Rheumatoid Arthritis (RA)
Pathogenesis, Prediction and Prevention

DOM Grand Rounds

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Disclosures

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Investigator initiated research grants and consulting with Inova and Janssen

Investigator initiated research grants with Pfizer

Consulting with ThermoFisher and Microdrop

Demoruelle

Investigator initiated research funding from Pfizer

Evidence-based reviews

Rheumatoid arthritis: pathogenesis, prediction and prevention – an emerging paradigm shift. Deane KD, Holers VM. Arthritis Rheumatol 2020

Rheumatoid arthritis and the mucosal origins hypothesis: protection turns to destruction. Holers VM, Demoruelle MK, Kuhn KA, Buckner JH, Robinson WH, Okamoto Y, Norris JM, Deane KD. Nat Rev Rheumatol. 2018

Primary Goal

Leave you with enthusiasm that within the next few years, rheumatology will be taking 'new' Intent to Prevent* approaches for RA

Overview

Pathogenesis

Prediction

Prevention

Opportunities and challenges, and progress

*Marvin Fritzler, Univ of Calgary

What is RA?

- Systemic, autoimmune disease
- INFLAMMATORY ARTHRITIS (IA) as hallmark
- AUTOANTIBODIES in ~80% of individuals with RA

Pathogenic, diagnostic, prognostic

~1% prevalence

~3 to 1 female to male

~Up to 8% in high-risk populations e.g. first-degree relatives, Indigenous North American populations

Smolen et al. Lancet 2016

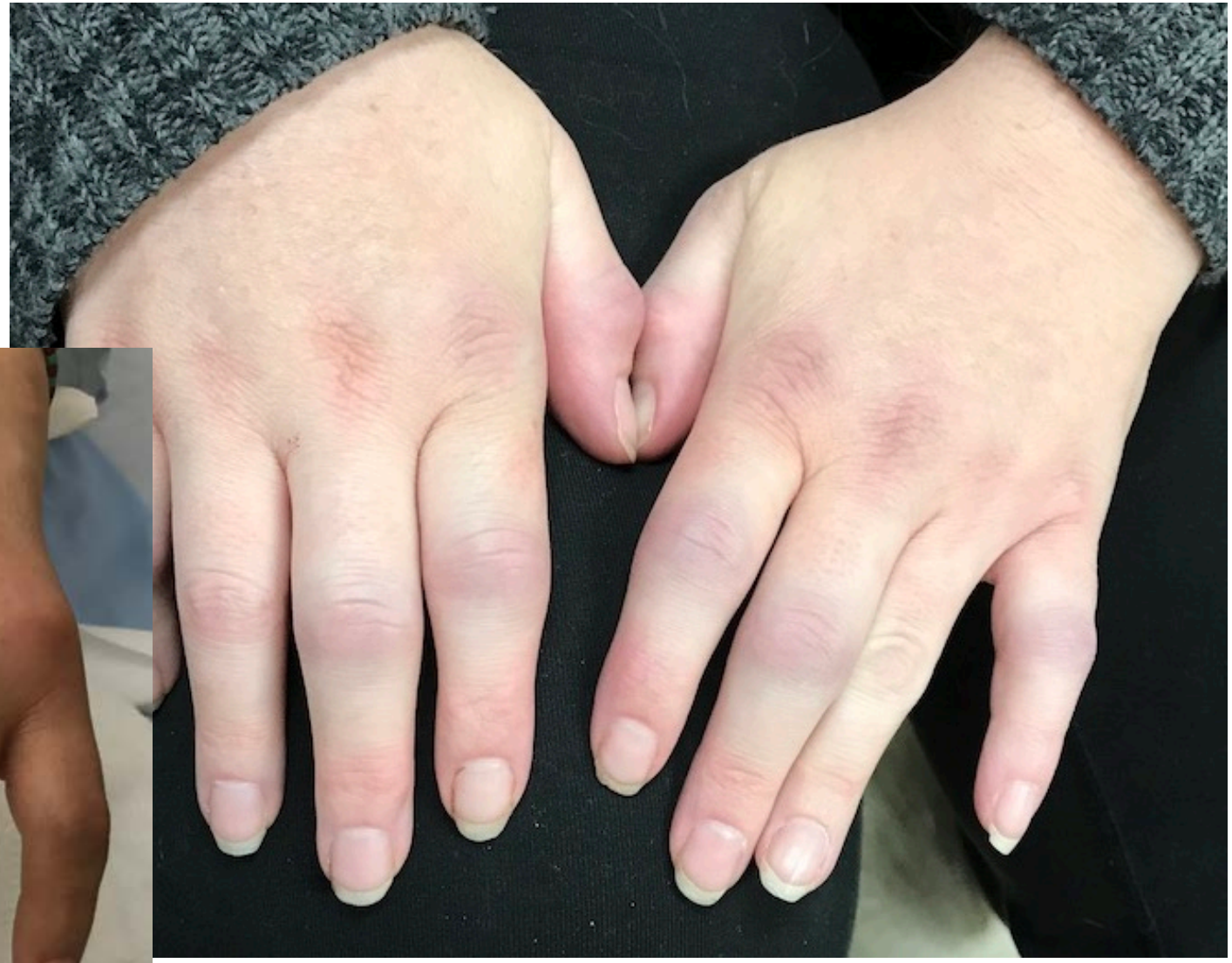
What is RA? **Individual experience**

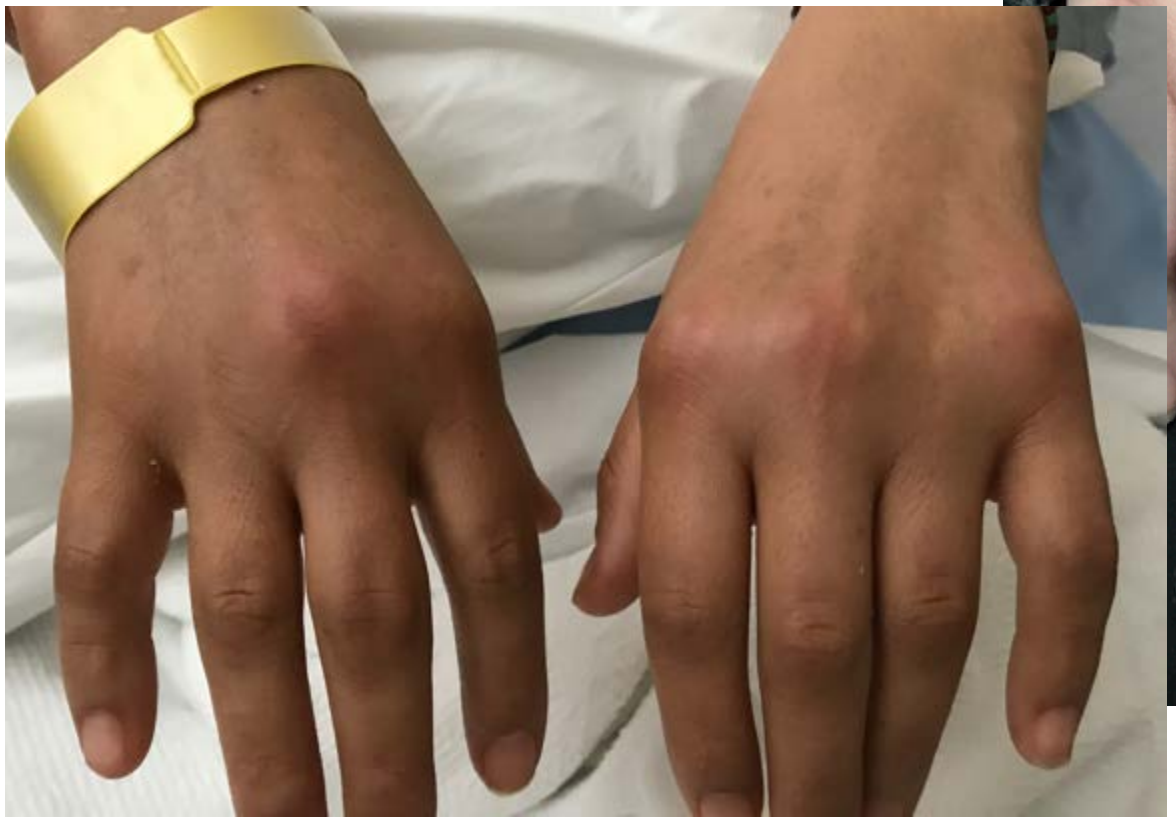
- Joint pain, stiffness and swelling, lack of mobility
- Fatigue, malaise
- Greatly improved treatments with good responses in most individuals

