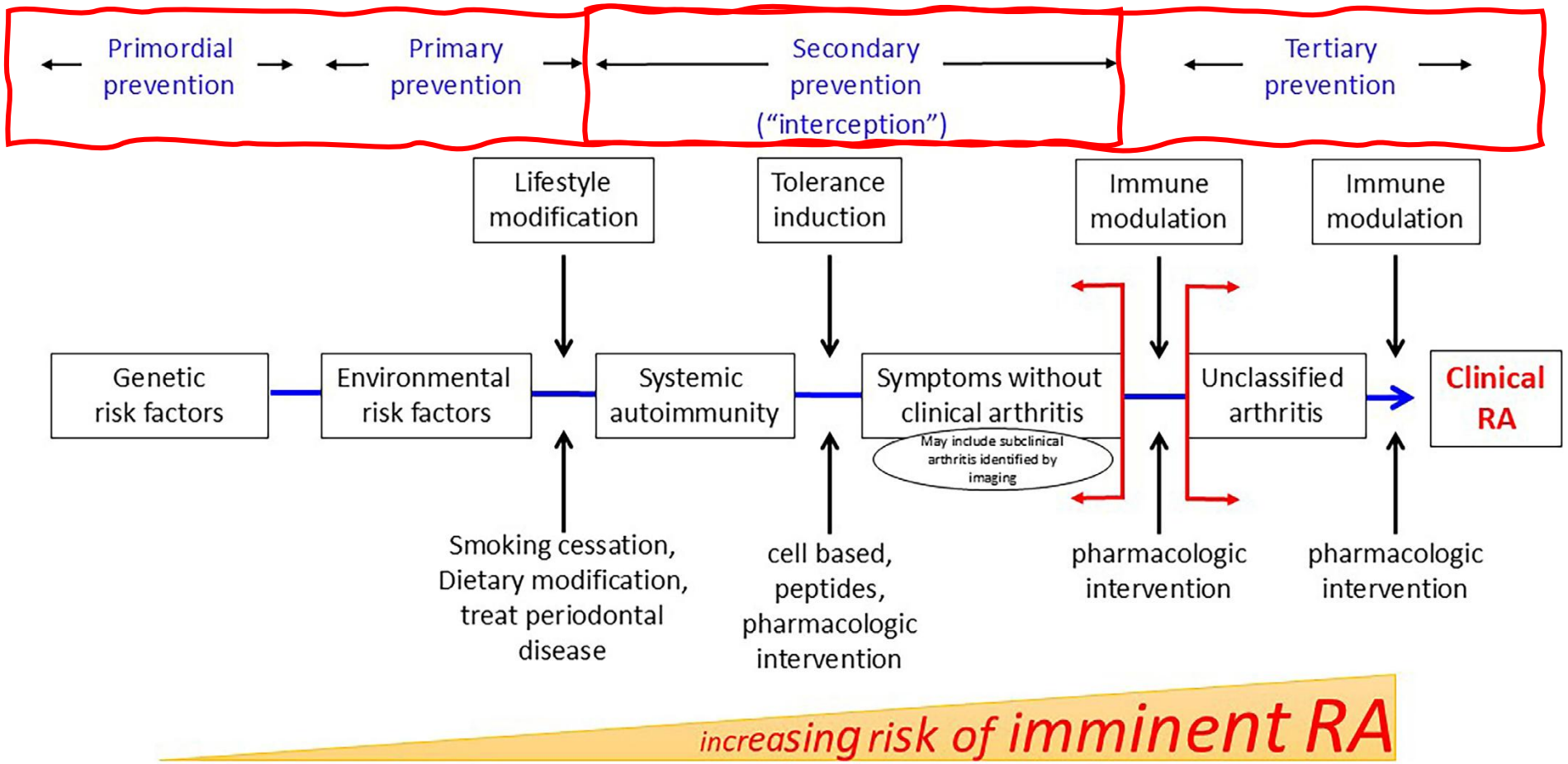
- ✓ Clinical data
- ✓ Cellular-molecular analysis
  - ➢ Synovium
  - ➢ Peripheral blood
- ✓ Comment - perspectives for clinical correlations:
  - ➢ response to treatment
  - ➢ prognosis (bDMARDs use, damage)

RA has a chronic immunological process before symptoms development



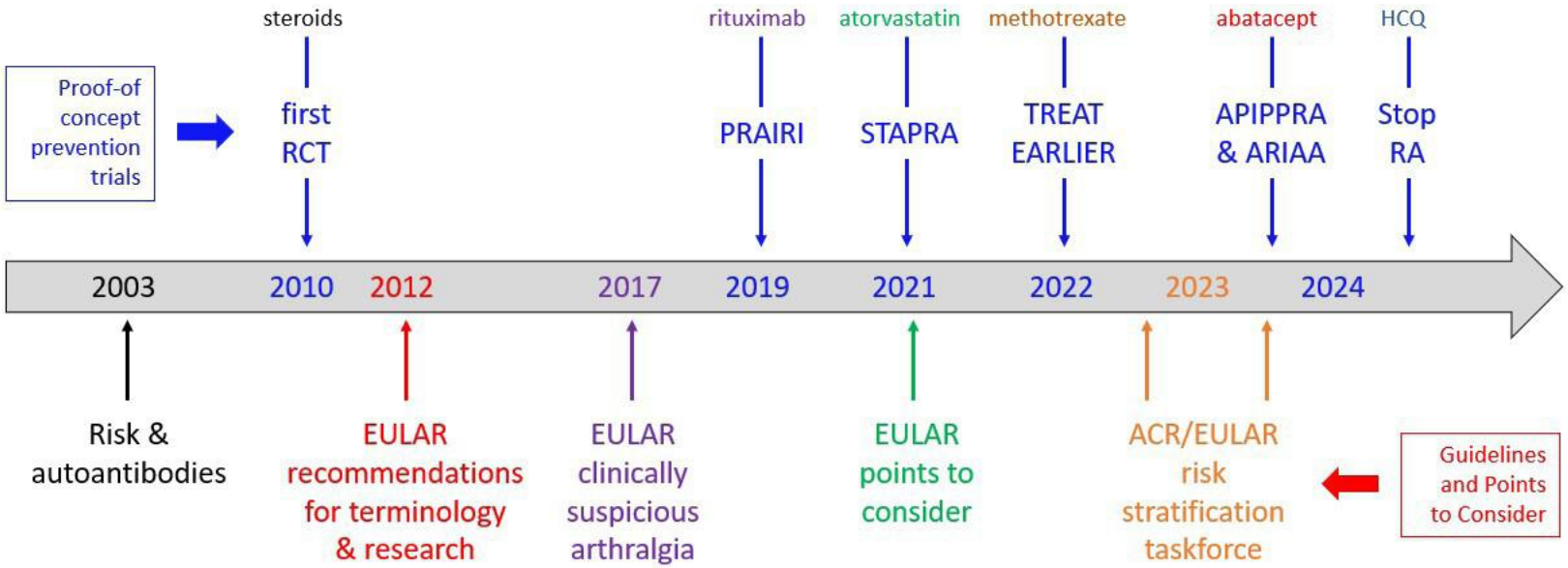
A.P. Cope, BPRC Rheumatology (2017)

Therapeutic intervention has evolved: from early treatment to prevention



Deane KD, et al. Ann Rheum Dis 2024

Preventive trials in Pre-RA
Clinical trials in individuals at risk for future clinical RA



Deane KD, et al. Ann Rheum Dis 2024

Clinical trials in individuals at risk for future clinical RA

What is the evidence?

- **Negative studies:** Limited courses of corticosteroids, atorvastatin and hydroxychloroquine **do not alter incidence** rates of clinical RA

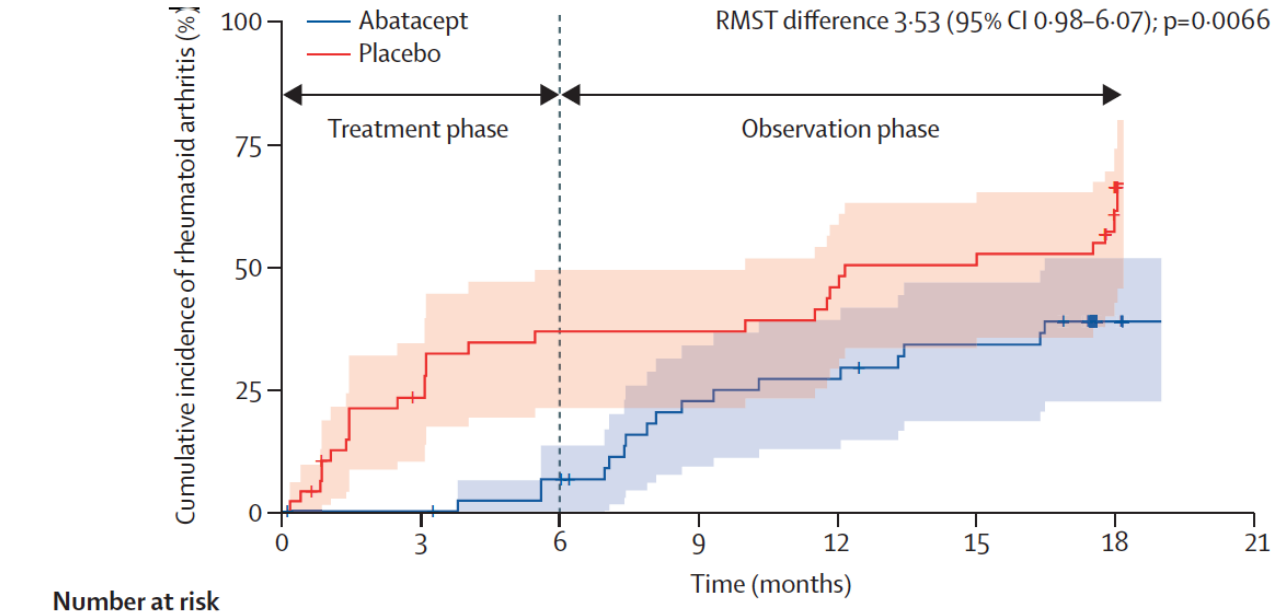
However,

- Methotrexate has transient effects
- Rituximab delays clinical RA onset
- **Abatacept delays clinical RA onset but does not fully prevent onset of RA after treatment cessation.**

….a limited course of abatacept reduced:

- ✓ Rates of progression to clinical RA within the trial period,
- ✓ Multiple aspects of the symptom burden
- ✓ Subclinical joint inflammation.

Nevertheless, time-limited interventions **were not sufficient to conclusively 'prevent' RA, indicating that challenges remain to further advance prevention in RA.**



Number at risk (number censored)							
Abatacept	49 (2)	47 (2)	42 (4)	34 (5)	32 (5)	28 (6)	6 (26)
Placebo	49 (0)	32 (4)	28 (4)	28 (4)	24 (4)	22 (4)	7 (15)

Lancet. 2024 Mar 2;403(10429):850

Overall 80% of early arthritis is classified as RA @ 10yrs

3 EU cohorts of “early arthritis” (ESPOIR, Reade, Leiden EAC)

Box 1 Phenotypes of early arthritis

	RA classification
⇒ Autoimmune inflammatory polyarthritis (AIPA).	>90%
⇒ Mild inflammatory polyarthritis (MIPA).	60-90%
⇒ Autoimmune inflammatory oligoarthritis of upper limbs (AIOAUL).	50-65%
⇒ Mild inflammatory oligoarthritis of upper limbs (MIOAUL).	20%
⇒ Oligoarthritis of lower limbs (OALL).	2-15%

The rest is Undifferentiated Arthritis

Table 4 Fulfilment of RA classification criteria across latent classes of EA in each cohort

Latent class / 2010 criteria	RA	No RA		% Classification
Reade				
AIPA	243	22	265	92
MIPA	39	25	64	61
OAUL	27	29	56	48
Total	309	76	385*	80
ESPOIR				
AIPA	358	23	381	94
MIPA	103	16	119	87
OAUL	177	82	259	68
OALL	3	16	19	16
Total	641	137	778*	82
EAC				
AIPA	422	68	490	86
MIPA	158	275	433	36
AIOAUL	101	53	154	66
MIOAUL	67	325	392	17
OALL	7	402	409	2
Total	755	1123	1878	40

RMD Open 2023;9:e003611

Phenotypic transitions @ 10yrs

Polyarthritis hands: 100% stable phenotype irrespective of labs

Olygoarthritis of hands: <30% transition to polyarthritis

Lower limbs arthritis: stable

Table 5 Latent transition analysis in ESPOIR (10 years) and EAC (1 year)

Baseline / Follow-up	AIPA	MIPA	OAUL	AIOAUL	MIOAUL	OALL
ESPOIR (N=504)						
AIPA	100	0	0	NA	NA	NE
MIPA	0	100	0	NA	NA	NE
OAUL	21.0	10.2	68.7	NA	NA	NE
OALL	NE	NE	NE	NA	NA	NE
EAC (N=1261)						
AIPA	100	0	NA	0	0	0
MIPA	0	100	NA	0	0	0
AIOAUL	14.2	0	NA	85.8	0	0
MIOAUL	0	2.9	NA	0	97.1	0
OALL	0.3	1.0	NA	0.3	6.6	91.7

Values come from LTA models with full invariance and are transition probabilities across classes from the baseline to the follow-up visit (10 years in ESPOIR and 1 year in EAC).
AIOAUL, autoimmune inflammatory OAUL; AIPA, autoimmune inflammatory polyarthritis; EAC, early arthritis clinic; ESPOIR, Etude et Suivi des Polyarthrites Indifférenciées Récentes; LTA, latent transition analysis; MIOAUL, mild inflammatory OAUL; MIPA, mild inflammatory polyarthritis; NA, not applicable (class not identified); NE, not possible to estimate; OALL, oligoarthritis of lower limbs; OAUL, oligoarthritis of upper limbs.

