Polyarticular JIA:
Nomenclature, presentation, and relationship to RA

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FDA/UMD CERSI pJIA Drug Development Workshop
Bethesda, October 2, 2019 (remotely)

DISCLOSURES

Consulting: Sobi, AbbVie, Pfizer, Quench Bio, Simcere, Miach Ortho, XBiotech

Research grants/support: Novartis, Genentech, Pfizer, BMS

None related to this talk

Thanks to Bob Colbert for the use of his slides to prepare for this presentation.

“The regulatory question” in polyJIA

Is polyJIA close enough to RA to allow efficacy to be extrapolated from one to the other?

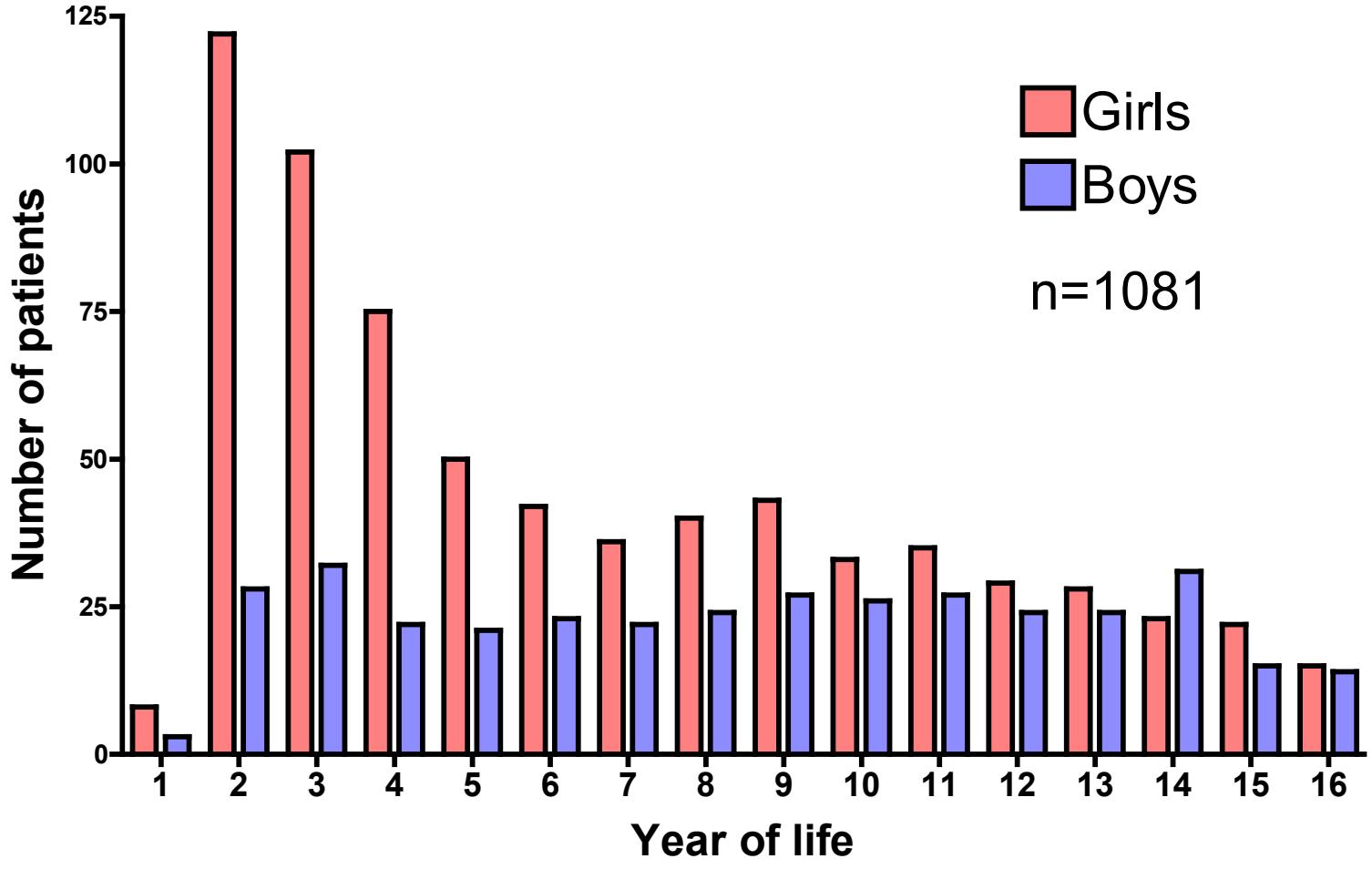
1. What is polyJIA?
2. What is RA?
3. What is the evidence for relevant similarities & differences?

Definition of juvenile idiopathic arthritis

- Arthritis lasting > 6wk
- Age of onset < 16y
- No other cause

Petty *J Rheum* 2004;31:390-2.

Heterogeneity within JIA: age of onset



adapted from Saurenmann *Arthritis Rheum* 2010;62:1824

Classification within JIA

1. Oligoarticular persistent
2. Oligoarticular extended*
3. Polyarticular JIA, RF neg*
4. Polyarticular JIA, RF pos*
5. Psoriatic JIA*
6. Enthesitis related arthritis*
7. Systemic JIA*
8. Other

} less than 5 joints in first 6 months

} 5 or more joints in first 6 months

poly JIA ~20% of JIA
** poly-course JIA >30% of JIA*

Petty *J Rheum* 2004;31:390-2.
Rosenberg and Oen, *Textbook of Ped Rheum* 2016, 7th Ed, Petty *et al*., eds.

Presentation and course of polyJIA

- Demographics: F:M >3:1, prevalence in US ~3 per 10,000
- Age of onset: throughout childhood, largely sparing infancy
- Joint predilection: mixed small and large joints
- Uveitis: 4-14% (early onset subgroup; 25-30% extended oligos)
- Sub-forms
  - Seronegative 80-90% (no RF +/- ACPA)
  - Seropositive 10-20% - older onset, rarely of ever remits, can have nodules
- Prognosis: RF+ = lifelong, RF- = rare remissions

Rosenberg and Oen, *Textbook of Ped Rheum* 2016, 7th Ed, Petty *et al*., eds.
Heiligenhaus *Rheumatology* 2007;46:1015
Saurenmann *A&R* 2007;56:647

Relationship between pJIA and RA?

Arthritis in children and adults: *no overlap in names*

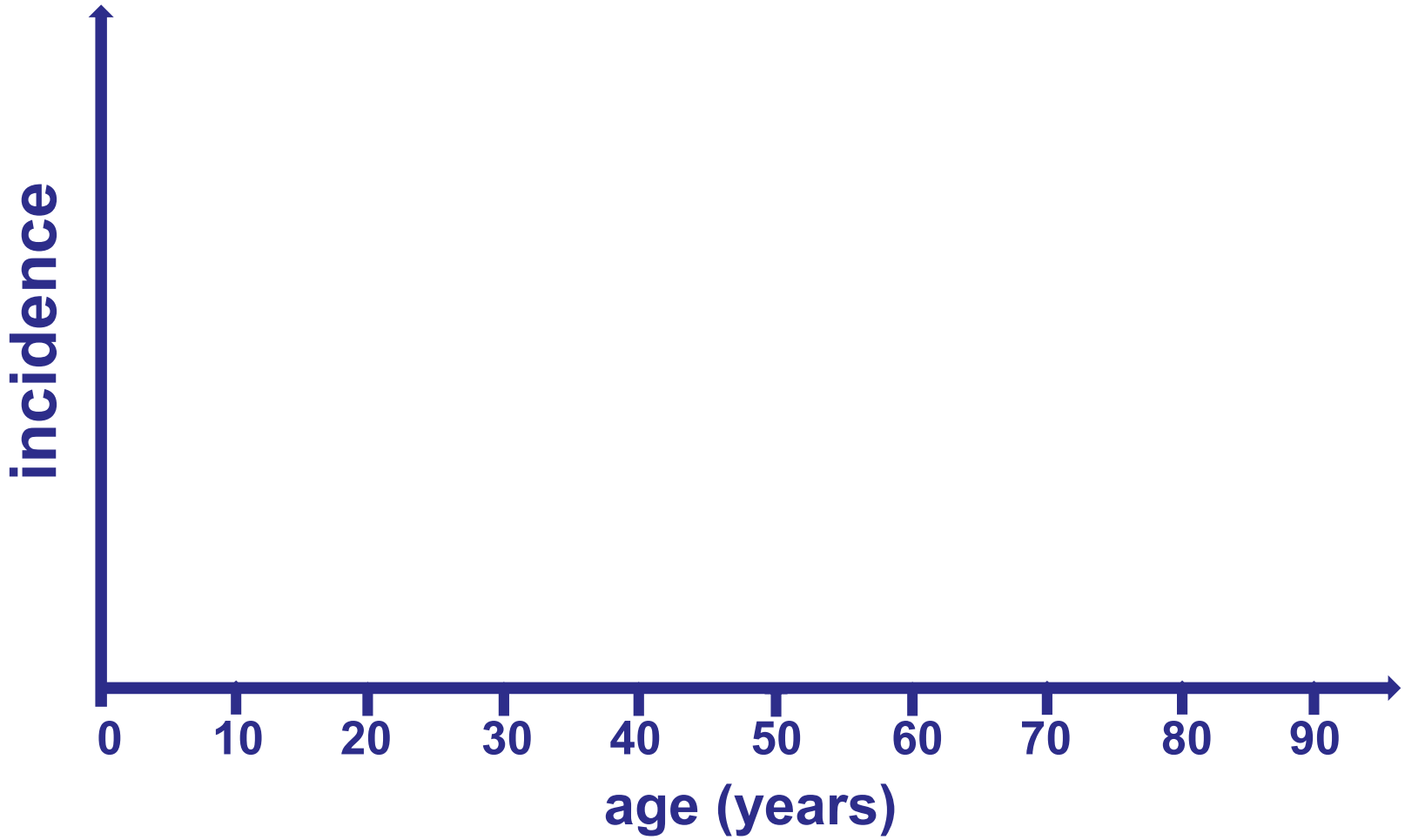
JIA – ILAR

- Oligoarticular persistent
- Oligoarticular extended
- Polyarticular JIA, RF neg
- Polyarticular JIA, RF pos
- Psoriatic JIA
- Enthesitis related arthritis
- Systemic JIA
- Other