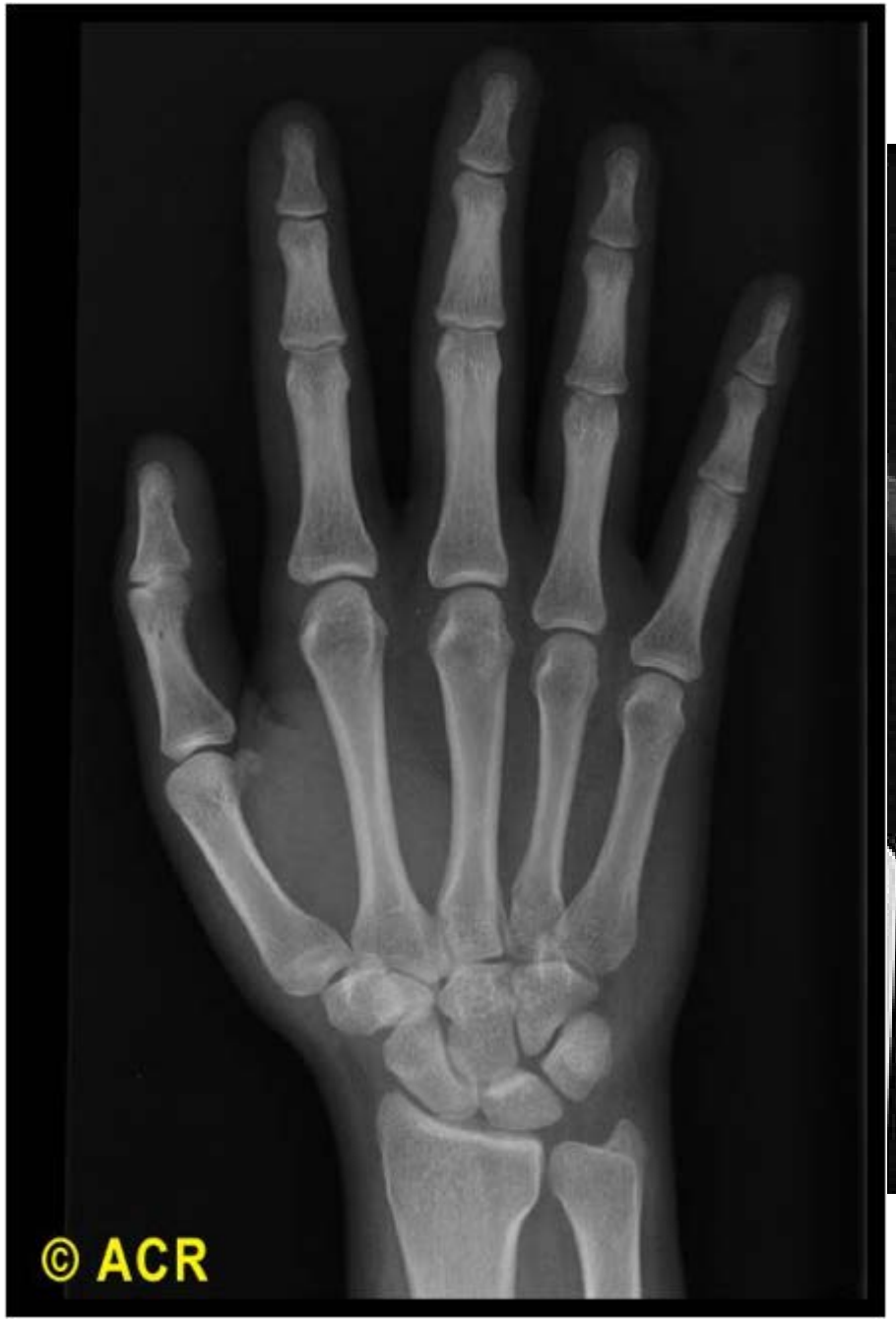
STILL

- Lifelong disease, lots of health-care visits and bloodwork, work loss, expense (~15K+/yr)
- Treatment side-effects
- ”Great” disease control doesn’t occur in all individuals
- Comorbid conditions: premature heart disease, osteoporosis, infections, lung disease
- Most people with RA wish they never gotten it, and they don’t want their family to get it!

Gul et al. Rheumatology 2019



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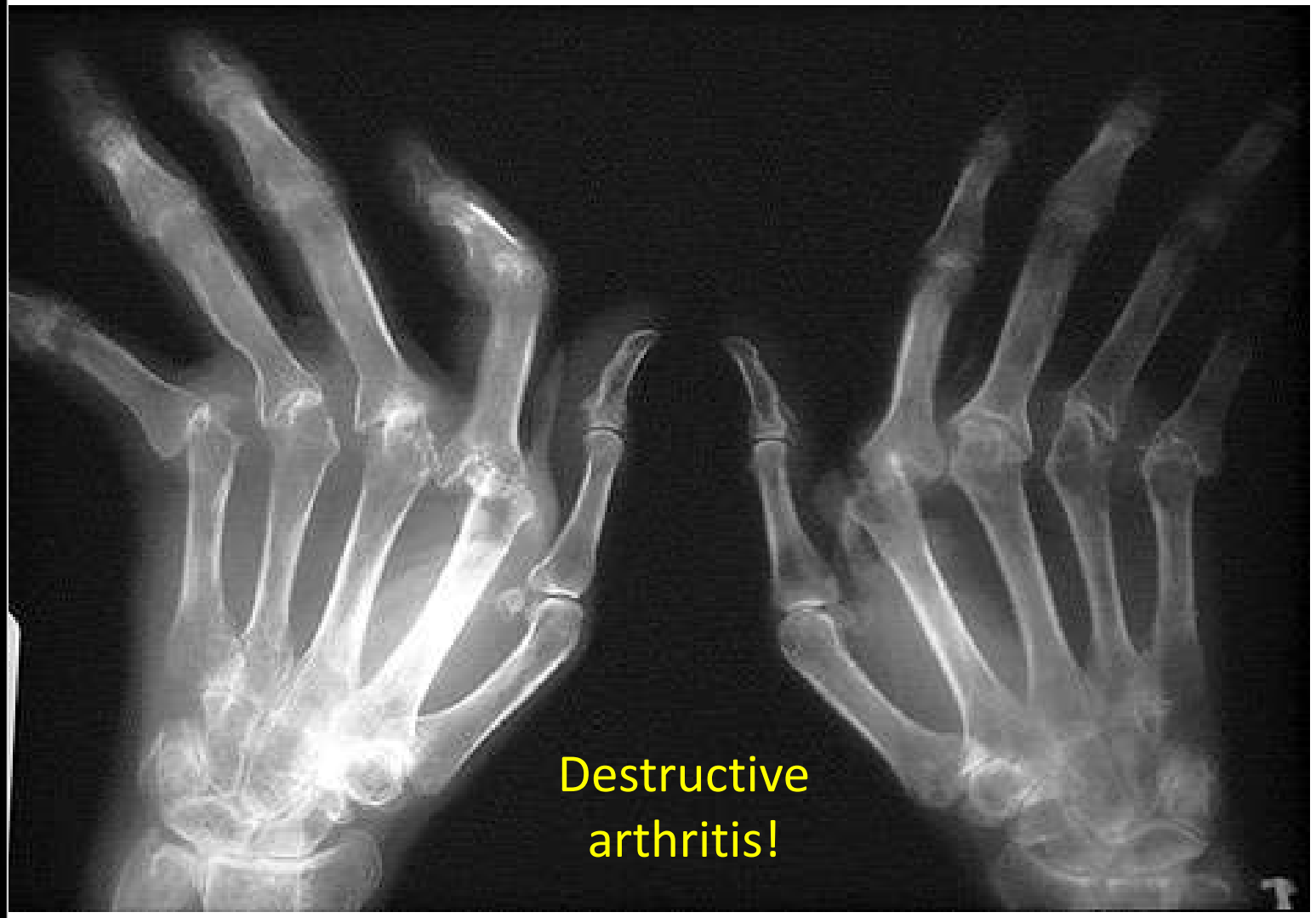
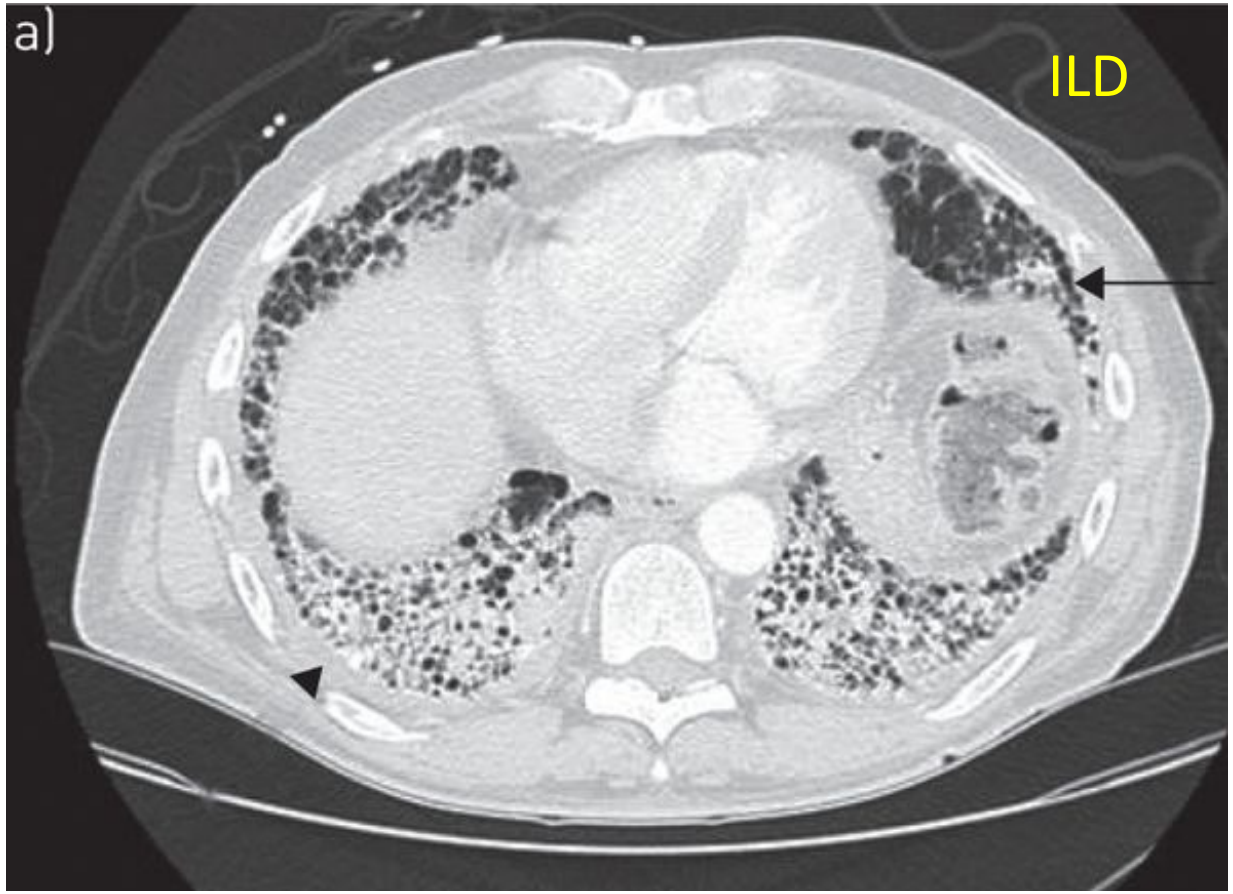
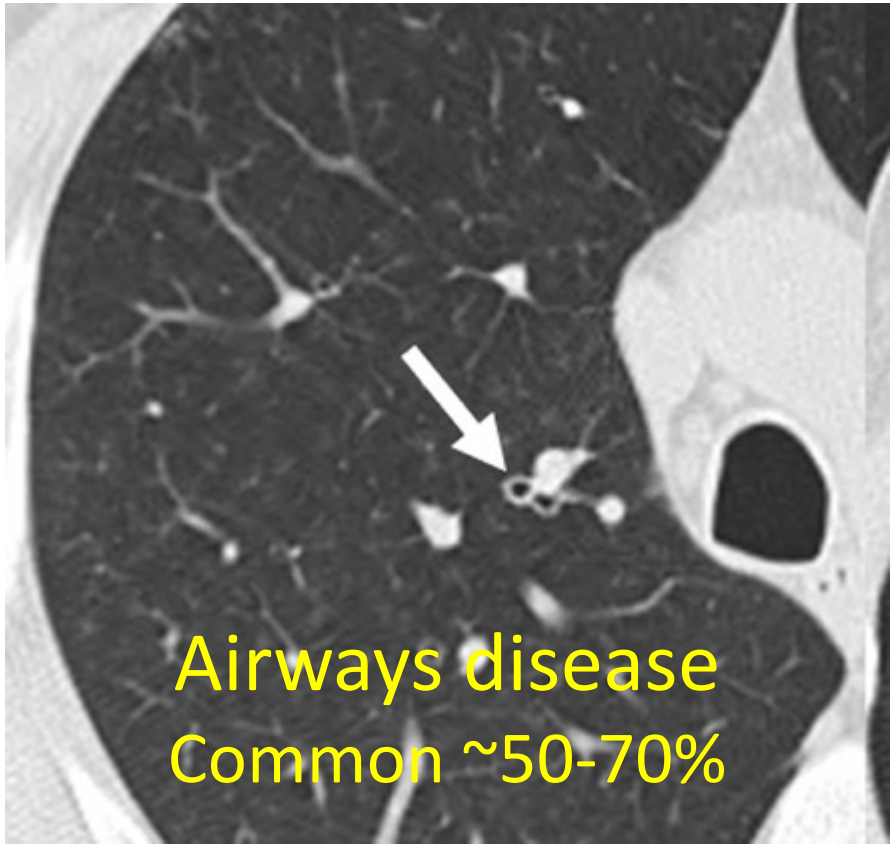

