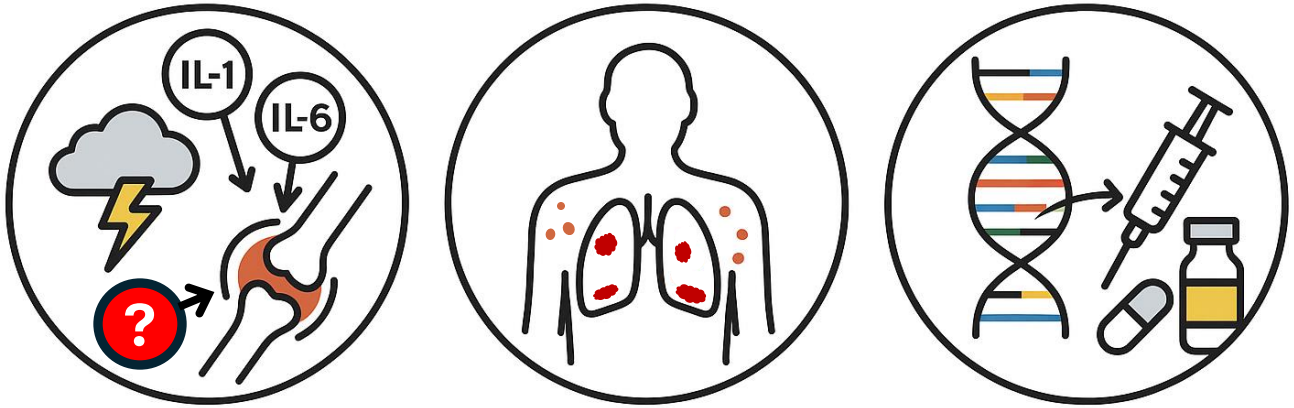
Still's Disease Across the Ages



National Institute of Arthritis and Musculoskeletal and Skin Diseases

Michael J. Ombrello, MD

Principal Investigator
Translational Genetics and Genomics Section
Intramural Research Program, NIAMS, NIH

Disclosures

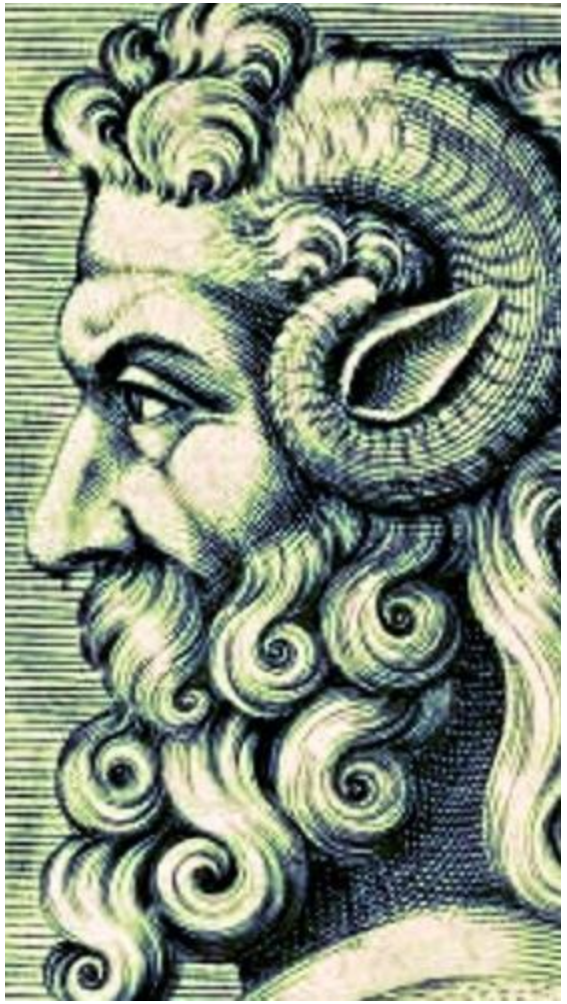
- I have no conflicts of interest to disclose

- I will discuss non-FDA approved therapies for Still's disease:
  - Anakinra
  - JAK inhibitors
  - mTOR inhibitors

Two faces of Still's disease

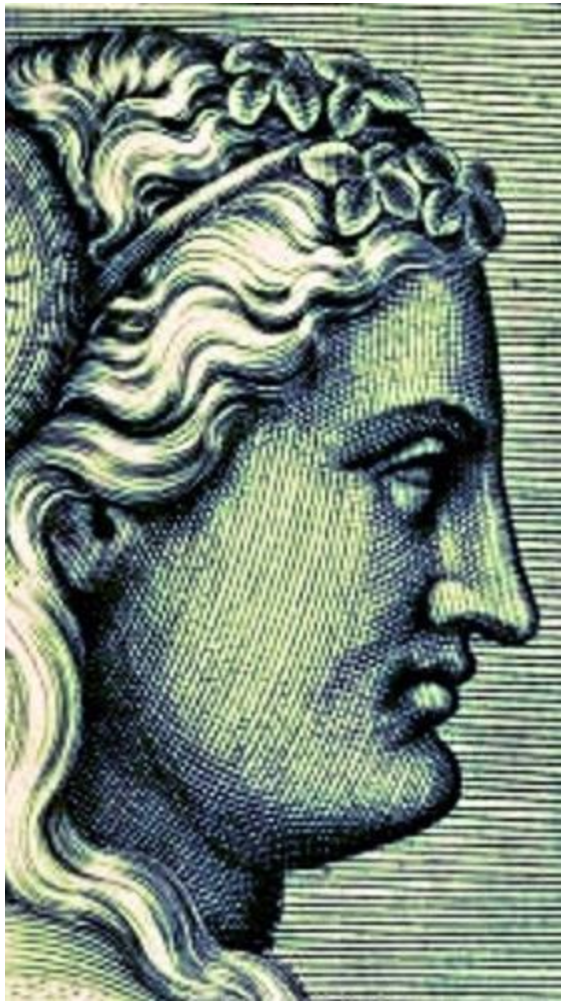
32-year-old female with AOSD

- Persistent polyarthritis, LAD, persistent inflammation, elevated LFTs and LAD
- Flares with MAS
- Infusion reactions
  - Tocilizumab, abatacept, infliximab
- Injection site reactions
  - Anakinra, adalimumab
- Treated with glucocorticoids and DMARDs



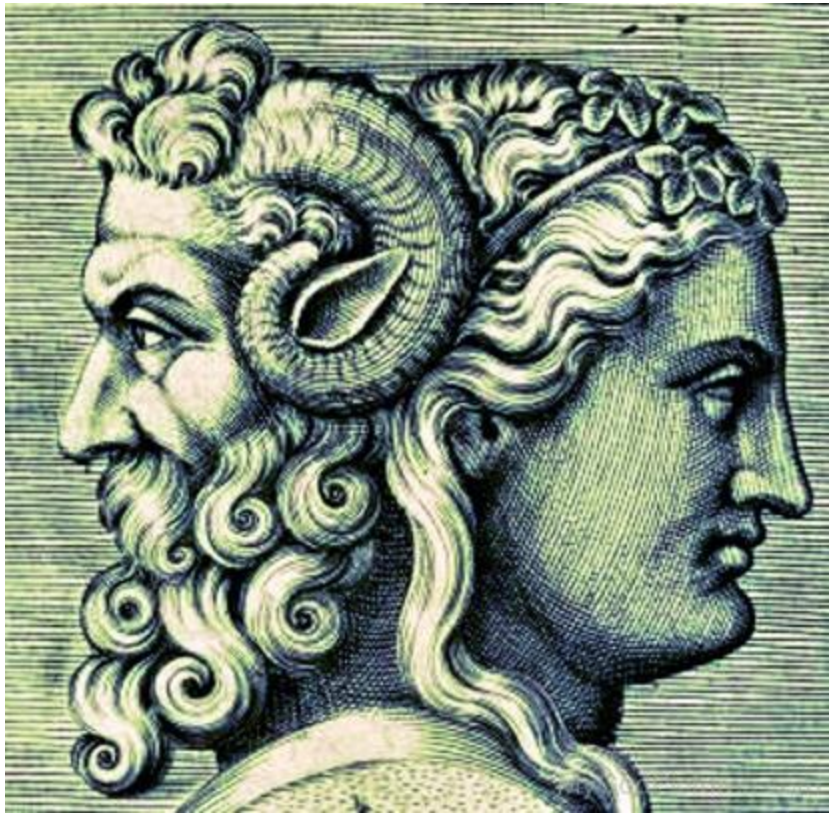
Two faces of Still's disease

- **5-year-old male with sJIA debut**
  - Prolonged fever, arthritis, rash, LAD
  - Flared during glucocorticoid taper
  - Remission on anakinra, occasional flares
- **4-year-old female with sJIA debut**
  - Prolonged fever, arthritis, LAD, myalgia
  - Clinical remission on glucocorticoids
  - No recurrence
- **12-year-old female with sJIA x 5 years**
  - Wheelchair bound, cushingoid
  - S/p multiple joint replacements
  - Many drug reactions, chronic steroids

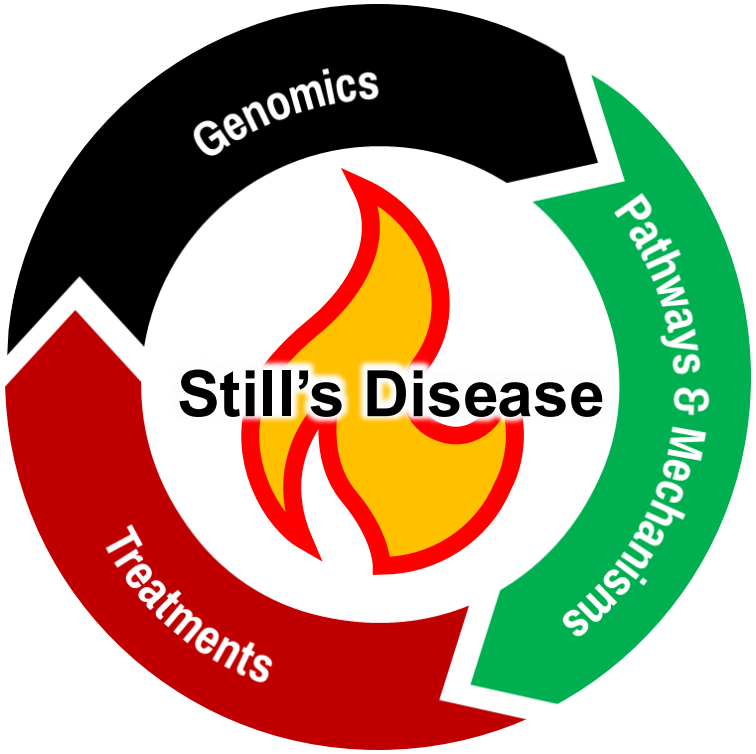


Challenges in Still's disease

- **Problems**
  - Incomplete effectiveness
  - Severe therapy-associated complications
  - AOSD studies and care lag behind sJIA
- **Solutions**
  - New therapeutic targets
  - Personalized medicine approaches
  - Education and collaboration among adult rheumatologists



The Ombrello Lab: Translational Investigations of Still's Disease



Collaborations/Consortia

- INCHARGE sJIA cohort
- CARRA (sJIA and sJIA-lung disease)
- FROST Investigators (sJIA)
- *PLCG2* Immune Dysregulation Consortium

Clinical Center

NIAID IRP

SYNERGY

NIAMS IRP

NHGRI IRP

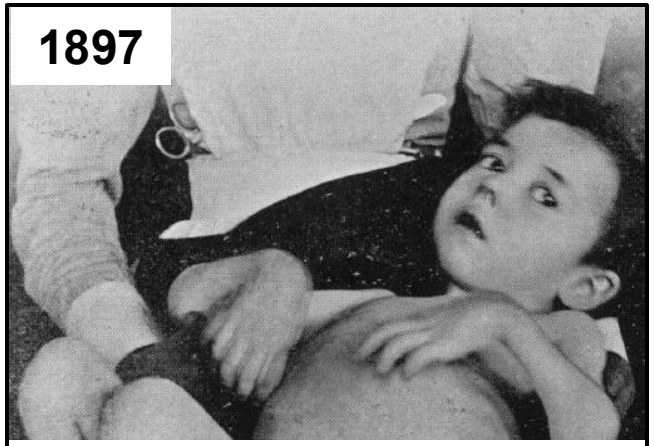
Local Study Cohort

- Still's disease in children and adults
- *PLCG2*-associated immune dysregulation
- Undiagnosed inflammatory disease

National Institute of Arthritis and Musculoskeletal and Skin Diseases

What is Still's disease?

1897



ON A

FORM OF CHRONIC JOINT DISEASE IN CHILDREN

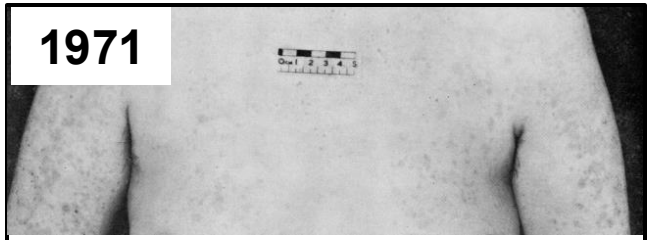
BY

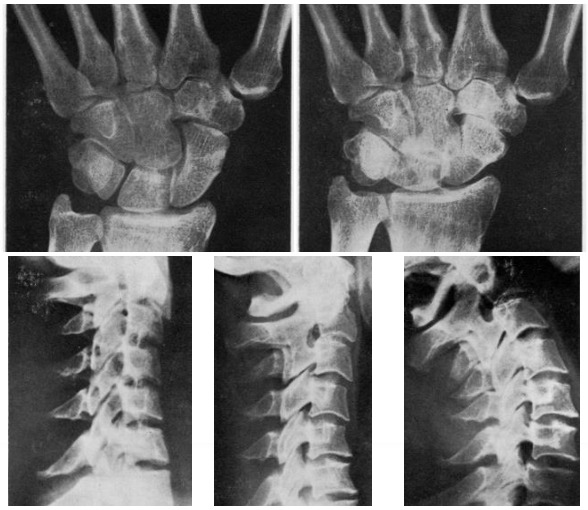
GEORGE F. STILL, M.A., M.D., M.R.C.P.
MEDICAL REGISTRAR AND PATHOLOGIST TO THE HOSPITAL FOR SICK CHILDREN, GREAT ORMOND STREET, LONDON

COMMUNICATED BY DR. ARCHIBALD E. GARROD

Received April 23rd—Read November 10th, 1896

1971





Ann. rheum. Dis. (1971), **30**, 121

Still's disease in the adult

E. G. L. BYWATERS
From the Department of Medicine, Royal Postgraduate Medical School, London, Council Rheumatism Unit, Taplow, Berks.

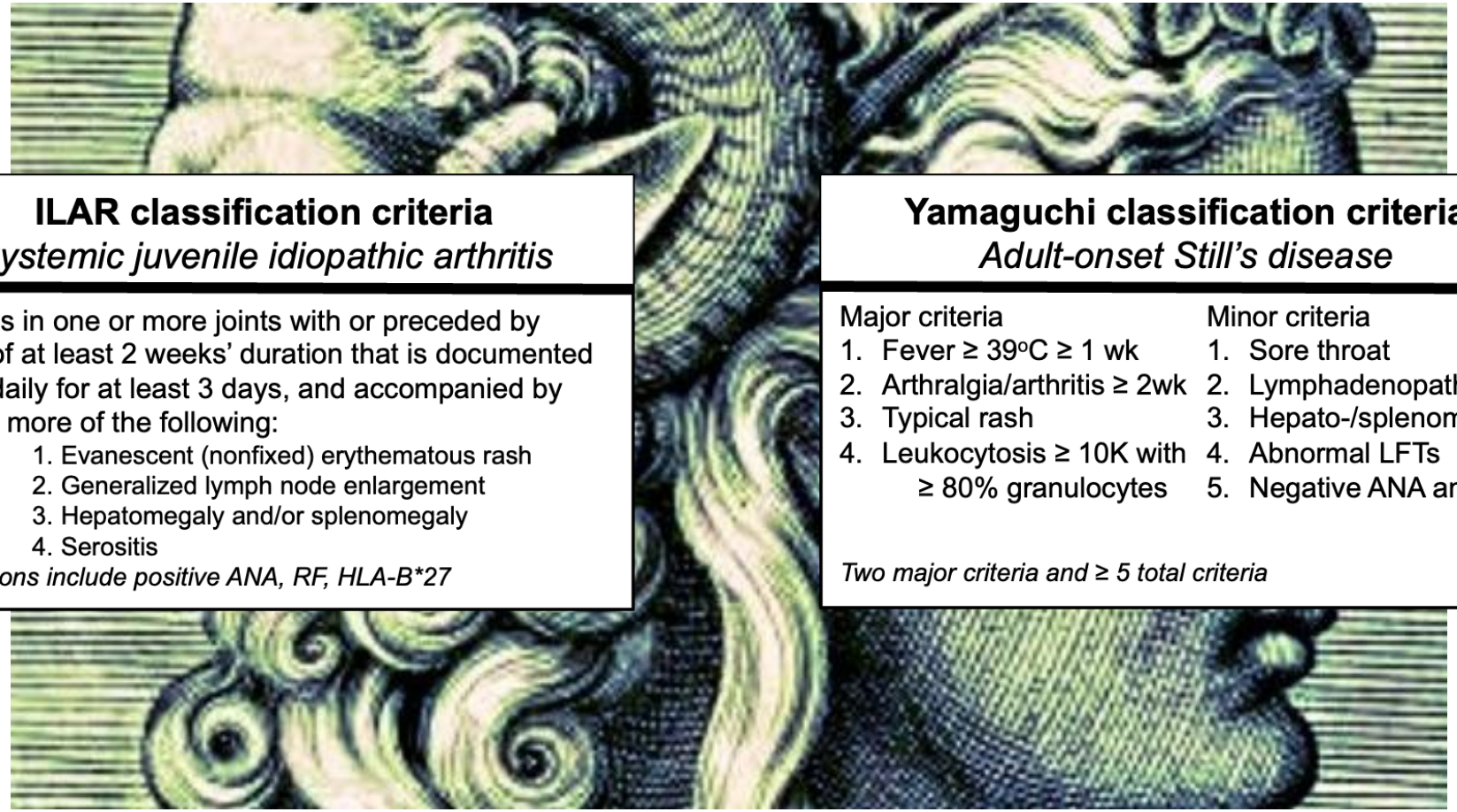
Prototypic features of Still's disease in 22 children and 14 adults

- Fever
- Rash
- Severe, progressive arthritis
- Lymphadenopathy
- Serositis

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Still GF, 1897 (PMID 20896907)
Bywaters EG, 1971 (PMID 5315135)

What is Still's disease?