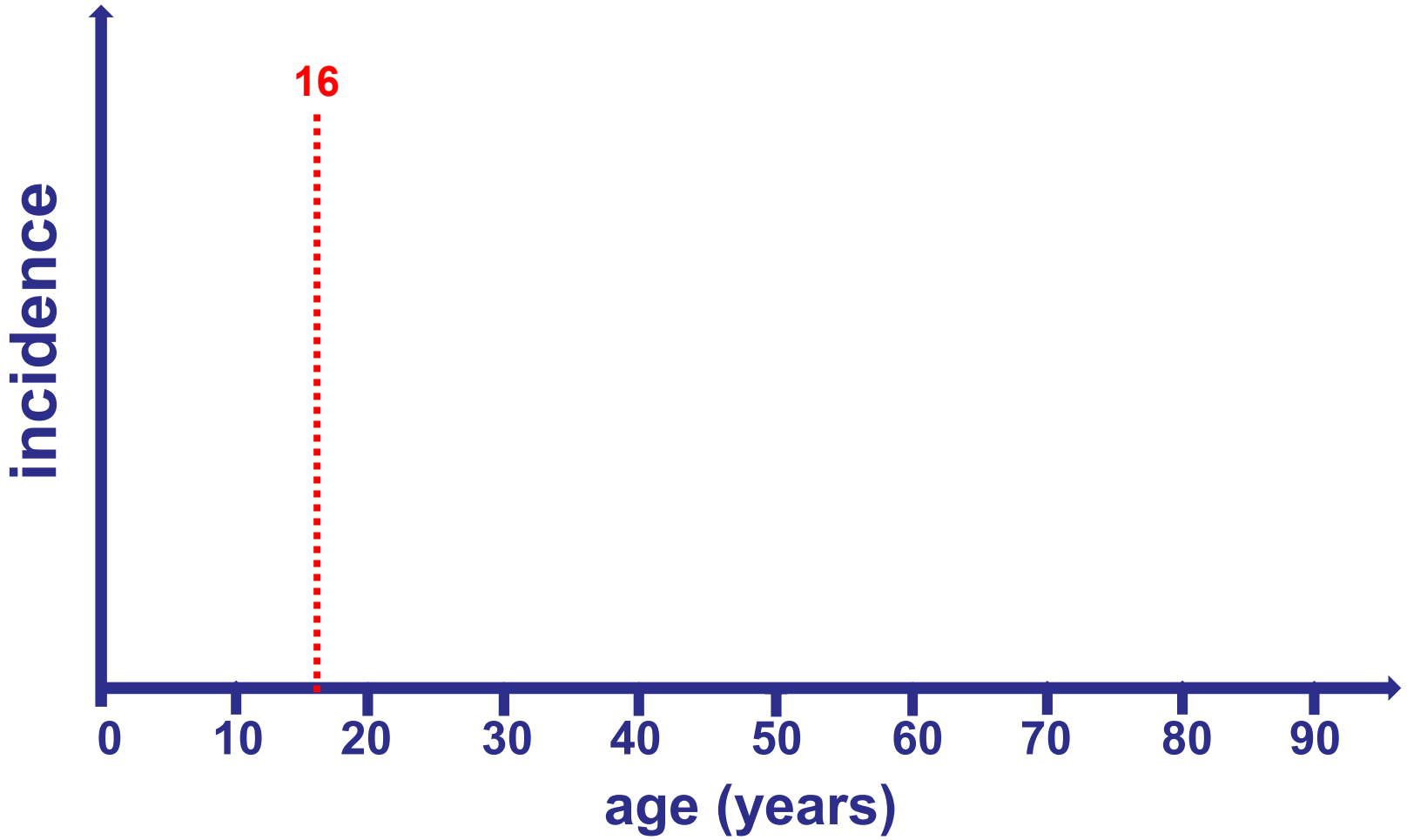
Adult arthritis

- Rheumatoid arthritis
  - seropositive RA
  - seronegative RA
- Spondyloarthritis
- Adult onset Still's disease

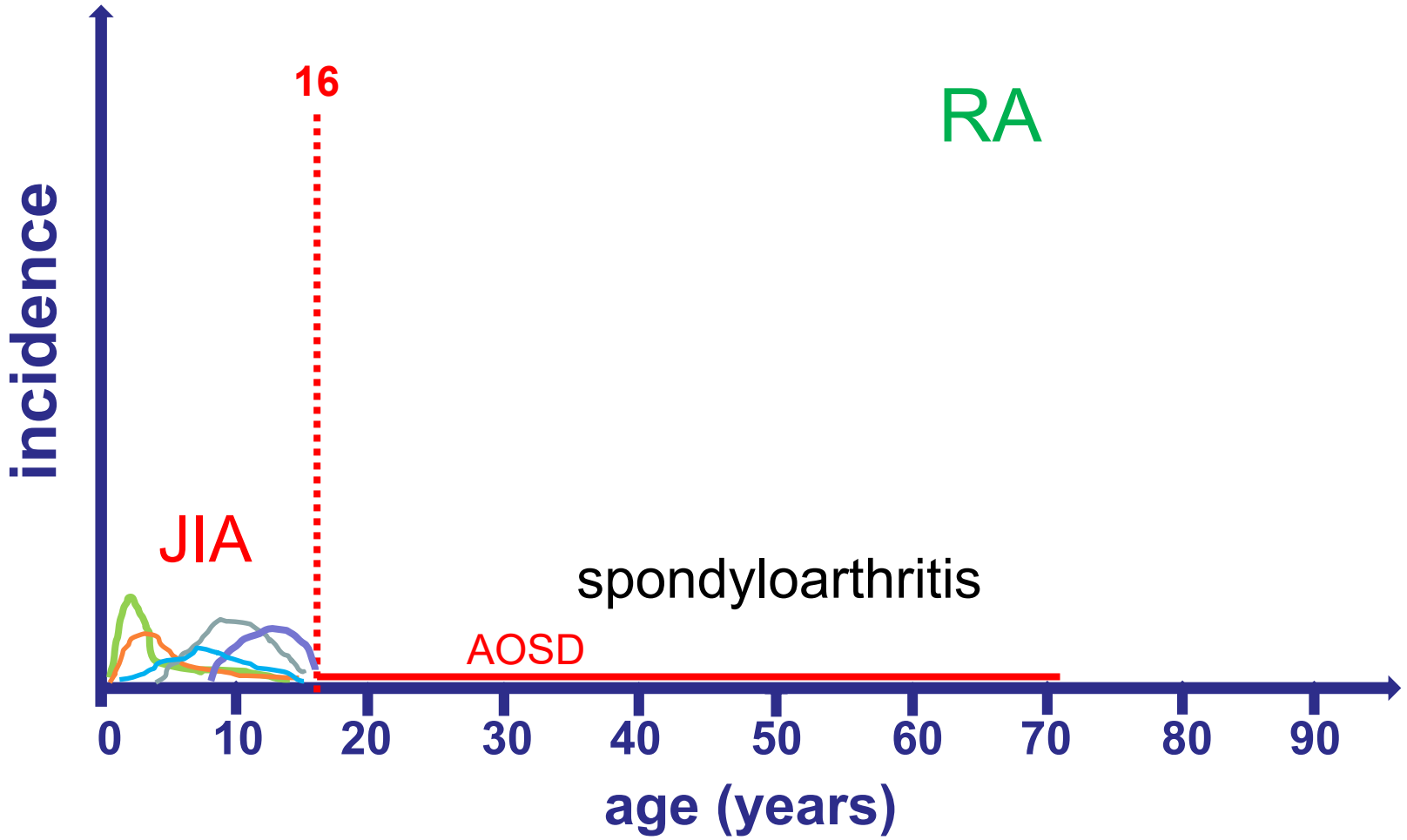
Arthritis across the age spectrum



Arthritis across the age spectrum



Arthritis across the age spectrum



A sharp discontinuity between pJIA and RA is *unlikely*

- *Age 16 cutoff was never founded on data of any kind*
- *No other specialty divides diseases categorically by age cutoff*

- Similarities between pJIA and RA:
  - F>M
  - small + large joints, C-spine, but sparing axial skeleton
  - synovial fluid / infiltrates: CD4, CD8, B cells, fibroblast expansion, fluid neutrophils
  - HLA II association
  - Some are RF+; these are also often ACPA+, share joint distribution, nodules
  - Drug response: MTX, SSZ, TNFi, CTLA4-IG, IL-6R blockade…

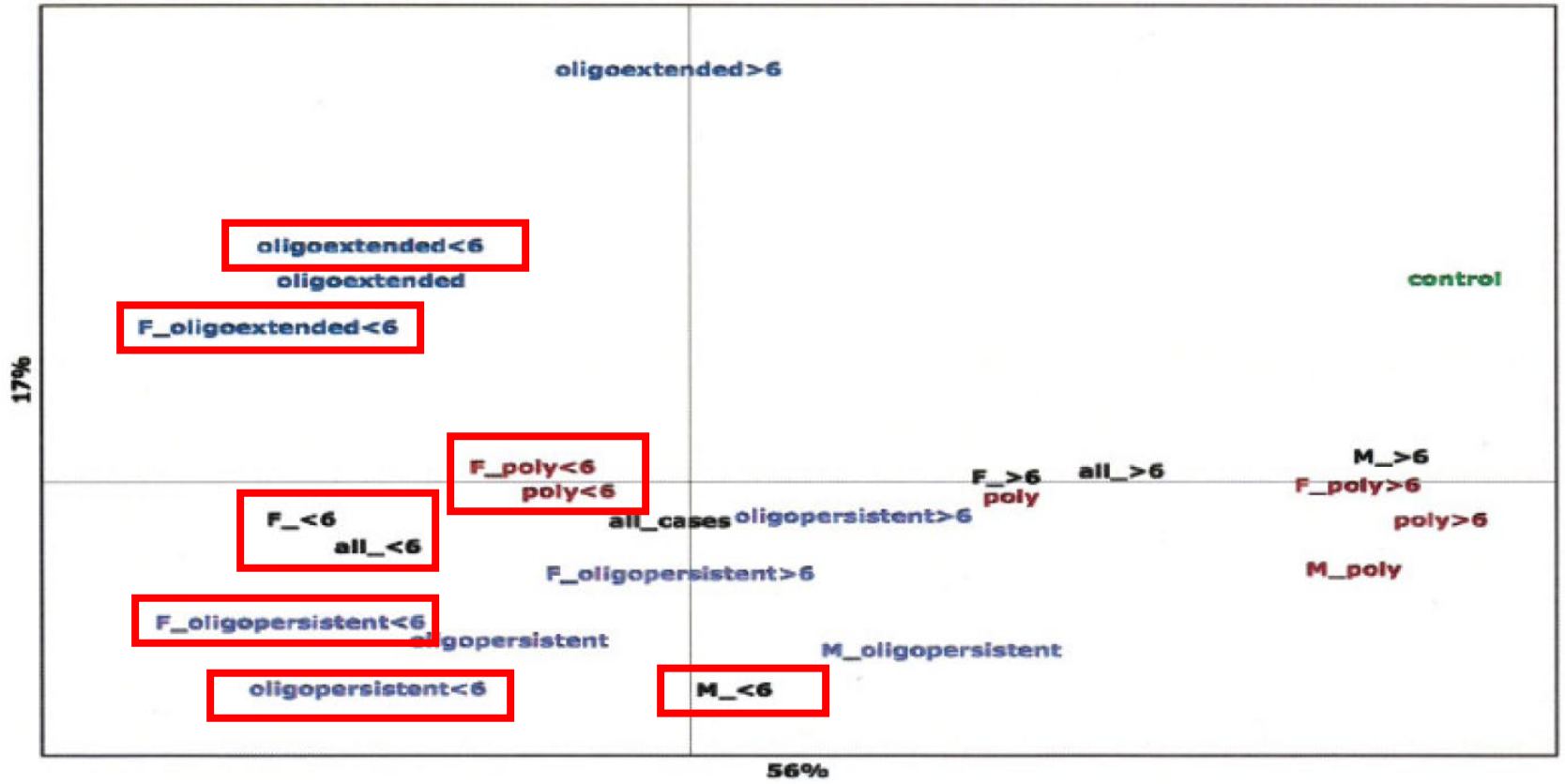
- Dissimilarities: chronic anterior uveitis in the very young