Destructive
arthritis!

Additional manifestations





Turesson Curr Opin Rheum 2013

RA: Autoantibodies

Rheumatoid factor (RF)

~80% sensitive

80% specific

Good biomarker

Pathogenic

Antibodies to Citrullinated Protein Antigens (ACPA)

Commercially-available = anti—Cyclic Citrullinated Peptide antibody

anti-CCP

~80 sensitive (and typically elevated earlier in disease)

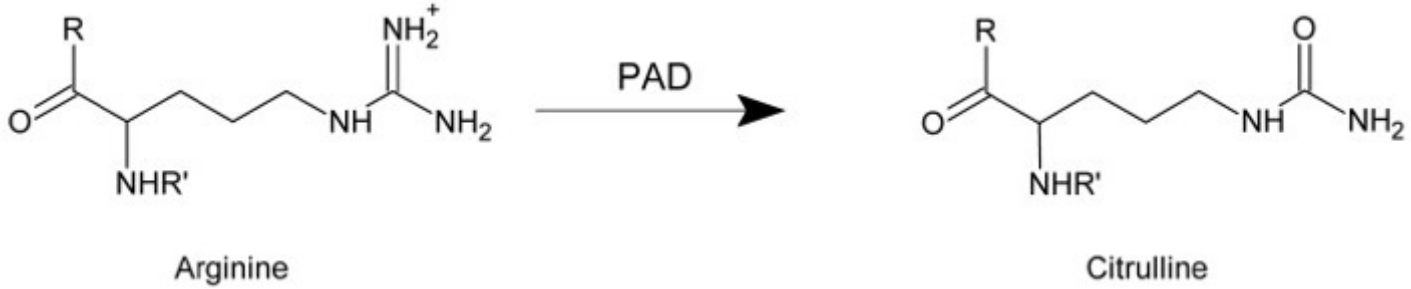
>95% specific

<u>Great</u> biomarker

Pathogenic

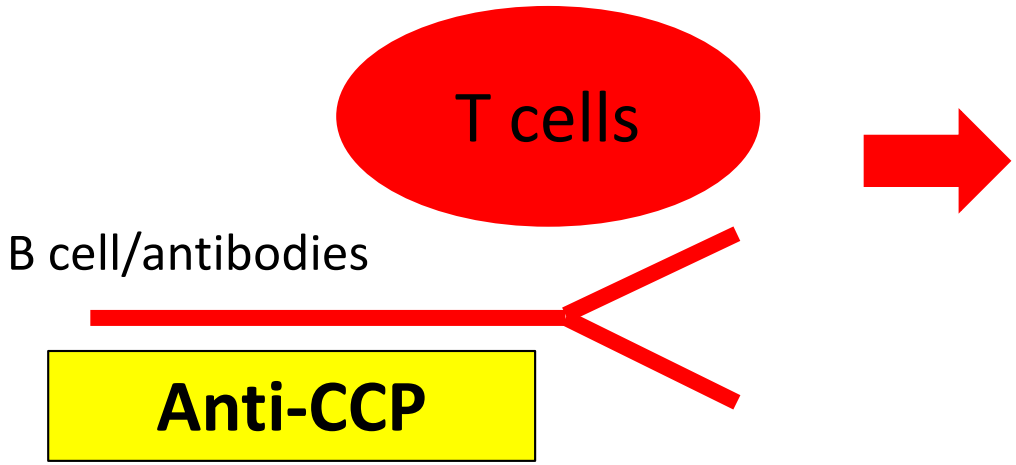
Derksen et al Semin Immunopathol 2017

Citrullination: happens in all of us, all the time (e.g. wound healing, apoptosis) – but immune responses to citrulline are highly specific for RA



Darrah et al Curr Opin Rheum 2018

X-X-Cit-X-X



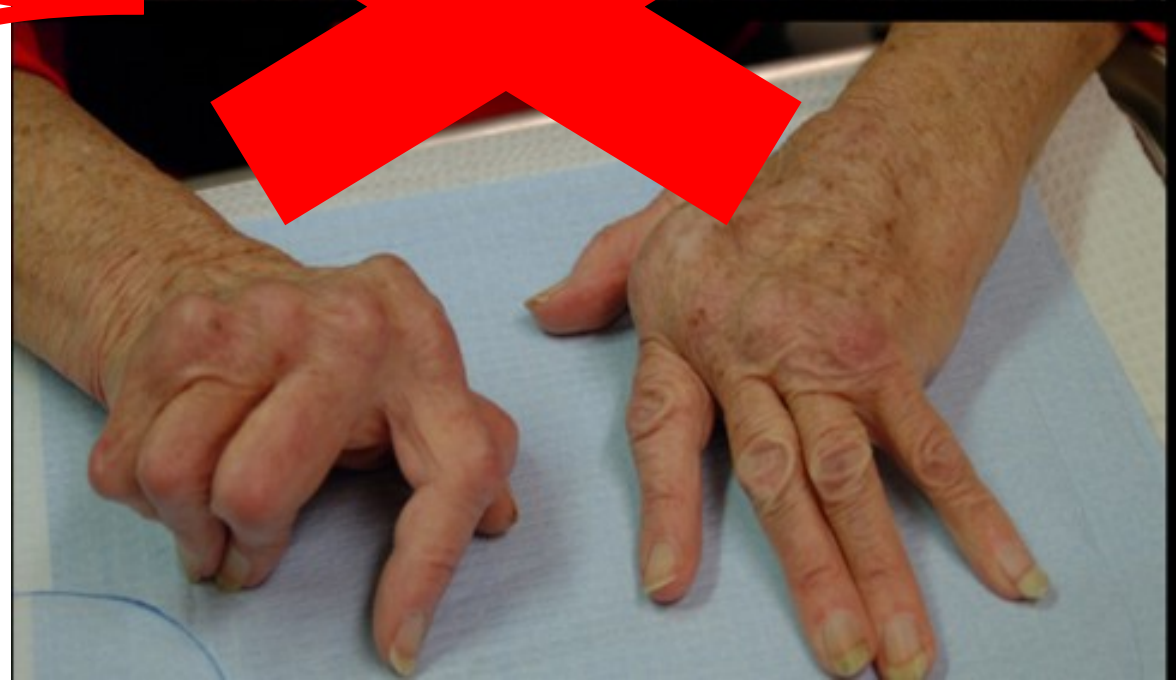
Many peptide and proteins contain citrullinated residues and are targeted in RA: fibrinogen, vimentin, enolase, histones

How is RA treated NOW?