ILAR classification criteria
Systemic juvenile idiopathic arthritis

Arthritis in one or more joints with or preceded by fever of at least 2 weeks' duration that is documented to be daily for at least 3 days, and accompanied by one or more of the following:

1. Evanescent (nonfixed) erythematous rash
2. Generalized lymph node enlargement
3. Hepatomegaly and/or splenomegaly
4. Serositis

*Exclusions include positive ANA, RF, HLA-B*27*

Yamaguchi classification criteria
Adult-onset Still's disease

Major criteria
1. Fever ≥ 39°C ≥ 1 wk
2. Arthralgia/arthritis ≥ 2wk
3. Typical rash
4. Leukocytosis ≥ 10K with ≥ 80% granulocytes

Minor criteria
1. Sore throat
2. Lymphadenopathy
3. Hepato-/splenomegaly
4. Abnormal LFTs
5. Negative ANA and RF

Two major criteria and ≥ 5 total criteria

NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases

Petty RE et al, 2004 (PMID 14760812)
Yamaguchi M et al, 1992 (PMID 1578458)

Clinical features of Still's disease

Comparison of children and adults

Clinical Feature	ILAR	Yamaguchi	Children[1,2]	Adults[3]
Fever	+	+	98-100%	91-100%
Lymphadenopathy	+	+	31-49%	28-64%
Pharyngitis		+		31-62%
Joint complaints	Arthritis	Arthralgia	80-88%	47-95%
Organomegaly	+	+	12-22%	25-60%
Rash	+	+	81-91%	62-80%
Leukocytosis		+	75%*	73-100%
Serositis	+		10-14%	25-60%
Transaminitis		+	25%*	50-62%

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Behrens EM et al, 2008 (PMID 18085728)
Foley CM et al, 2023 (PMID 37780048)
Extracted from Efthimiou P et al, 2021 (PMID 34175791)

What is Still's disease?

431 children vs. 579 adults

Inflammatory arthritis

OPEN ACCESS

CLINICAL SCIENCE

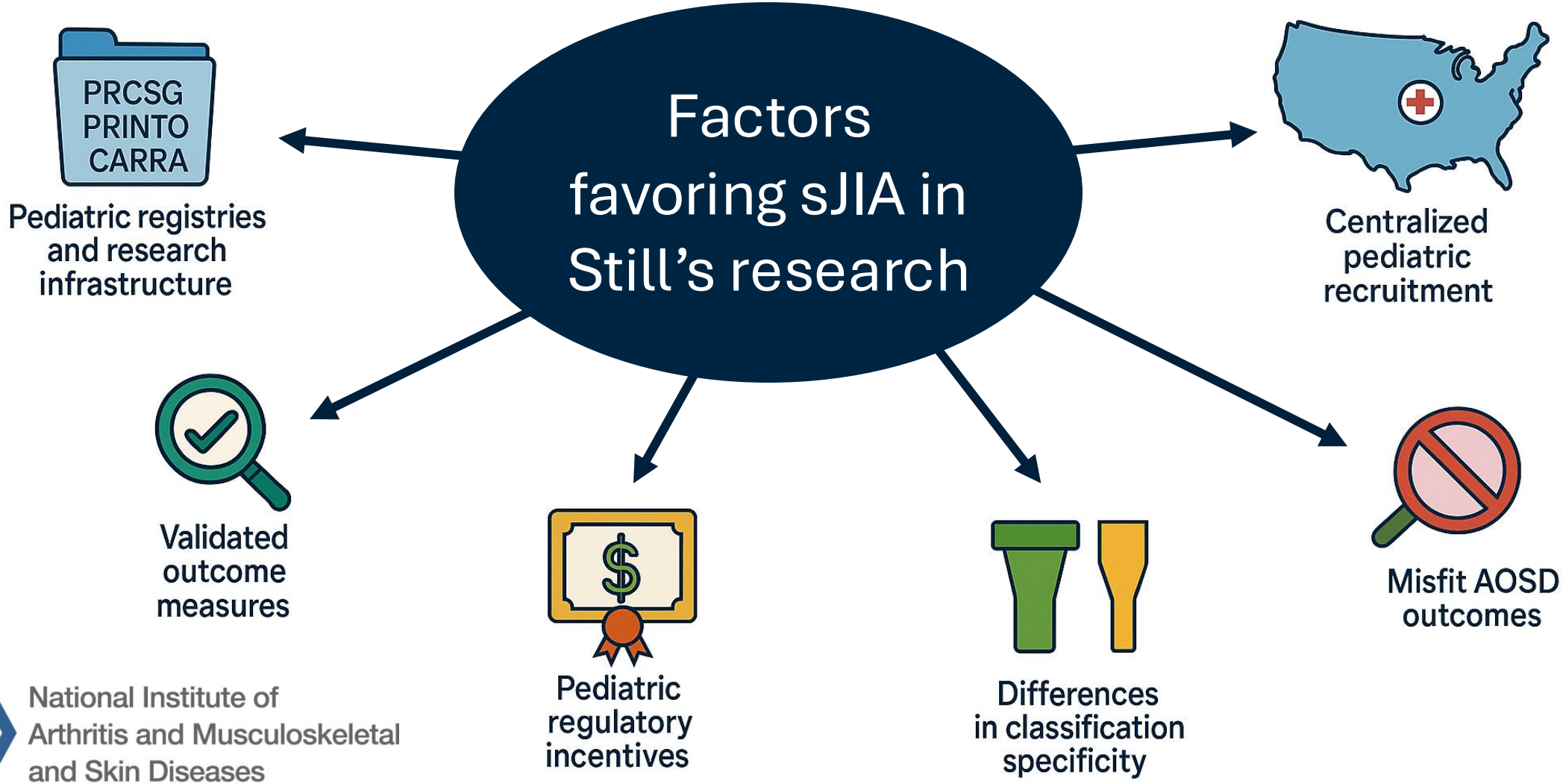
Systemic juvenile idiopathic arthritis and adult-onset Still's disease are the same disease: evidence from systematic reviews and meta-analyses informing the 2023 EULAR/PReS recommendations for the diagnosis and management of Still's disease

Arianna De Matteis [1], Sara Bindoli [2], Fabrizio De Benedetti [1], Loreto Carmona [3], Bruno Fautrel [4,5,6], Stéphane Mitrovic [4,5]

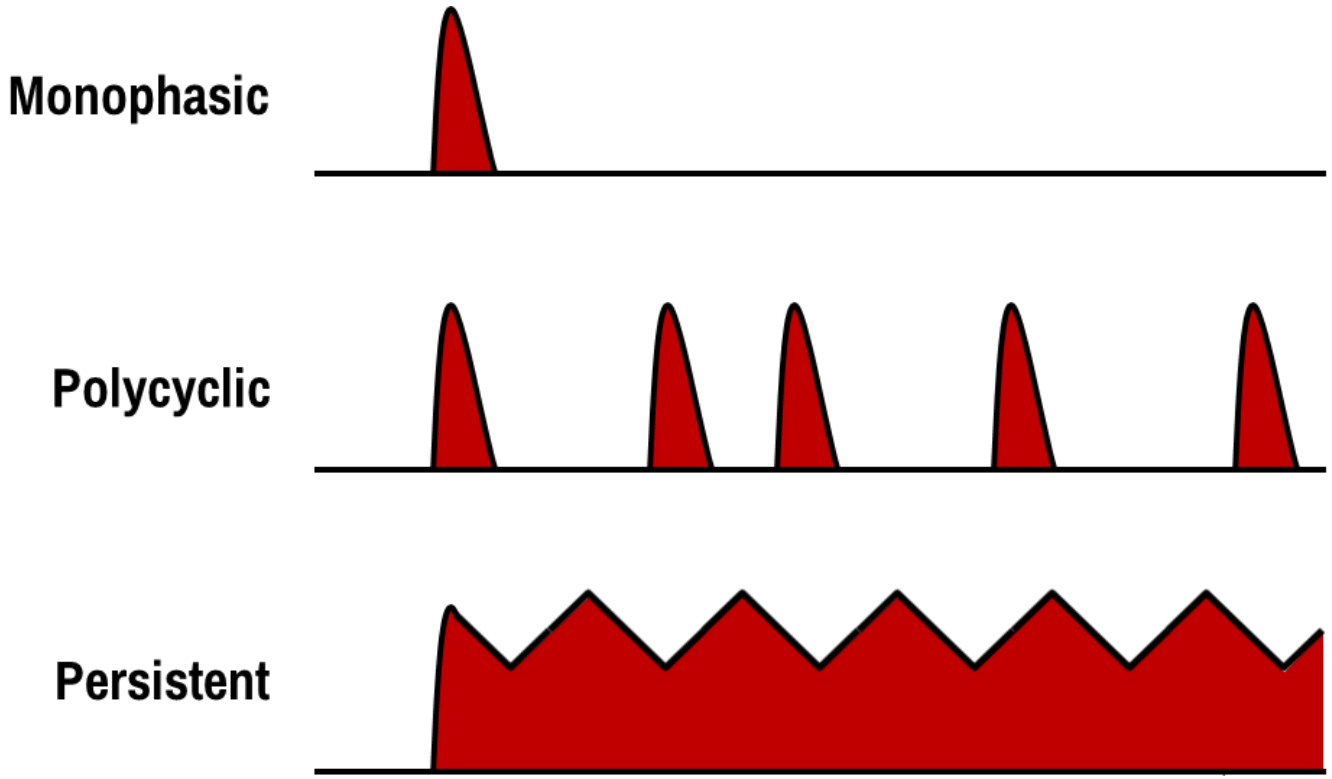
National Institute of Arthritis and Musculoskeletal and Skin Diseases

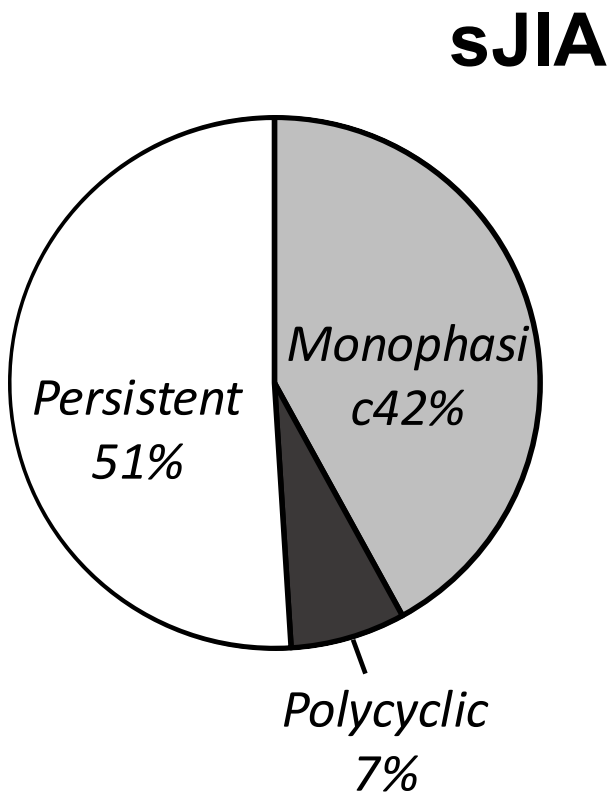
De Matteis A et al, 2024 (PMID 39317414)

Still’s research skewed toward sJIA



Heterogeneous disease courses in Still's disease

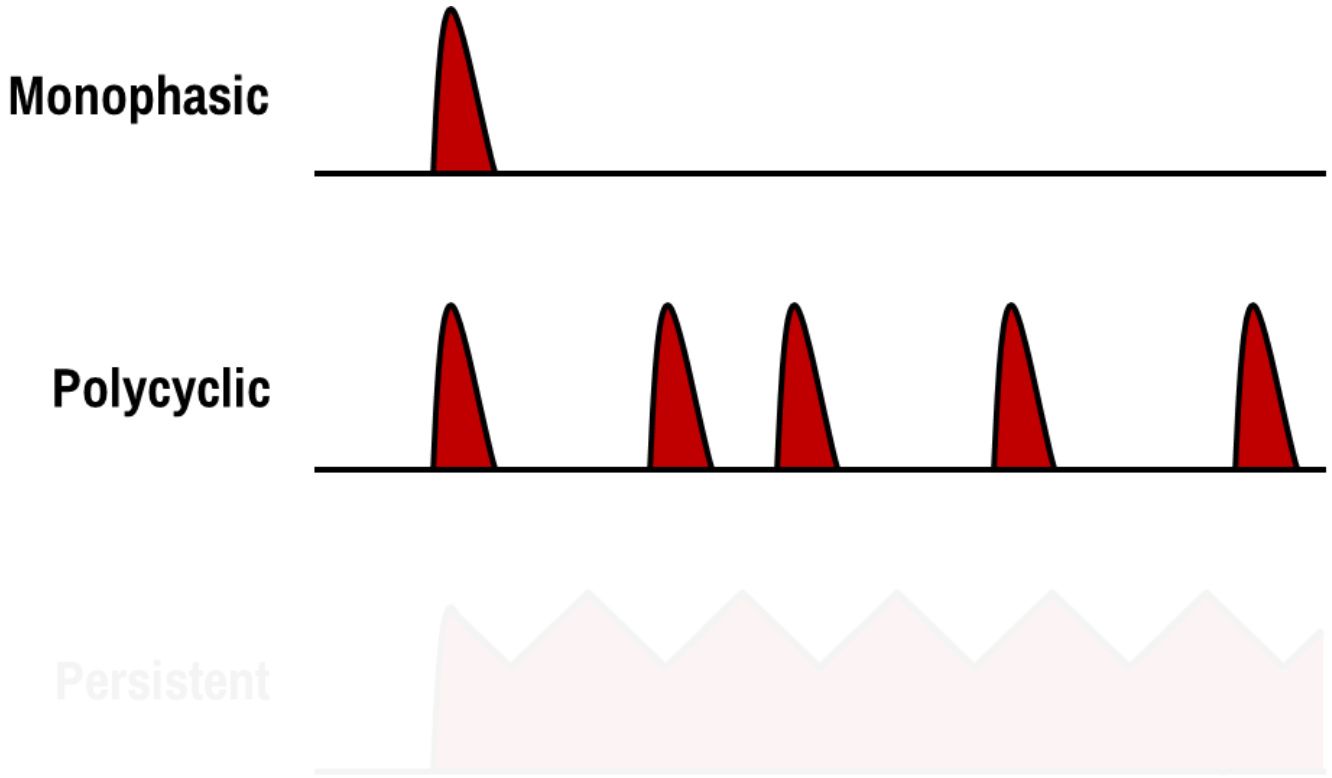


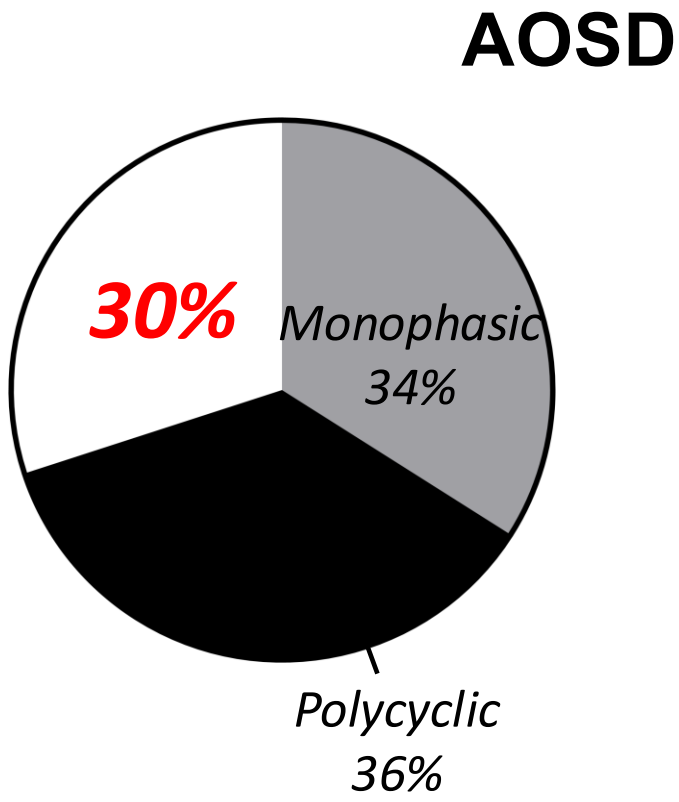


National Institute of Arthritis and Musculoskeletal and Skin Diseases

Singh-Grewal D et al, 2006 (PMID 16645998)