Note 1. Oligo-poly split within JIA is probably wrong

Red box:
onset < age 6y

Cluster by age
not oligo/poly

Principal components analysis of HLA subtypes in JIA

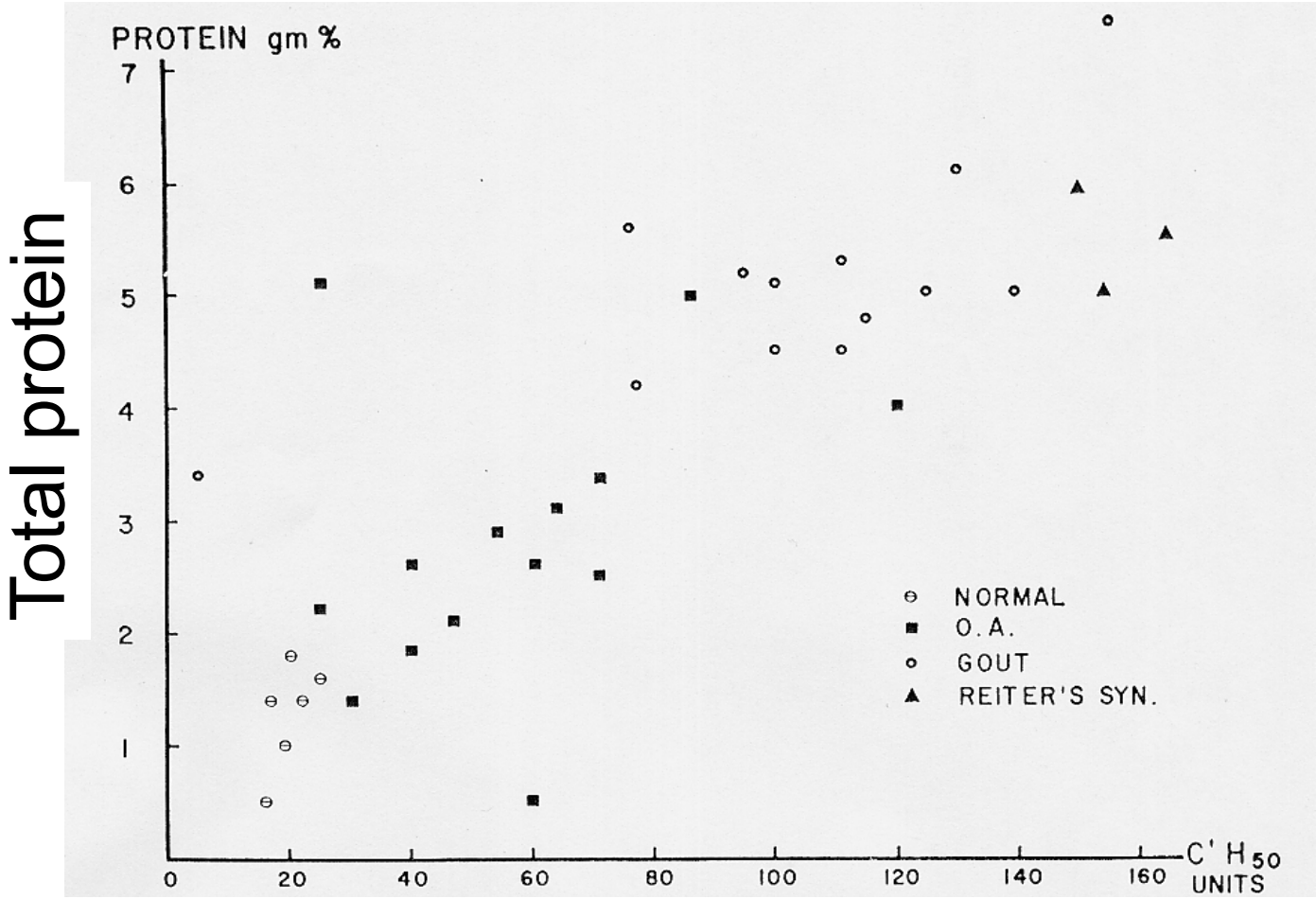


Hollenbach *Arthritis Rheum* 2010;62:1781.

PBMC gene expression also – see Barnes *Arthritis Rheum* 2010;62:3249.
Martini *J Rheum* 2003;30:1900-3. **Martini *J Rheum* 2019;46:190-197.**

Note 2. RA is not a single disease either

Complement in synovial fluid (non-RA)



Total protein

Joint fluid complement

Pekin & Zvaifler *JCI* 1964;43;1372

Complement in RA synovial fluid

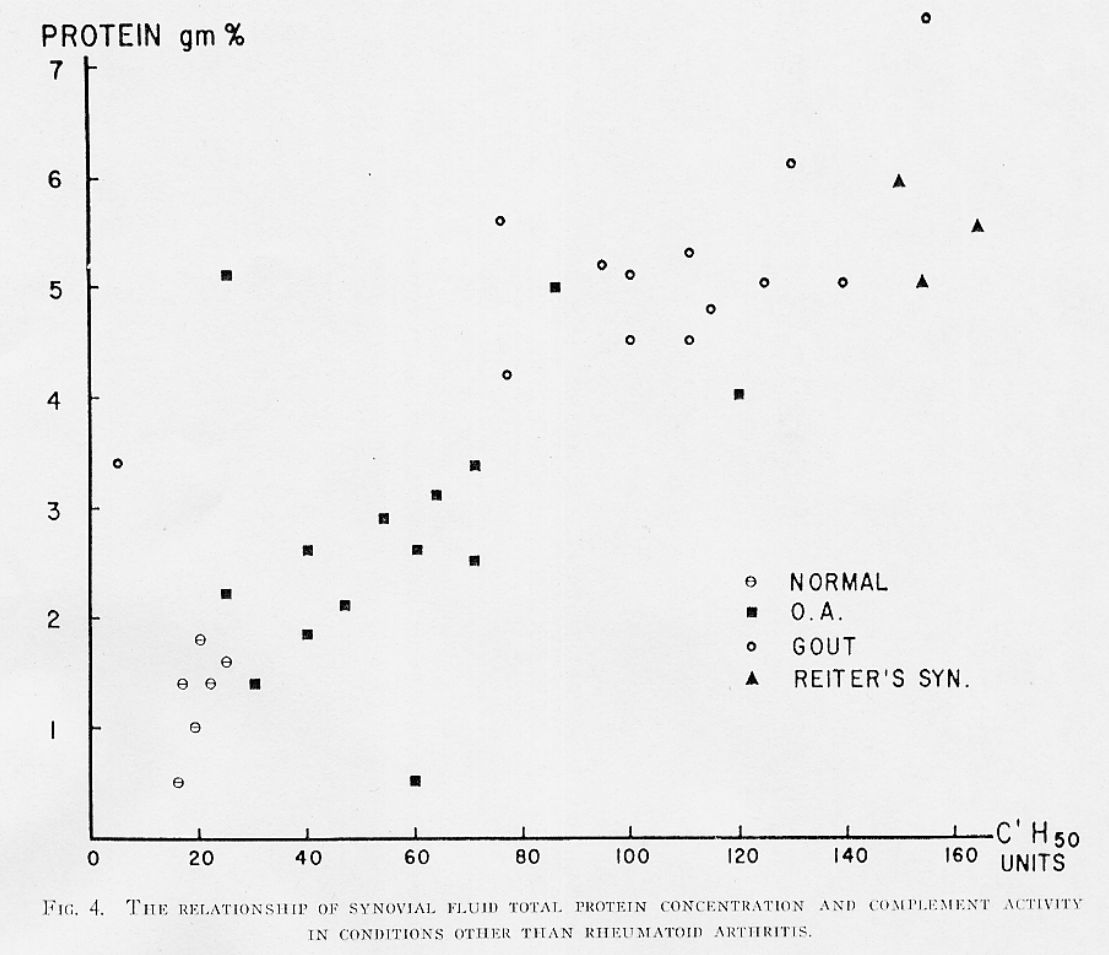


FIG. 4. THE RELATIONSHIP OF SYNOVIAL FLUID TOTAL PROTEIN CONCENTRATION AND COMPLEMENT ACTIVITY IN CONDITIONS OTHER THAN RHEUMATOID ARTHRITIS.