- We wait until someone is “sick” with clinically-apparent IA
- Apply disease modifying therapy *Ideally start <3 months after onset of symptoms*
- Therapy is based on growing understanding of the biology and natural history of RA

Stack et al BMK Open 2019; Singh et al Arthritis Rheumatol 2015

DMARDS
Steroids
Hydroxychloroquine
Sulfasalazine
Methotrexate
Leflunomide
JAK/STAT inhibition
Anti-TNF
Anti-IL6
B cell depletion



www.cdaarthritis.com/.../ images_slides_29.htm

1992

2002

Wiesenhutter

Case Presentation

47 y/o female

Mom had RA

Aches and pains off/on for the past 8 months

Hands and feet, sometimes shoulders

Morning stiffness ~15 minutes some days

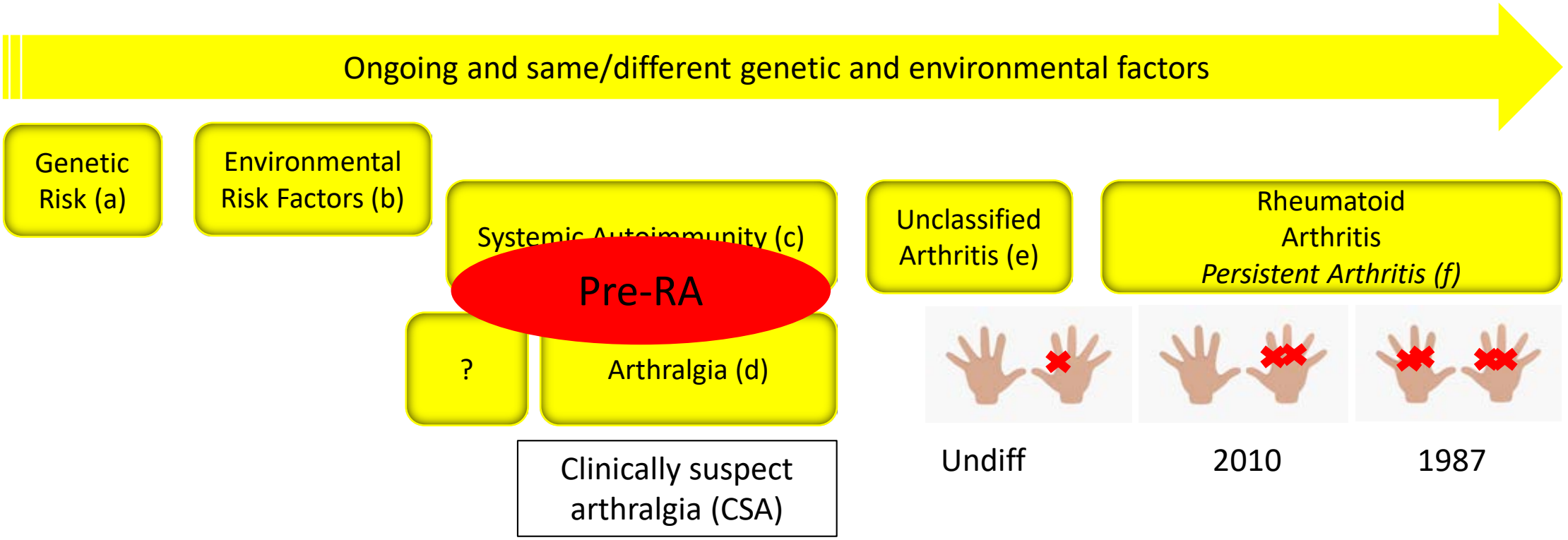
On exam, no tender or swollen joints consistent with IA

Autoantibody testing:

anti-CCP 68 units (normal <20)

RF 44 (normal <6)

Overview of RA development: PRE-RA



EULAR Recommendations for Terminology and Research in Rheumatoid Arthritis Development

Somewhat controversial politically and biologically

Deane and Holers Arthritis Rheumatol 2020
Gerlag et al Annals Rheum Dis 2014
Van Steenbergen Annals Rheum Dis 2017

How have we learned about Pre-RA?

Well-developed prospective natural history studies

Akimel O'odham (Pima) people *Del Puente 1988* (~20 yr study!)

RA prevalence ~5%

British family study Silman 1991

Fortuitously collected biospecimens

Finnish biobank *Aho multiple 1980s/90s*

Swedish biobank Rantapaa-Dahlqvist 2003

Dutch biobank *Nielen 2004*

US military biobank *Majka 2008 (CU)*

How have we learned about Pre-RA?

Ongoing prospective Studies

Studies of the Etiology of RA (SERA)
Holers/Norris/Deane/Demoruelle (and a cast of thousands…)

First Nations Studies El-Gabalawy multiple

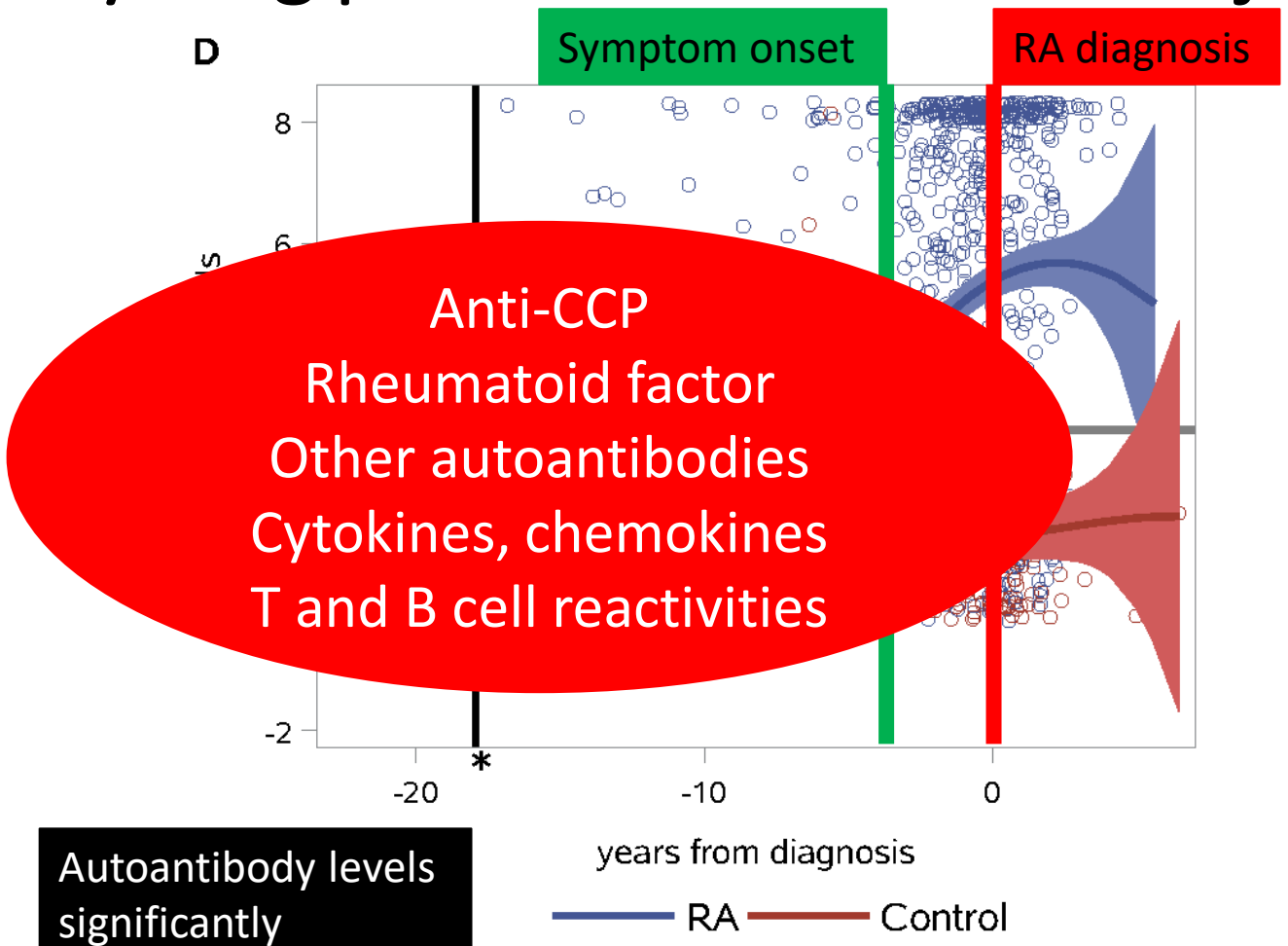
Dutch ACPA+/Arthralgia Cohorts Bos/van Schaardenburg multiple

Mexican FDR studies *Ramos-Remus 2015*

UK ACPA+ in clinics *Rakieh, Emery multiple*

Others

Pathophysiology: Initiation and propagation of autoimmunity long prior to the first swollen joint!



Kelmenson et al A+R 2020

There is no IA during much of Pre-RA (exam, imaging, biopsy)

HYPOTHESIS:

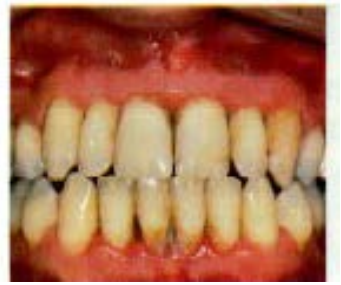
RA-RELATED AUTOIMMUNITY STARTS OUTSIDE JOINTS

Where?