RMD Open 2023;9:e003611

Overall improvement in function over the long term. Comparable disability between subgroups

There was an improvement over time for function (ESPOIR):

- ✓ SF36 physical (PCS)
  - ✓ baseline 35–40 ☛ 12 years: 43–51
- ✓ SF-36 mental (MCS)
  - ✓ baseline: 34–41 ☛ 12 years: 40–48
- ✓ HAQ
  - ✓ baseline: 0.7–1.2 ☛ 12 years: 0.3-0.6

Comparable functional evolution between different phenotypes!!!

Table 6 Prognosis of EA phenotypes: impact of the different classes on outcomes over time

	HAQ (0–3) β (95% CI)*	SF36 PCS (0–100) β (95% CI)*	SF36 MCS (0–100) β (95% CI)*
Reade			
MIPA vs AIPA	**0.22 (0.10; 0.33)**	NA	NA
OAUL vs AIPA	0.04 (–0.17; 0.10)	NA	NA
ESPOIR			
MIPA vs AIPA	0.01 (–0.1; 0.08)	0.20 (–1.46; 1.06)	0.21 (–1.75; 1.34)
OAUL vs AIPA	**0.07 (–0.13; –0.01)**	0.45 (–0.50; 1.40)	0.74 (–1.95; 0.47)
OALL vs AIPA	0.04 (–0.19; 0.10)	0.97 (–3.36; 1.42)	1.73 (–5.14; 1.69)
EAC			
MIPA vs AIPA	**0.09 (–0.18; 0.00)**	NA	NA
AIOAUL vs AIPA	0.01 (–0.11; 0.12)	NA	NA
MIOAUL vs AIPA	0.08 (–0.16; 0.01)	NA	NA
OALL vs AIPA	0.06 (–0.18; 0.05)	NA	NA

RMD Open 2023;9:e003611

Low incidence of radiological damage

Higher radiographic damage in polyarthritis/hands/autoAb+ve (AIPA)

Table 6 Prognosis of EA phenotypes: impact of the different classes on outcomes over time

	SvdH (0–448) β (95% CI)*
Reade	
MIPA vs AIPA	**7.00 (–9.42; –4.52)**
OAUL vs AIPA	2.73 (–5.94; 0.49)
ESPOIR	
MIPA vs AIPA	**4.33 (–6.47; –2.18)**
OAUL vs AIPA	0.79 (–3.05; 1.47)
OALL vs AIPA	**4.48 (–6.80; –2.17)**
EAC	
MIPA vs AIPA	**18.5 (–25.2; –11.9)**
AIOAUL vs AIPA	0.7 (–5.3; 6.7)
MIOAUL vs AIPA	6.3 (–15.1; 2.6)
OALL vs AIPA	6.8 (–19.2; 5.5)

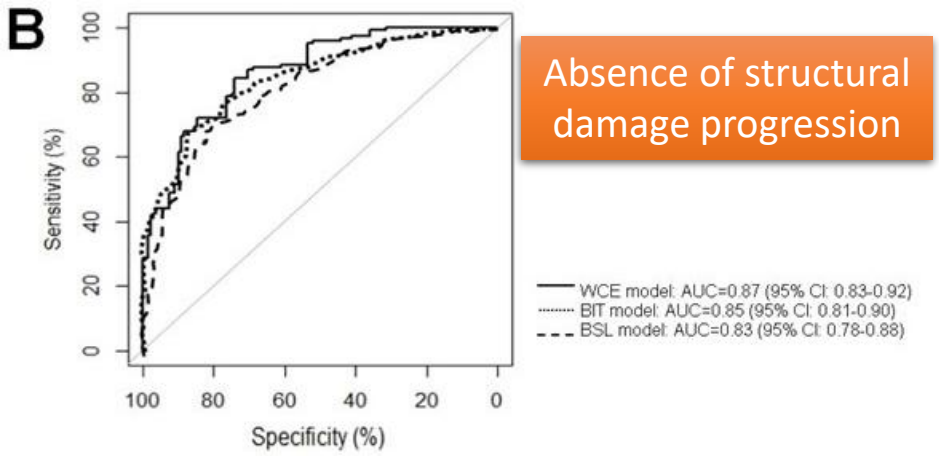
Clinical interpretation:

the data suggest that EA patients presenting without known prognostically unfavourable features (eg, elevated APR and autoantibodies) do not necessarily have better clinical outcomes on the long-term as compared with those who have these markers at presentation

75% of early arthritis do not have damage @ 10 yrs (ESPOIR)

Damage Progression in early arthritis @ 10 years

- 26.5% had structural damage progression (SDP)
- Mean progression in progressors of 34.4±22.8 (vSHS)



Absence of structural damage progression

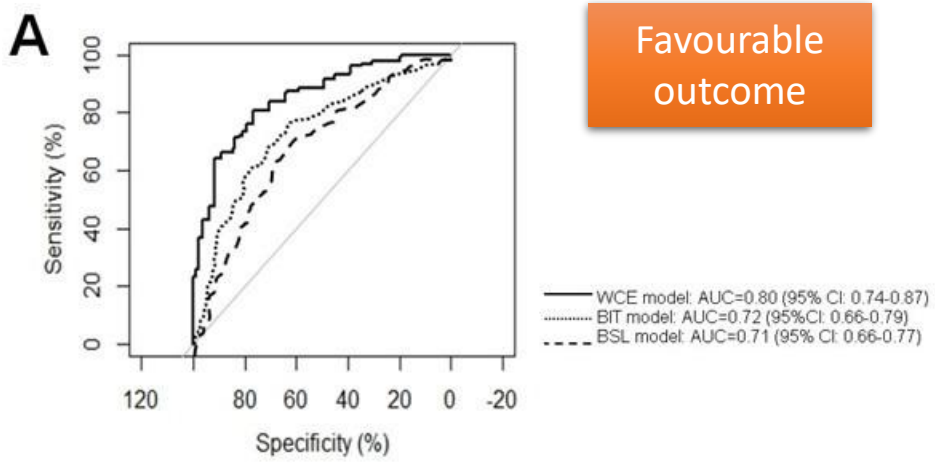
Baseline model (BSL)

age at onset
DAS28, HAQ, patient global
fatigue
total mean vSHS
Low income

BIT model (BIT)

BSL + csDMARD/bDMARD Y/N

Favourable outcome @ 10 years: 50%
DAS28-ESR <2.6 and HAQ-DI <0.5



Favourable outcome

WCE model (WCE)

BSL + csDMARD/bDMARD dose

RMD Open 2022;8:e002040

The majority 75% of RA patients do not have radiographic damage: 2 groups: progressors and not progressors

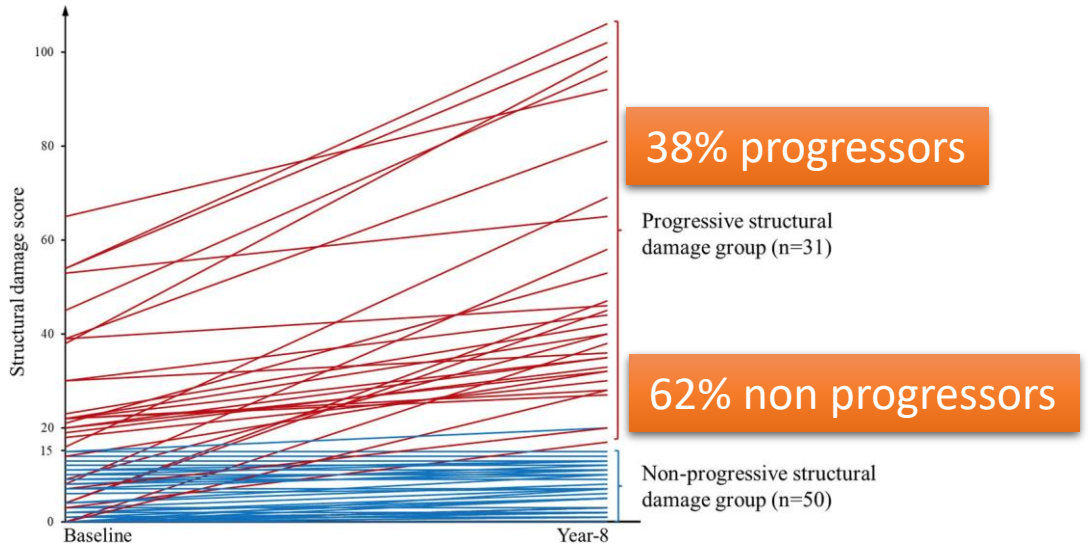
In a cohort of early RA @ 8 yrs:
25% with erosive disease on Xrays and 38% on MRI

Radiographic structural damage (SHS score) "progressed":

@ baseline, 93% (75/81) had none/mild radiographic damage
@ year-8, 75% (61/81) still had none or mild damage.

- ✓@ baseline 2.2 ± 4.4 increased ☛
- ✓@ 1st year 3.9 ± 6.5 ☛
- ✓@ 8th year 6.3 ± 8.9 ($p < 0.001$)

MRI: 38% progressors



Wu et al. European Radiology, 2025

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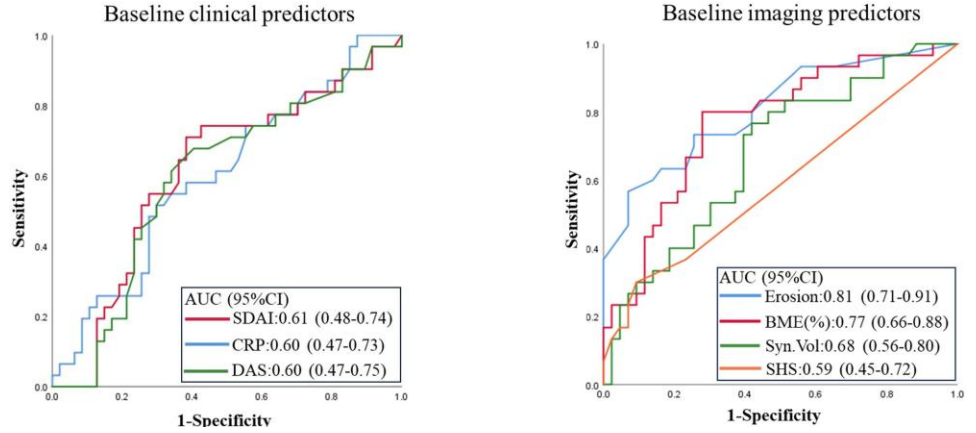
Clinical predictors: not valid
Baseline MRI findings better predict 8 yrs damage



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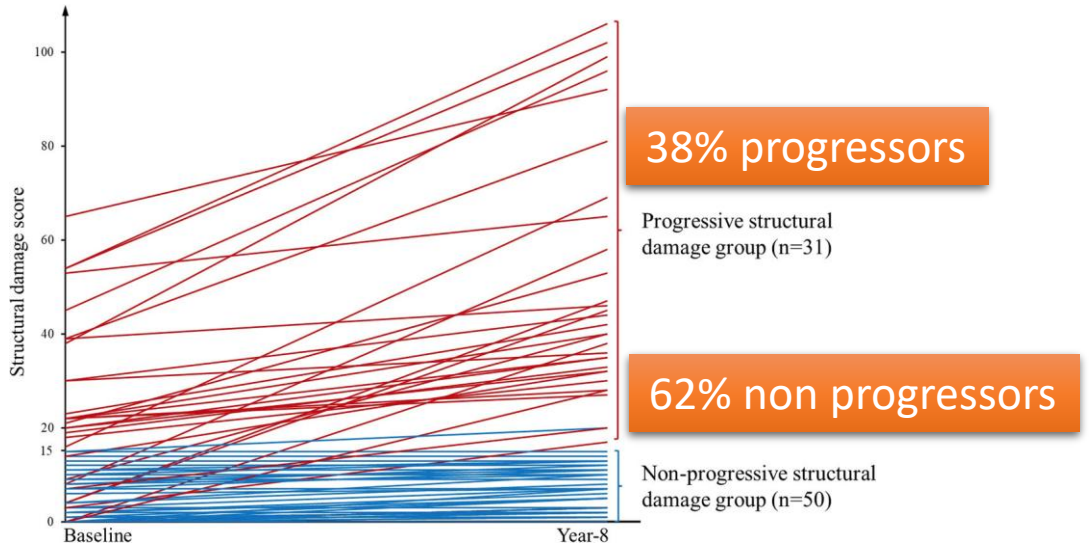

Wu et al. European Radiology, 2025

bDMARDs in early RA cohorts: do we treat early enough?