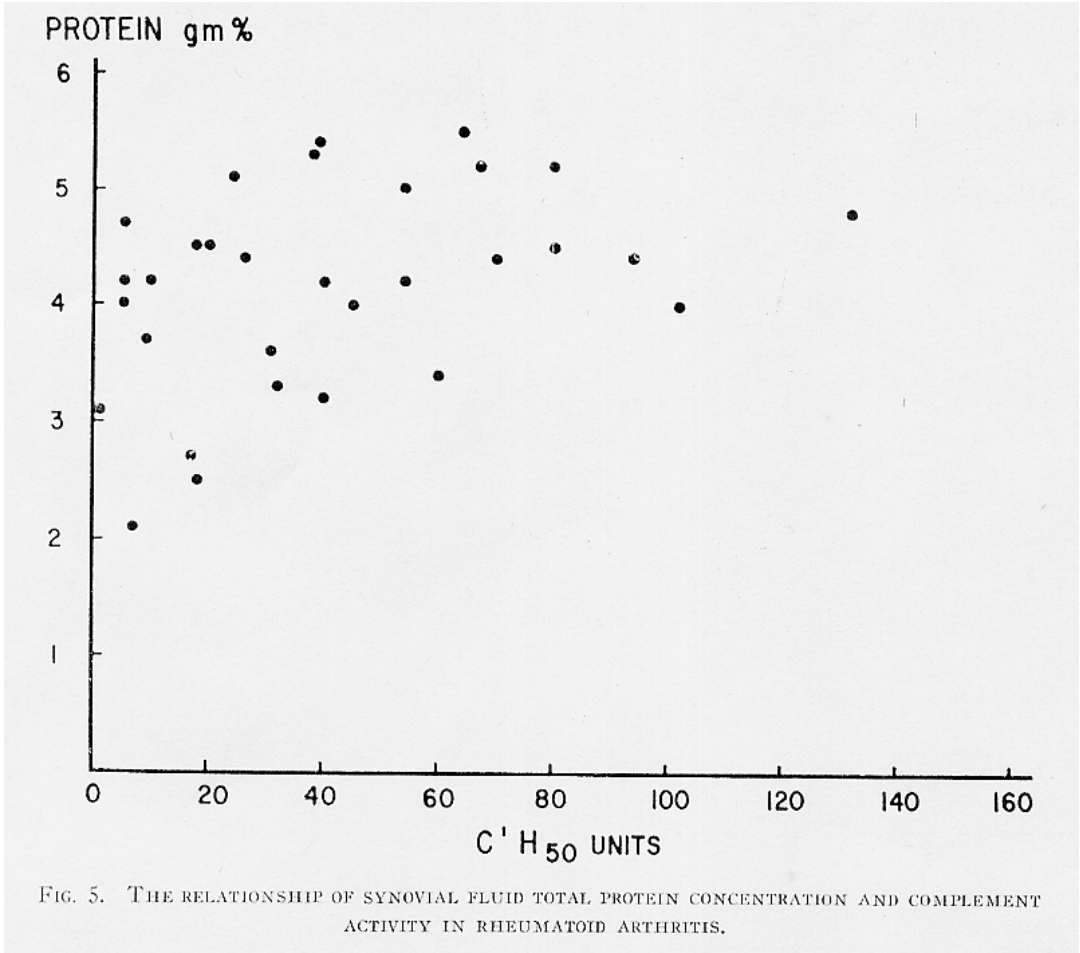
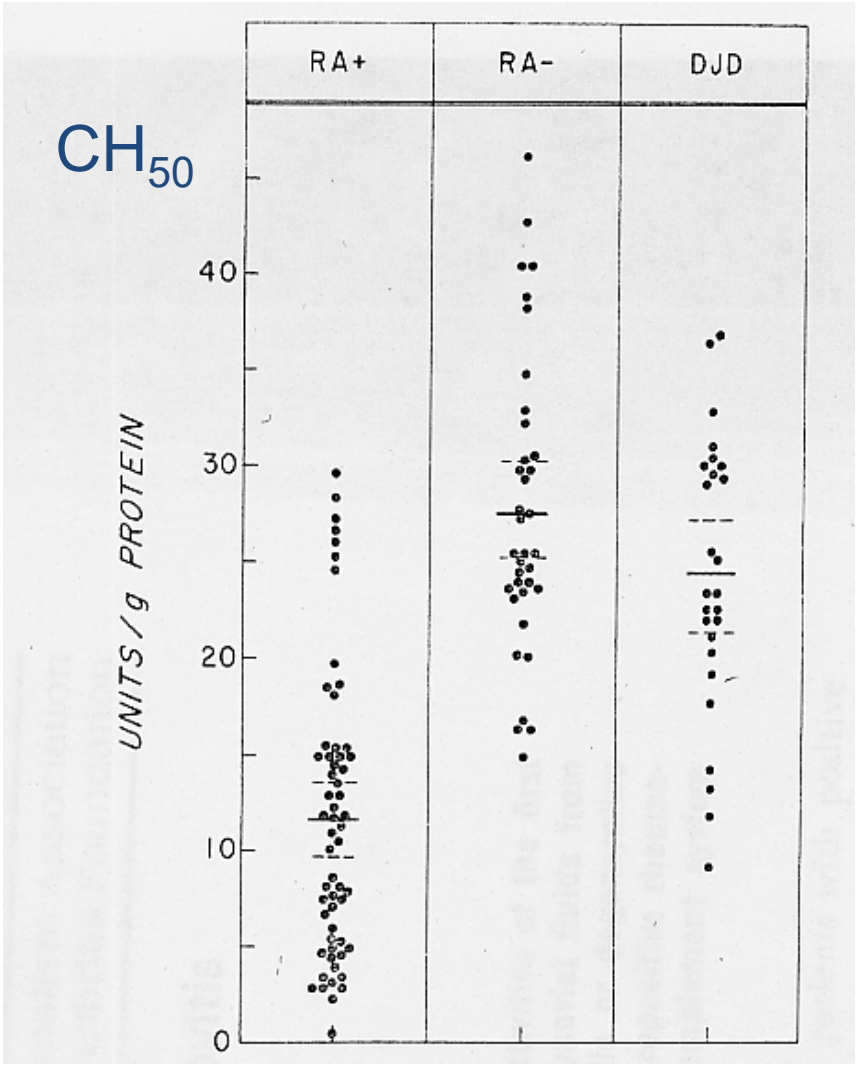


FIG. 5. THE RELATIONSHIP OF SYNOVIAL FLUID TOTAL PROTEIN CONCENTRATION AND COMPLEMENT ACTIVITY IN RHEUMATOID ARTHRITIS.

C' is consumed in RA but not selected other arthritides

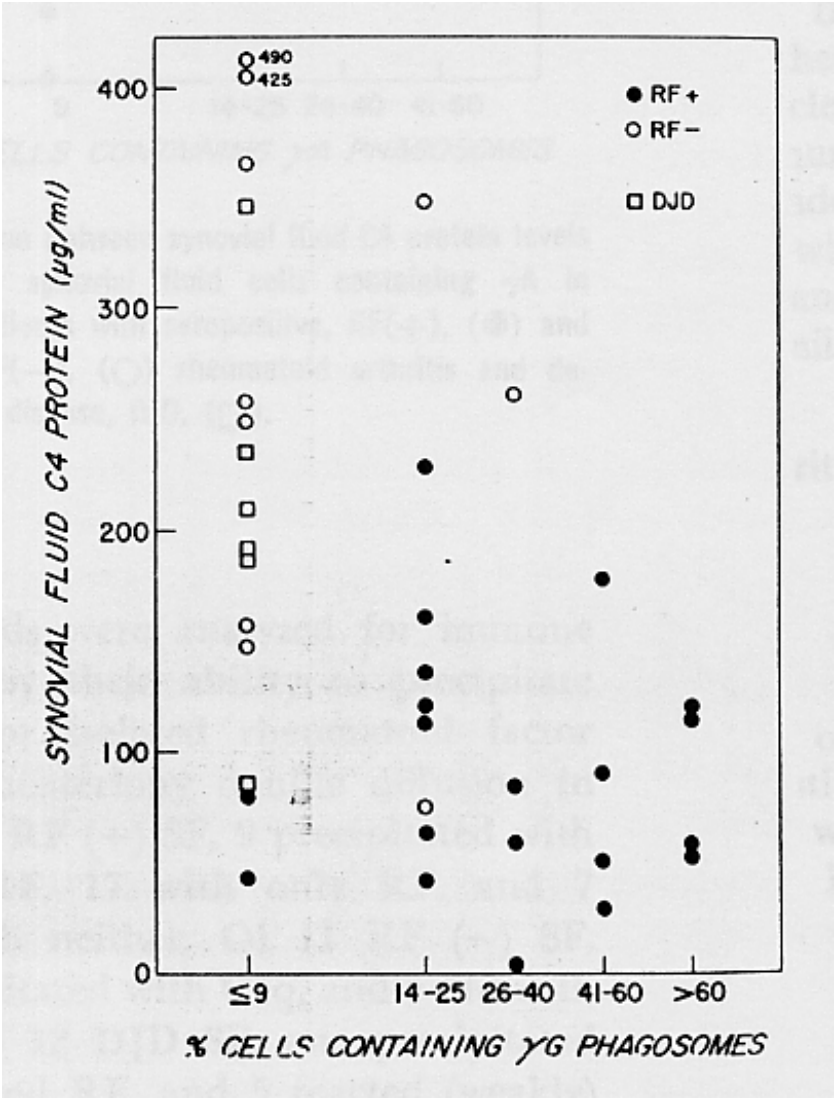
Pekin & Zvaifler *JCI* 1964;43;1372

SF hypocomplementemia restricted to **seropositive RA**



Ruddy & Austen *Arthritis Rheum* 1970;13:713

IgG ICs in seropositive RA



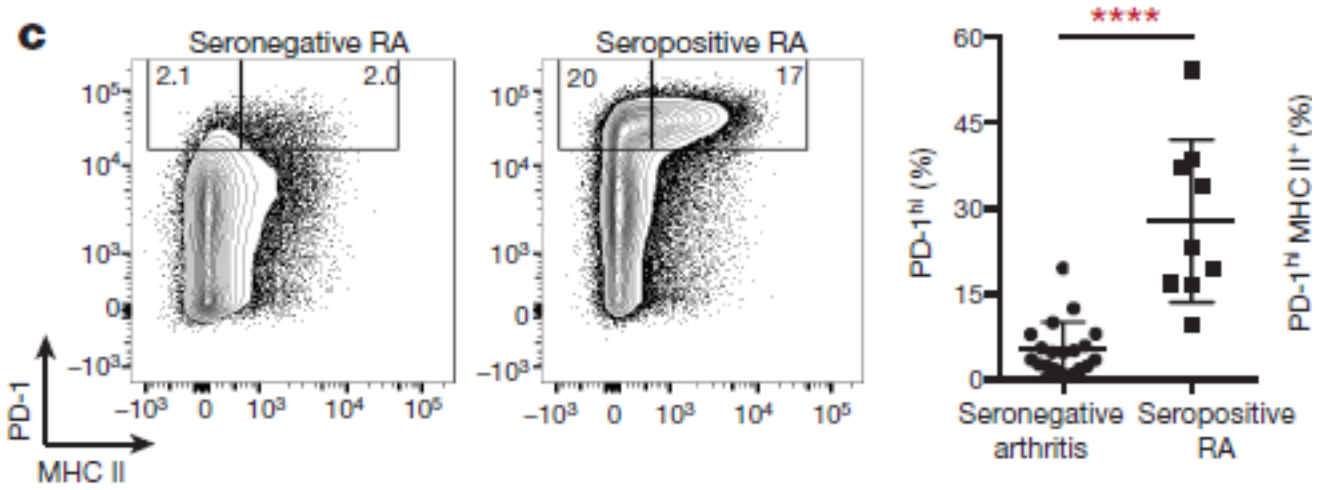
Britton & Schur, *Arthritis Rheum* 1971;14:87