Highly likely to be mucosal site

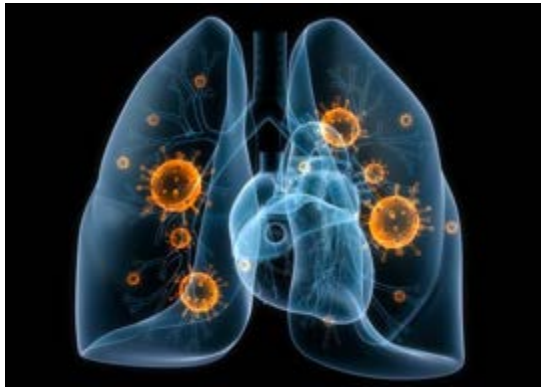
Holers et al Nature Rev Rheum 2018

Multiple potential mucosal sites where autoimmunity may originate in RA



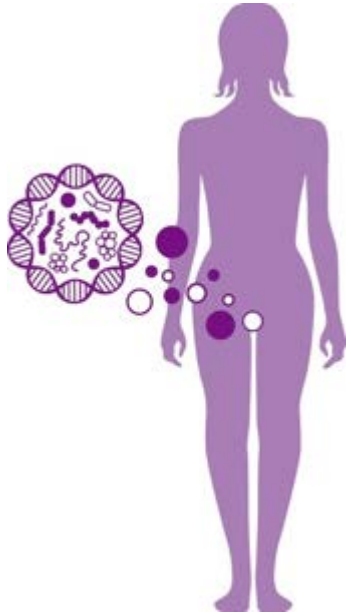
Periodontium

Lung



Intestine

Genital Tract



Holers et al. Nature Reviews Rheum 2018

Multiple studies suggest a link between the lungs and RA

In established RA

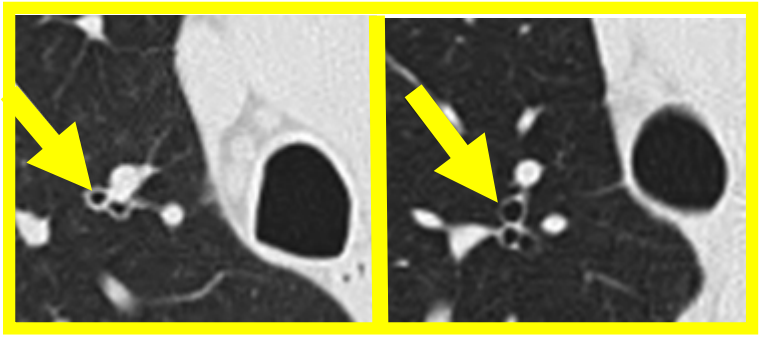
- High prevalence of airways and parenchymal abnormalities on lung HRCT
  - 66% airways and 54% parenchymal - in early RA
- Increased prevalence of clinically significant interstitial lung disease in RA
  - 5-10% in RA vs. 0.1% in the general population
- Increased prevalence of asthma and COPD in RA
  - RA vs. general population - 17% vs. 14% asthma and 7% vs. 4% COPD

Reynisdottirr et al Arthritis Rheum 2013
Olson et al. Am J Respir Crit Care 2011
Nikiphorou et al. Rheumatology 2020

Airways inflammation in pre-RA

HRCT imaging of the lung in 42 pre-RA subjects and 15 controls

- Inflammatory airways were more prevalent in pre-RA
  - 76% vs. 33%, p=0.005
- Subsequent studies - asthma and COPD are risk factors for RA



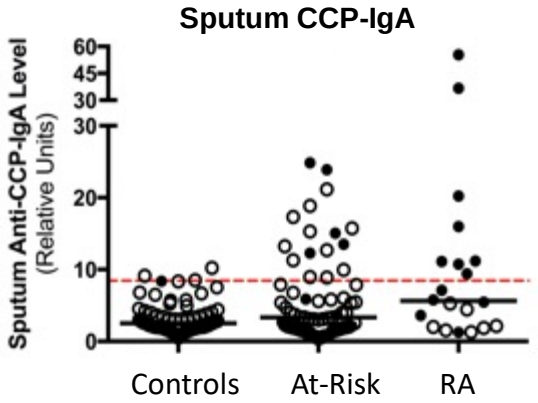
Anti-CCP(+) Case with bronchial wall thickening

Control with normal thin walled bronchus

Induced sputum in subjects At-Risk for RA, with RA and healthy controls

- At-Risk subjects had more sputum anti-CCP positivity than controls
  - 24% vs. 5%, p<0.01

●= serum CCP(+)
○= serum CCP(-)



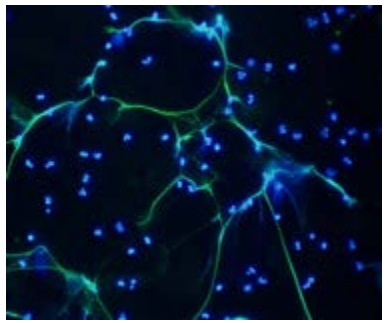
A portion were sputum anti-CCP+ in absence of serum anti-CCP supporting local generation in the lung

Demoruelle et al Arthritis Rheum 2012
Demoruelle et al. Arthritis Rheum 2017

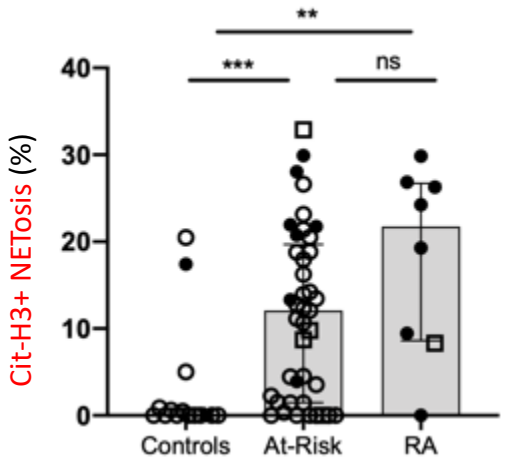
NETs and anti-CCP in the lung in pre-RA

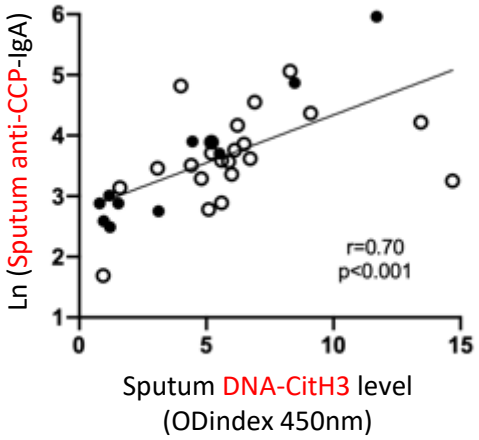
Neutrophil extracellular traps (NETs) = neutrophils decondense and expel their chromatin

- Externalize citrullinated proteins
- Increased in blood and joints in RA



Measured NET formation and NET remnants in sputum





NET formation increased in sputum neutrophils in pre-RA

NET remnants correlate with anti-CCP in sputum

- Particularly NETs containing citrullinated proteins

Suggesting excessive cit-protein containing NETs may be a trigger of anti-CCP generation in the lung

Okamoto et al. submitted

Going forward – SERA studies

Determine the effect of cytokines and bacteria on sputum NET induction associated with anti-CCP in pre-RA

Determine the role of NET clearance associated with anti-CCP in pre-RA

Hypothesis: Distinct factors increasing cit-protein expressing NETs and decreased NET clearance in the lung in pre-RA will be associated with anti-CCP generation and ultimately RA

NET formation and clearance may be novel treatment targets for RA prevention

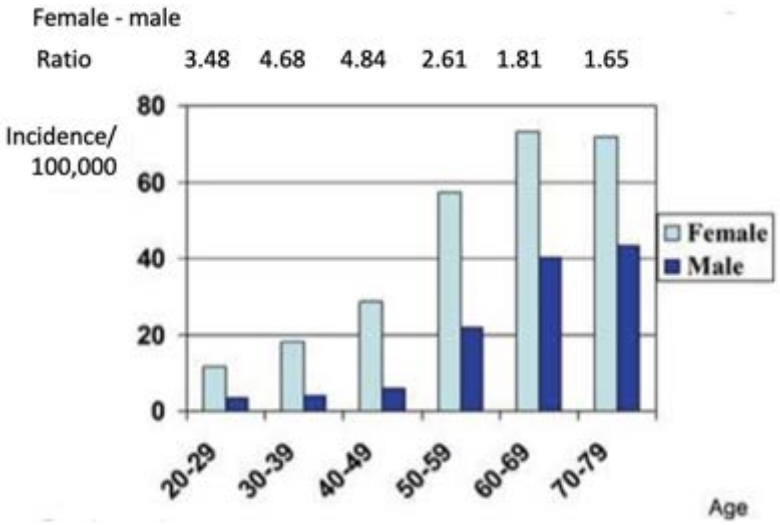
Female genital tract mucosa in RA

RA more common in women than men (3:1)