Heterogeneous disease courses in Still's disease

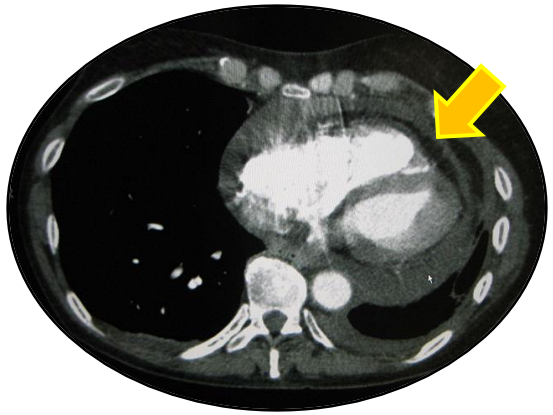




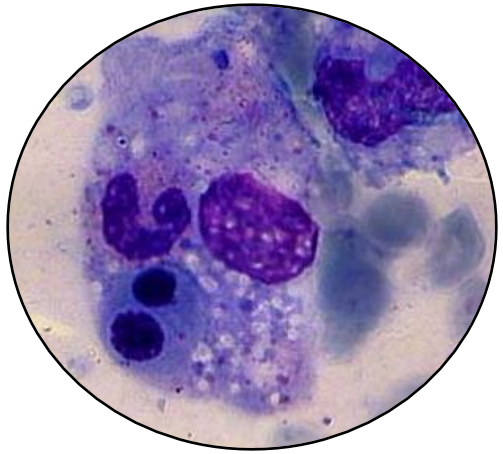
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Extracted from Efthimiou P et al, 2021 (PMID 34175791)

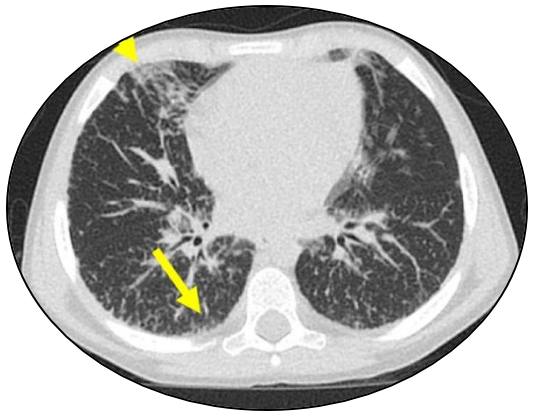
Heterogeneous complications of Still's disease



Pericardial Effusion
- Occurs in up to 30% of AOSD
- May be recurrent
- Tamponade may be fatal



Macrophage Activation Syndrome
- Hyperinflammatory cytokine storm
- Occurs in up to 15% of AOSD
- Lethal if untreated



Interstitial Lung Disease
- Multicentric, polymorphic histology
- Prominent alveolar proteinosis
- Rapidly progressive and lethal

National Institute of Arthritis and Musculoskeletal and Skin Diseases

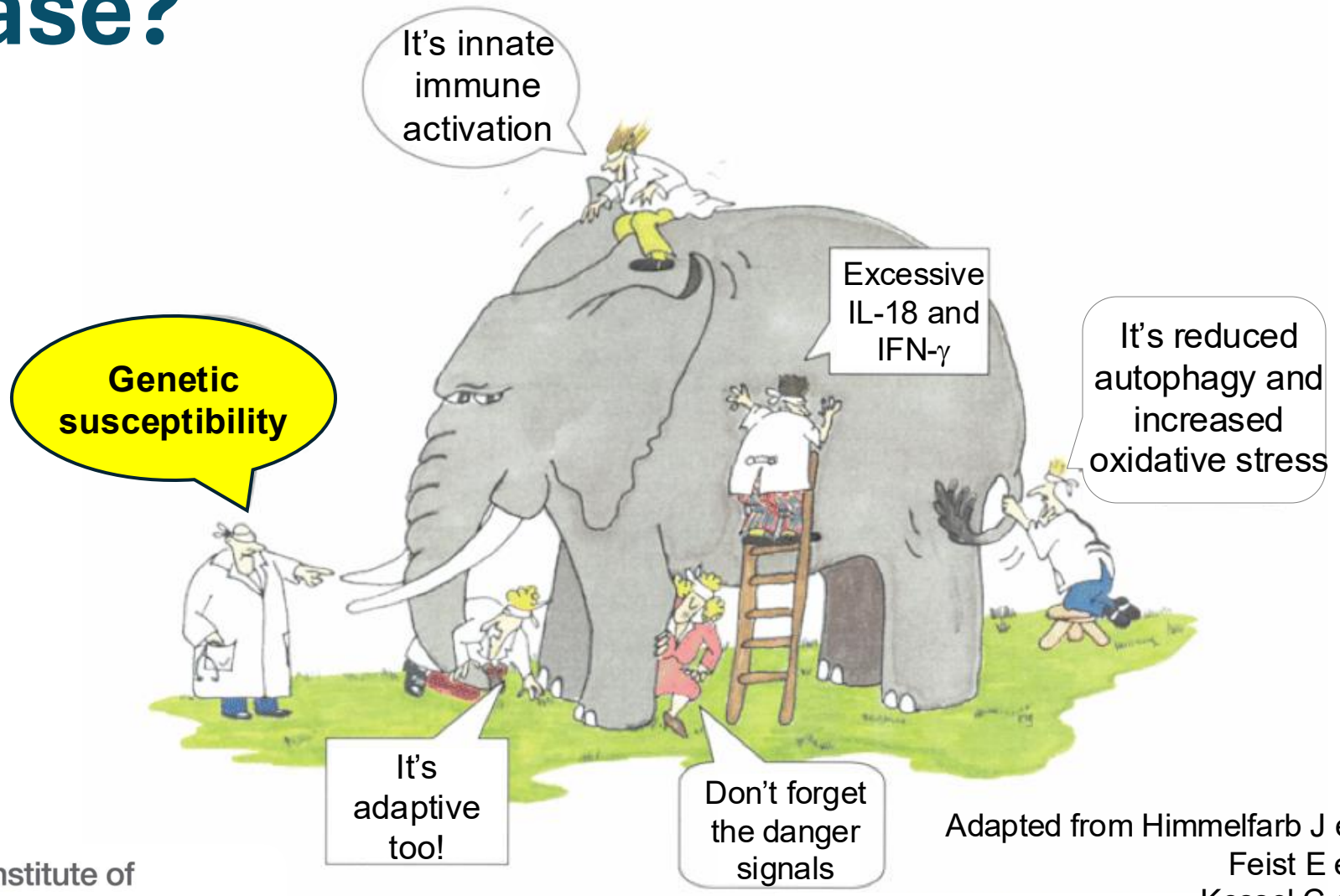
Schulert GS et al, 2019 (PMID 31379071)

What is *not* Still's disease?

- Still's disease is NOT a:
  - **Variant of a known monogenic autoinflammatory disease**
  - **Variant of a known form of arthritis (RA, SpA, PsA, etc.)**
  - **Autoimmunity with any specific autoantibodies**
  - **Subacute or chronic viral infection**
  - **Recurrent/chronic streptococcal infection with arthritis**
  - **Post-infectious autoimmunity**
  - **Lymphoproliferative disease**
  - **Paraneoplastic syndrome**
  - **Myelodysplastic syndrome**

- Clinically, this is critical for optimal management
- Excluding disparate pathophysiology is also critical to successfully investigating Still's disease

What is the pathophysiology of Still's disease?



Adapted from Himmelfarb J et al, 2002 (PMID 12371953)
Feist E et al, 2018 (PMID 30218025)
Kessel C et al, 2020 (PMID 31524322)
Ombrello MJ et al, 2014 (PMID 26598658)

Genetics and Still's disease

- **Candidate gene studies**
- **sJIA GWAS**
  - *HLA-DRB1*11*
  - Numerous other risk loci
  - *IL1RN* (low expression)
- **Rare variants**
  - HLH genes, *STXBP2*, *LYST*
- **Family-based studies**
  - *LACC1*
- **AOSD GWAS**
  - Multiple HLA alleles
  - *CSF1* (encoding M-CSF)

WHAT WE NEED:

✓ ***International AOSD genomics consortium***

✓ ***Combined studies of sJIA and AOSD***

Ombrello MJ et al, 2015 (PMID 26598658)
Ombrello MJ et al, 2017 (PMID 27927641)
Arthur VL et al, 2018 (PMID 29609200)
Wakil SM et al, 2015 (PMID 25220867)
Li Z et al, 2020 (PMID 31471296)
Chen Y et al, 2020 (PMID 32149159)

NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases

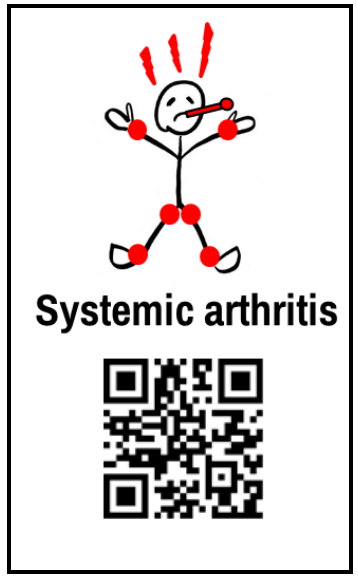
The treatment of Still’s disease

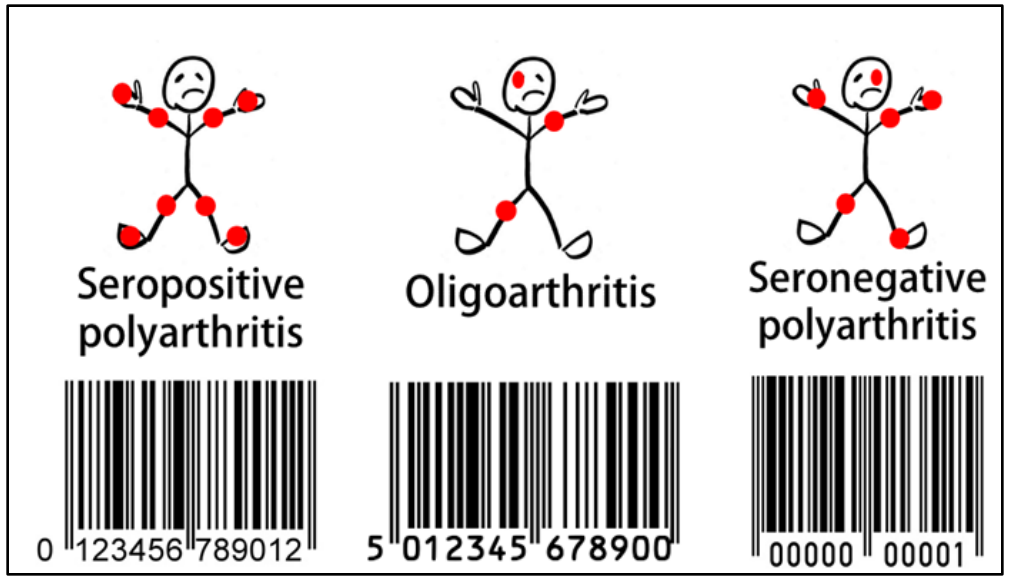
How *did* we treat Still's disease?

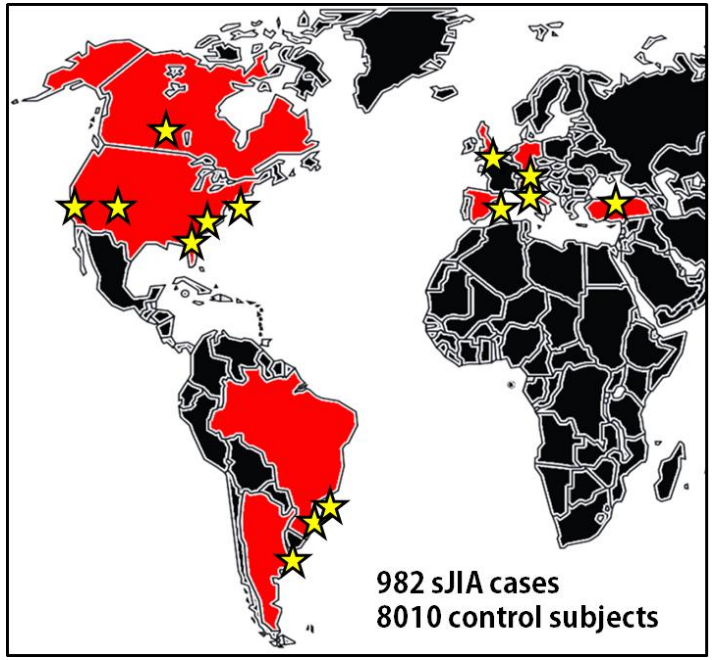
- No guideline figure from pre-biologic era!
- Repurposing from other conditions?
- NSAIDs, glucocorticoids, DMARDs, immunomodulators, IVIG, emerging biologics (TNF-blockers)?

NOT VERY WELL

Why hasn't drug repurposing been successful in Still's disease





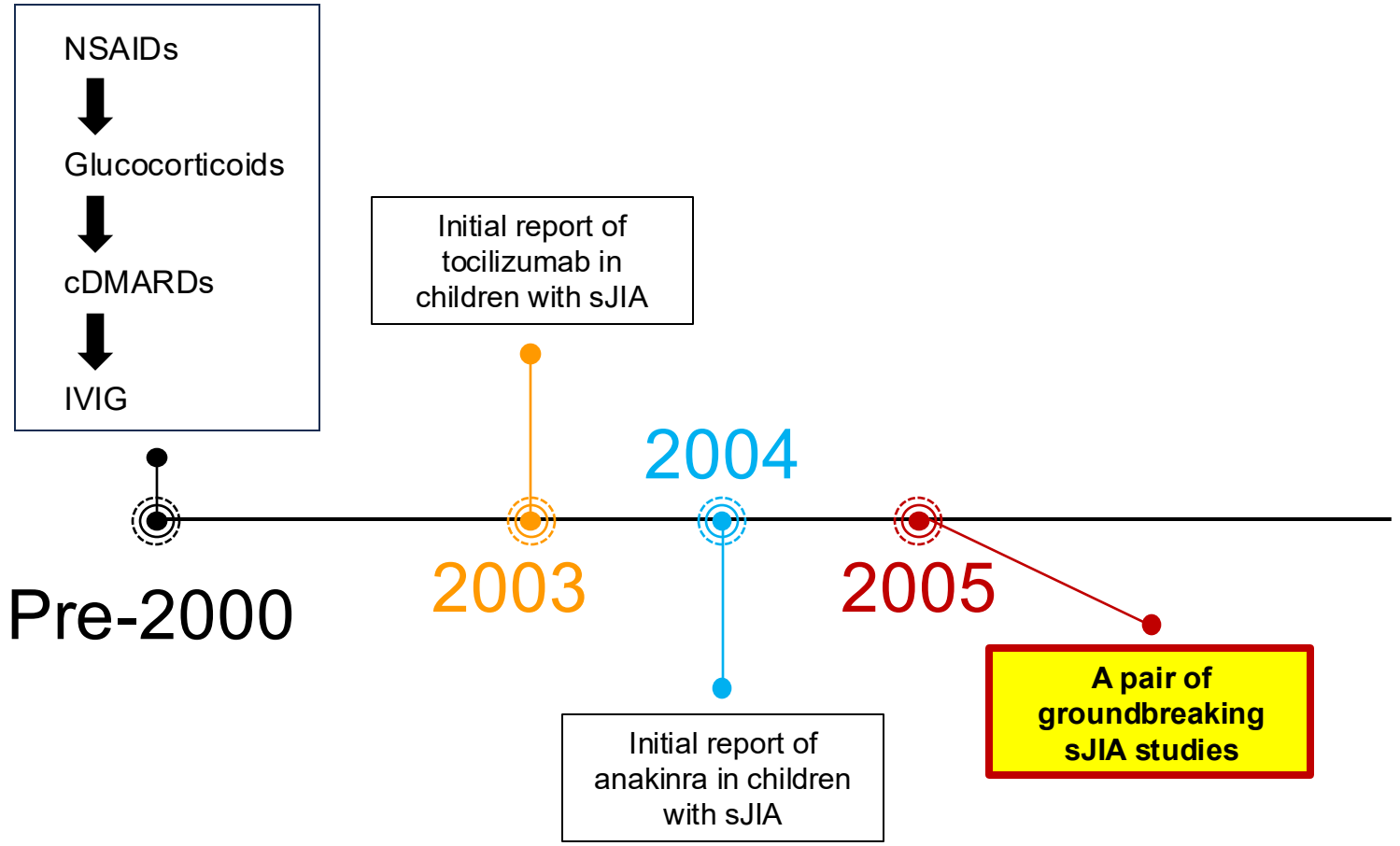


sJIA has a unique genetic architecture compared to other forms of JIA

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Ombrello MJ et al, 2017 (PMID 27927641)