8% @1yr ☛ 14% @2yrs ☛ 21% @5yrs

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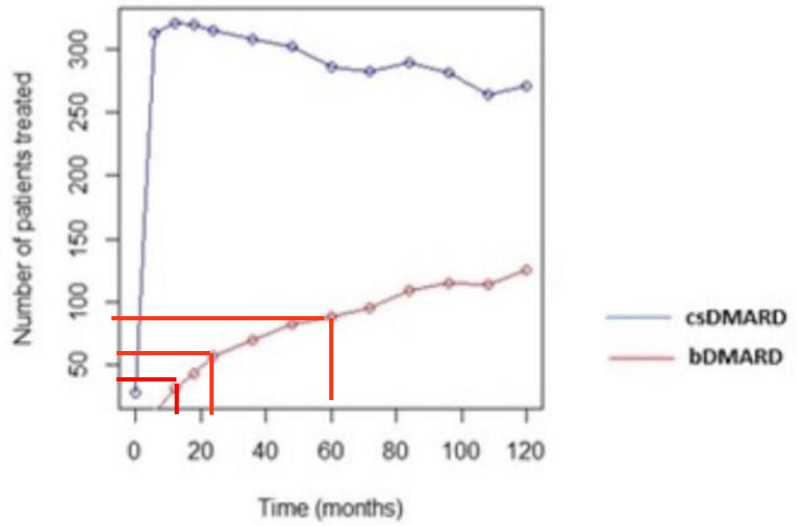
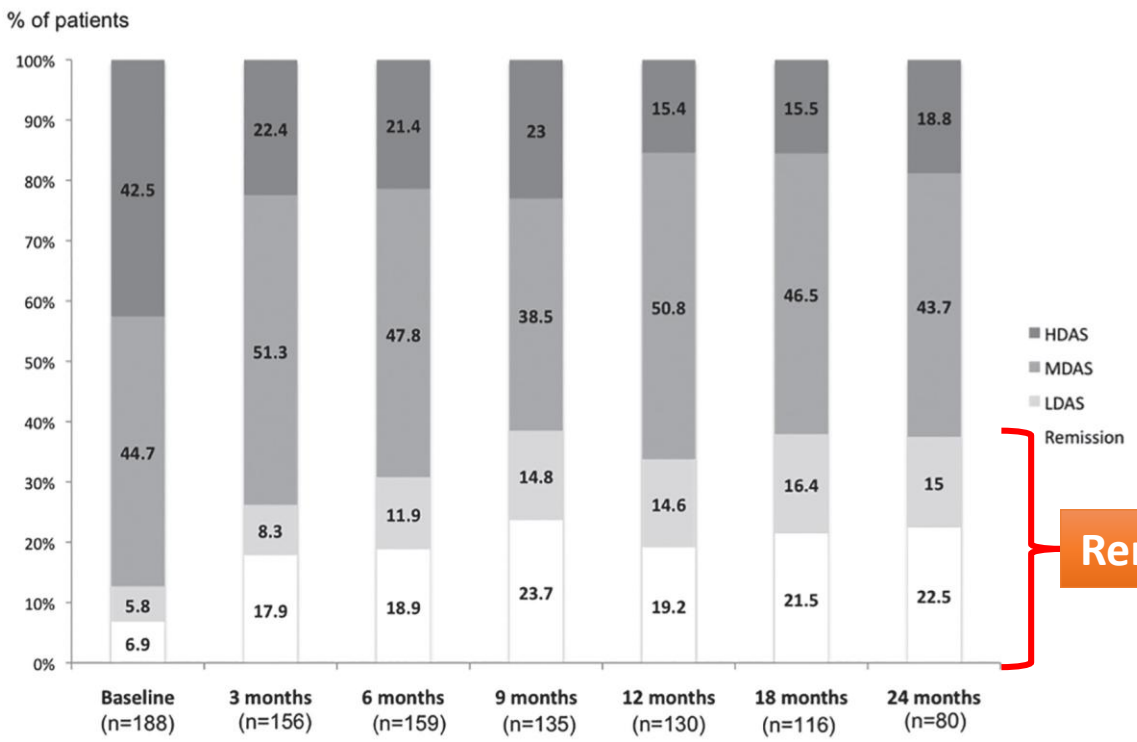


	M0	M6	M12	M18	M24	M36	M48	M60	M72	M84	M96	M108	M120
csDMARD	28 (6.7%)	312 (74.6%)	320 (76.6%)	319 (76.3%)	315 (75.4%)	308 (73.7%)	302 (72.3%)	286 (68.4%)	282 (67.4%)	289 (69.1%)	281 (67.2%)	264 (63.2%)	271 (64.8%)
bDMARD	0 (0.0%)	12 (2.9%)	32 (7.7%)	44 (10.5%)	57 (13.6%)	70 (16.8%)	83 (19.9%)	89 (21.3%)	96 (23.0%)	109 (26.1%)	152 (27.5%)	114 (27.3%)	125 (29.9%)

RMD Open 2022;8:e002040

Early arthritis clinic – University Hospital of Heraklion : @ years prospective follow-up:

30-40% remission /LDA @ 6-24 μήνες



Remission/LDA

14% on bDMARD @ 2 years

Mean time of bDMARD start : 10 (6 SD) m

Fanouriakis A et al. Clin Exp Rheumatol. 2018;36(5):806

Early arthritis clinic – University Hospital of Heraklion : @ years prospective follow-up:

Increased HAD @baseline and high DAS28 @ 6 months predict 2 years outcome:

Variable	DAS28 >5.1 at 2 years		HAQ >1 at 2 years		Start of biologic DMARD	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Duration of symptoms (weeks)	1.00 (1.00-1.01)		1.06 (1.00-1.01)	1.00 (1.00-1.01)	1.00 (1.00-1.01)	1.00 (1.00-1.01)
Baseline DAS28	2.13 (1.18-3.86)		1.19 (0.82-1.72)		1.30 (0.95-1.76)	
Baseline HAQ	4.85 (1.31-17.99)	2.85 (0.69-11.76)	11.27 (3.24-39.18)	**12.63 (2.67-59.78)**	2.25 (1.09-4.65)	2.12 (0.77-5.80)
Baseline CRP	0.66 (0.29-1.52)		0.67 (0.37-1.21)		0.78 (0.55-1.11)	
Baseline ESR	0.99 (0.97-1.02)		0.98 (0.95-1.01)		0.98 (0.95-1.00)	**0.95 (0.90-0.99)**
RF (+)	3.33 (0.67-16.47)		1.21 (0.22-6.57)		2.45 (0.84-7.10)	3.71 (0.70-19.82)
Anti-CCP (+)	0.87 (0.16-4.61)		0.25 (0.03-2.08)		1.85 (0.65-5.23)	
DAS28 at 3 months	2.41 (1.23-4.74)	**2.62 (1.20-5.72)**	2.26 (1.33-3.82)	**2.31 (1.14-4.71)**	2.10 (1.41-3.13)	**2.22 (1.36-3.62)**
HAQ at 3 months	3.72 (1.15-11.97)		3.90 (1.45-10.49)		1.95 (1.01-3.78)	

Fanouriakis A et al. Clin Exp Rheumatol. 2018;36(5):806

Main points (Clinical)

- Pre RA phase: we need better predictors to identify high-risk individuals for RA progression
- Early RA or Undifferentiated arthritis:
  - Mostly permanent, when in hands mostly RA
  - Prognosis comparable between phenotypes
  - Phenotype/labs do not predict outcome
- Only 25-30% @ 10 yrs has damage (Rx), but function is limited!

High-throughput technologies in early arthritis cohorts: Detailed molecular taxonomy reveals novel pathogenetic pathways and therapeutic targets

Tissue:
- ✓ Synovium
- ✓ Peripheral blood

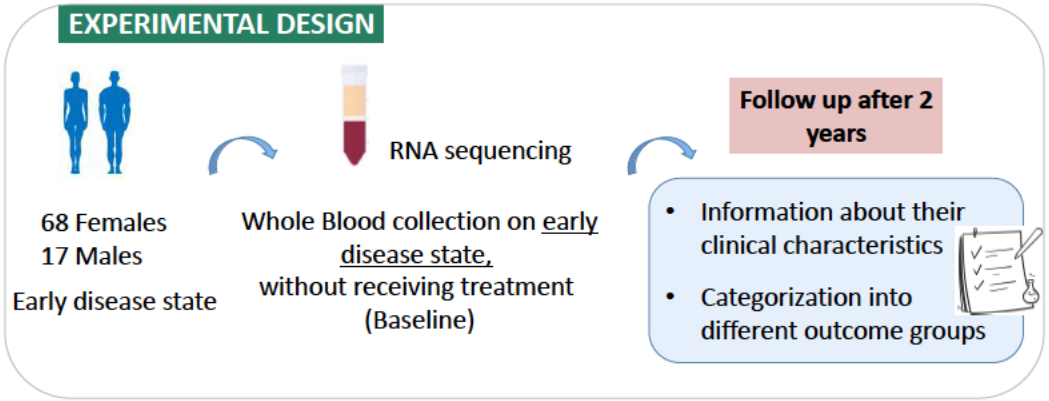
Methodology:
- ✓ RNAseq
- ✓ Single cell RNA analysis
- ✓ CyTOF……..

Current
- Autoantibodies
- Clinical imaging
- Clinical lab testing: complement levels and split products
- Soluble mediators: cytokines, chemokines, and solub receptors
- Transcriptomics: molecular signatures
- Genetics: disease-associated variants
- Immunophenotyping: flow cytometry
- Tissue histology

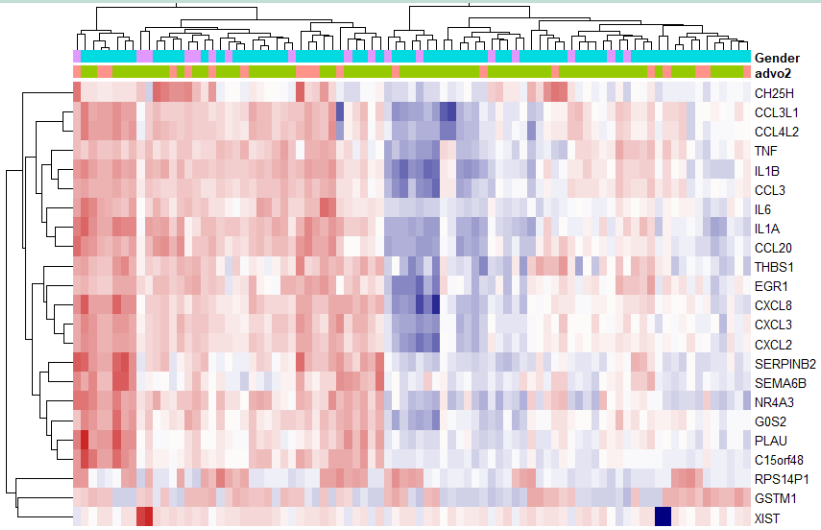
Emerging
- Genetics: genetic load, polygenic risk scores, extended HLA haplotypes
- Transcriptomics: cell-specific expression/signatures (scRNA-seq)
- Immunophenotyping: single-cell proteomics (CyTOF), proteogenomics (CITE-seq), repertoire immunomics
- Perturbomics (multi-omic evaluation after stimulation or other perturbation conditions)
- Spatial tissue analytics: multiplex tissue imaging (CODEX, serial IHC)
- Imaging mass cytometry (Hyperion, IonPath)
- Epigenomics (sorted cell and single cell): DNA methylation, histone modification, chromatin conformation (ATAC-seq), protein–DNA interactions (CUT&RUN)
- Mass spectroscopy (biofluid) and imaging mass spectrometry (tissue): proteomics, metabolomics, lipidomics, and glycomics
- Environmental factors: microbiomics, exposomics

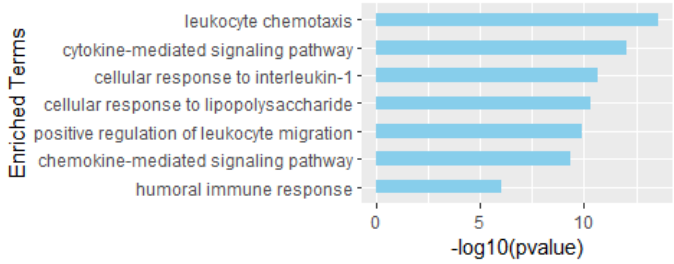
Early RA or UA have many upregulated genes associated to immune/inflammatory responses

Early Arthritis Cohort -CRETE



a. Heatmap and **b**. functional enrichment analysis of the top 25 most variable genes.