Despite decades of research, still unclear why

New concepts may be needed to explain sex differences in RA

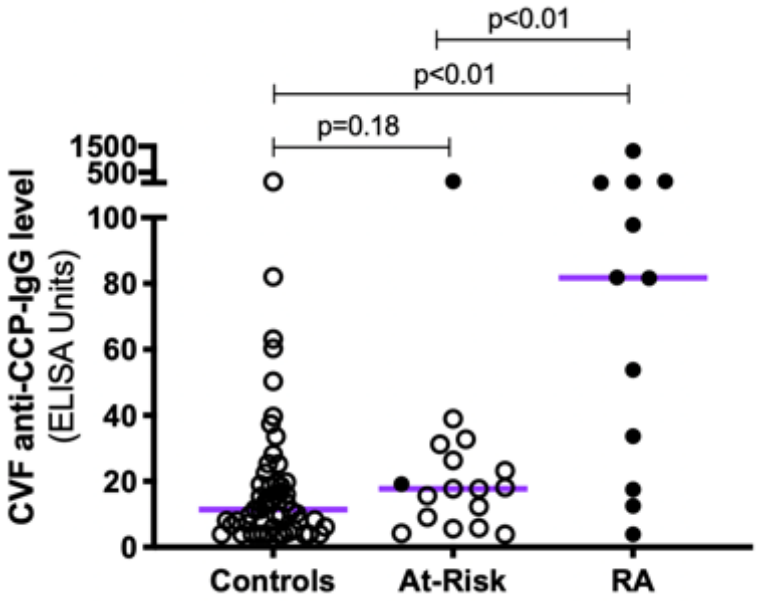
- Mucosal Origins Hypothesis in RA



Cervicovaginal (CV) mucosa may be a mucosal site where inflammation and autoimmunity originate in RA that is unique to women

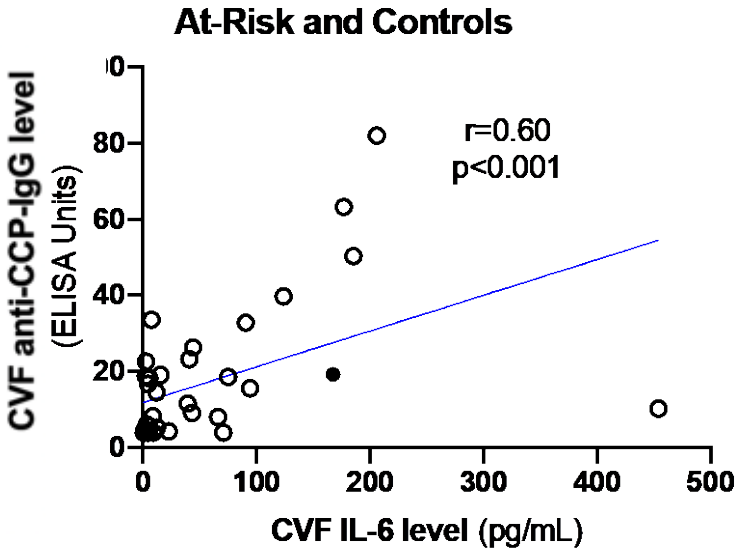
Uhlig T et al. J Rheumatol 1998

Anti-CCP generation in the female genital tract



CVF anti-CCP is elevated in RA but also in a portion of At-Risk and healthy premenopausal women

Anti-CCP associated with inflammation in female genital tract in women with and without RA



CVF anti-CCP strongly correlates with local inflammation

Demoruelle et al. unpublished

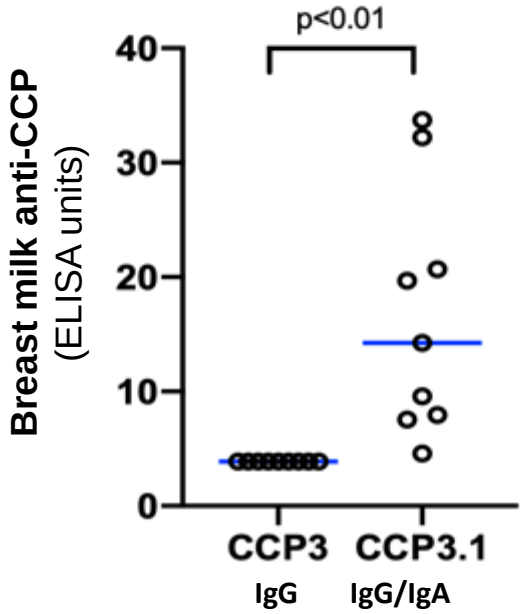
RA and the post partum period

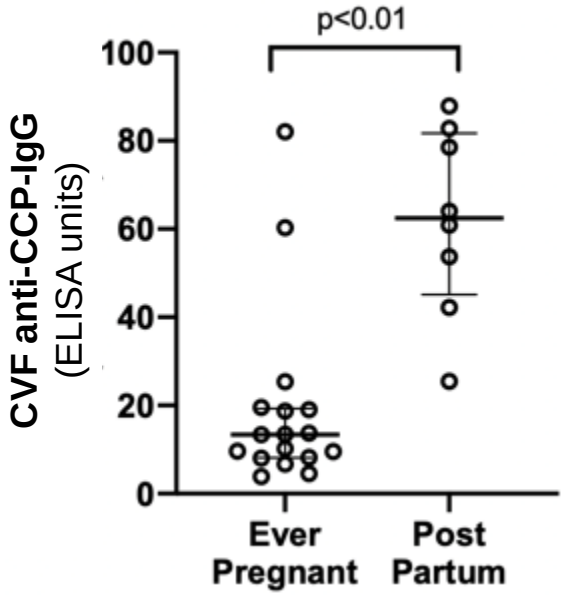
Incidence of RA increases during the first-year after childbirth

- Up to 6-fold increase
- Mechanism unknown

We collected breast milk and CVF samples in 9 women without RA who were in the 1st year postpartum

Anti-CCP are present in breast milk and CVF in a portion of healthy women postpartum





Demoruelle et al. unpublished

Oral mucosa in RA

Multiple data link the gingival mucosa, anti-CCP and RA

- Anti-CCP present in gingival crevicular fluid in periodontitis patients without RA
- *Porphyromonas gingivalis*
  - Expresses PAD that can citrullinate human proteins
- *Aggregatibacter actinomycetemcomitans*
  - Expresses a leukotoxin that hypercitrullinates neutrophils

Wegner et al. Arthritis Rheum 2010; Konig et al. Sci Transl Med 2016

Gut mucosa in RA

Gut dysbiosis and certain bacteria are associated with RA

- *Prevotella copri*
  - Expanded in stool in RA and activates T cells in RA
- Anti-CCP in the stool of subjects with RA and pre-RA
  - Distinct bacteria associated with anti-CCP and pre-RA

Wegner et al. Arthritis Rheum 2010; Konig et al. Sci Transl Med 2016

Multiple mucosal sites demonstrate RA-related antibody generation in pre-RA

- Often in the absence of serum anti-CCP supporting initial generation at these mucosal sites

- Present in a modest portion of healthy controls suggesting the possibility of a 'natural' mucosal response to local inflammation and citrullinated proteins
  - May resolve with resolution of inflammation

Hypothesis: Dysregulation of a natural mucosal immune response could progress to aberrant anti-CCP generation and ultimately RA

Using mucosal site immune dysregulation to predict RA

Using mucosal site immune dysregulation to predict RA

49 serum anti-CCP+ pre-RA subjects were followed for 3 years

- 10/49 (20%) developed RA

Compared baseline factors associated with incident RA

	Developed RA (N=10)	Did not develop RA (N=39)	p-value
Sputum anti-CCP+ or RF+	78%	20%	0.002

Sputum RA-related antibodies could enhance prediction of RA in a high-risk population

Perhaps, decreasing inflammation and antibody generation in the lung could be a future therapeutic strategy in the treatment or prevention of RA

Case Presentation

47 y/o female

Mom had RA

Aches and pains off/on for the past 8 months

Hands and feet, sometimes shoulders

Morning stiffness ~15 minutes some days

On exam, no tender or swollen joints consistent with IA

Autoantibody testing:

anti-CCP 68 units (normal <20)

RF 44 (normal <6)

Prediction of future clinically-apparent IA/RA

In **case-control and prospective** studies, serum elevations of anti-CCP

Positive predictive value of 30-60% for clinically-apparent inflammatory arthritis within 2-6 years

Higher PPV if symptoms are present, RF also positive, HLADR4 allele present

Rantapaa-Dahlqvist 2003; Nielen 2004; Van de Stadt 2012; Rakieh 2014; Deane 2010; Sokolove PLoS One 2012; Erlandsson 2018; van Steenbergen 2016

Case Presentation

47 y/o female

Mom had RA

Aches and pains
months

Hands and feet, s

Morning stiffness
days

On exam, no tender or swollen jo
consistent with synovitis

20)