LETTER

doi:10.1038/nature20810

Pathologically expanded peripheral T helper cell subset drives B cells in rheumatoid arthritis

Deepak A. Rao[1], Michael F. Gurish[1], Jennifer L. Marshall[2], Kamil Slowikowski[1,3,4,5,6], Chamith Y. Fonseka[1,3,4,6,7], Yanyan Liu[1], Laura T. Donlin[8,9], Lauren A. Henderson[10], Kevin Wei[1], Fumitaka Mizoguchi[1], Nikola C. Teslovich[1,3,4], Michael E. Weinblatt[1], Elena M. Massarotti[1], Jonathan S. Coblyn[1], Simon M. Helfgott[1], Yvonne C. Lee[1], Derrick J. Todd[1], Vivian P. Bykerk[11,12], Susan M. Goodman[11,12], Alessandra B. Pernis[9,12,13], Lionel B. Ivashkiv[8,9], Elizabeth W. Karlson[1], Peter A. Nigrovic[1,10], Andrew Filer[2], Christopher D. Buckley[2], James A. Lederer[14], Soumya Raychaudhuri[1,3,4,5,15,16] & Michael B. Brenner[1]



T peripheral helper (Tph) cells (PD-1^{hi}CXCR5^{neg}MHCII^{pos}CD4+)

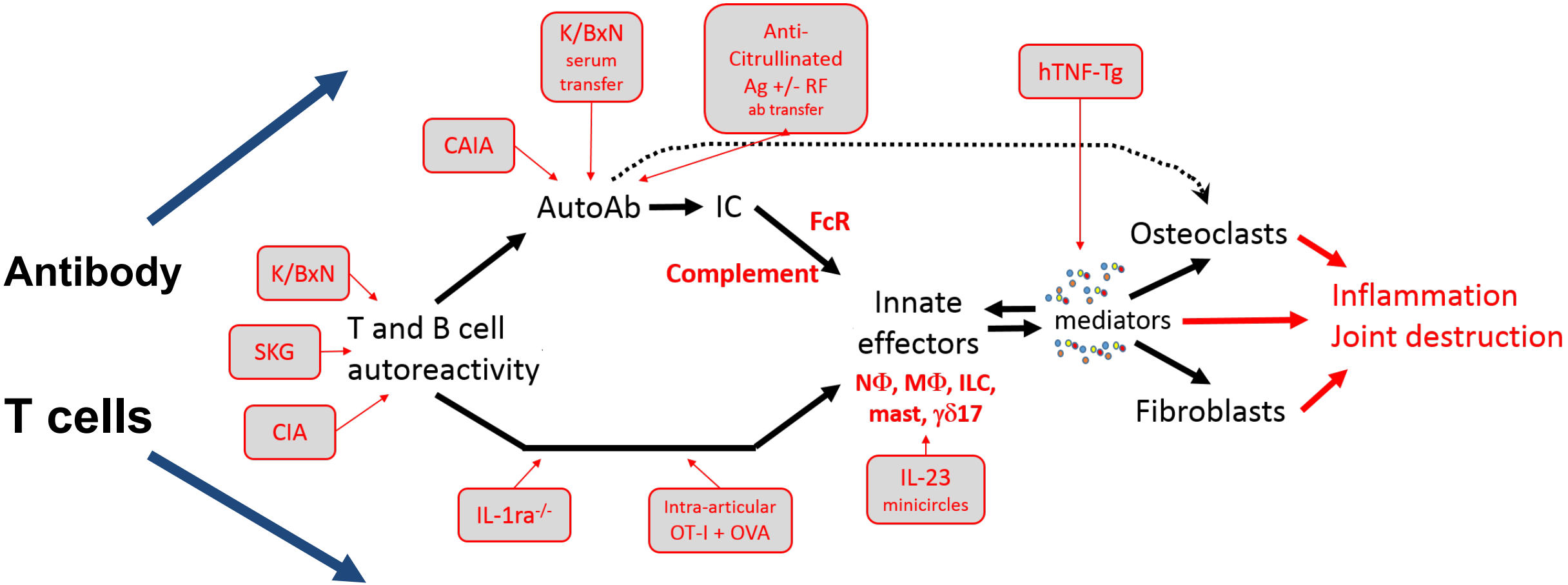
Nature 2017;542:110.

- **F > M**
- **polyarticular**
- **distal > proximal**
- **erosive**
- **symmetric**

	Seropos RA	Seroneg RA
Immune complexes	YES	NO
C’ consumption	YES	NO
Tph cells in synovium	YES	NO
Smoking as risk factor	YES	NO

Chang & Nigrovic. Mechanisms of antibody-dependent and -independent arthritis. *JCI Insight* 2019 Mar 7;4:125278.

Two pathways to autoimmune arthritis in animal models

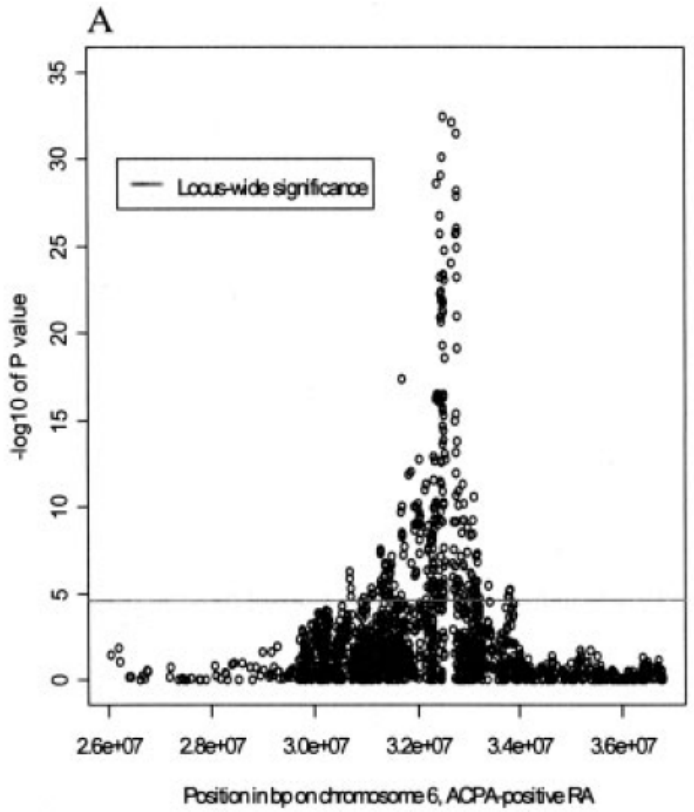


Chang & Nigrovic. Mechanisms of antibody-dependent and -independent arthritis. *JCI Insight* 2019 Mar 7;4:125278.

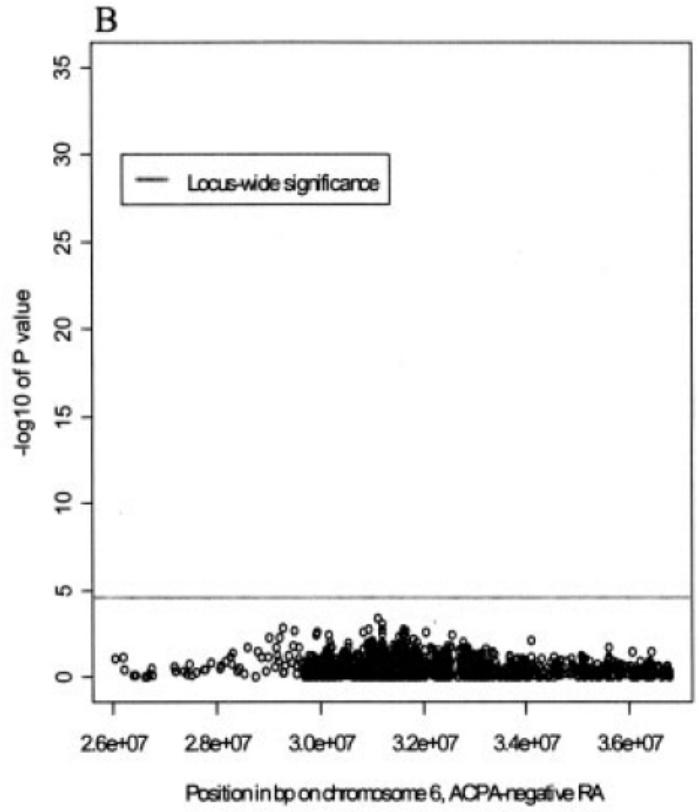
Genetics also distinguishes seropos / seroneg RA

HLA locus

ACPA pos



ACPA neg



Ding *Arth Rheum* 2009:60;30–38.