Evolution of Still's disease therapy



National Institute of Arthritis and Musculoskeletal and Skin Diseases

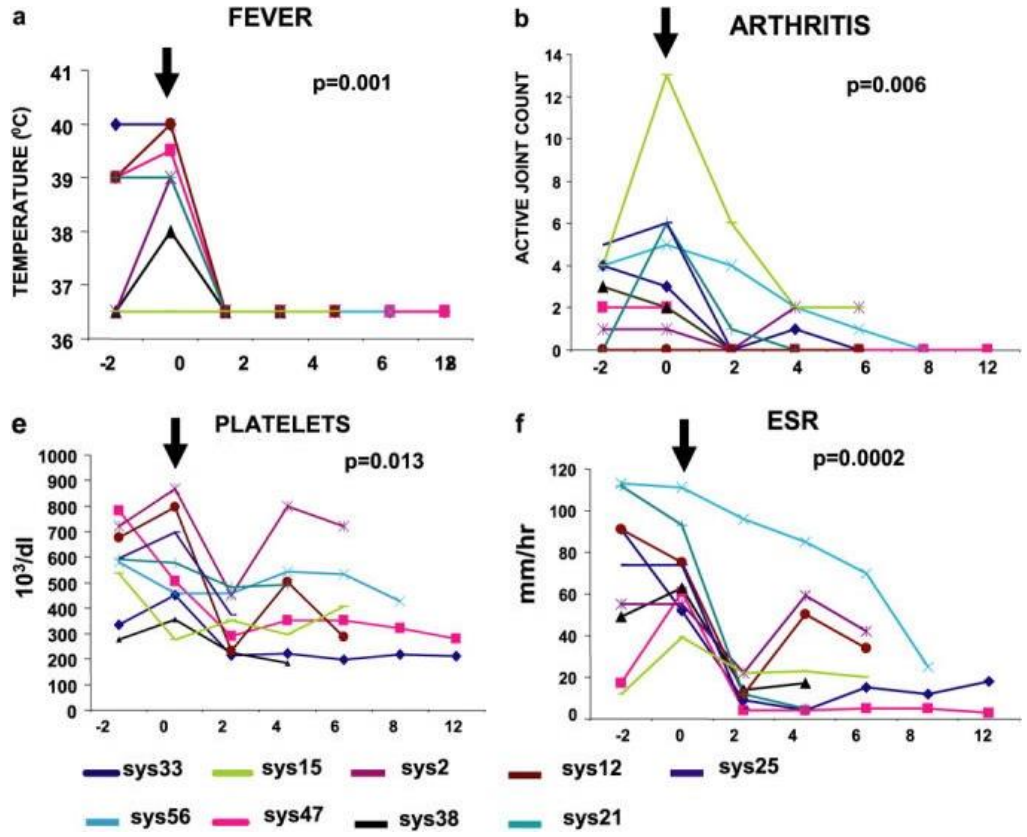
Cytokine inhibition in Still's disease

Interleukin-1β targeting therapy in Still's disease

1. **IL-1β is elevated in Still's disease**

2. **Landmark mechanistic rationale**
   - IL-1β transcriptional signal
   - Reciprocal induction of IL-1β ex vivo
   - Clinical proof of principle

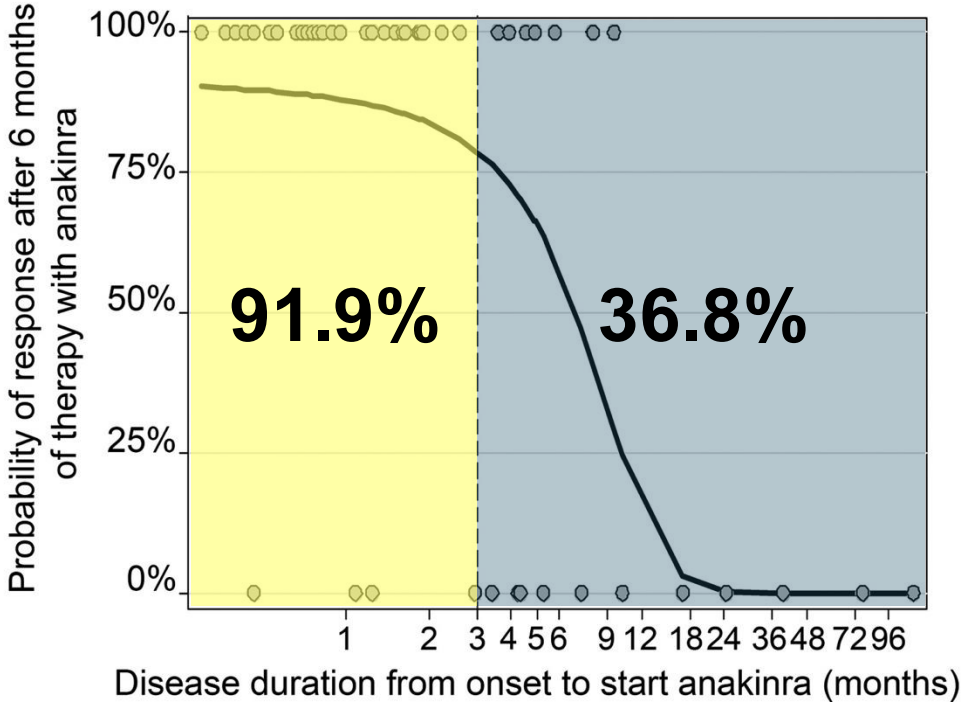
3. **Many clinical trials**
   - Observational >> RCT



Pascual V et al, 2005 (PMID 15851489

Anakinra in Still's disease

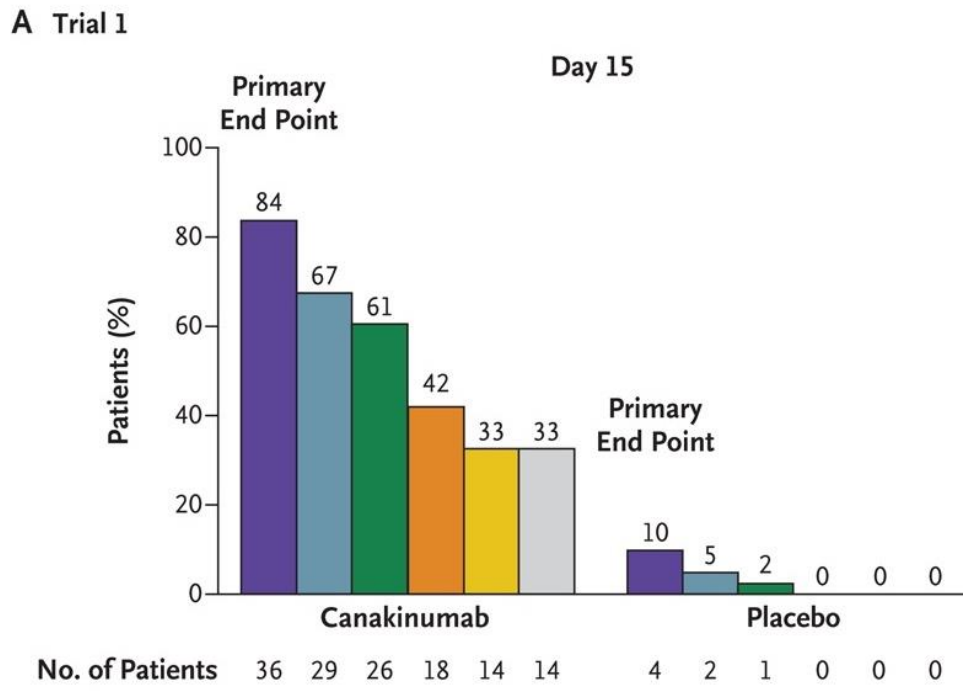
- Human recombinant IL-1Ra
- Highly effective, but not FDA approved
- AEs: Infection, injection site reaction, pruritic eruption, hepatic injury
- ***Early treatment improves prognosis***
- ***High expression IL1RN promoter variation may predict non-response***



Quartier P et al, 2010 (PMID 21173013)
Nigrovic PA et al, 2011 (PMID 21280009)
Vastert SJ et al, 2014 (PMID 24757154)
Vastert SJ et al, 2019 (PMID 31769856)
Pardeo M and Rossi MN et al, 2021 (PMID 33615724)
Arthur VL et al, 2018 (PMID 29609200)

Canakinumab in Still's disease

- Human IgG1 anti-IL-1β mAb
- Highly effective in clinical trials
- FDA approved in sJIA and AOSD
- AE: infections, MAS, injection site reactions, pruritic eruptions



National Institute of Arthritis and Musculoskeletal and Skin Diseases

Ruperto N et al, 2012 (PMID 23252526)
Ruperto N et al, 2012 (PMID 21953497)

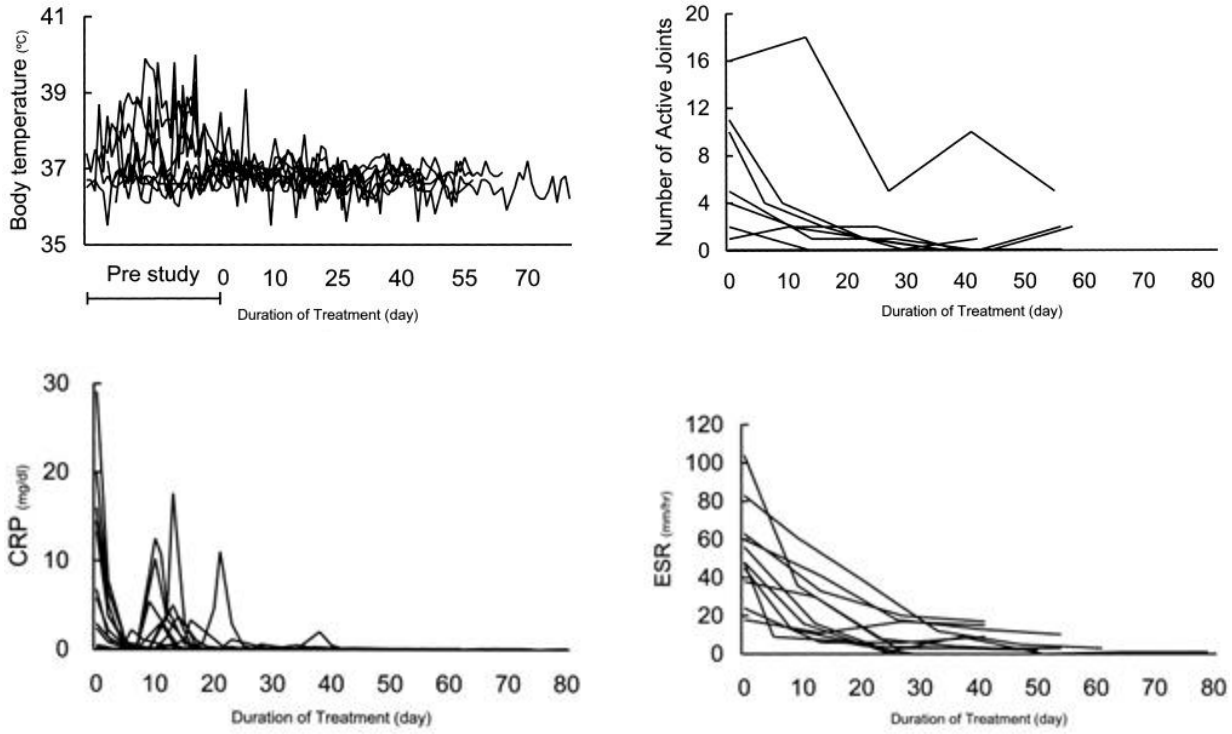
Cytokine inhibition in Still's disease

Interleukin-6 targeting therapy in Still's disease

1. **IL-6 is elevated in Still's disease**

2. **Strong clinical correlations with levels**
   - Fever, joint inflammation
   - CRP, ferritin
   - Clinical proof of principle

3. **Many clinical trials**
   - Observational
   - RCT

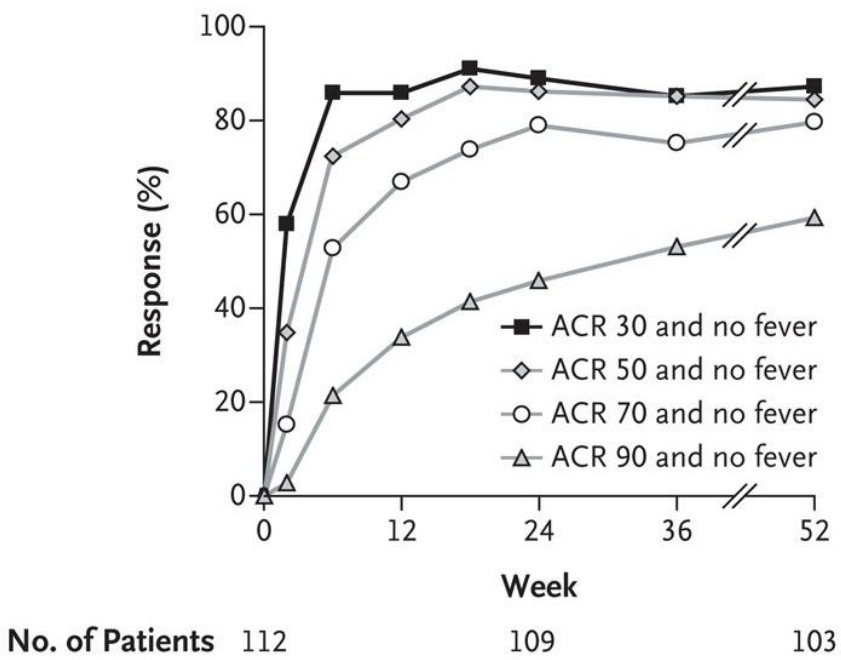


National Institute of Arthritis and Musculoskeletal and Skin Diseases

Yokota S et al, 2005 (PMID 15751095)

Tocilizumab in Still's disease

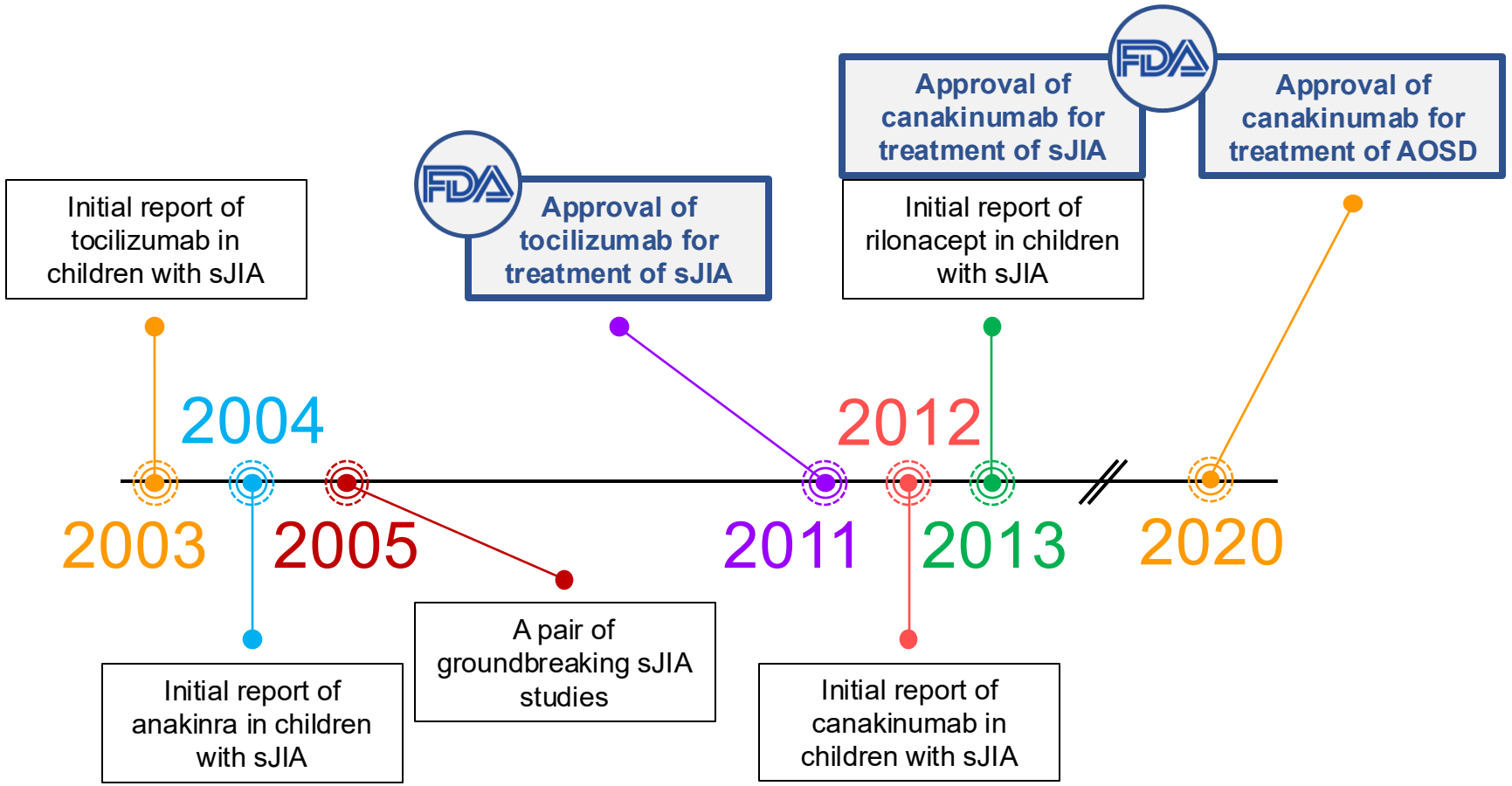
- Humanized IgG_1 anti-IL-6R mAb
- Highly effective in clinical trials
- FDA approval in sJIA
- AE: infection, MAS, elevated LFTs, anaphylaxis, hypercholesterolemia