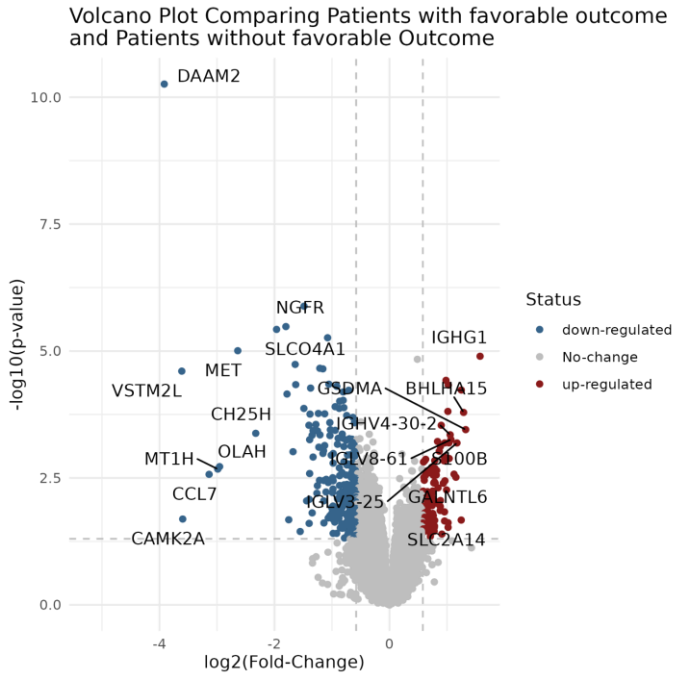


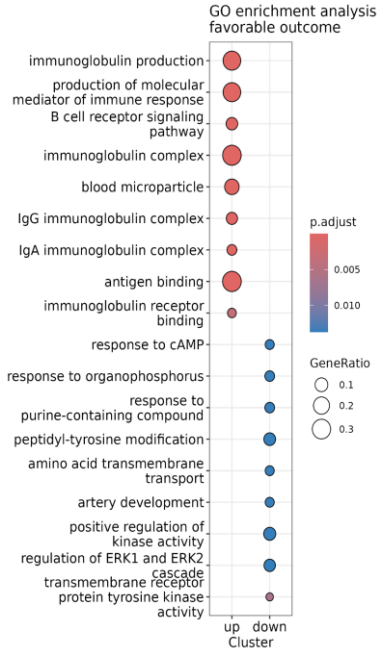


Differentially expressed genes according to long-term outcome:

genes associated to immune/inflammatory responses, metabolism, DNA damage repair

FavOut vs not FavOut:
137 genes were up-regulated and 356 down-regulated





Upregulated in patients with favorable outcome

- ✓ DNA damage repair machinery (*RAD5* and *KIF18B*),
- ✓ Metabolism/anti-inflammatory (*GLP1R)*
- ✓ Anti-angiogenic molecules (*CRIP-2*)
- ✓ Tregs homing in inflamed tissues (*GPR15*)
- ✓ B cell function (*MZB1*)

Down-regulated in patients with favorable outcome

- ✓ chemokines receptors (*ACKR3* and *CCRL2*)
- ✓ chemokines (*CCL20*)
- ✓ lipids with inflammatory action (*CH25H*, *OLAH*)
- ✓ NETosis-associated genes (*CRYBG1* and *SLC19A2*)
- ✓ Innate immune response (*PTX3, CSF3*)
- ✓ inflammatory responses of DCs (*NGFR*)

High-throughput technologies reveals molecular grouping corelated to phenotype

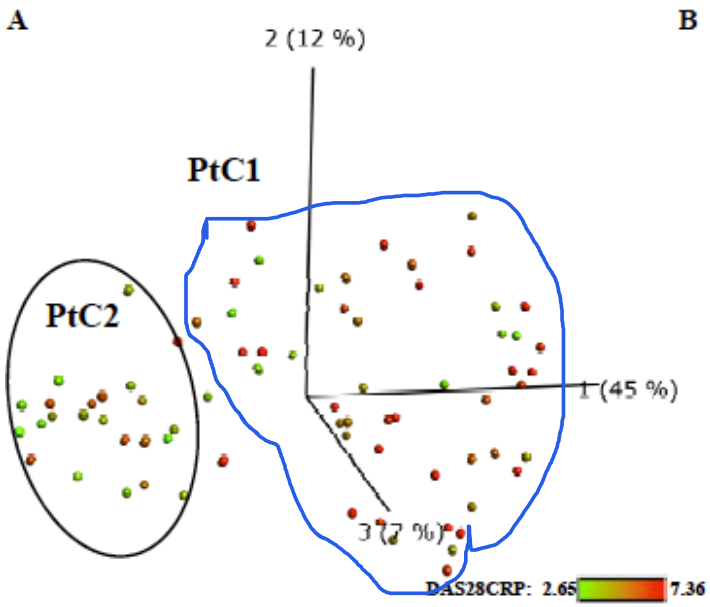
Molecular clustering based on gene expression analysis

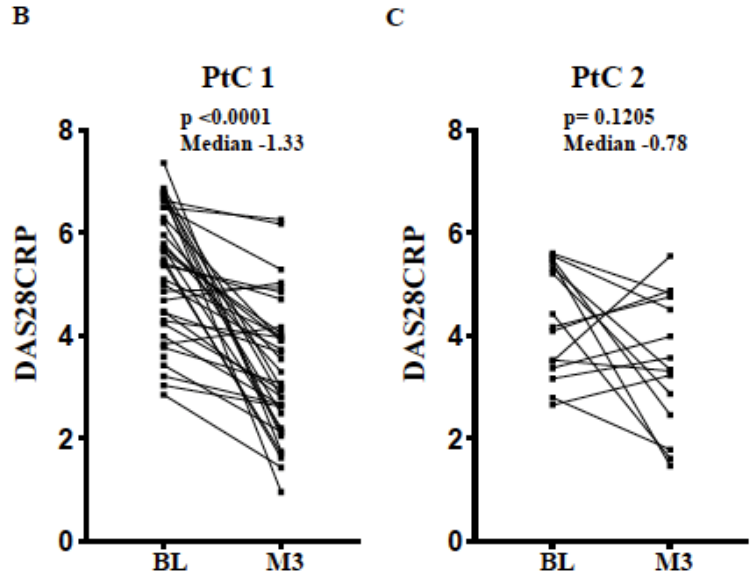
PtC1 vs PtC2: higher inflammation and better responses @ 3 m to MTX responses

	PtC1 (n=52)	PtC2 (n=22)	Uncorrected p-value
DAS28CRP	**5.56** [4.46-6.46]	**4.09** [3.47-5.34]	**0.0003**
SJC28 Q50	**9.5** [5-13.75]	**3** [1.75-6]	**<0.0001**
TJC28 Q50	**8.5** [4-14.75]	**3.5** [2-7.5]	**0.0073**
CRP (mg/dl)	**2.3** [0.9-4.15]	**0.85** [0.4-2.53]	**0.0214**
PhGA	**50** [35.75-60]	**34** [23.5-50]	**0.0121**
PtGA	**70** [40-84.25]	**56** [35-72.5]	0.1368
HAQ	**1.63** [1.13-2.1]	**1.0** [0.57-1.75]	**0.0346**
EROSIONS	**34.6%** (18/34)	**10%** (2/20)	**0.0252**
ACPA and/or RF	**61.5%** (32/20)	**72.7%** (16/6)	0.43
ACPA	**50%** (26/26)	**72.7%** (16/6)	0.08
FEMALE	**82.7%** (43/9)	**81.8%** (18/4)	0.99
AGE (years)	**50.9** [41.4-66.5]	**45.9** [33.4-57.3]	0.0542
KNEE BIOPSY	**65.4%** (34/18)	**95.5%** (21/1)	**0.0077**
RIN	**7.85** [7.3-8.4]	**7.65** [6.85-8.35]	0.2589
MTX-TREATED (n=51)	**PtC1 (n=36)**	**PtC2 (n=15)**	**Uncorrected p-value**
STEROID (any)*	**52.4%** (18/17)	**20%** (3/12)	0.0606
STEROID (>7.5mg/d)*	**8.6%** (3/32)	**13.3%** (2/13)	0.6293

Molecular clustering based on gene expression analysis

PCA based on gene expression



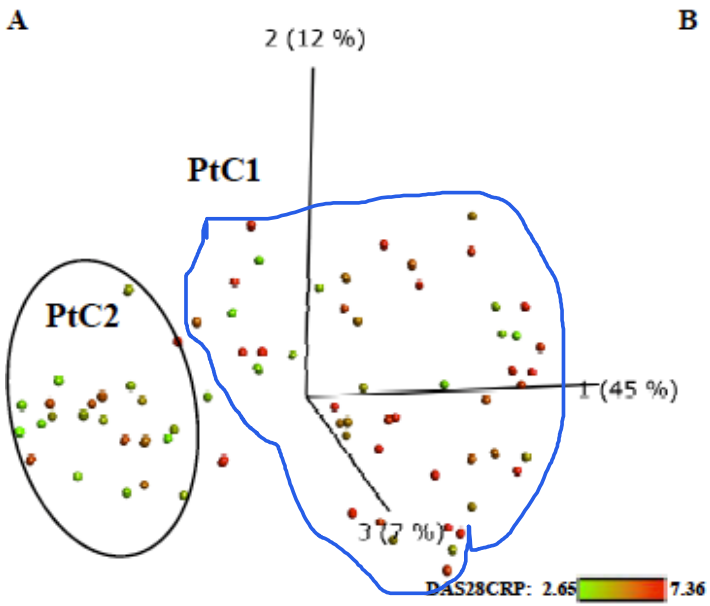


Triaille C, et al. Ann Rheum Dis 2023;82:1538

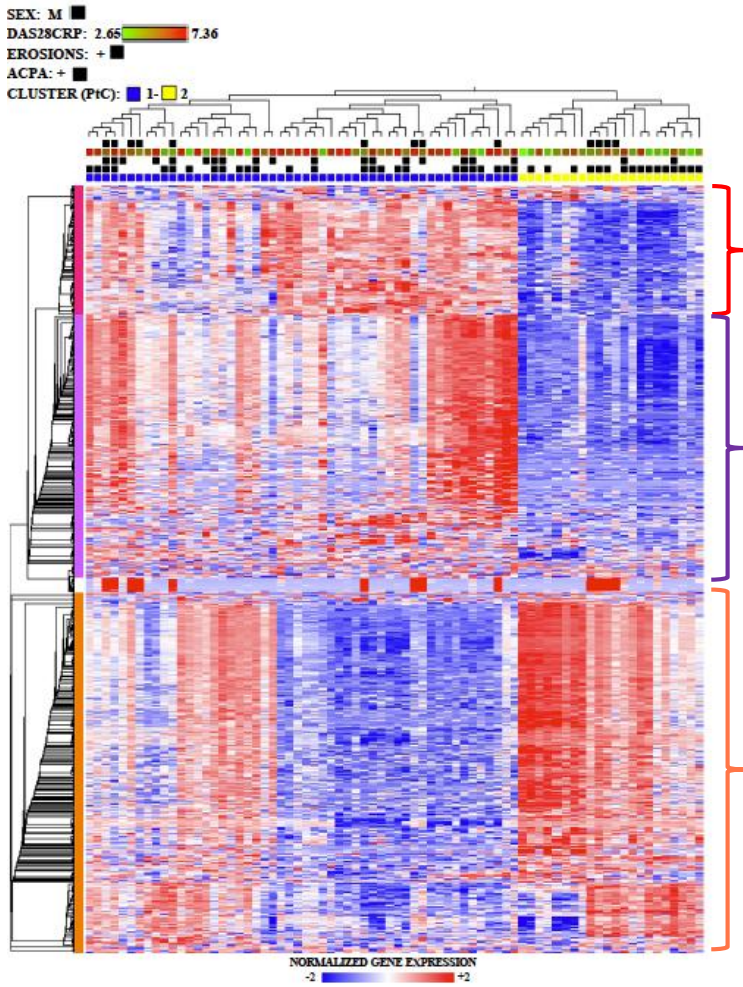
High-throughput technologies reveals molecular endotypes associated to inflammation and metabolism