OPEN ACCESS

EXTENDED REPORT

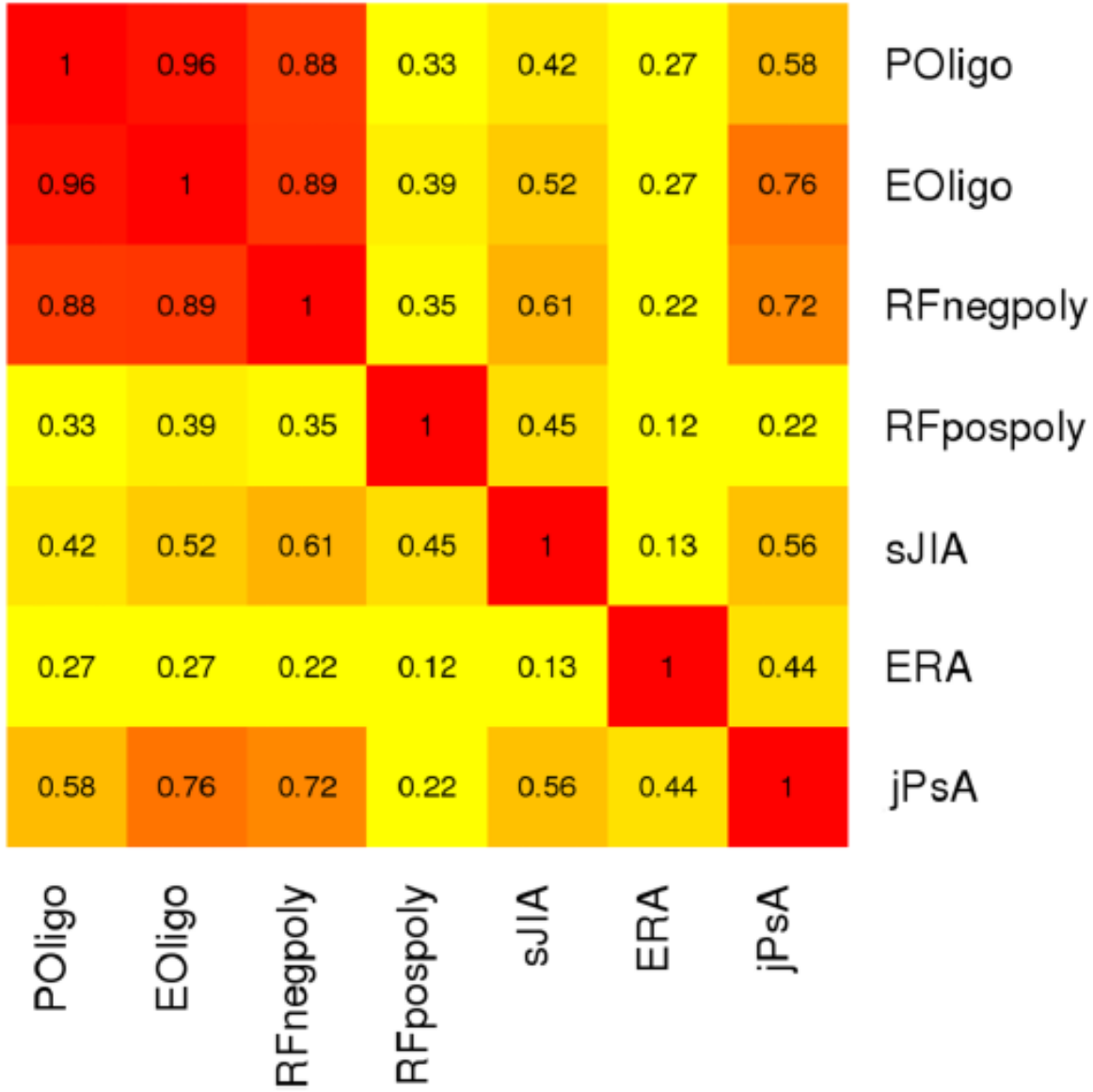
Fine-mapping the MHC locus in juvenile idiopathic arthritis (JIA) reveals genetic heterogeneity corresponding to distinct adult inflammatory arthritic diseases

A Hinks,[1] J Bowes,[1] J Cobb,[1,2] H C Ainsworth,[3] M C Marion,[3] M E Comeau,[3] M Sudman,[4] B Han,[5,6] Juvenile Arthritis Consortium for Immunochip, M L Becker,[7] J F Bohnsack,[8] P I W de Bakker,[9] J P Haas,[10] M Hazen,[11] D J Lovell,[12] P A Nigrovic,[11,13] E Nordal,[14] M Punnaro,[15,16] A M Rosenberg,[17] M Rygg,[18] S L Smith,[1] C A Wise,[19,20] V Videm,[18] L R Wedderburn,[21,22] A Yarwood,[1] R S M Yeung,[23] S Prahalad,[24] C D Langefeld,[3] S Raychaudhuri,[1,5,25,26] S D Thompson,[4] W Thomson[1,2]

5,043 JIA cases, 14,390 controls

Hinks, Bowes et al. *Ann Rheum Dis* 2016;76(4):765-72.

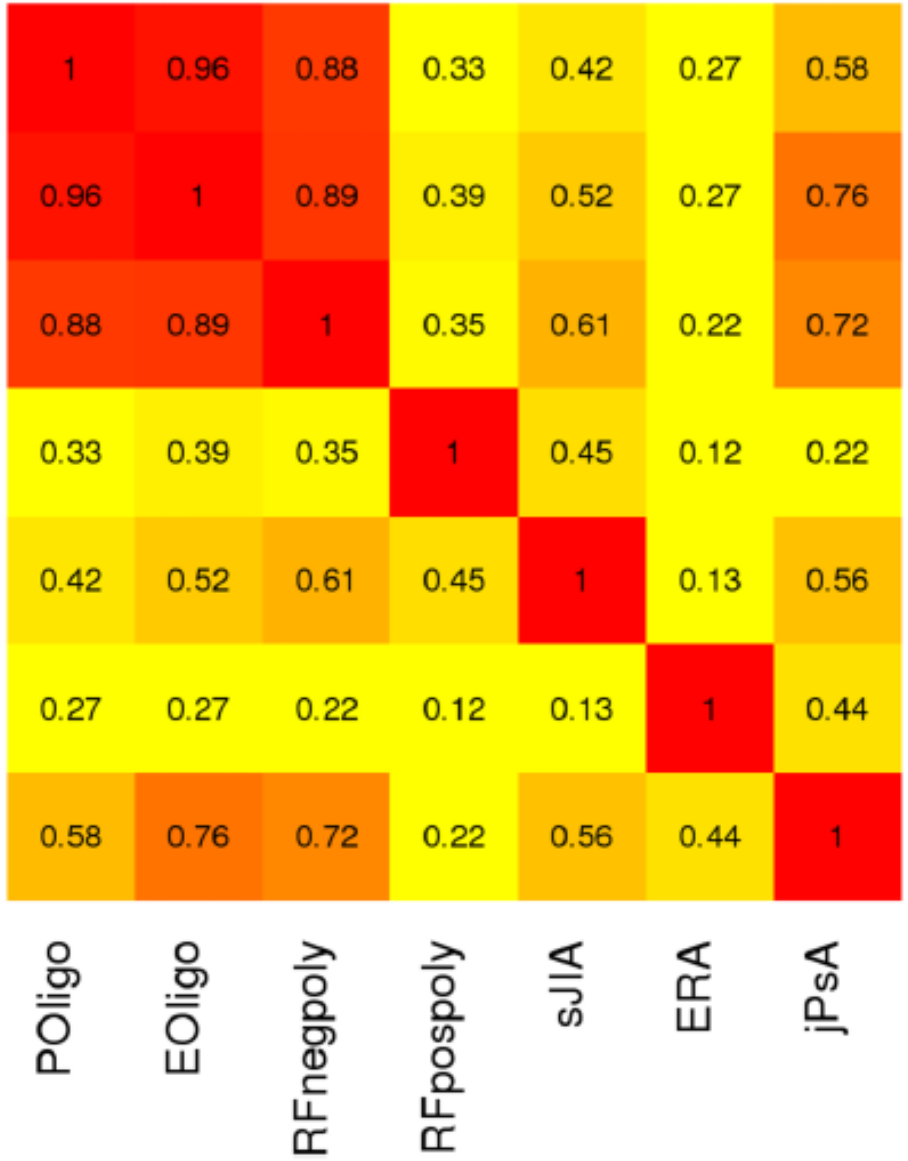
Correlation matrix



"pJIA"

Hinks, Bowes et al. *Ann Rheum Dis* 2016;76(4):765-72.

Correlation matrix



"pJIA"

POligo
EOligo
RFnegpoly } = seroneg adult RA

RFpospoly = seropos adult RA

sJIA

ERA = adult AS (HLA-B27)

jPsA ≈ adult PsA

Hinks, Bowes et al. *Ann Rheum Dis* 2016;76(4):765-72.

Beyond the HLA: Genetic Risk Scores (GWAS-wide)

Immunochip: RF+ polyJIA ≈ adult-onset (seropos) RA

BRIEF REPORT

The Genetic Profile of Rheumatoid Factor–Positive Polyarticular Juvenile Idiopathic Arthritis Resembles That of Adult Rheumatoid Arthritis

Anne Hinks,[1] Miranda C. Marion,[2] Joanna Cobb,[3] Mary E. Comeau,[2] Marc Sudman,[4] Hannah C. Ainsworth,[2] John Bowes,[1] Juvenile Idiopathic Arthritis Consortium for Immunochip, Mara L. Becker,[5] John F. Bohnsack,[6] Johannes-Peter Haas,[7] Daniel J. Lovell,[4] Elizabeth D. Mellins,[8] J. Lee Nelson,[9] Ellen Nordal,[10] Marilynn Punaro,[11] Ann M. Reed,[12] Carlos D. Rose,[13] Alan M. Rosenberg,[14] Marite Rygg,[15] Samantha L. Smith,[1] Anne M. Stevens,[16] Vibeke Videm,[15] Carol A. Wallace,[17] Lucy R. Wedderburn,[18] Annie Yarwood,[1] Rae S. M. Yeung,[19] Carl D. Langefeld,[2] Susan D. Thompson,[4] Wendy Thomson,[3] and Sampath Prahalad[20]

Hinks…Prahalad. *Arth Rheum* 2018;70:957-62.

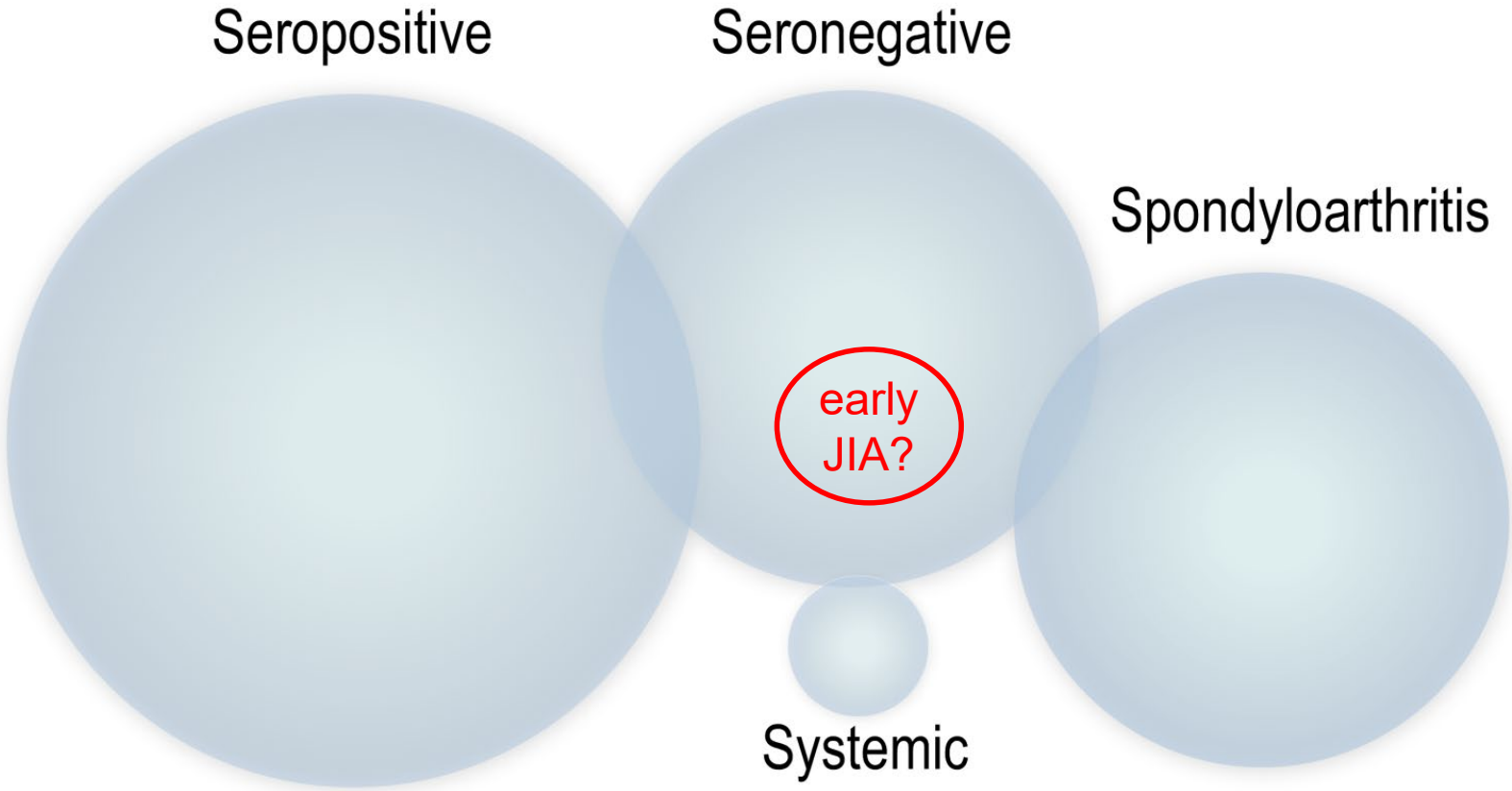
Seroneg JIA vs. seroneg RA – very limited data, but compatible

Nigrovic, Martínez-Bonet, Thompson. *Curr Opin Rheumatol*. 2019 Sep;31(5):401-410.

Genetics / biology: the “split” is seropos vs. seroneg, not pJIA vs RA

burden of proof *on those who wish to split kids and adults*

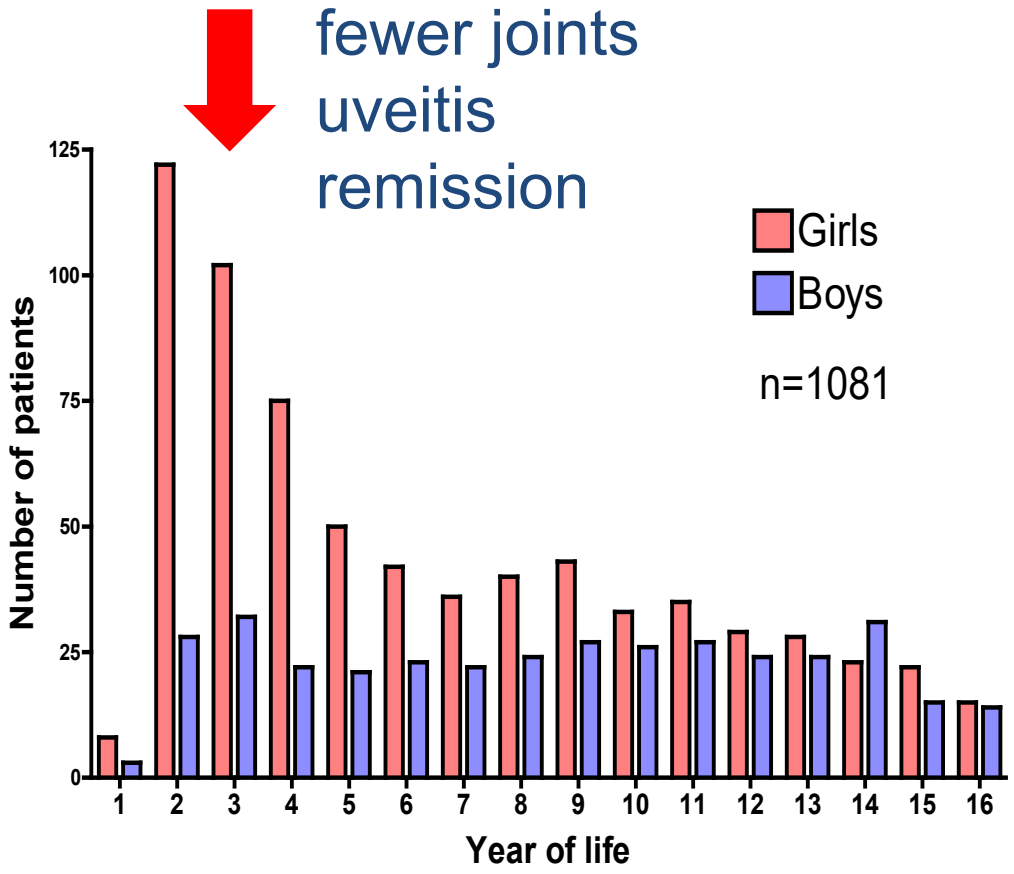
…but what about early-onset JIA?



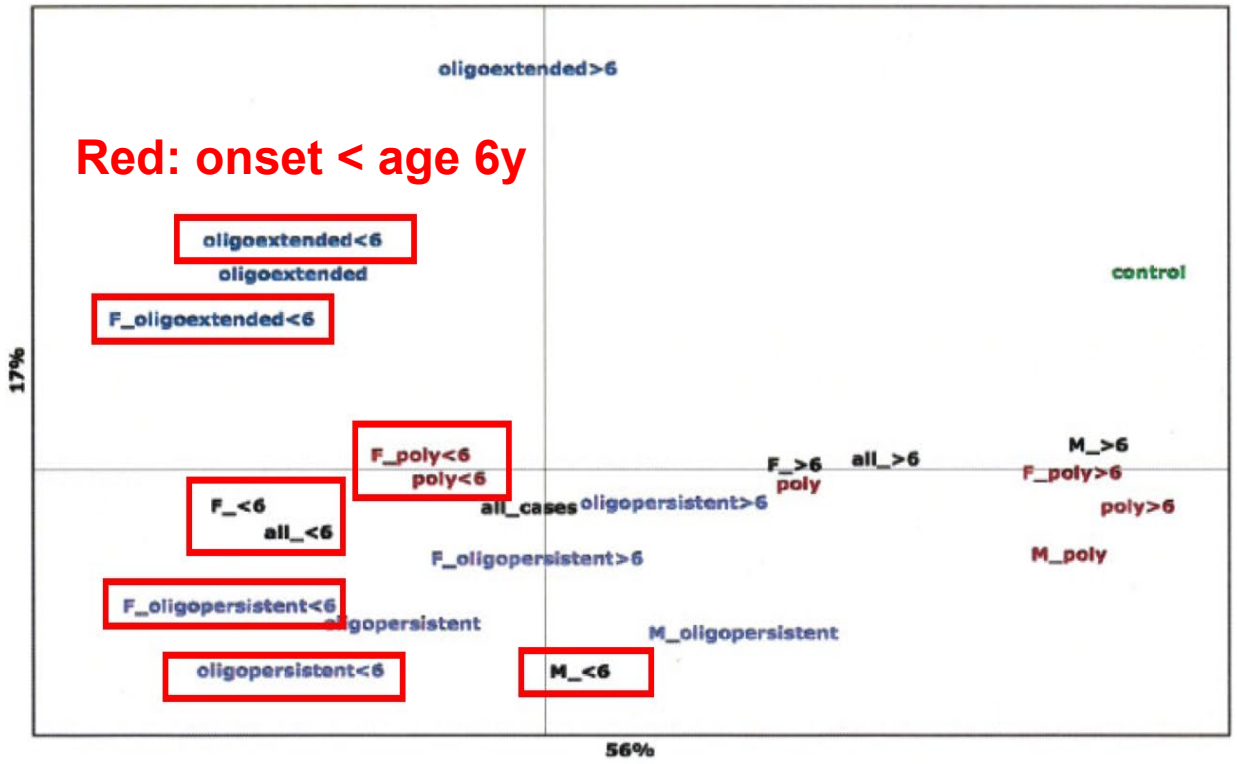
Nigrovic, Raychaudhuri, Thompson. Genetics and the classification of arthritis in adults and children. *Arthr Rheum* 2018;70:7-17.

Nigrovic, Martínez-Bonet, Thompson. Implications of JIA genetic risk variants for disease pathogenesis and classification. *Curr Opin Rheumatol*. 2019 Sep;31(5):401-410.

** Early childhood arthritis may be different **



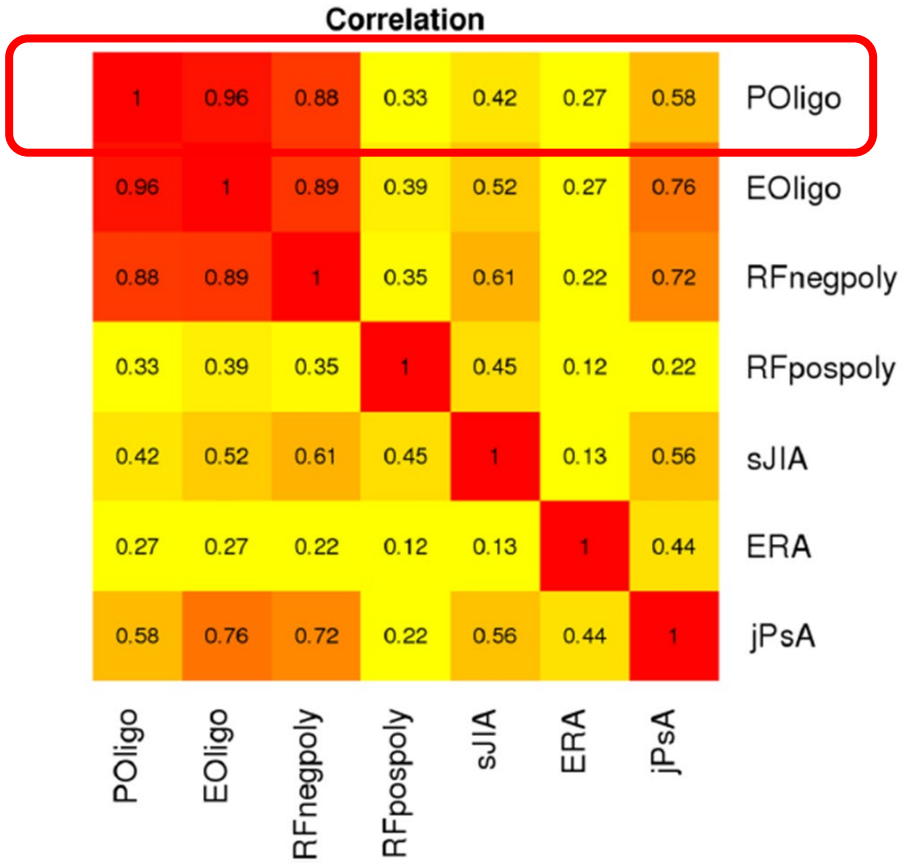
PCA of HLA associations in oligo/poly JIA



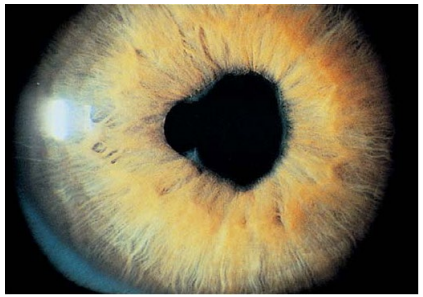
adapted from Saurenmann *A&R* 2010;62:1824

Hollenbach *A&R* 2010;62:1781.