National Institute of Arthritis and Musculoskeletal and Skin Diseases

Yokota S et al, 2008 (PMID 18358927)
De Benedetti F et al, 2012 (PMID 23252525)

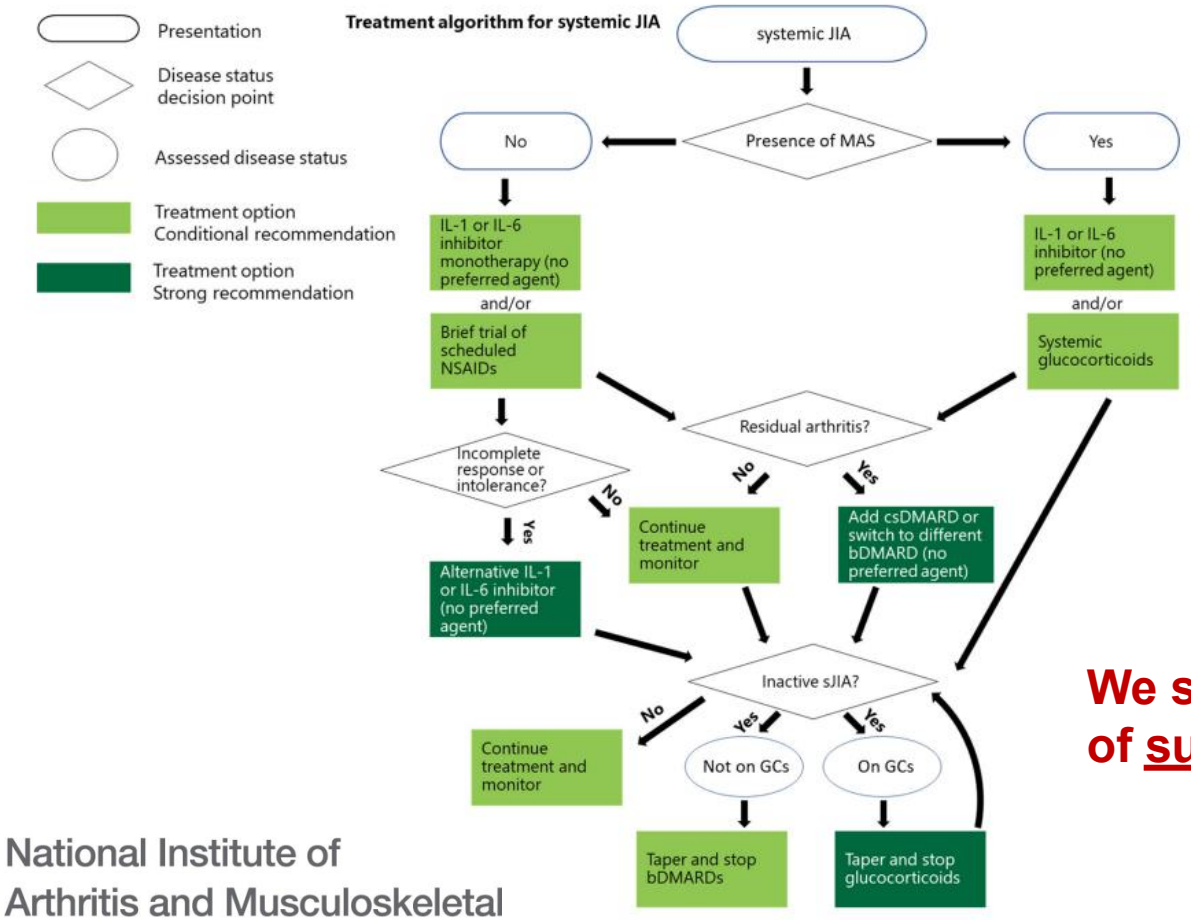
Evolution of Still's disease therapy



National Institute of Arthritis and Musculoskeletal and Skin Diseases

Treatment of Still's Disease

2021 ACR Guidelines for Management of sJIA



Summary of Recommendations

1. Brief NSAID monotherapy
2. Biologic DMARDS are priority
3. Minimize glucocorticoids

We should recalibrate our goal and treat to target of sustained, steroid-free clinical remission

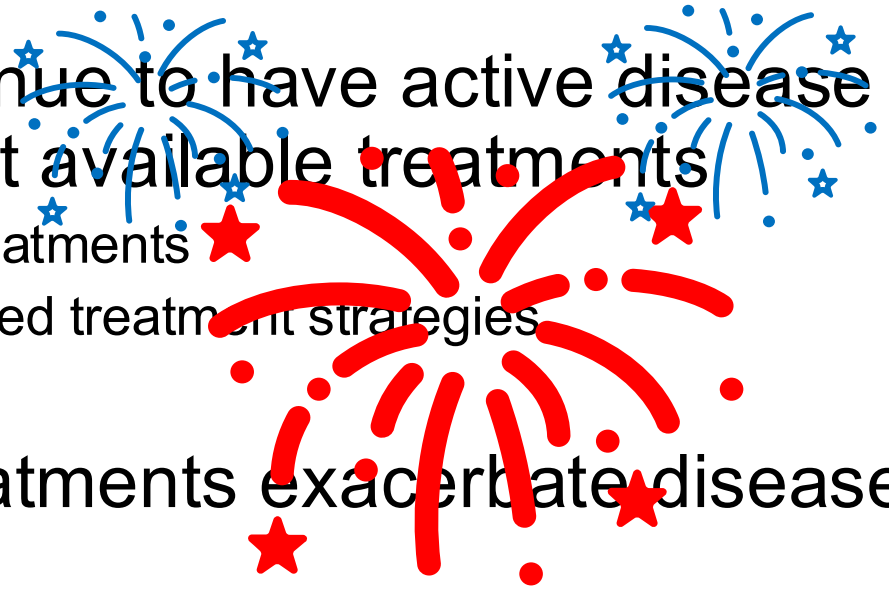
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Onel KB et al, 2022 (PMID 35233993)

Treatment of Still's Disease

Beyond clinical trials: real world experiences

- IL-1 and IL-6 blockade revolutionized Still's disease treatment
- Up to half continue to have active disease or require steroids despite the best available treatments
  - Need new treatments
  - Need optimized treatment strategies
- Sometimes treatments exacerbate disease activity



National Institute of Arthritis and Musculoskeletal and Skin Diseases

Janow G et al, 2016 (PMID 27307527)
Horneff G et al, 2017 (PMID29166924)
Ter Haar N et al, 2019 (PMID 30848528)
Saper VE*, Ombrello MJ* et al, 2022 (PMID 31562126)

Treatment refractory Still's disease

- **Chronic arthritis**
- **Recurrent MAS**
- **Lung Disease**

- Many never achieve sustained steroid-free clinical remission
  - 20-35% of Still's disease cannot achieve sustained remission
  - Over 50% of Still's disease cannot taper steroids

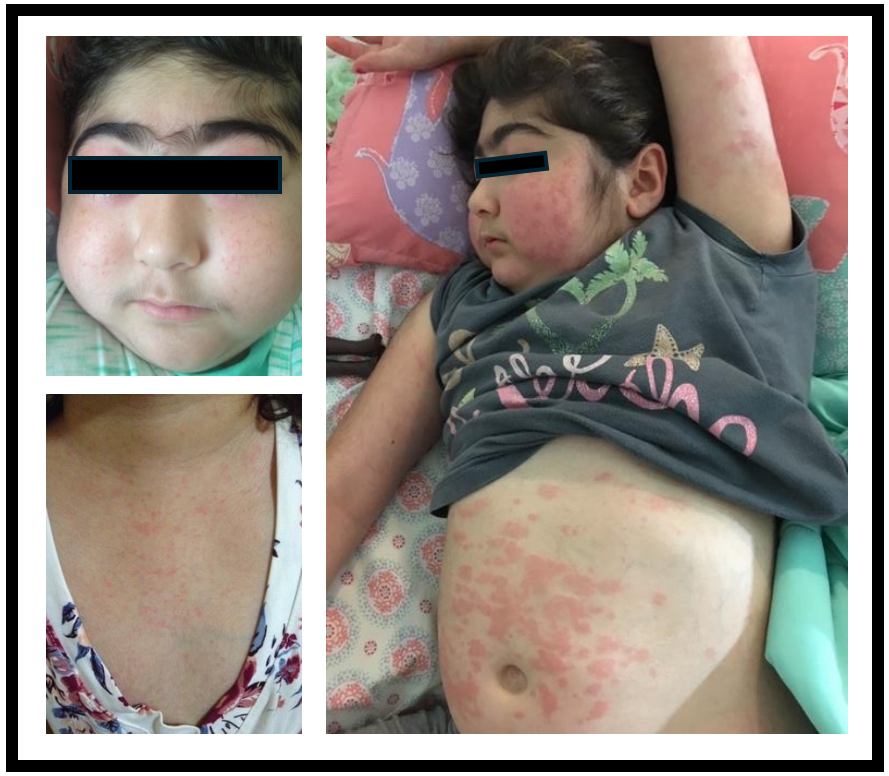
These cases highlight the need for new therapies and subtype-specific precision medicine approaches

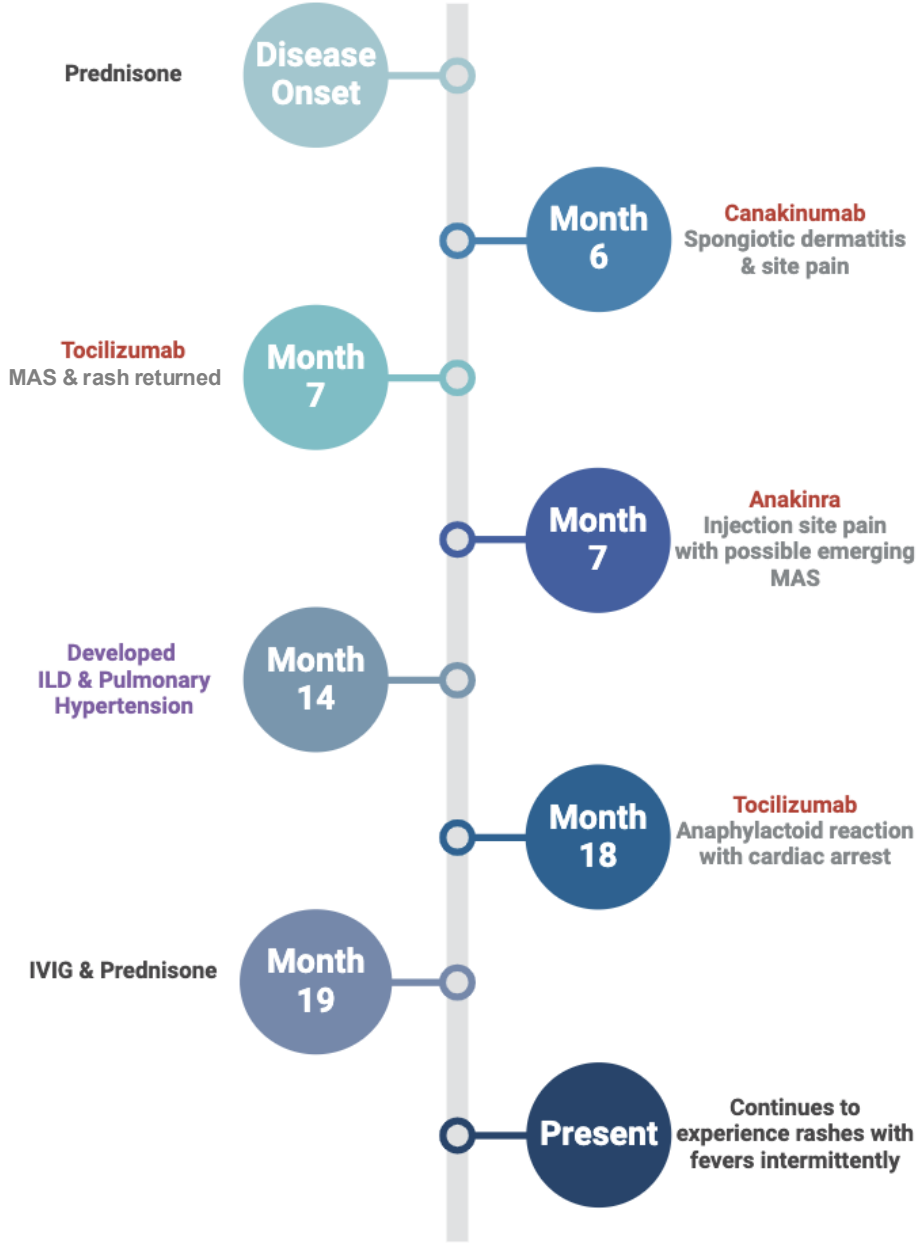
Erkens R et al, 2021 (PMID 34635293)
Ambler W et al, 2022 (PMID 35786149)
Foley CM et al, 2024 (PMID 37780048)
Ruscitti P et al, 2024 (PMID 38302170)

NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases

The Changing Face of Still's Disease

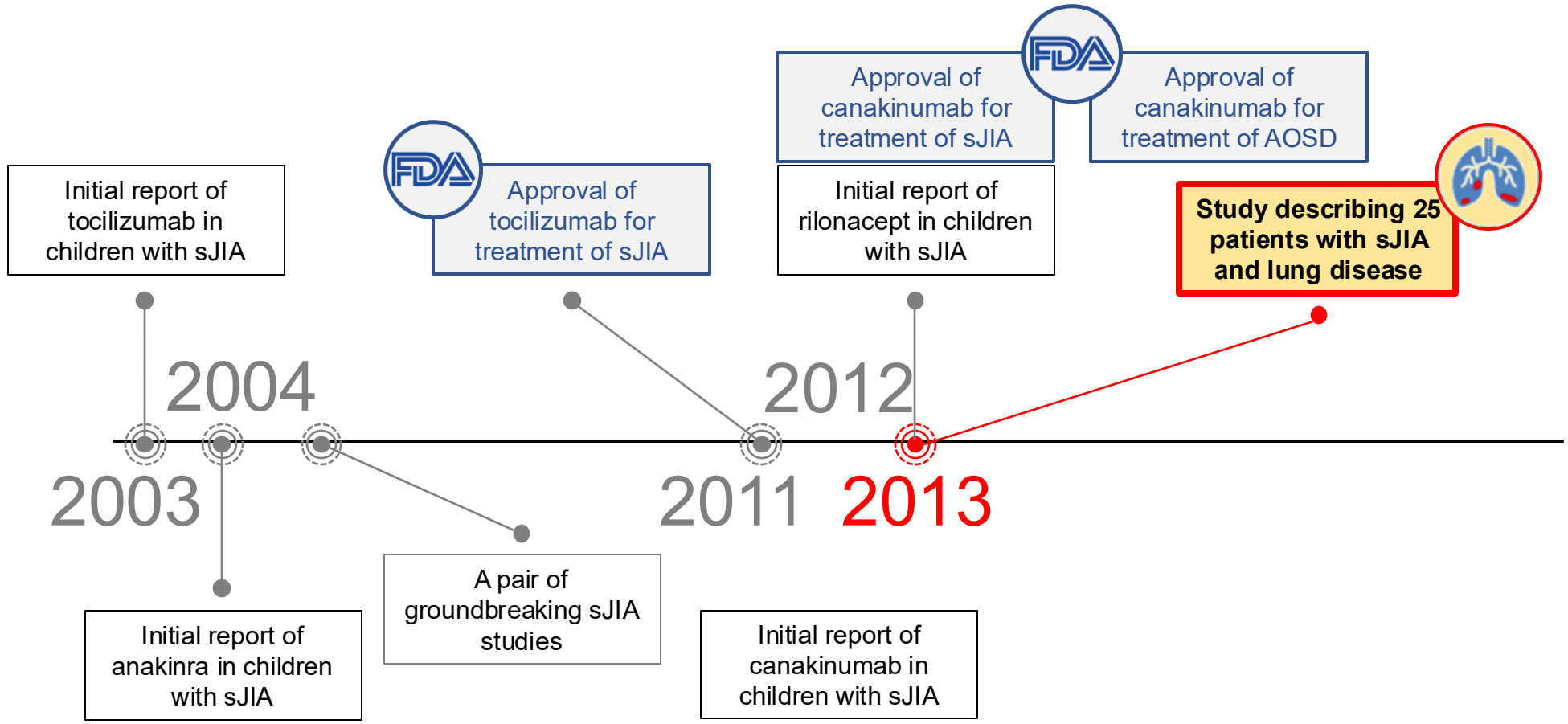
Case presentation





National Institute of Arthritis and Musculoskeletal and Skin Diseases

Emergence of Still's lung disease



National Institute of Arthritis and Musculoskeletal and Skin Diseases

Still's-associated lung disease

- **Series of sJIA with cardiopulmonary manifestations**
  - 6 had lung disease (PAP, ILD or both)
  - 12 had pulmonary arterial hypertension (PAH)
  - 7 had PAH & lung disease (PAP, ILD or both)

More severe disease (treatments, systemic symptoms)

88% had received IL-1 or IL-6 inhibition

Roughly 2X more than CARRA registry (n=389)

Kimura Y et al, 2013 (PMID 23139240)

Is Still's lung disease emergent?