Molecular clustering based on gene expression analysis

PCA based on gene expression



Unsupervised clustering

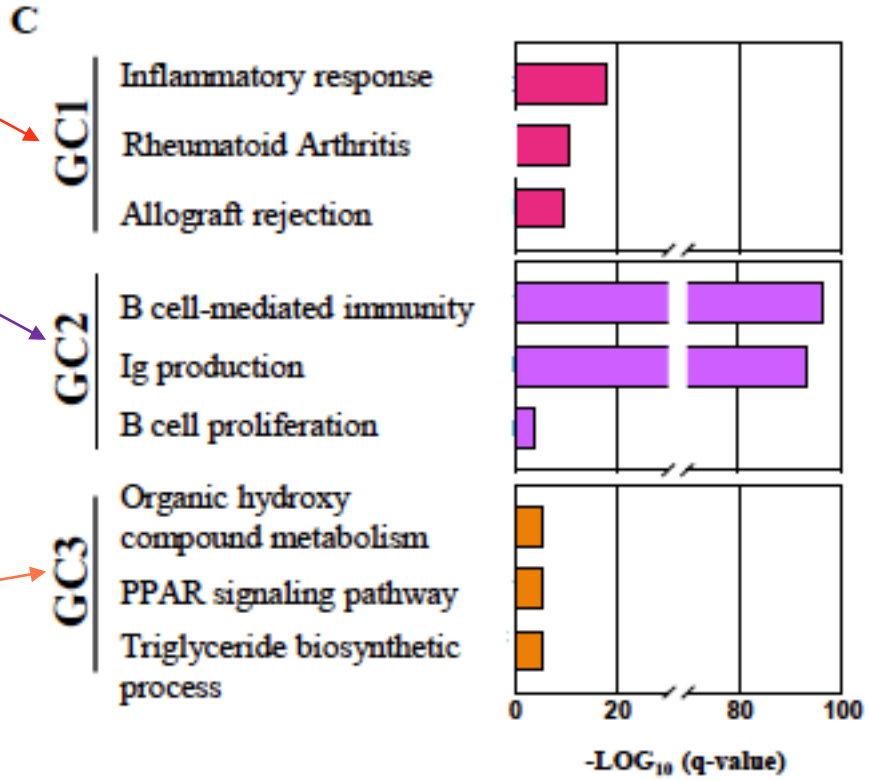


Molecular clustering: Pathways analysis

GC1: inflammatory response and RA pathways

GC2: B cell activation

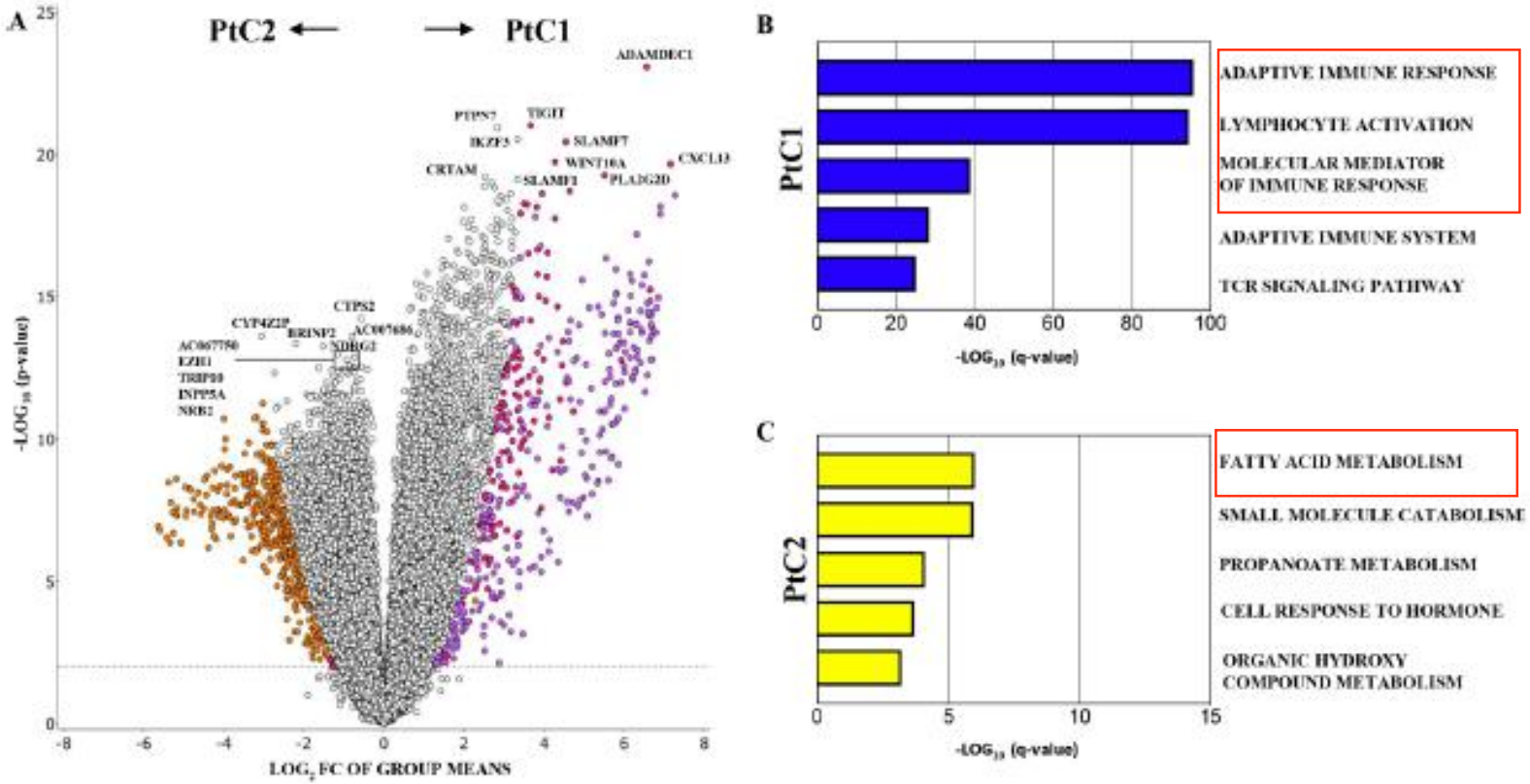
GC3: fatty acid metabolism and PPAR signalling



Triaille C, et al. Ann Rheum Dis 2023;82:1538

High-throughput technologies reveals molecular endotypes associated to inflammation and metabolism

Supervised analysis of the differentially expressed genes between PtC1 vs PtC2

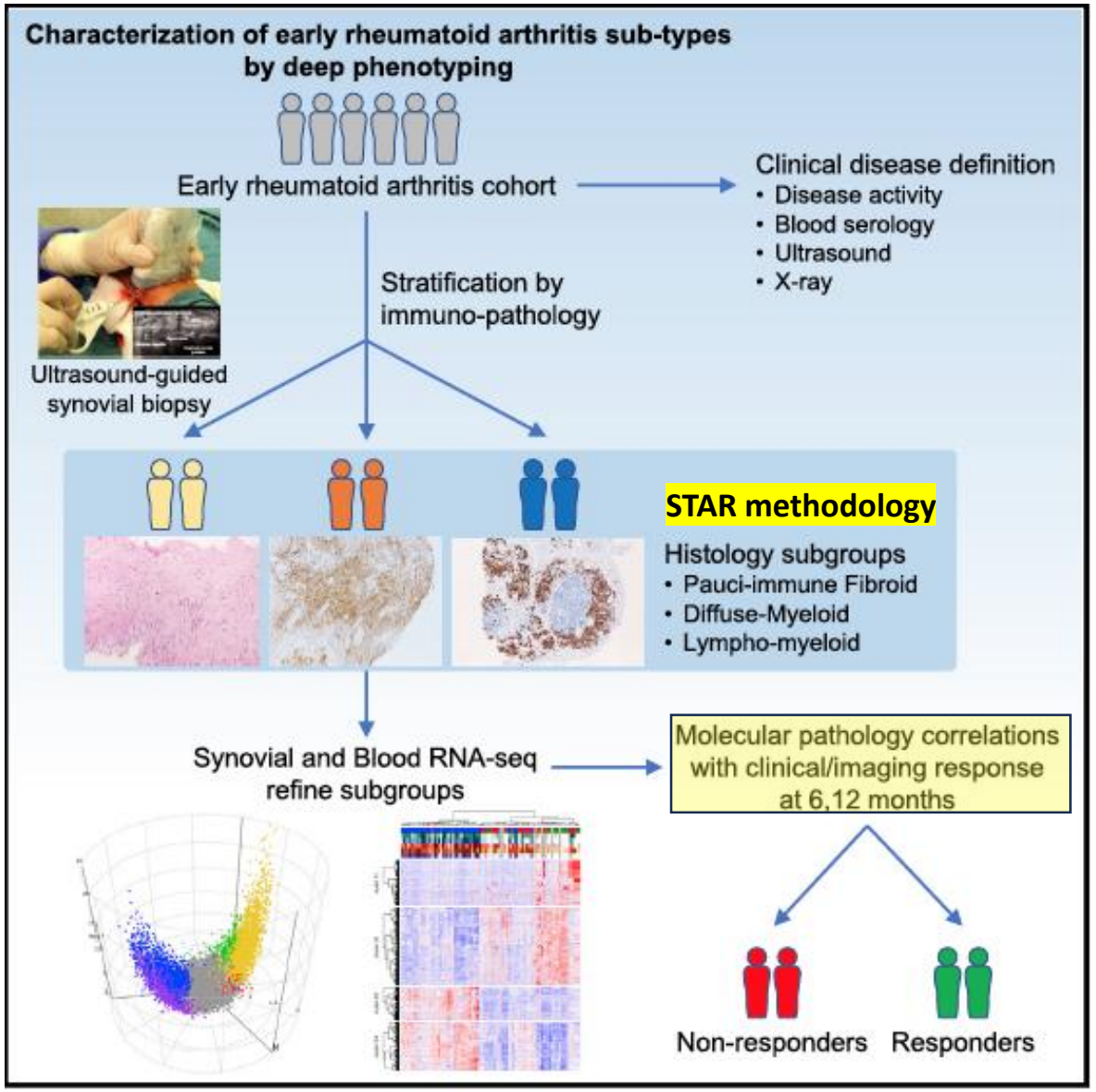


Conclusion

In this large series of early, untreated RA, we show that the synovial transcriptome closely mirrors clinical disease activity and correlates with synovial inflammation.

Triaille C, et al. Ann Rheum Dis 2023;82:1538

High-throughput technologies:
Detailed molecular taxonomy reveals novel pathogenetic pathways and associates to phenotype



PEAC cohort:
Early RA- treatment naive

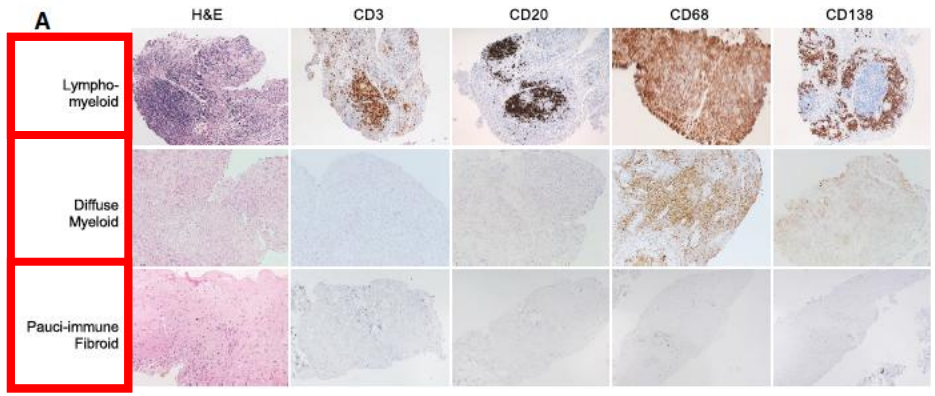
- N=90 RA patients (from 355-individual PEAC cohort).
- Symptom duration: 5.6-months
- DAS28- ESR:5.8 ± 1.3

Lewis et al., 2019, Cell Reports 28, 2455

Immune cell Gene expression analysis is a detailed analysis grouping patients based on cellular signatures and correlates to histological pathotypes

Immunohistochemistry of synovial biopsies:

- ✓ lympho-myeloid (50%)
- ✓ diffuse myeloid (20%)
- ✓ pauci-immune fibroid (20%)

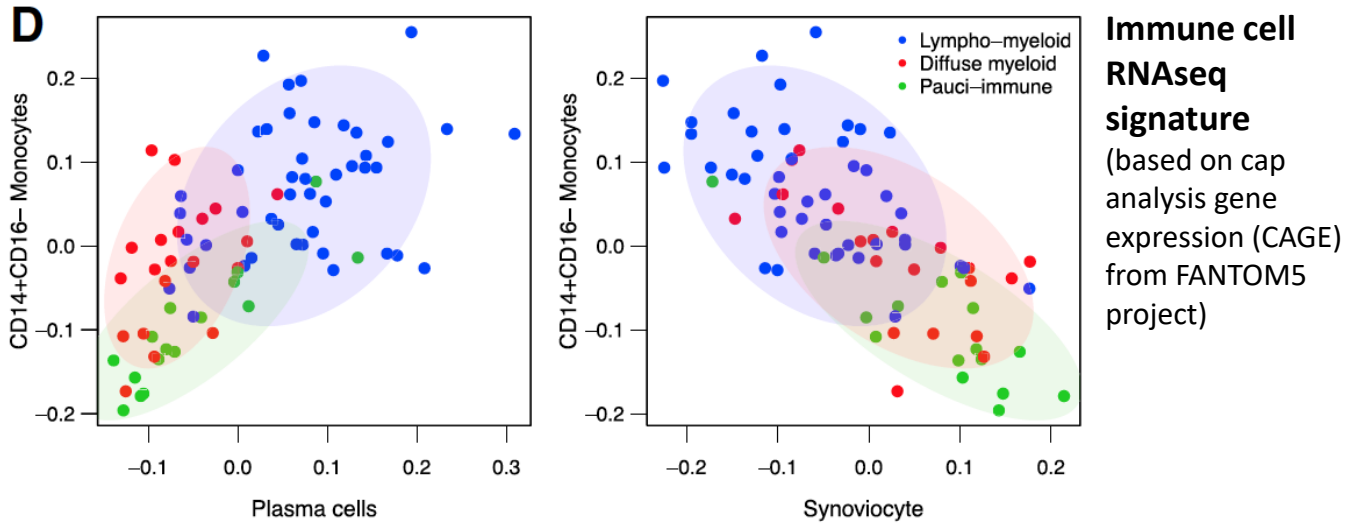


Synovial tissue heterogeneity represents a divergent continuum with:

- ✓ **pauci-immune fibroid samples**, low on all types of immune-inflammatory cells at one end
- ✓ **lympho-myeloid** at the other end with the full range of immune-inflammatory cells including macrophage, T, B, and plasma cell infiltration,
- ✓ **diffuse-myeloid samples** prevalent macrophage infiltration but largely lack T, B, and plasma cell infiltration

Immune cell gene signature

Plasma cell, B cell, monocyte, and synoviocyte **RNA-seq cell-specific modules segregate** the histologically defined pathotypes