Is early-onset arthritis really different after all?

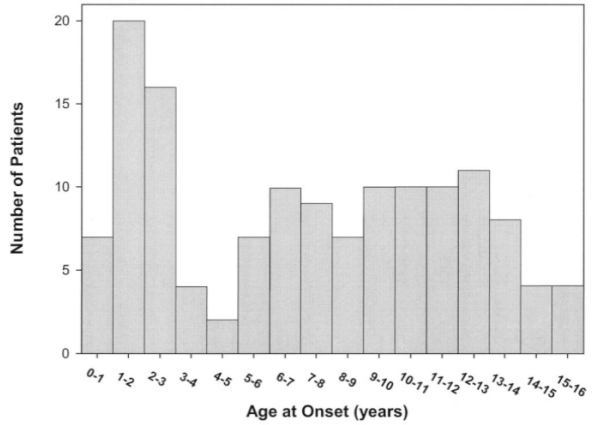


Hinks, Bowes et al. *Ann Rheum Dis* 2016;76(4):765-72.



occurs in young children without JIA

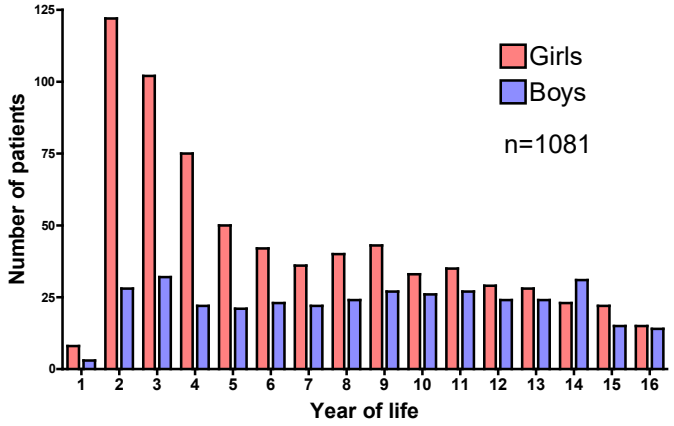
Juvenile psoriatic arthritis



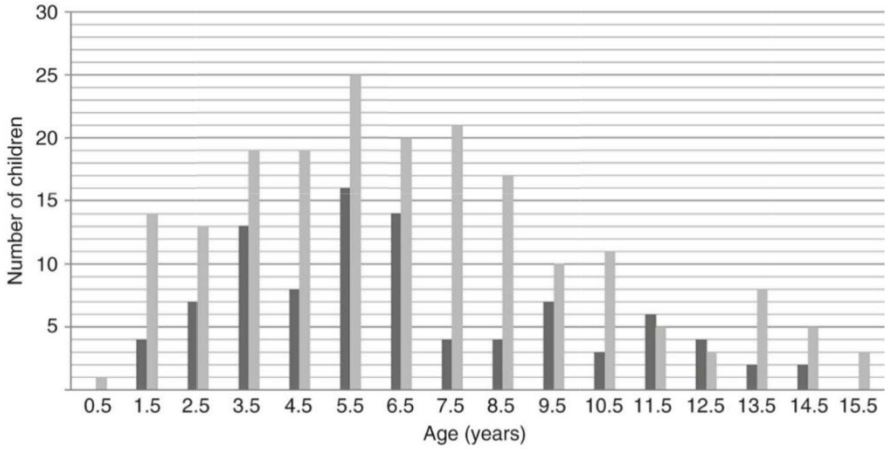
Stoll…Nigrovic *Arth Rheum* 2006;54:3564

Different diseases? Or different “substrate”, exposures, …?

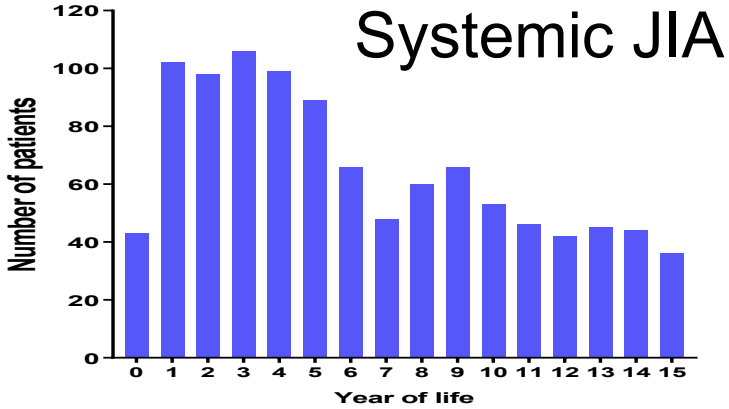
JIA



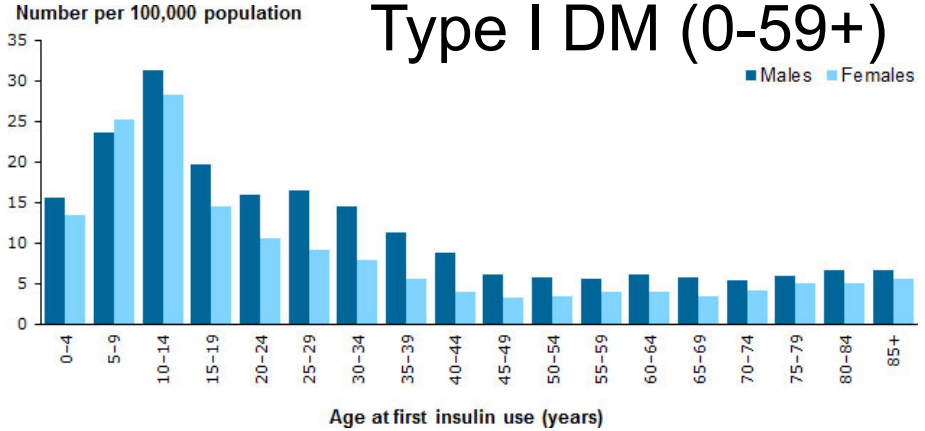
Juvenile Dermatomyositis



Systemic JIA



Type I DM (0-59+)



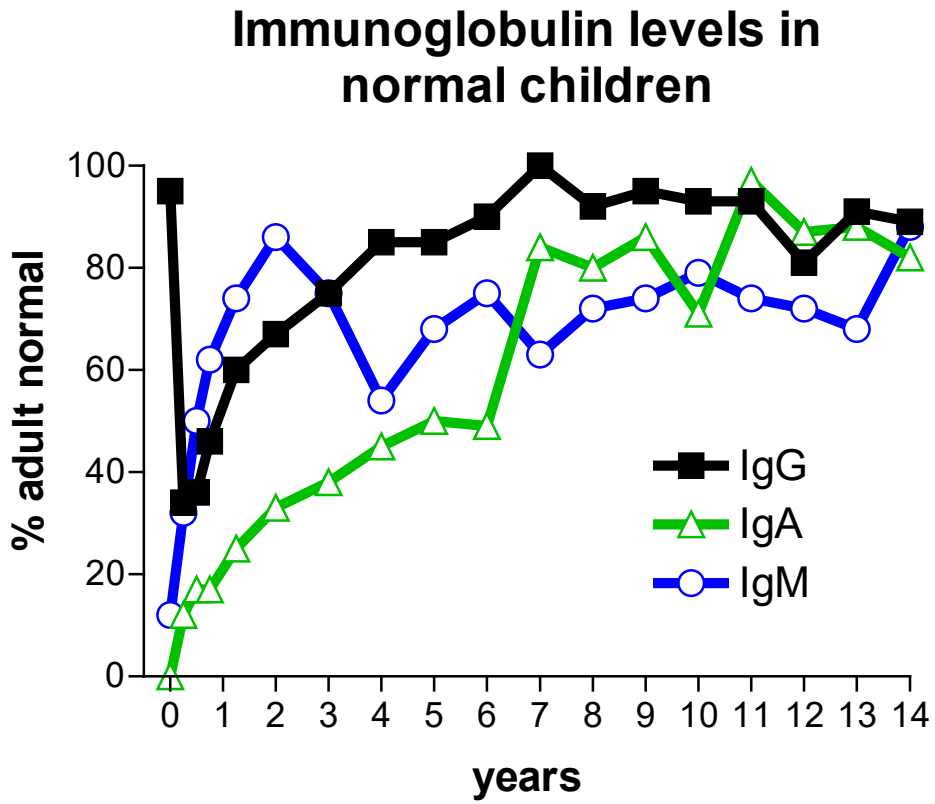
How should early-onset disease factor into our thinking about pJIA vs. RA?

1. As likely as not to be the “same” disease, different substrate

2. Known differences between early & later-onset JIA (and RA) are <u>smaller than</u> the differences between RF+ and RF- RA
   - ** pediatric rheumatologists do not treat early / late pJIA differently **

3. Our treatments to date seem not mechanism-sensitive
   - e.g. RF+ and RF- RA mostly respond to same drugs in same way
   - suggests relatively non-specific anti-synovitis mechanism of action

Yet kids are (in some ways) not little adults



Lewis & Tu in Steihm et al. (eds.) *Immunological Disorders in Infants and Children, 5th Ed., 2004*

- **Pharmacokinetics/metabolism**
- **Growth and development**
  - Immunological maturation
  - Linear growth / growth plates
  - Bone mineralization
  - Sexual development
  - Psychological maturation
- Needed regulatory emphasis
  - PK/PD
  - Toxicity

Big picture: polyJIA ≅ RA

- seroneg pJIA ≅ seronegRA
- seropos pJIA = seroposRA *(the very same disease)*

From the regulatory point of view…

- The FDA tolerates differences within “RA” (RF pos vs. neg, onset 16 vs. 35 vs. 80 years)
- Differences between <16 and ≥16 y onset are smaller than these
- Regulatory focus should be on PK / PD / toxicity → REGISTRIES

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