Pediatric reports

Two singleton reports of PAH

- Primary PAH without parenchymal lung disease

Three singleton reports of PAP

- Two cases exposed to anakinra

Adult reports

Pleuritis and ARDS have been described

- "Parenchymal" LD, not PAP/ELP pattern

Two singleton reports of PAH

- Primary PAH without parenchymal lung disease

One singleton report of ILD

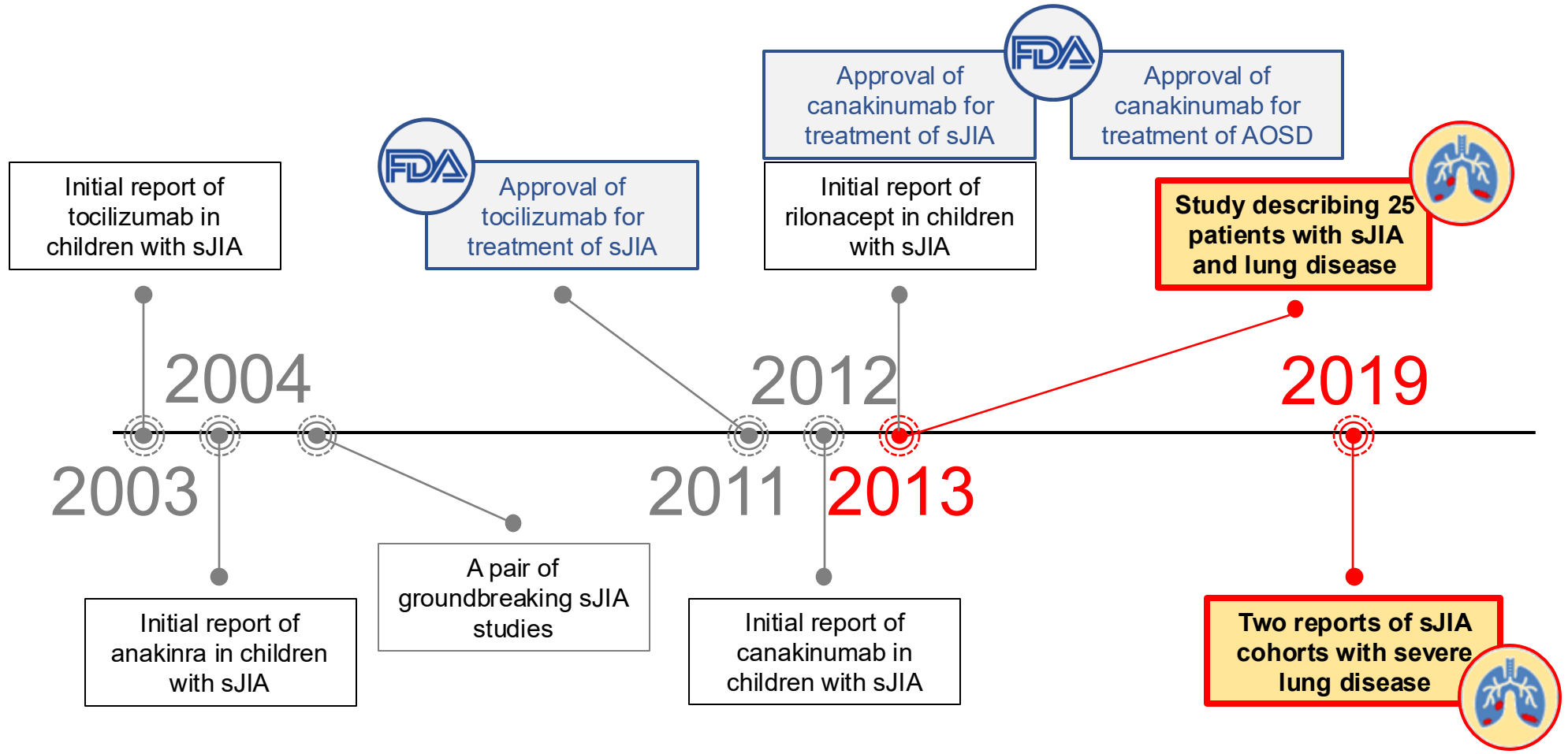
- PAP-like pattern

No other PubMed publications describing PAP/ELP-like lung disease or pulmonary hypertension in Still's disease until Kimura et al 2012.

Padeh S et al 1991 (PMID 1747143)
Schultz R et al, 2001 (PMID 11596165)
Nolan PK et al, 2005 (abstract CHEST 2005)
Weiss JE et al, 2008 (abstract ACR 2008)
Dharia S and Noe J, 2010 (doi:10.1378/chest.9858)
Zen A et al, 1990 (PMID 2377940)
Cheema GS and Quismorio FP, 1999 (PMID 27472698)
Van Hoeyweghen RJ et al, 1993 (PMID 8258247)
Mubashir E, et al 2007 (PMID 16871352)

NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases

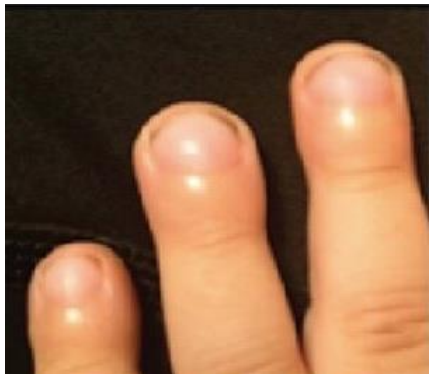
Emergence of Still's lung disease

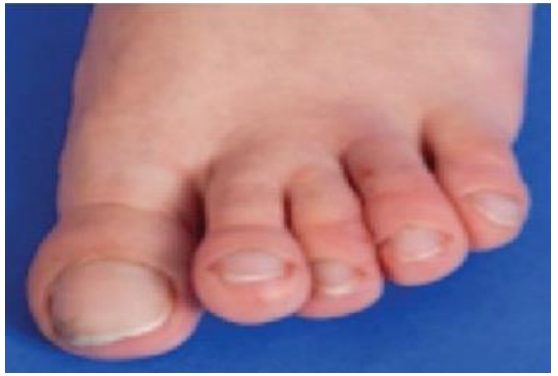


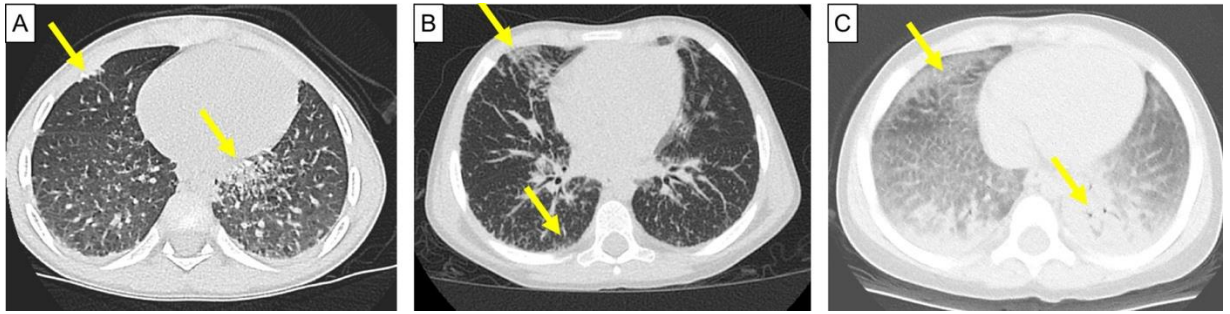
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Still's-associated lung disease

- Pulmonary Alveolar Proteinosis
- Unusual features
  - Eosinophilia
  - Atypical skin rash
  - Anaphylaxis to tocilizumab
  - Injection site reactions
- Risk factors
  - Young age (<2 years)
  - Trisomy 21
  - Recurrent MAS
  - High IL-18







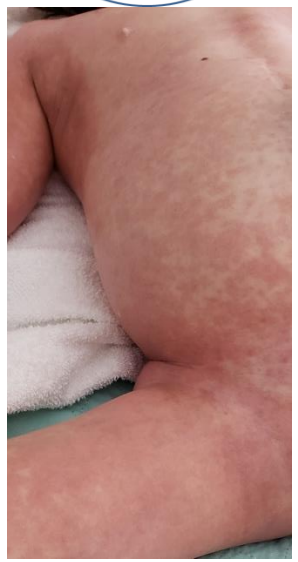
Initial cohorts had mortality > 50%

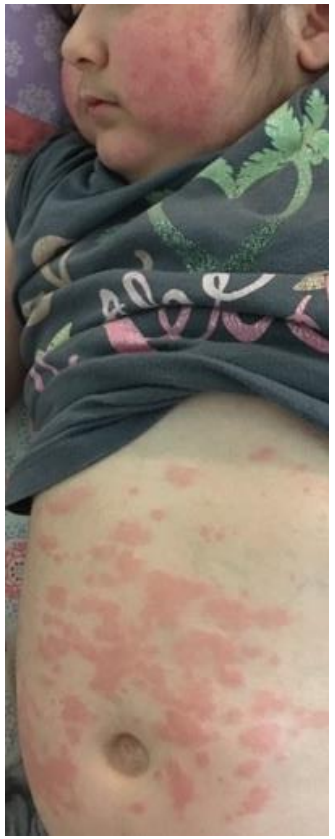
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Schulert GS et al, 2019 (PMID 31379071)
Saper VE et al, 2019 (PMID 31562126)

Still's-associated lung disease is associated with HLA-DRB1*15

47 Still's LD patients (42 sJIA, 5 AOSD)





HLA-DRB1*15 allele frequencies:

Still's-LD (0.82) vs. INCHARGE sJIA (0.26)

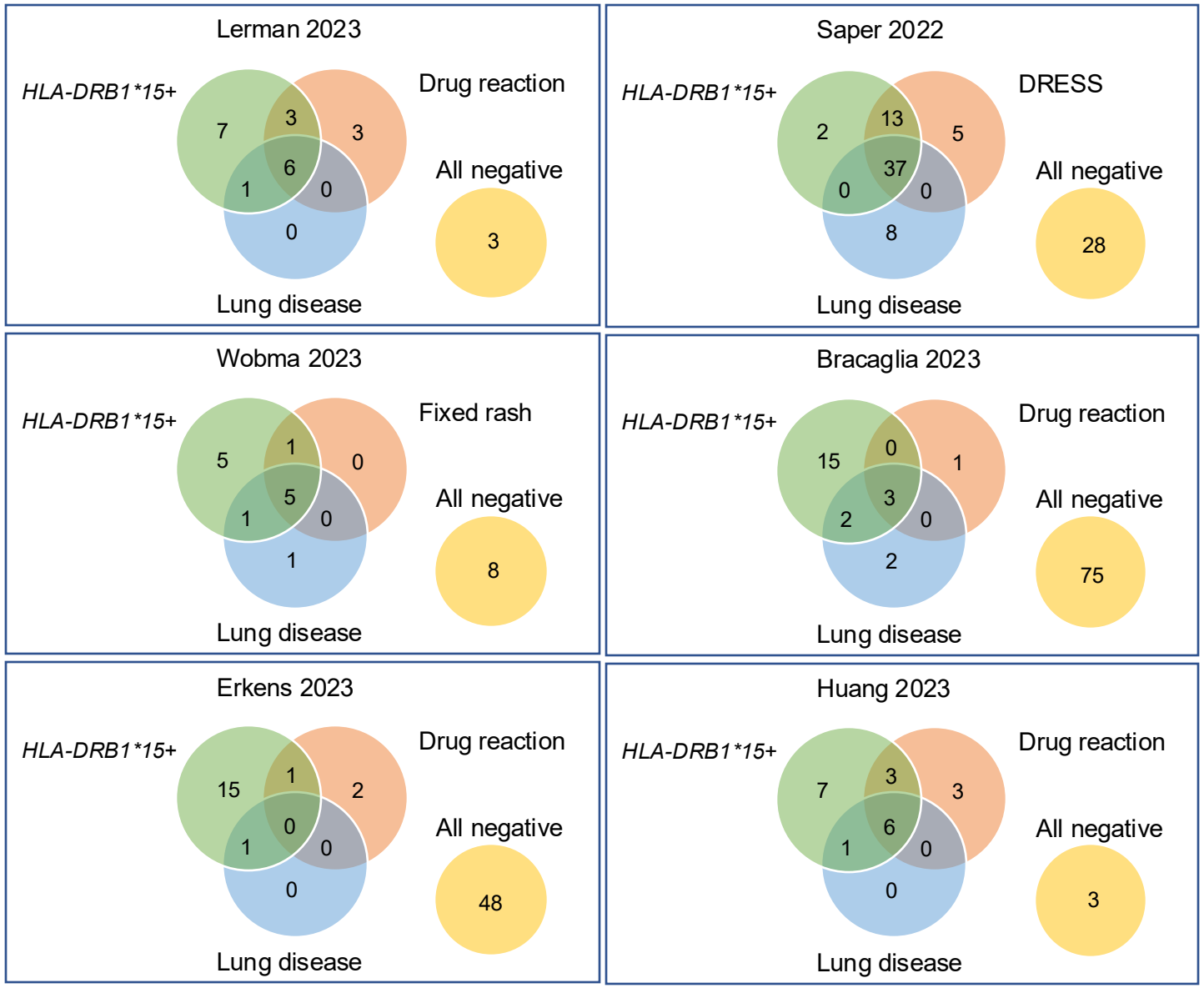
OR of 14.1 [6.4, 31]

Still's-LD (0.82) vs. "drug tolerant" sJIA (0)

OR 57.6 [11.5, 288]

NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases

Saper VS*, Ombrello MJ* et al, 2022 (PMID: 34789453)



National Institute of Arthritis and Musculoskeletal and Skin Diseases

HLA-DRB1*15 in Lung Disease: 77/92 (83.7%)

Still's-associated drug reactions (DRESS) associates with HLA-DRB1*15

18 Still's with drug reactions, no LD

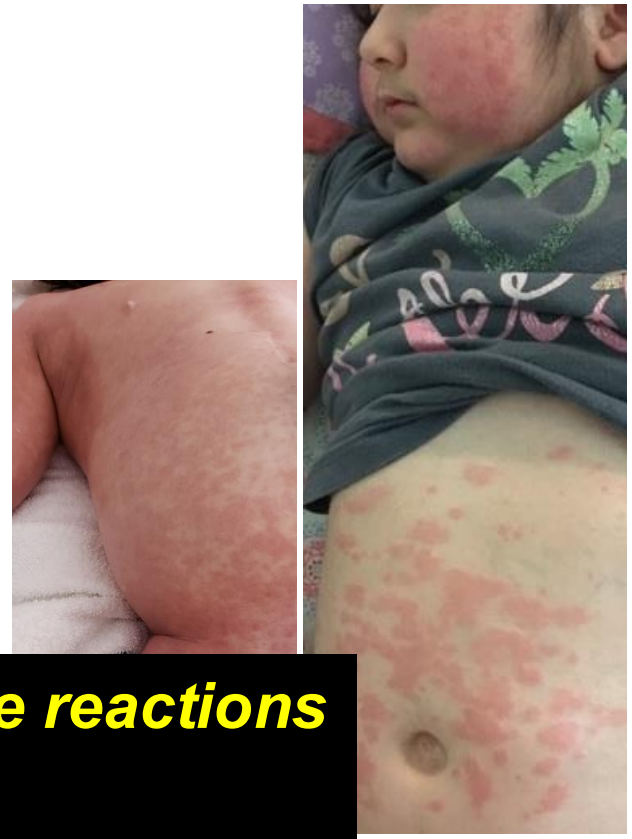
HLA-DRB1*15 allele frequencies:

Still's DR no LD (0.82) vs. INCHARGE sJIA (0.26)

OR 11.0 [4, 30.1]

Still's DR + LD (0.82) vs. "drug tolerant" sJIA (0)