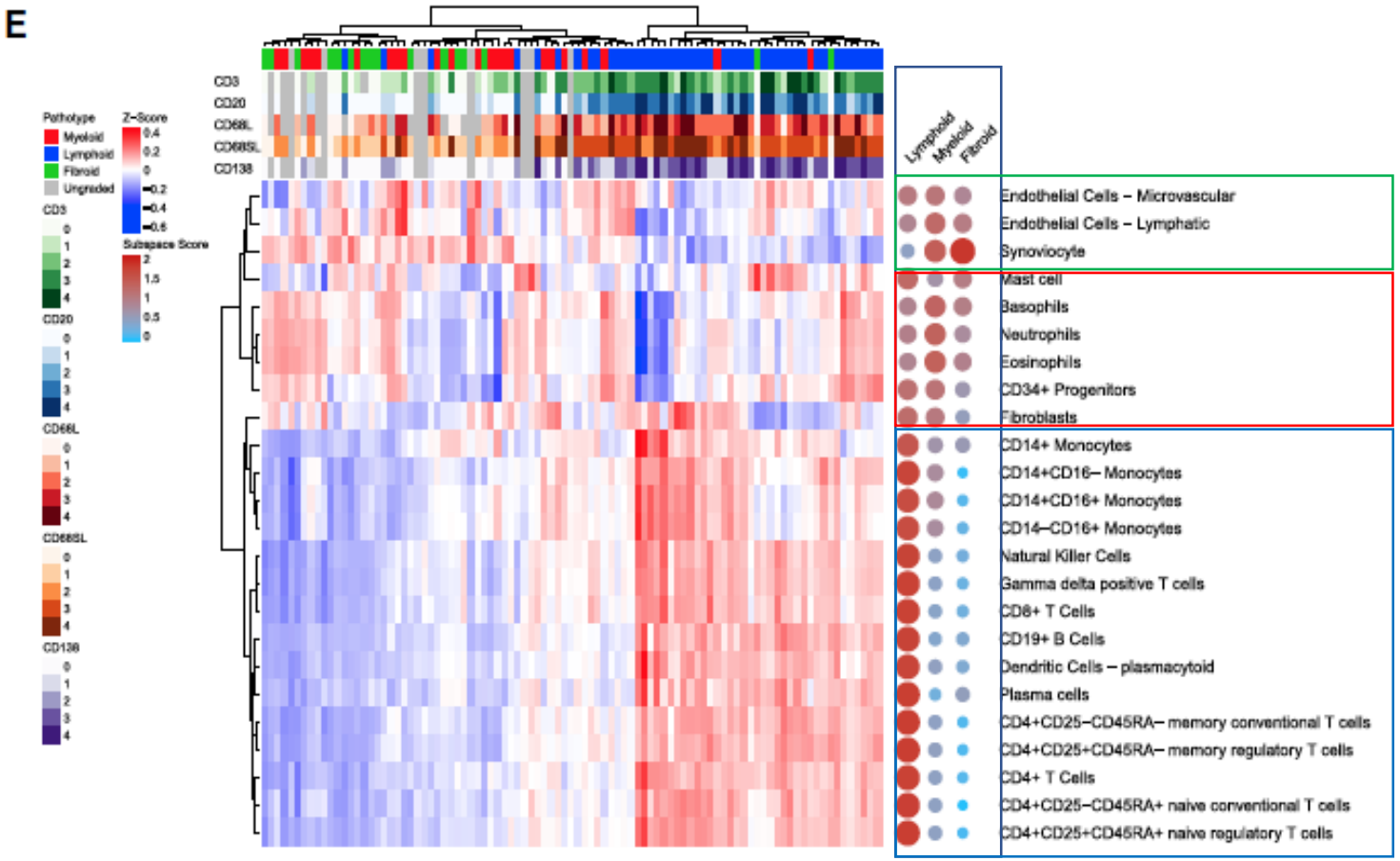


Immune cell RNAseq signature (based on cap analysis gene expression (CAGE) from FANTOM5 project)

Lewis et al., 2019, Cell Reports 28, 2455

Cell specific Gene expression analysis (RNA-seq) segregates patients based on cellular signatures and correlates to histological pathotypes

Synovium RNA Sequencing (cell specific gene signatures)
Correlates with Histological Pathotype in Early RA

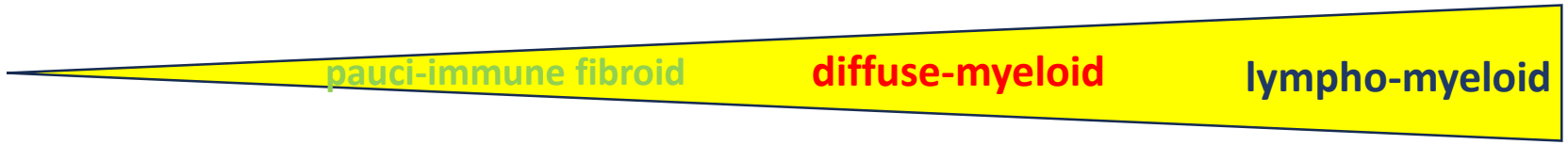


Lewis et al., 2019, Cell Reports 28, 2455

Gene expression analysis offers a detailed analysis of synovial pathology and correlates to histological pathotypes

Synovial tissue heterogeneity represents a divergent continuum with:

- ✓ **pauci-immune fibroid samples**, low on all types of immune-inflammatory cells at one end
- ✓ **lympho-myeloid** at the other end with the full range of immune-inflammatory cells including macrophage, T, B, and plasma cell infiltration,
- ✓ **diffuse-myeloid samples** prevalent macrophage infiltration but largely lack T, B, and plasma cell infiltration



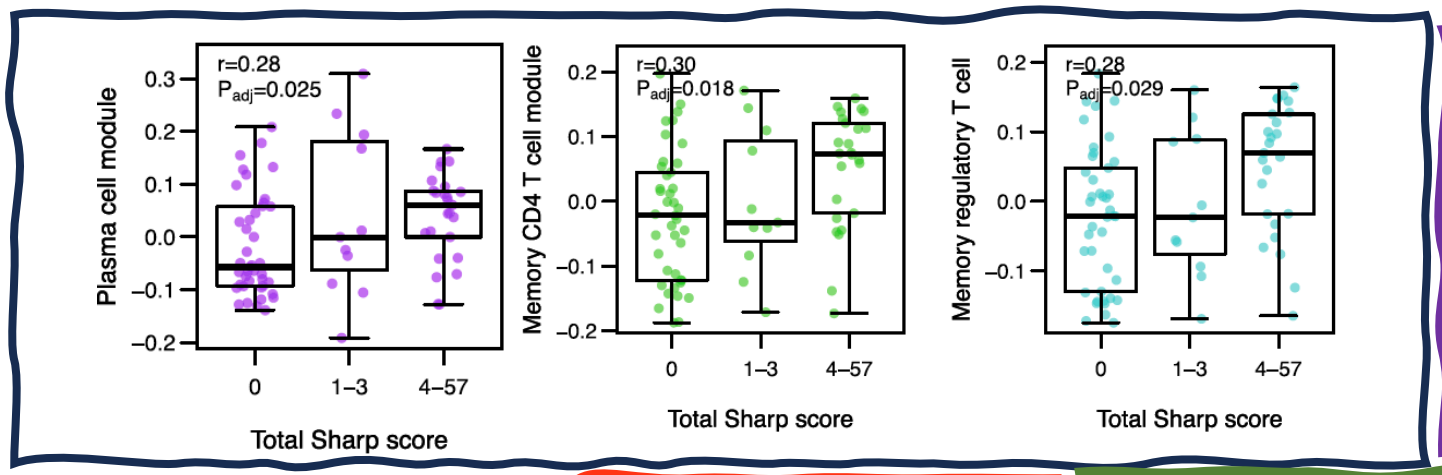
Lewis et al., 2019, Cell Reports 28, 2455

Cell specific Gene expression analysis correlates to RA characteristics: immune cell infiltration corelates to damage, synovitis, seropositivity, VAS pain

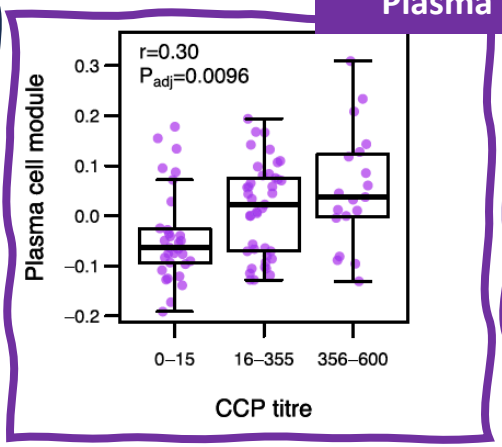
Synovial tissue heterogeneity correlates with clinical characteristics:

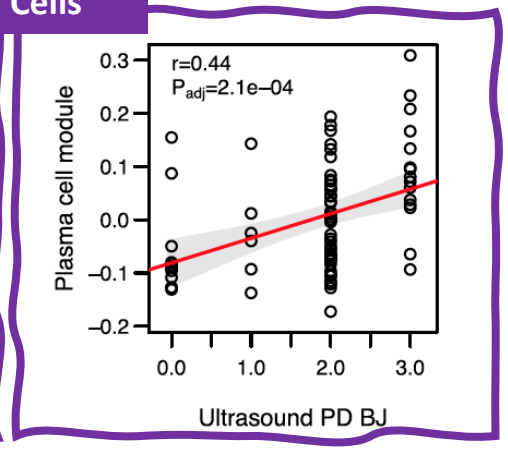
- ✓ Several **cell type modules** (**B- & T cells**) showed significant correlation with **radiographic damage,**
- ✓ **The plasma cell gene module was the strongest predictor of ultrasonographic synovial thickness AND** was associated to CCP titres
- ✓ Inverse correlation between ultrasound scores and synoviocyte gene expression (pauci-immune fibroid pathotype)

radiographic damage

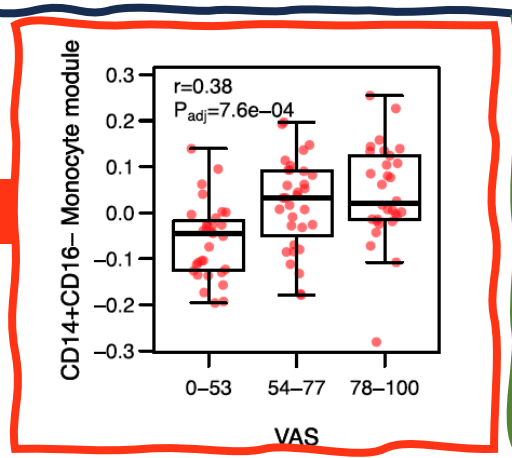


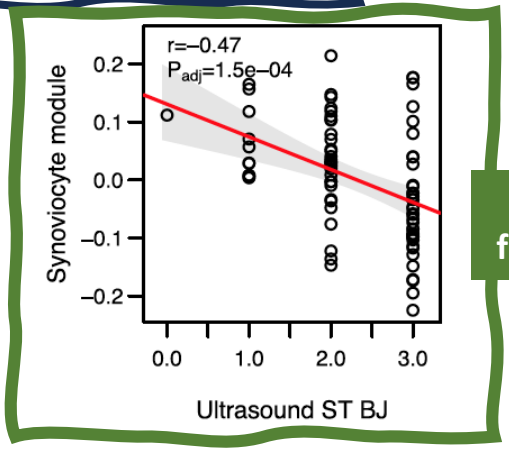
Plasma Cells





Myelocytes





pauci-immune fibroid pathotype

Lewis et al., 2019, Cell Reports 28, 2455

*“These data suggest that **infiltration of multiple immune cell types** associated with ectopic lymphoid responses in the synovial tissue may be **linked to more destructive disease from early on** in the course of RA.”*

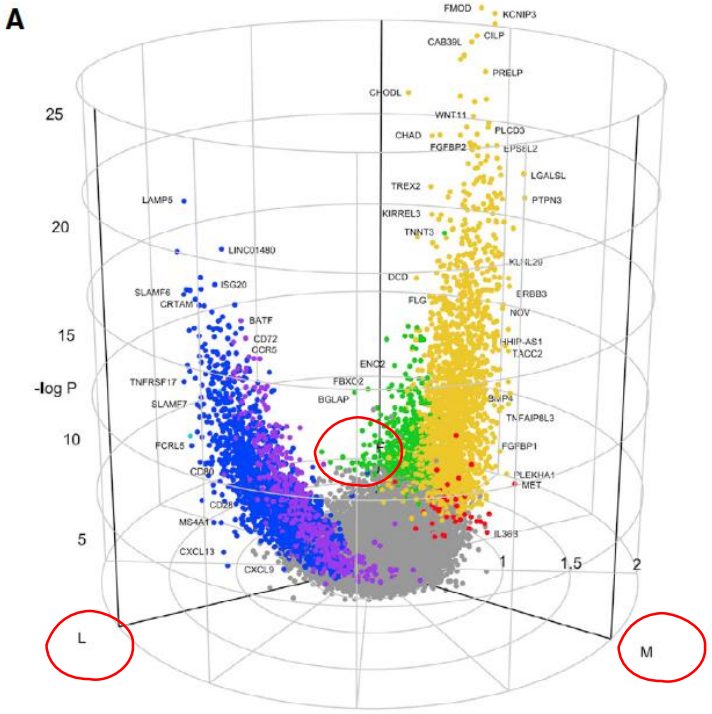
Gene expression analysis RNAseq (clustering and PCA) and patients' classification:

the synovium gives clean delineation of the different histological subtypes while the blood transcriptome shows significantly less differentiation