>50% risk for clinically-apparent inflammatory arthritis in 3-5 years

Prevention

<u>Underpinned by:</u>

Prediction models

Established therapies

Growing identification of ‘at-risk’ subjects

Completed RA prevention trials
Stop/delay the first joint with IA on exam

PRAIRI Study

Inclusion

81 subjects

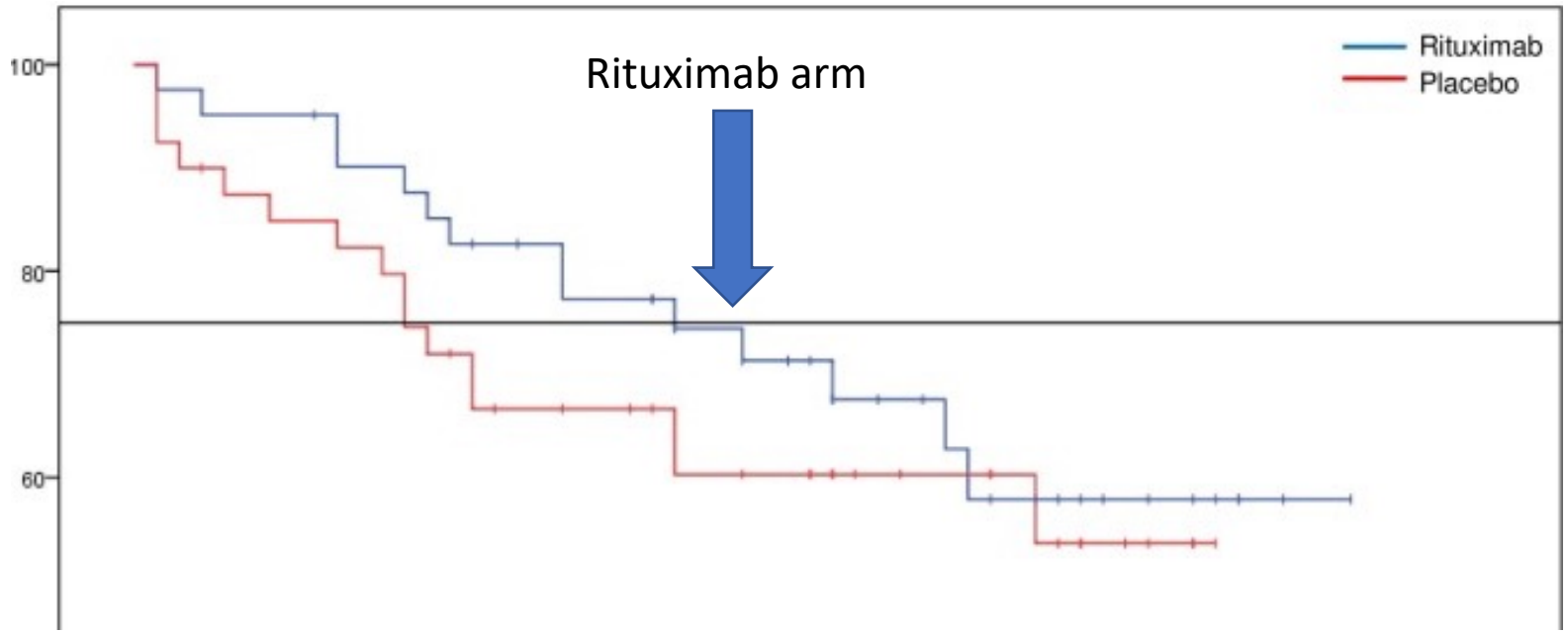
Arthralgia

No examination IA

Anti-CCP and RF

Intervention

Rituximab 1000 mg x 1



37% developed RA over a mean of 29 months (range 0-54): 40% vs. 34%

Rituximab delayed the time at which 25% of subjects had developed IA by ~12 months

Gerlag et al Ann Rheum Dis 2019

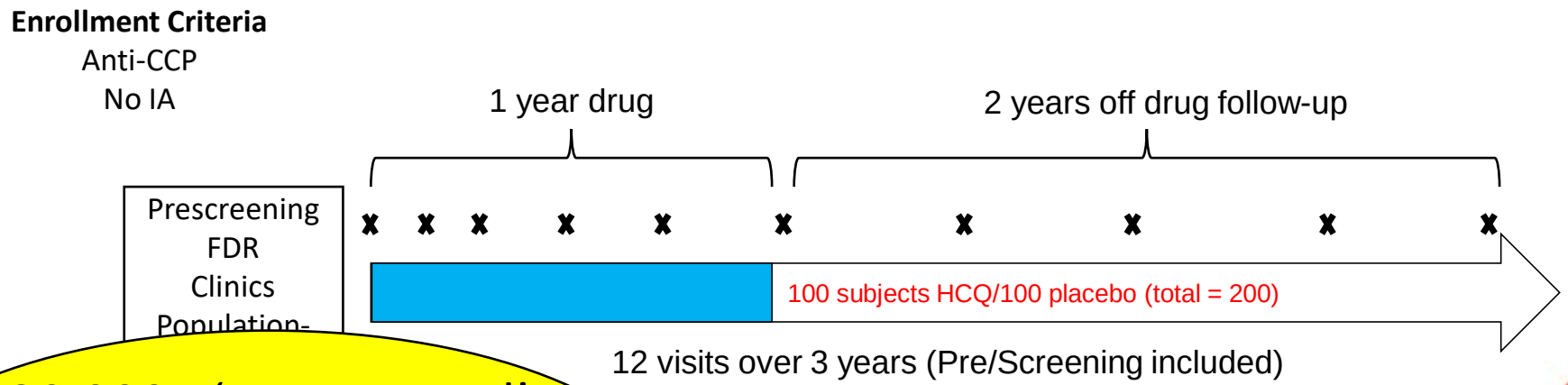
Ongoing RA prevention trials

Acronym	Inclusion: Biomarker*	Inclusion: symptoms	Intervention	Primary Outcome	Location
StopRA	Anti-CCP >2x	-	Hydroxychloroquine x 1 year	RA 2010	USA
APIPPRA	Anti-CCP+RF or anti-CCP >3x	arthralgia	Abatacept x 1 year	RA 2010	UK
StapRA	RF+anti-CCP or anti-CCP >3x and arthralgia	arthralgia	Atorvastatin 40 mg x 1 year	RA 2010	Dutch
TreatEarlier	Subclinical joint inflammation on MRI	arthralgia	MTX x 1 year, initial dose of IM methylprednisolone	RA 2010	Europe
CuPRAA	Anti-CCP any elevated level	-	Curcumin, omega-3, vit D	Anti-CCP levels*	Indigenous/ First Nations Canada

***serum levels**

StopRA: Study Design

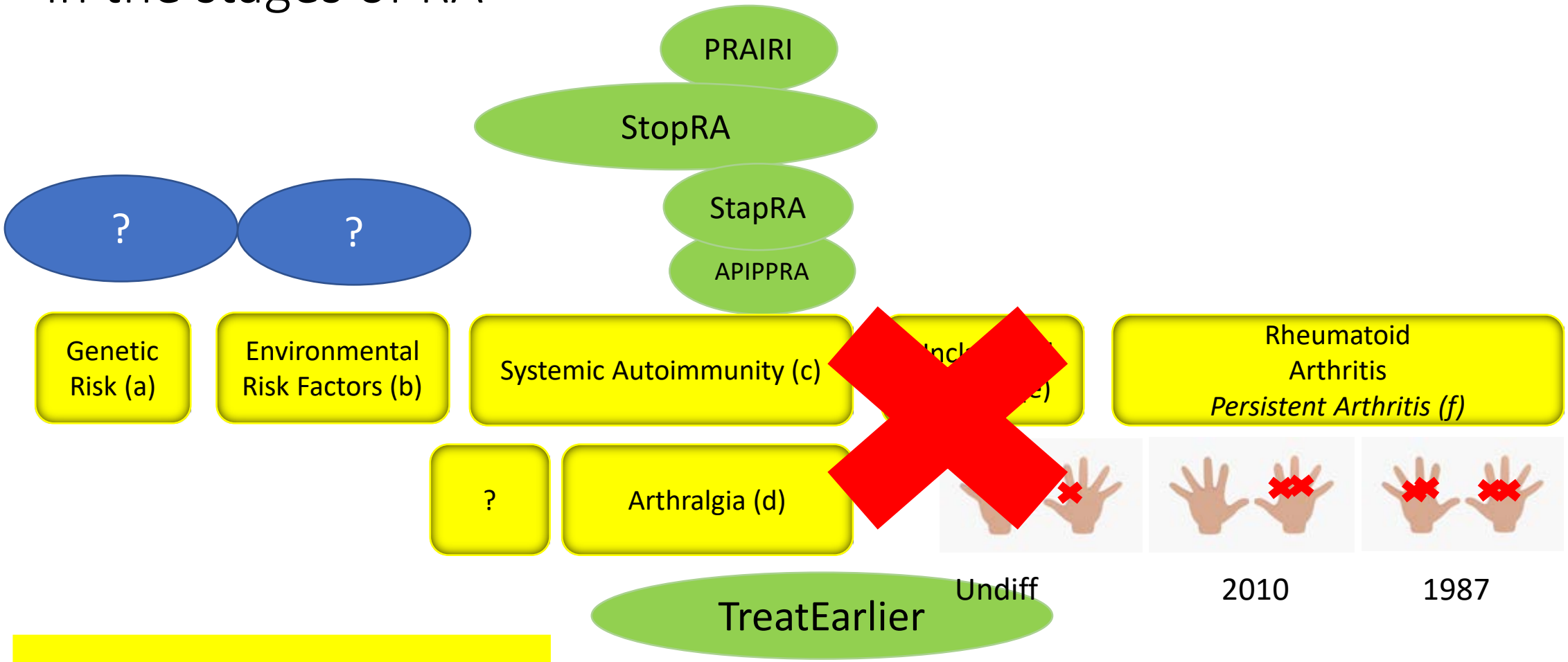
Funding:
NIH/NIAID
Autoimmunity Center of Excellence



30,000+ 'Prescreened' in ~3.5 yrs to randomize ~130 so far!

www.stop-ra.org

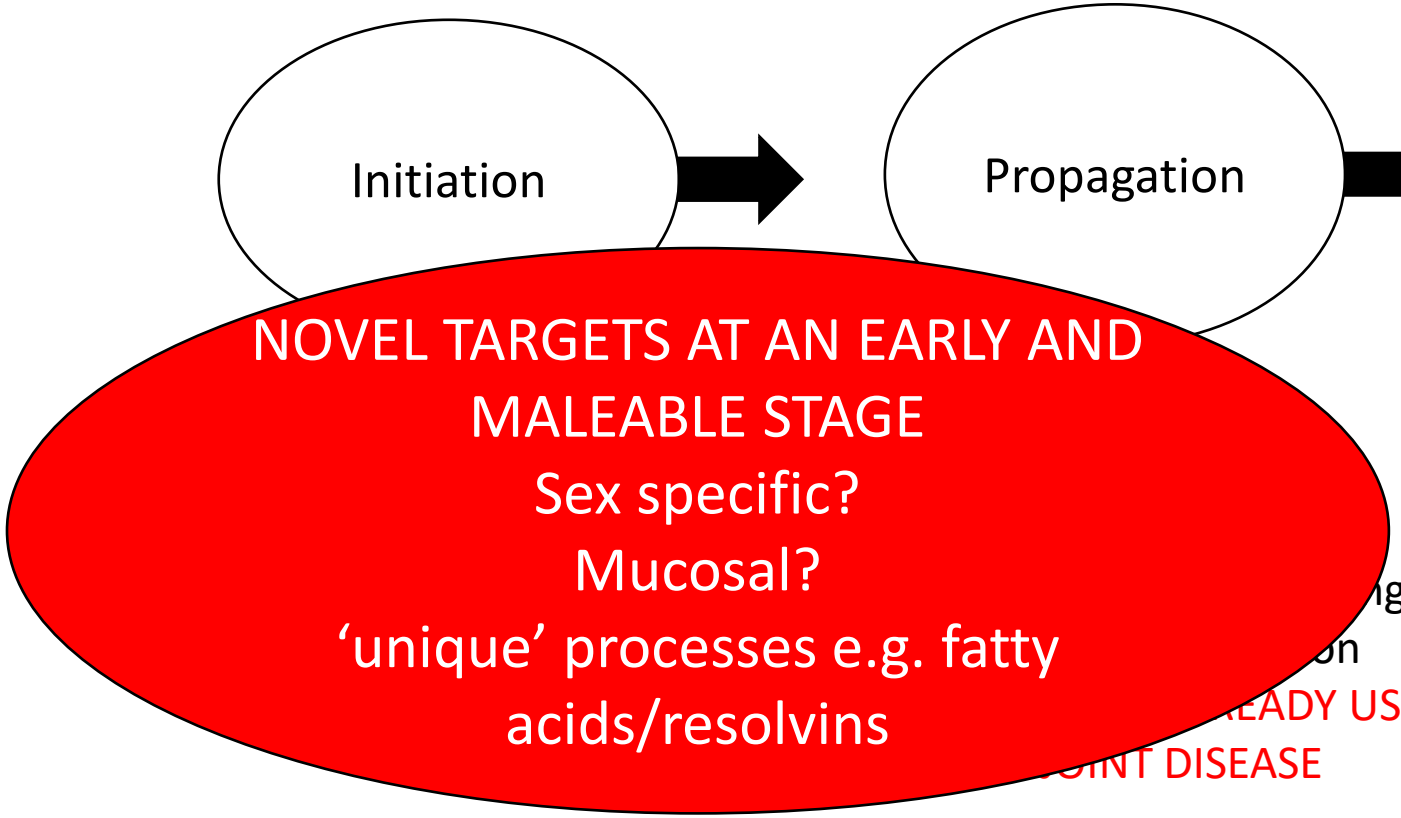
The trials have different targets and different times in the stages of RA

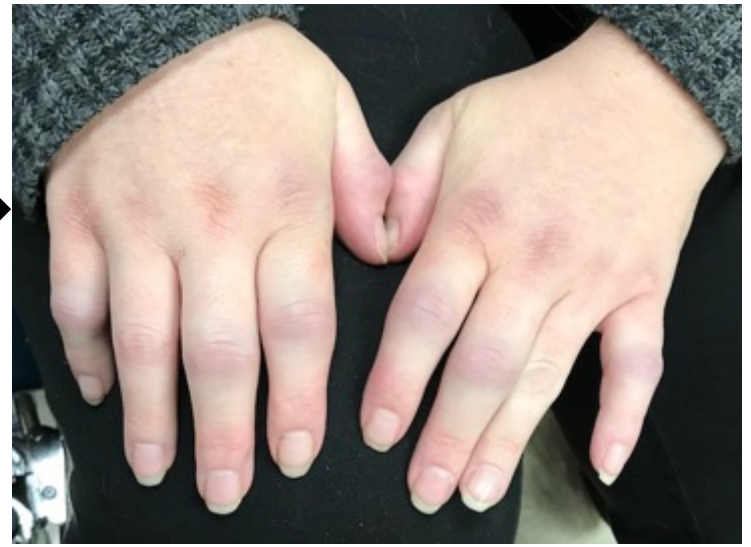


Where an individual is may dictate intervention: type, risk, cost

Opportunities and challenges

Current preventive interventions: science and convenience – but do we need better?





This is where we have experience

Gan et al Rheumatology (Oxford) 2017
Gan et al Ann Rheum Dis 2017

Move known drugs earlier

Major Challenges and Opportunities

- **What will these current trials tell us? PREDICTION, RESPONSE TO THERAPY AND NOVEL TARGETS**
- **Build infrastructure for trials TYPE 1 DM AND TRIALNET (Teplizumab, Herold et al NEJM 2019)**
- **What is success in prevention? DRUG-FREE REMISSION? STOP THE FIRST FLARE BUT CONTINUE LIFELONG THERAPY?**
- **Individual preferences and delivery ESPECIALLY TO HIGH-RISK GROUPS (racial groups, women, family members)**
- **Expansion to other diseases E.G. LUPUS, PSORIATIC ARTHRITIS**
- **Business model for prevention PUBLIC HEALTH, INSURANCE, PHARMA, DIAGNOSTICS**

Conclusion

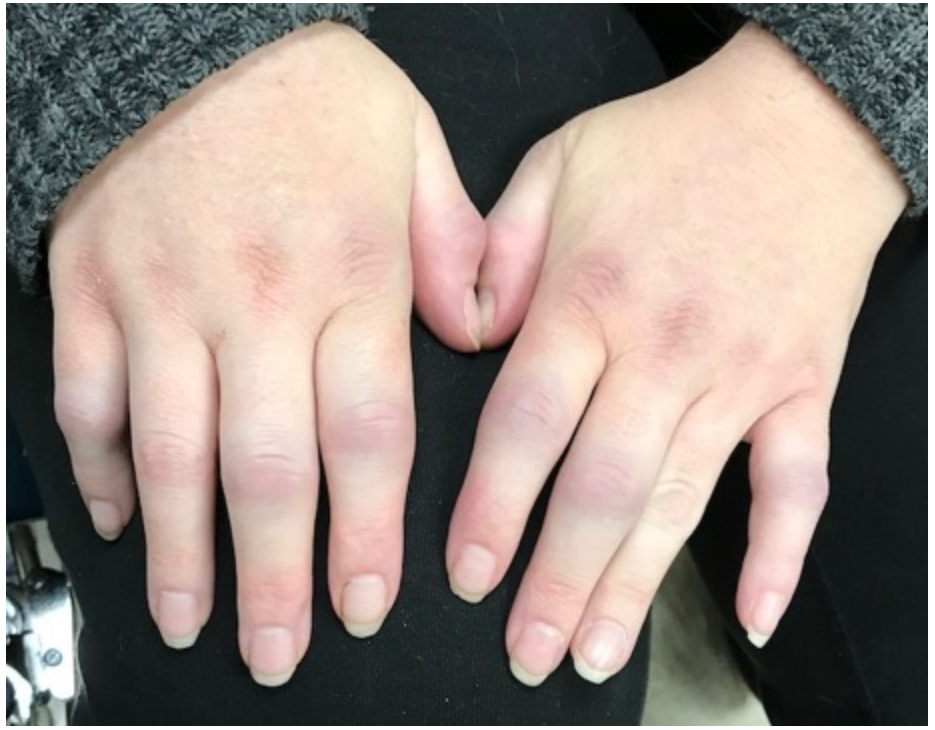
RA

Pathogenesis

Prediction

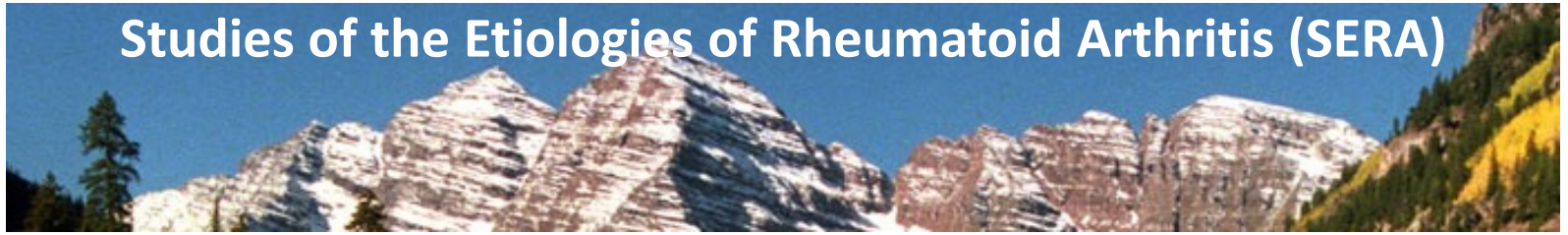
Prevention

Opportunities and challenges



Studies of the Etiology of RA (SERA)

Studies of the Etiologies of Rheumatoid Arthritis (SERA)



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Finding a Cure for Rheumatoid Arthritis

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Pfizer
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Questions

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