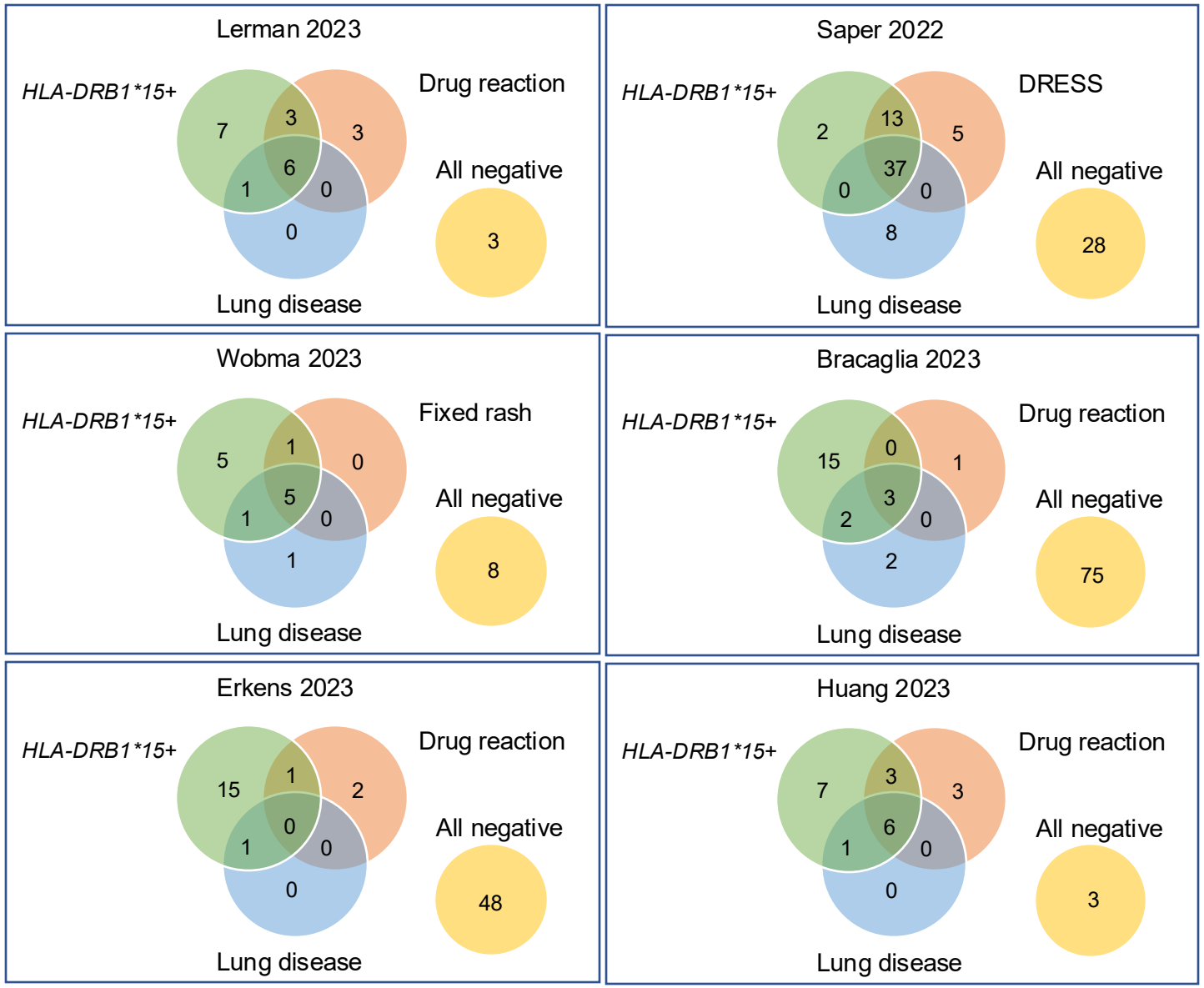
OR 54.9 [11.6, 261]



1. Unique combination of immediate and delayed-type reactions
2. Reactions induced by multiple different drugs
3. Reactions relatively specific to Still's disease

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Saper VS*, Ombrello MJ* et al, 2022 (PMID: 34789453)



National Institute of Arthritis and Musculoskeletal and Skin Diseases

HLA-DRB1*15 in drug reaction (surrogate): 78/92 (84.8%)

The changing face of Still's disease

More than lung disease…

- **Schulert 2013** "adverse reactions to biologic therapy" or "immune-mediated reactions"
- **Saper 2013:** "atypical features" or "unusual clinical features"
- **Saper and Ombrello 2022:** "Hypersensitivity" or "DRESS"
- Binstadt and Nigrovic 2022 (accompanying editorial)
    - *Not DRESS, what about a compensatory cytokine shift?*

Schulert GS et al, 2019 (PMID 31379071)
Saper VE et al, 2019 (PMID 31562126)
Saper VS*, Ombrello MJ* et al, 2022 (PMID: 34789453)
Binstadt B, Nigrovic P 2022 (PMID 35413159)

What connects HLA-DRB1*15 with Still's LD and drug reactions?

- ***Coexistent LD and drug reaction with shared HLA association suggests shared pathophysiology, but a specific mechanism unclear***
  1. Reaction to the drug (active ingredient)
  2. Reaction to the drug (not active ingredient)
  3. Still's disease-specific compensatory shift (biologic effect of drug)
  4. Related to viral infection, exogenous modifier or new exposure
  5. Related to another gene co-inherited on DR15 haplotype
  6. Something beyond the bounds of my imagination

Imperfect screening tool →
but is it better than running blind?

Still's LD with DAIR in adults associates with HLA-DRB1*15

- **AOSD cases with cardiopulmonary manifestations**
  - 16 had PAH, 12 with coexistent LD (PAP or ILD)
  - *Only 1 case developed before 2010*

Compared 16 PAH to 111 AOSD patients:

Female sex	**100%** vs 67%
MAS	**62.5%** vs 14.4%
Eosinophilia	**69%** vs 7%
Drug reactions	**38%** vs. 7%
Mortality	**37.5%** vs 0.9%
HLA-DRB1*15	**73%** vs. 30%

NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases

Boucly A et al, 2025 (PMID 40379524)

How can we predict who will develop Still's-LD?

Predictive clinical features?

- Macrophage activation syndrome (after starting meds)?
- Early age of onset (in children)?
- Eosinophilia?
- Drug reactions?

How should we treat new Still's disease? How do we screen?

Boston Children's Hospital sJIA Pulmonary Screening Algorithm

Baseline cardiac and pulmonary evaluation
Check red flags (including HLA typing)
Treat with IL-1 or IL-6 directed therapies
Careful monitoring Q6 months
If they develop it, consider more aggressive therapy
~~***No recommendation to stop or avoid*~~

We disagree

Wobma H et al, 2023 (PMID 37688362)

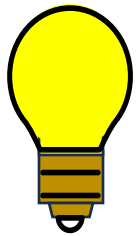
Does Still's LD improve if IL-1/IL-6 inhibitors are discontinued?

Observation	Stopped inhibitor group (n = 52)	Continued inhibitor group (n = 37)	P-value
Pulmonary complication at first reaction	75% (39/52)	76% (28/37)	NS
Resolution of pulmonary complications	67% (26/39)	**0%** (0/28)	$p = 1.5 \times 10^{-8}$
Survival / mortality improvement	8% (4/52)	41% (15/37)	p = 0.005 (MV regression)
Rates of macrophage activation syndrome (MAS) while on inhibitor	51 in 29,295 person-days	36 in 28,511 person-days	p = 0.169
Rates of macrophage activation syndrome (MAS)	Pre-stop: 51 in 29,295 Post-stop: 1 in 19,441		p < 0001 RR 33.8 (95% CI 5.81–1363)

National Institute of Arthritis and Musculoskeletal and Skin Diseases

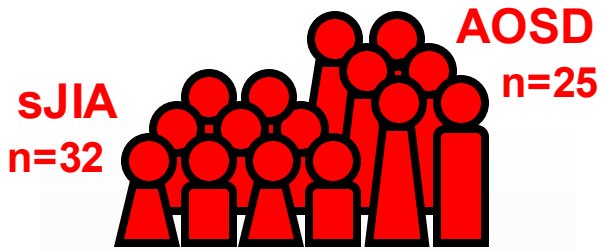
Saper VE et al, 2024 (PMID 39002722)

We need a biomarker to identify or predict lung disease and drug reactions in Still's disease?



Type I interferon signature?

Study Design



Consecutive Still's disease patients

Measure whole blood ISG expression (ISG-28 score)

Custom Nanostring nCounter Assay

Stratify patients by ISG-28 score

Compare top ISG-28 quartile with larger population

1. *Demographics and features (Age, sex, treatments, HLA-DRB1*15)*
2. *Historical complications (MAS, DHR, LD)*
3. *Candidate genes (with rare recessive, X-linked or de novo variants)*

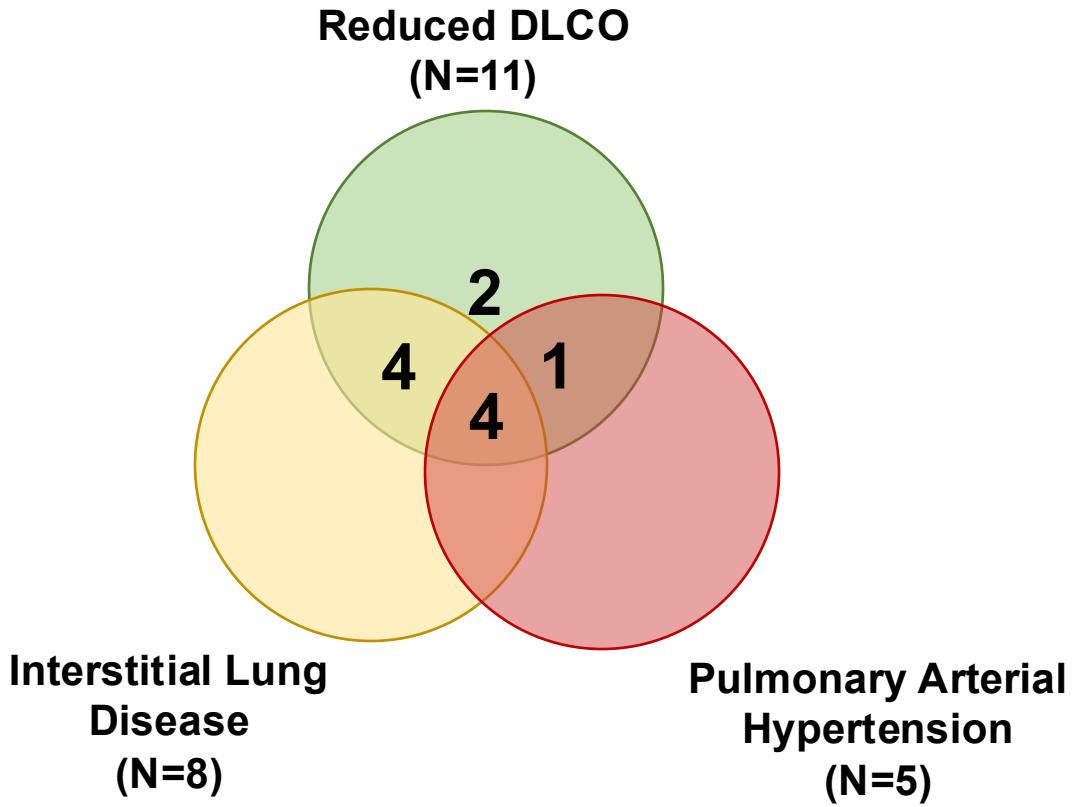
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Correia Marques M et al. in revision

Still's-associated lung disease in NIH Still's disease cohort

Still's Lung Disease	n (of 11)
Interstitial Lung Disease	4
Pulmonary Arterial Hypertension	1
ILD + PAH	4
Isolated reduction in DLCO	2

19% of cohort have lung disease

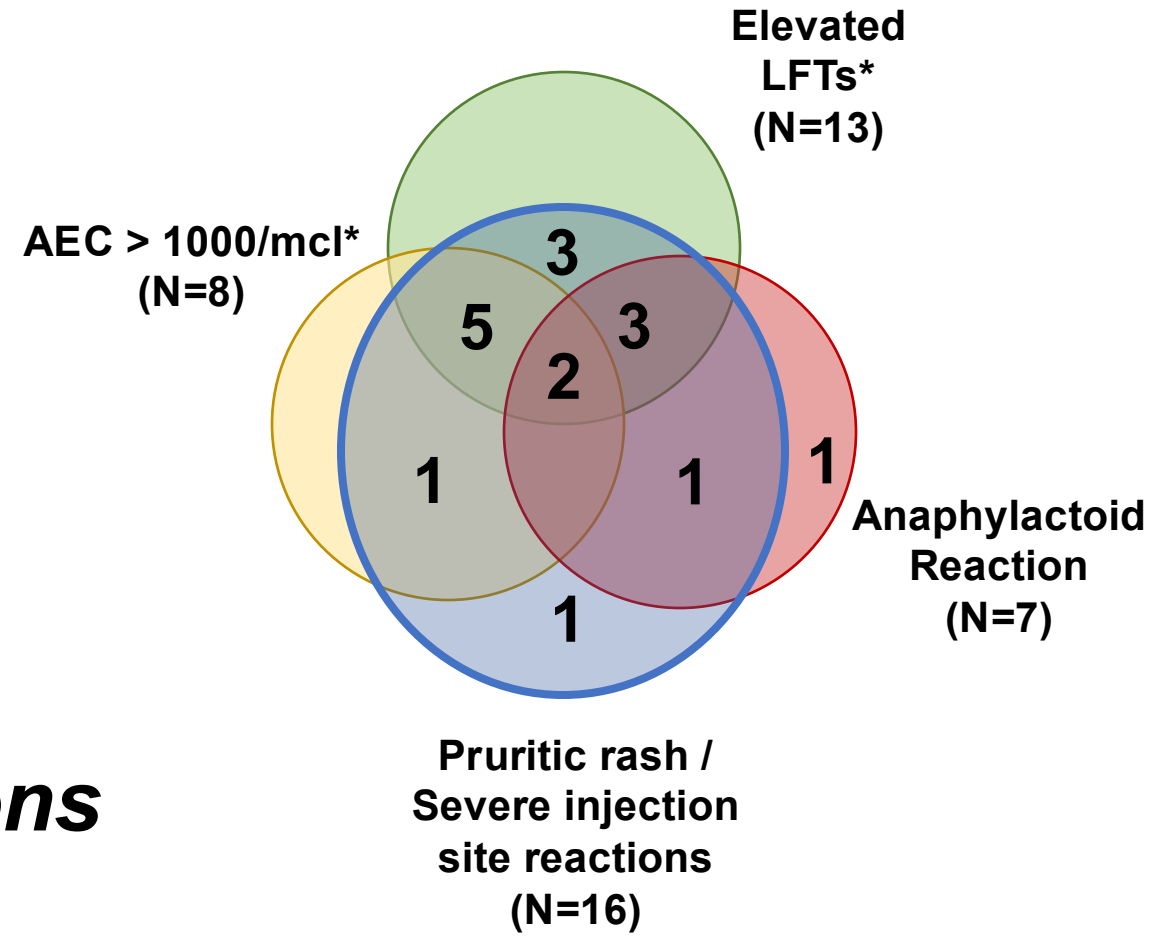


National Institute of Arthritis and Musculoskeletal and Skin Diseases

Correia Marques M et al. in revision

Drug-associated immune reactions in NIH Still's disease cohort

Hypersensitivity	n (of 17)
Pruritic rash	16
Elevated LFTs > 2.5x ULN	13
Peripheral eosinophilia > 1K	8
Anaphylactoid reaction	7
Two or more above features	15
MAS with med change	***12***

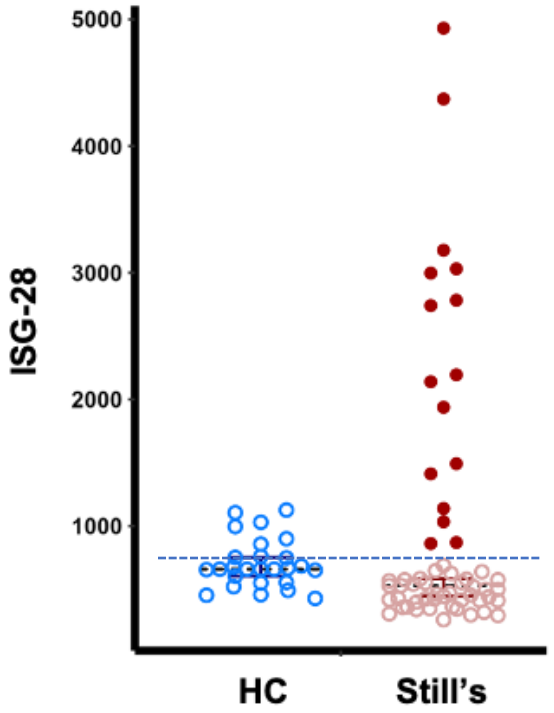


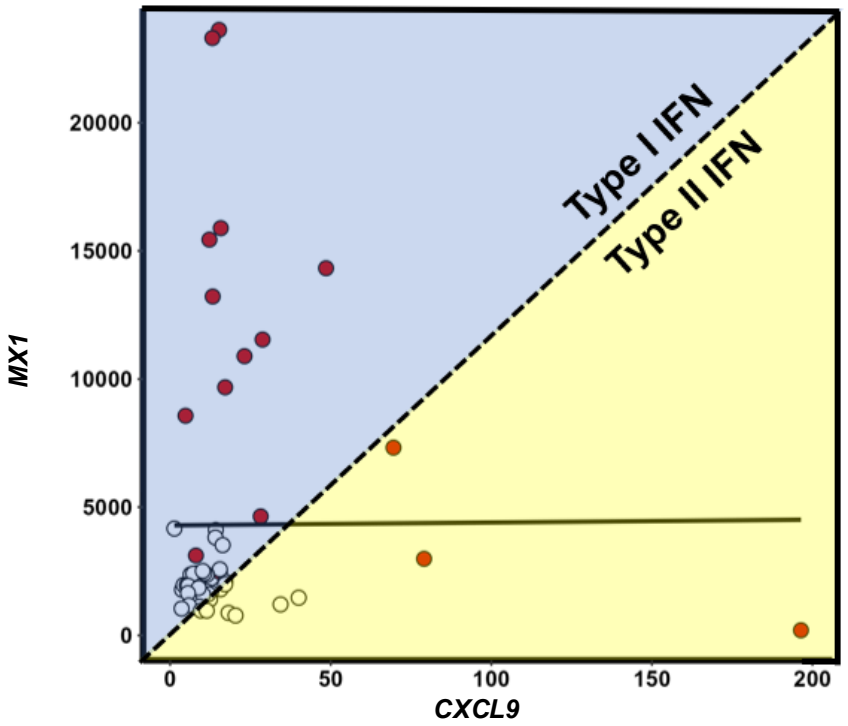
30% of cohort had drug-associated immune reactions