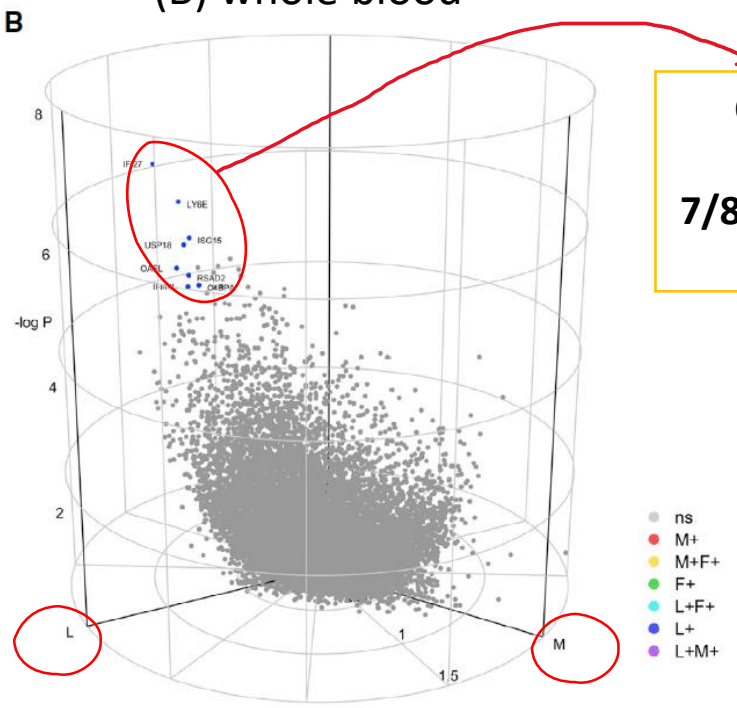
Differentially expressed genes comparing RNA sequencing of (A) **synovial tissue** and (B) **whole blood**

3,000 transcripts in synovium compared to only 8 differentially expressed (increased in L) in matched peripheral blood

(A) synovial tissue

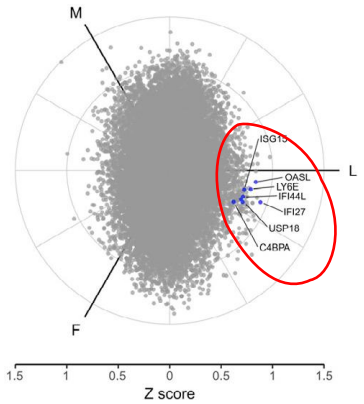


(B) whole blood



Only 8 differentially expressed ☛ Increased in Lymphoid

7/8 are type I interferon response genes: IFI27, ISG15, IFI44L, OASL, USP18, RSAD2, and LY6E

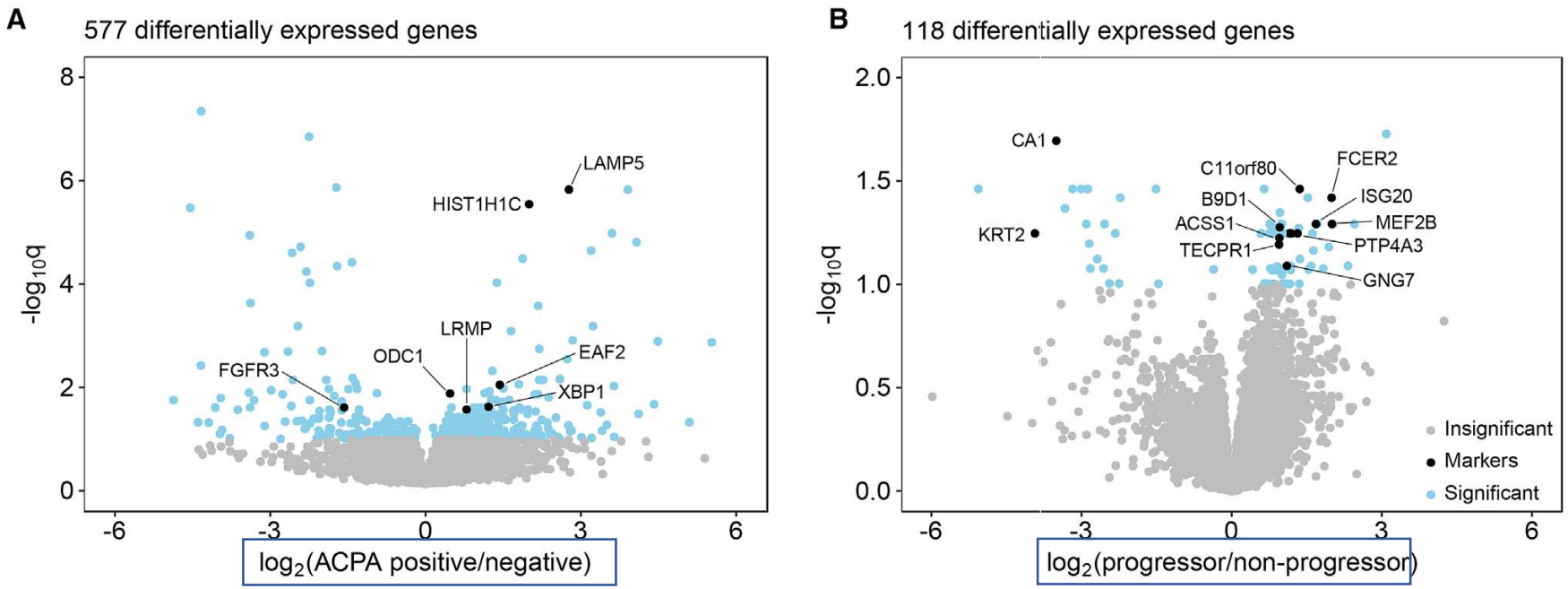


Lewis et al., 2019, Cell Reports 28, 2455

Differentially Gene Expression is Associated with Clinical Parameters:

Synovium Plasma Cell Gene Expression :
- Is Associated with Anti-CCP Antibody
- Predicts Join Damage at 12 Months

Differential gene expression in synovium RNA-seq revealed signatures associated with ACPA and progression

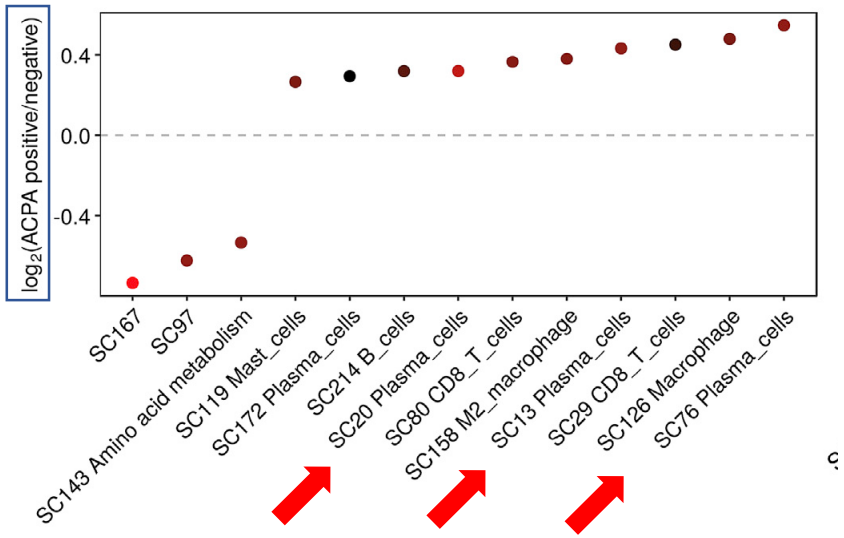


Lewis et al., 2019, Cell Reports 28, 2455

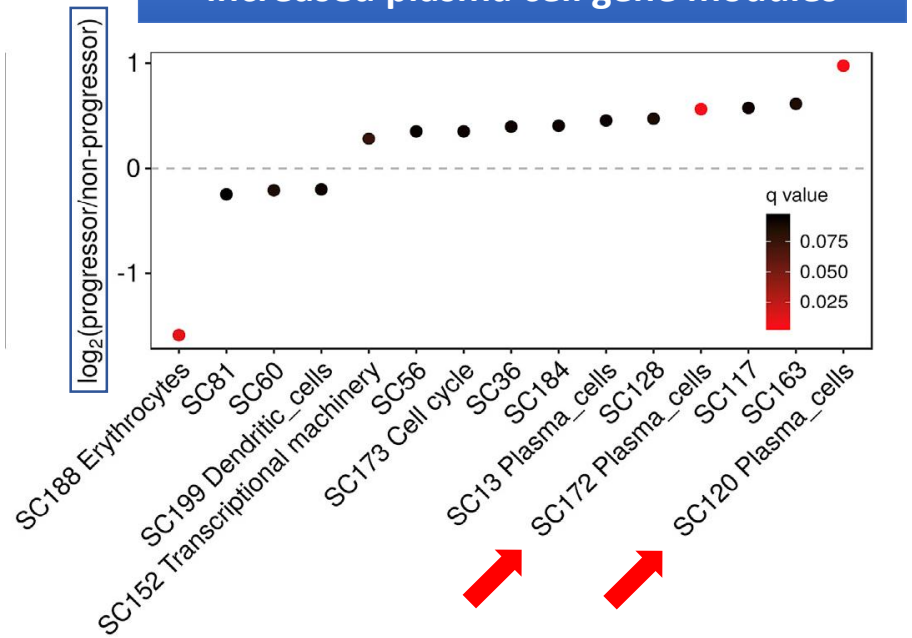
Clinical Correlations:
Plasma cell signatures are associated to ACPA and damage progression

RNA-seq-annotated WGCNA modular analysis showed that:

ACPA positivity was associated with **increased plasma cell and macrophage gene modules**



Damage progression was associated with **increased plasma cell gene modules**



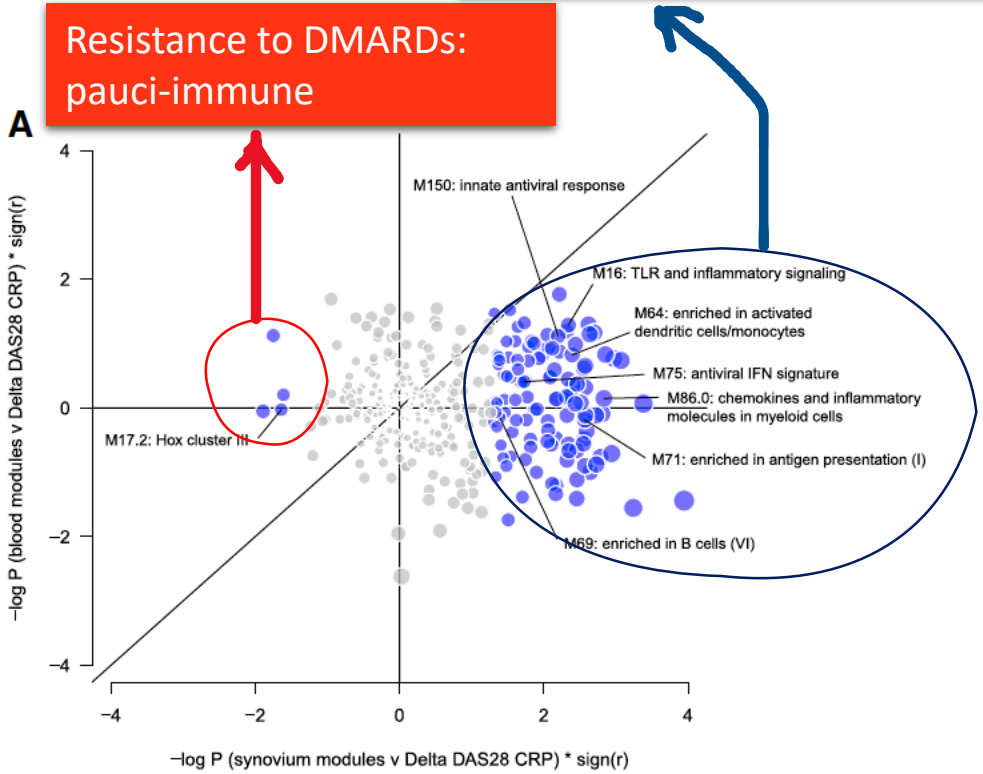
Lewis et al., 2019, Cell Reports 28, 2455

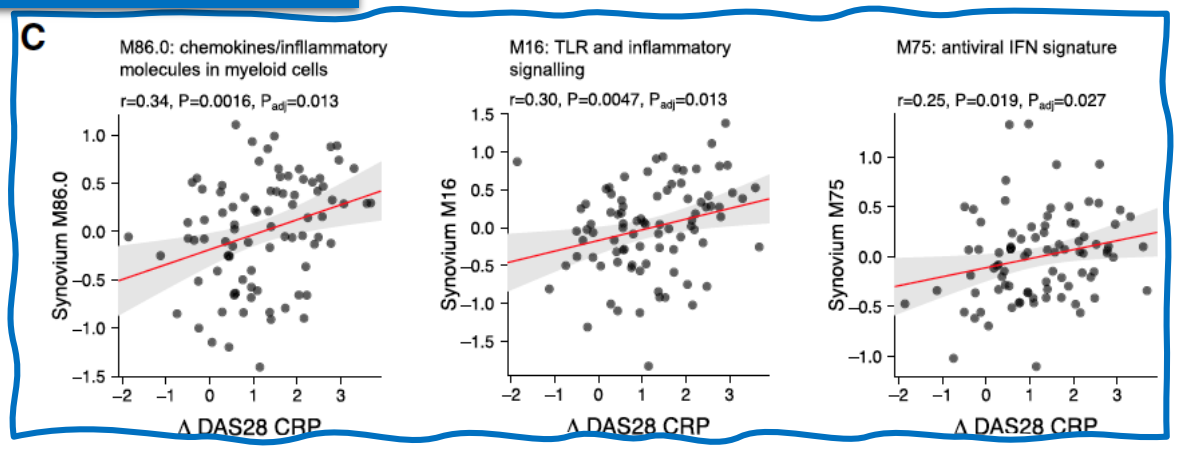
Baseline Synovium gene expression analysis (RNAseq) is more informative for clinical correlations than peripheral blood: clinical responses and radiographic progression

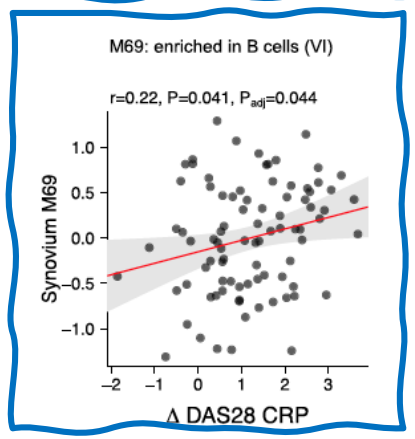
Synovial modules correlated with response to treatment @ 6 mo (ΔDAS28):

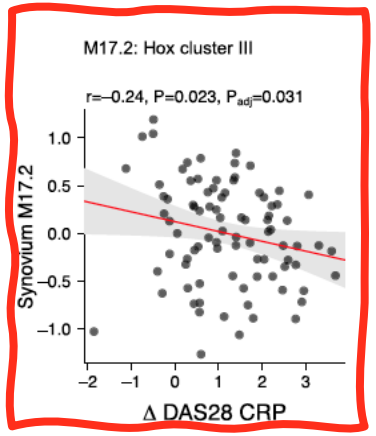
- ✓ type I IFN signature and antiviral modules
- ✓ monocyte and chemokine modules
- ✓ dendritic cell and antigen presentation
- ✓ B cell modules

Resistance to DMARDs: pauci-immune







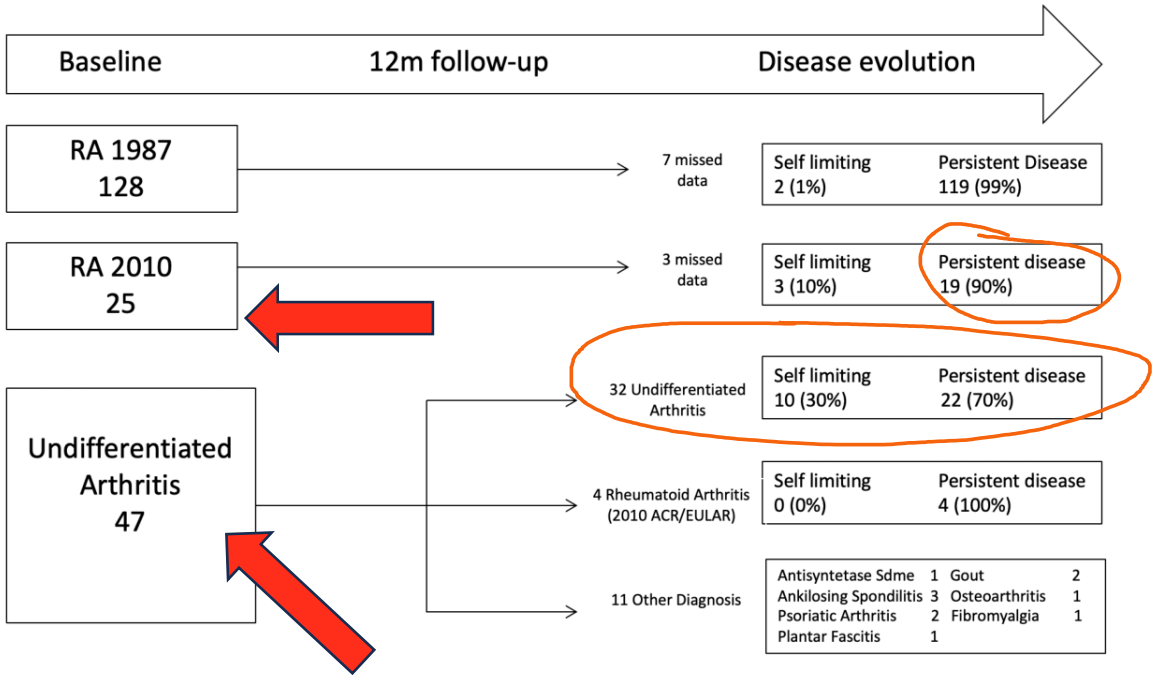


Synovium gene signature more informative than peripheral blood signature and histology

EULAR responses @ 6 months

- ✓ Blood gene expression or pathotype per se were not strong predictors of overall clinical response
- ✓ Molecular signatures associated to response
  - ✓ Modules for CD8+ T cells, mast cells, and TLR signaling were significantly increased in EULAR moderate and good responders at 6 months compared to nonresponders
  - ✓ whereas a CD55+ type 1 fibroblast module was lower in responders

✓ **In early inflammatory arthritis (either RA or undifferentiated):**
- Histology is comparable
- Evolution is comparable



Between the RA2010 and UA group
Comparable in synovitis score:
CD3 +T, CD20 +B, CD68 +L or SL macrophage or CD138 +PCs !!!

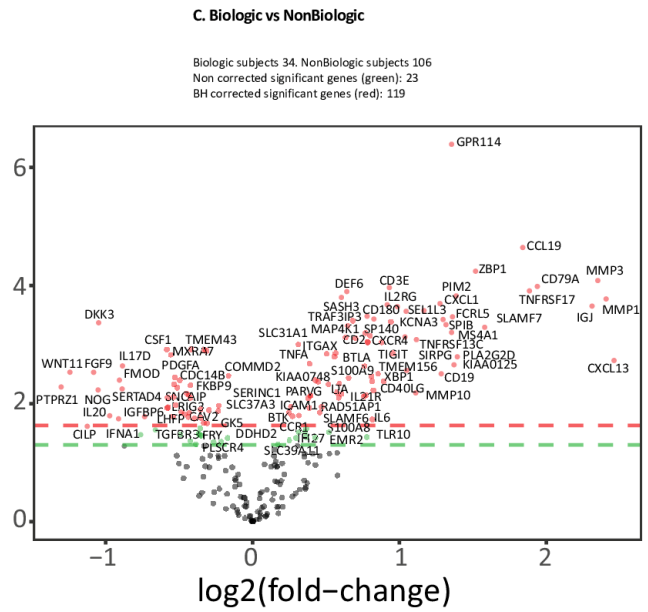
N 179	RA 1987 (RA 1987 + / RA 2010 +) N 121	RA 2010 (RA 1987 - / RA 2010 +) N 22	UA (RA1987 -/ RA2010-) N 36	p-value
Self limiting N 15 (%)	2 (13%)	3 (20%)	10 (64%)	<0.001*
Persistent disease N 164 (%)	119 (72%)	19 (12%)	26 (16%)	

Lliso-Ribera G. Ann Rheum Dis 2019 Dec;78(12):1642-1652

1. Histology did NOT predicted responses
2. Disease duration was not associated to bDMARD use
3. Baseline Synovium gene expression analysis (nanostring) was more informative to predict response /damage progression than clinical parameters

Nanostring: RNA expression of 238 preselected genes

119 differentially expressed genes

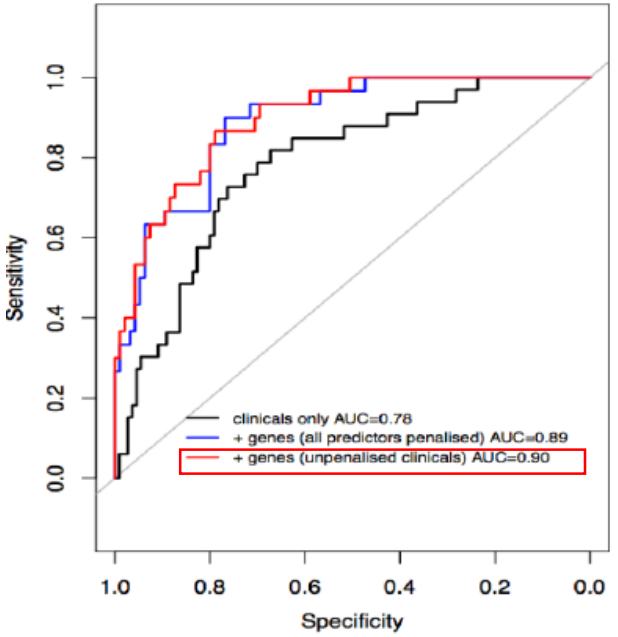


11-13 genes independent of disease duration predict bDMARD use

<u>Optimal predictor of need for bDMARDs (AUC 0.9):</u>

Model including both clinical covariates and genes

	All predictors penalised	Unpenalised clinicals
(Intercept)	-0.372	-3.572
Pathotype		-0.324
CRP	-0.015	-0.037
TJC		-0.061
DAS28	0.246	0.88
GPR114	0.242	0.295
IL8	0.26	0.265
CSF1	-0.08	-0.034
MMP3	0.051	0.047
LTB	0.017	
HIVEP1	-0.143	-0.182
IL20	-0.221	-0.239
UBASH3A	0.049	
MMP10	0.149	0.16
NOG		-0.038
IFNB1		-0.023



Lliso-Ribera G. Ann Rheum Dis 2019 Dec;78(12):1642-1652

Combined models based on gene expression and clinical characteristics predict better clinical outcomes (bDMARDs use % Rx progression)

Nanostring: RNA expression of 238 preselected genes

119 differentially expressed genes

AUC was 0.9

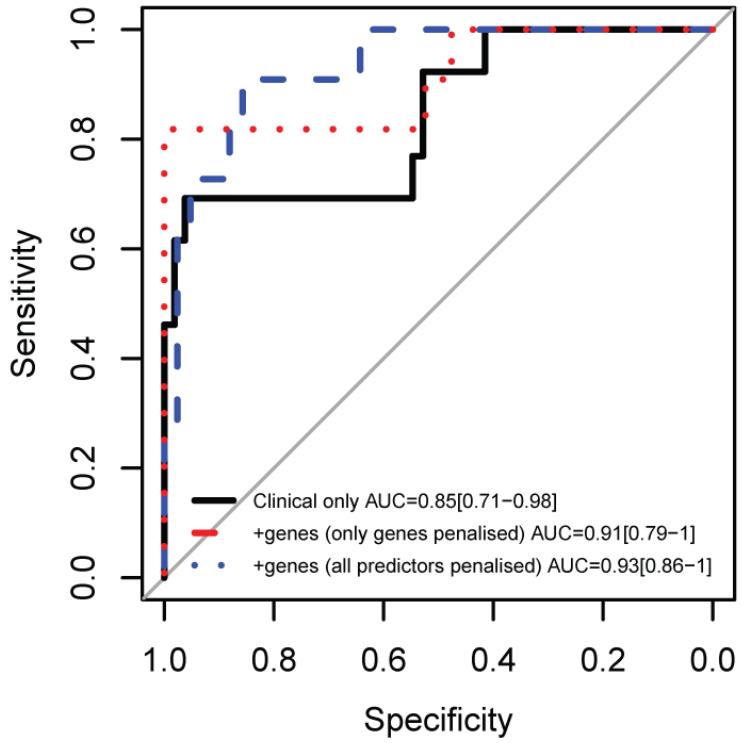
<u>Optimal predictor of radiographic progression</u>

A model incorporating RF titre, and the expression of 7 genes (SDC1, CSF2, DENND1C, CD180, UBASH3A, CXCL1, MMP10)

Model on clinical covariates :

- ✓ baseline RF titre,
- ✓ disease duration,
- ✓ VAS, swollen joint number, DAS28-ESR
- ✓ baseline pathotype,
- ✓ 12 max US ST and US PD scores.

AUC was 0.75



Humby F, et al. Ann Rheum Dis 2019;78:761

Early RA/undifferentiated cohorts and synovial RNAseq analysis

Treat Early to Remission Irrespective of the Phenotype- Classification Ccriteria

- ✓ RNA sequence analysis advances the understanding of RA pathogenesis:
  different gene expression signatures relevant to immune-inflammatory pathways

- ✓ This is suggestive that **early on disease onset IN BOTH RA AND UNDIFFERENTIATED disease divergent pathogenic pathways or activation disease states exist**

- ✓ **Molecular signatures better correlate to clinical outcomes (response, bDMARDs use, damage) than histology/clinical**:
  Promyeloid inflammatory synovial gene signatures correlated with clinical response to initial drug therapy
  Plasma cell genes identified a subgroup with progressive structural damage

What is missing?

A reliable, practical, easy to perform marker to support individual DMARD selection or long-term outcome characterization