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Correia Marques M et al. in revision

IFN signature in NIH Still's cohort

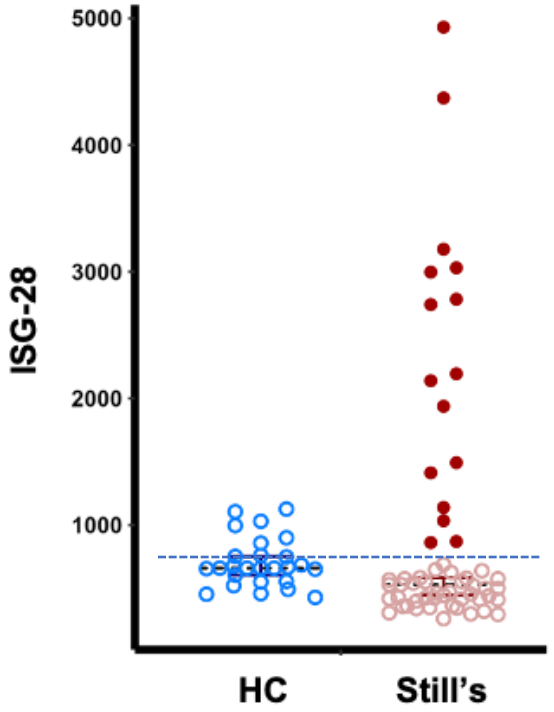




National Institute of Arthritis and Musculoskeletal and Skin Diseases

Correia Marques M et al. in revision

IFN signature in NIH Still's cohort



High ISG-28 score did not associate with

1. Disease activity
2. IL-18 levels
3. Any specific treatments

High ISG-28 score correlated with

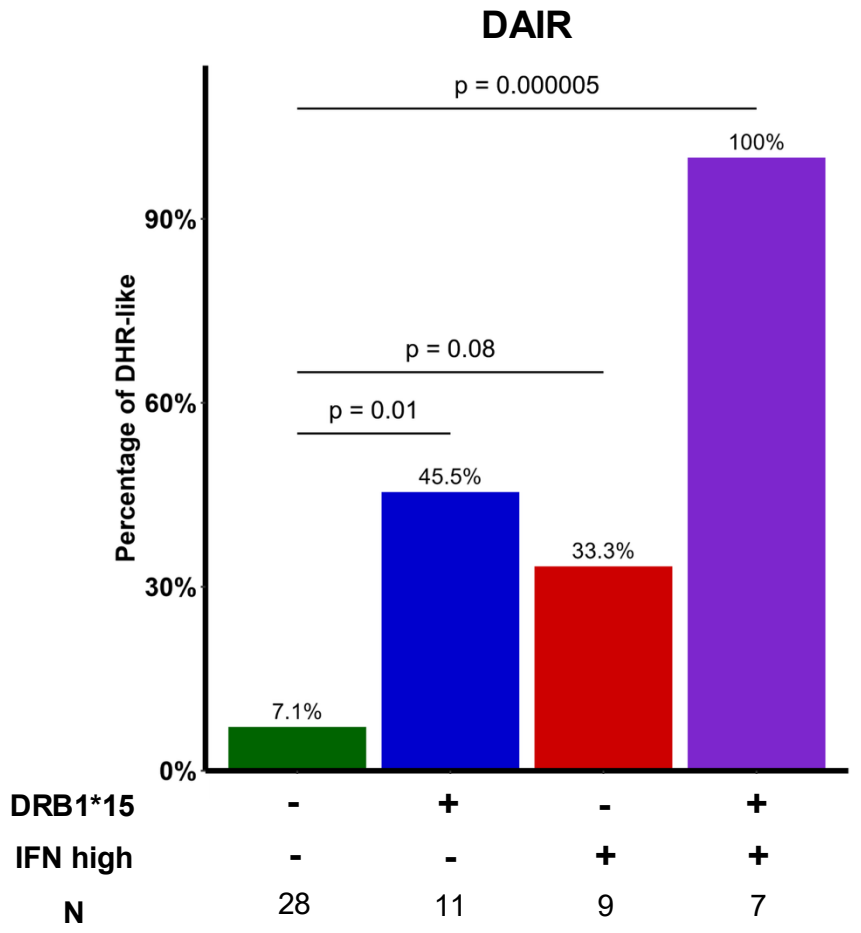
1. Lung disease
2. Drug reactions

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Correia Marques M et al. in revision

High ISG-28 Score + HLA-DRB1*15 Identify Highest and Lowest Risk DAIR Subgroups

	DR15+	IFN high	DR15+ & IFN high	DR15+ or IFN high
Sens.	0.71	0.59	0.41	0.88
Spec.	0.84	0.84	1.00	0.68
PPV	0.67	0.63	1.00	0.56
NPV	0.86	0.82	0.79	0.93

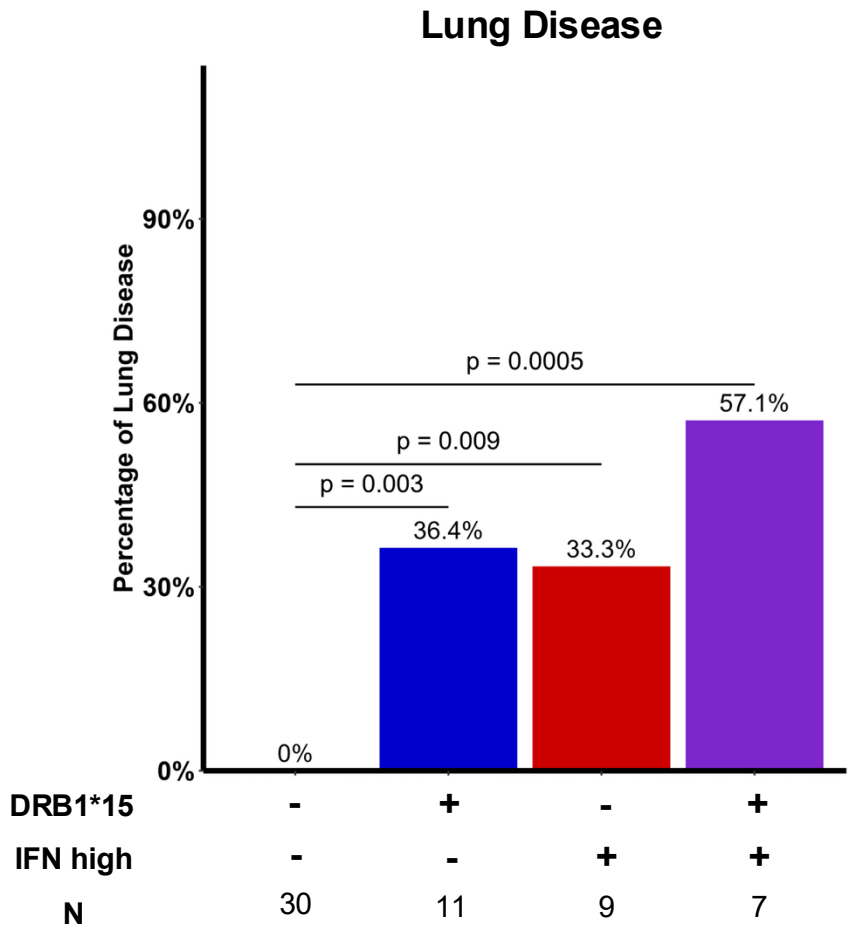


National Institute of Arthritis and Musculoskeletal and Skin Diseases

Correia Marques M et al. in revision

High ISG-28 Score + HLA-DRB1*15 Identify Highest and Lowest Risk LD Subgroups

	DR15+	IFN high	DR15+ & IFN high	DR15+ or IFN high
Sens.	0.73	0.64	0.36	1.00
Spec.	0.78	0.80	0.93	0.65
PPV	0.44	0.44	0.57	0.41
NPV	0.92	0.90	0.86	1.00

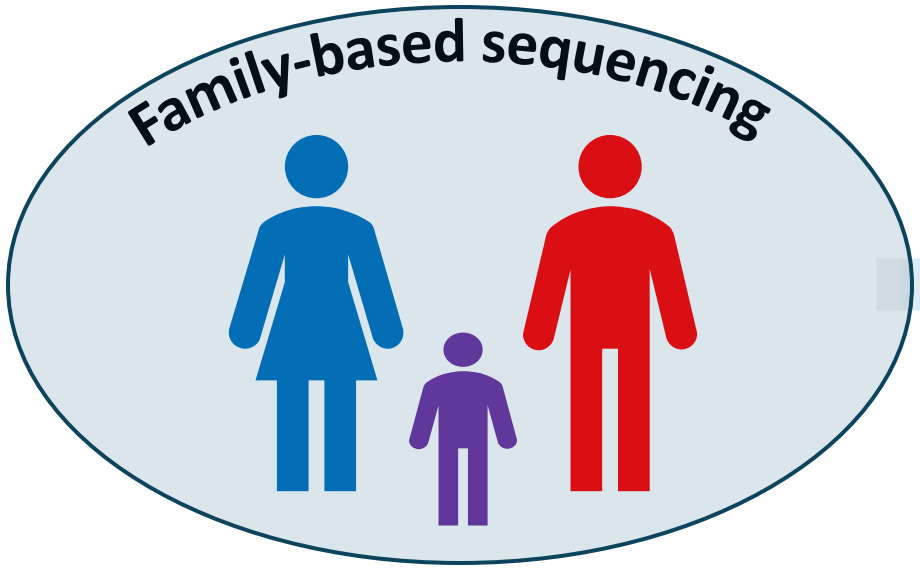


National Institute of Arthritis and Musculoskeletal and Skin Diseases

Correia Marques M et al. in revision

IFN signature in Still's disease

Is there a genetic contribution?



41 Still's disease trios

MAF < 0.01 in all reference populations

High ISG-28 score (16)
13 *de novo* variants
16 X-linked variants
63 recessive variants

Non-high ISG-28 (n=25)
13 *de novo* variants
12 X-linked variants
56 recessive variants

Pathway enrichment?

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Correia Marques M et al. in revision

GSEA of candidate genes from Still's disease with high IFN score

Gene Set	Description	Enrichment Ratio	P Value	FDR
GO:0031347	Regulation of defense response	4.0	1.05E-05	0.013
GO:0006954	Inflammatory response	3.7	2.12E-05	0.017
GO:0006914	Autophagy	4.2	6.27E-05	0.029
GO:0042116	Macrophage activation	10.4	1.21E-04	0.038
GO:0007010	Cytoskeleton organization	2.6	1.27E-04	0.040
GO:0140895	Cell surface toll-like receptor signaling pathway	13.0	2.52E-04	0.052
GO:0032606	Type I interferon production	9.0	2.44E-04	0.052

No enrichment in non-high ISG-28 group

NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases

Correia Marques M et al. in revision

How should we treat this endotype?

- **Stop medications linked with DAIRs**
- **Published case report and series using JAKi**
  - 8 French cases of sJIA with LD
  - 4 with clinical remission (2 off steroids)
  - 2 went on to BMT, 1 died, 1 partial response
- **Based on our observations and experience**
  - High dose steroids with slow taper + JAK inhibition
  - Type I IFN blockade, mTOR inhibition?
  - Allogeneic transplant?

Bader-Meunier B, et al, 2022 (PMID 32054604)
Côte G et al, 2024 (PMID 39447041)

OMBRELLO'S TOP TEN: TAKE HOME POINTS ABOUT STILL'S DISEASE IN 2025

10. Still's disease is the same condition in children and adults
9. Early treatment of Still's disease leads to better long-term outcomes
8. Still's disease is unique and drug repurposing is unsuccessful
7. IL-1 and IL-6 directed therapies are highly effective in many patients
6. Life-threatening LD and DAIR to IL-1/IL-6 inhibitors develop in some patients
5. HLA-DRB1*15 alleles is the strongest risk factor for Still's LD and DAIR
4. Discontinuing IL-1/IL-6 directed may improve clinical outcomes in Still's-LD
3. JAKi is promising in refractory Still's disease, but novel therapies are needed
2. Careful screening and early recognition of Still's LD are critical
1. We need to work together to better understand and treat Still's disease

NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases

How can we improve the care of people with Still's disease?

Make partnerships and work together

- **Pediatric and adult rheumatologists**
- **On the regional, national and international level**

I want to improve the care of Still's disease and I want to partner with you!

Michael.Ombrello@nih.gov
Office phone: (301) 435-4037
Cell phone: (301) 768-8066

NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases

Acknowledgements

Translational Genetics and Genomics Section, NIAMS

Mariana Correia Marques, MD
Krisztian Csomos, PhD
Dale Kobrin, MD
Paul Panipinto, PhD
Anthony Cruz
Emily Rosenbaum
Aditi Kodali
Hiroto Nakano, MD PhD
Kathleen Baysac, PhD
Ann Marie Szymanski, MD
Navid Choudhury, MD
Victoria Arthur, PhD
Chris Felicelli, MD
Alexis Bailey, MD
Andrew Patt, PhD
Brooke Boyd
Mallika Datta
Elizabeth Schmitz
Alana Platukus
Hannah Marcy
Danielle Rubin
Charles Fisher
Emily Shuldiner
Elizabeth Baskin

Office of the Clincal Director, NIAMS

Michelle Millwood
Carol Lake
Ly-Lan Bergeron
Estefania De Los Santos

Biodata Mining Section, NIAMS

Zuoming Deng, PhD
Stephen Brooks, PhD

Inflammatory Disease Section, NHGRI

Amanda Ombrello, MD
Elaine Remmers, PhD
Daniel Kastner, MD PhD

University of Cincinnati/ CCHMC

Grant Schulert, MD PhD
Alexei Grom, MD PhD

Stanford University

Elizabeth Mellins, MD PhD
Vivian Saper, MD

Children's Hospital of Philadelphia

Scott Canna, MD

University of California San Francisco

Jill Hollenbach, PhD

Boston Children's Hospital

Lauren Henderson, MD

INCHARGE Consortium

Jordi Anton, MD PhD
John Bohnsack, MD
Dirk Föll, MD
Marco Gattorno MD
Alexei Grom, MD
Johannes-Peter Haas MD PhD
Cladio Len MD
Alberto Martini MD
Kirsten Minden, MD
Elizabeth Mellins MD
Sheila Oliviera, MD PhD
Seza Ozen, MD PhD
Sampath Prahalad, MD
Elaine Remmers, PhD
Angela Rosen-Wolff, MD PhD
Alan Rosenberg, MD
Klaus Tenbrock, MD
Susan Thompson, PhD
Wendy Thomson, PhD
Lucy Wedderburn, MD PhD
Patricia Woo, MBBS PhD
Rae Yeung, MD PhD

We appreciate the selfless contributions of our patients and their families to our studies of sJIA and AOSD.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

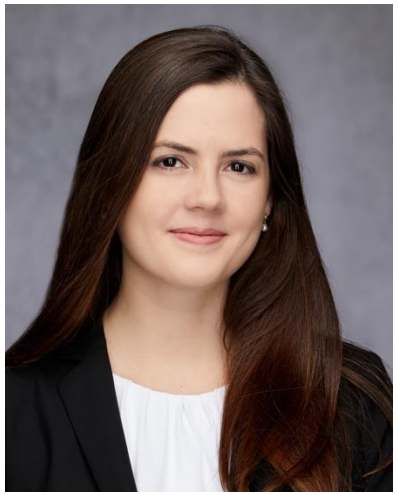
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Still's disease Clinical Team

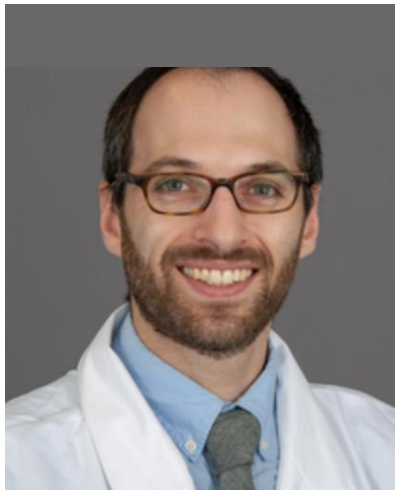
Michelle Millwood, BSN
Research Nurse

Carol Lake, FNP
Nurse Practitioner

Ly-Lan Bergeron, PA
Physician Assistant



Mariana Correia Marques, MD
Lawrence Shulman Scholar in Translational Research



Dale Kobrin, MD
Rheumatology Fellow

Estefania De Los Santos
Patient Care Coordinator

Thank you for your attention!

I want to improve the care of Still's disease and I want to partner with you!

Michael.Ombrello@nih.gov
Office phone: (301) 435-4037
Cell phone: (301) 768-8066

NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases