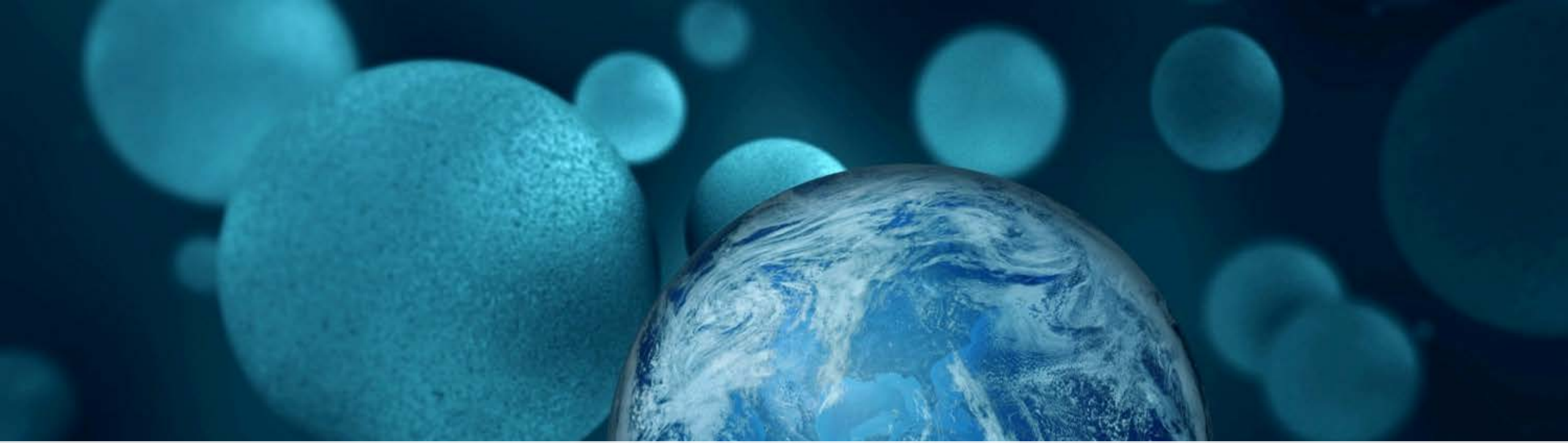


ThermoFisher SCIENTIFIC

Rheumatoid Arthritis Diagnosis
Avoiding CCP False Positives Through Test Selection

Dr. Teresa Tarrant
Duke University School of Medicine

Bio

Dr. Tarrant is a Clinical Immunologist, board certified in Allergy, Immunology and Rheumatology. She specializes in diseases of and related to Rheumatoid arthritis, Sjögrens syndrome, Inflammatory Eye disease, CVID, and Immunodeficiency in Aging.

After graduating from the University of Florida College of Medicine**,** she performed her fellowship and residency at Duke University Hospital in North Carolina. In addition to her active medical practice, over the last 10 years, Dr. Tarrant has held two other major roles in her daily work; first as a medical liaison, where she assists in the evaluation and selection of immunoassays, including authoring or co-authoring peer-reviewed scientific articles of their evaluations, and secondly as an Associate Professor, Medicine.

Her work began within the hospital system and school of medicine at the University of North Carolina (UNC), and **recently she became Associate Professor of Medicine at Duke University and Vice Chief of Translational Research, Rheumatology.**

UNC THURSTON ARTHRITIS RESEARCH CENTER

Duke University School of Medicine

Disclosure

Dr. Tarrant has received consulting fees as well as an honorarium for today's presentation. In addition, presentations are by their very nature, very brief overviews of complicated subject matter. No medical decision should be made solely based upon the information presented.

Program Objectives

After participating in this educational activity, participants will be able to:

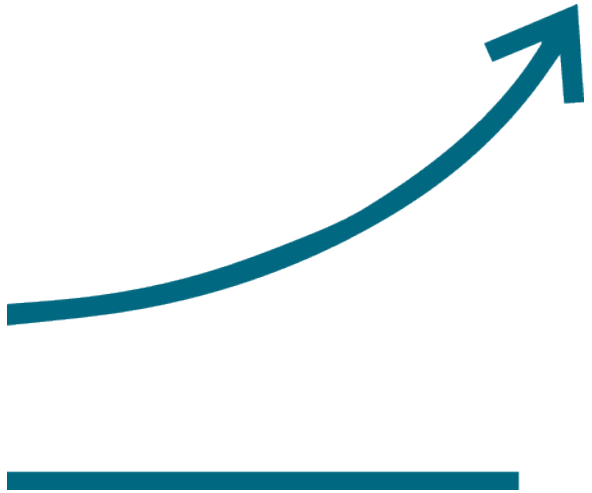
- Understand evidence-based approaches described in the American College of Rheumatology Guidelines for the diagnosis and management of Rheumatoid Arthritis (RA)
- Identify the importance of specificity in test selection, and the optimal usage of two recommended serologic markers for rheumatoid arthritis — anti-CCP and rheumatoid factor IgM
- Recognize how test efficacy and disease prevalence impact the accuracy of results, and when to consult with or refer the patient to a specialist

Prevalence of Disease

Rheumatoid Arthritis (RA) – An Autoimmune Disease

RA is the most common form of autoimmune arthritis[1]
RA can start at any age[2]

Adults age ≥ 18 have RA[2]



Average age has increased steadily over time[3]

1 www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Rheumatoid-Arthritis. Accessed September 5, 2016.
2 www.cdc.gov/arthritis/basics/rheumatoid.htm. Accessed September 5, 2016.
3 Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum*. 2008 Jan;58(1):15–25.

Rheumatoid Arthritis (RA) – An Autoimmune Disease Primarily in Women

Affects women 2–3x more than men[1]

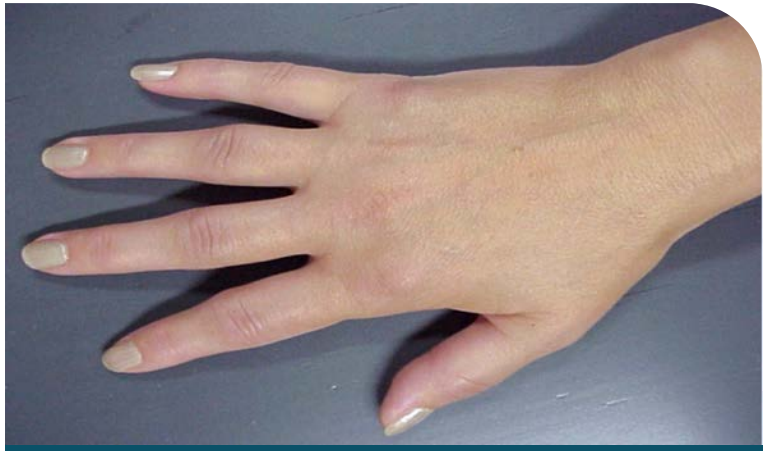
1–3 % of women may get rheumatoid arthritis in their lifetime.[1]

1 www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Rheumatoid-Arthritis. Accessed September 5, 2016.

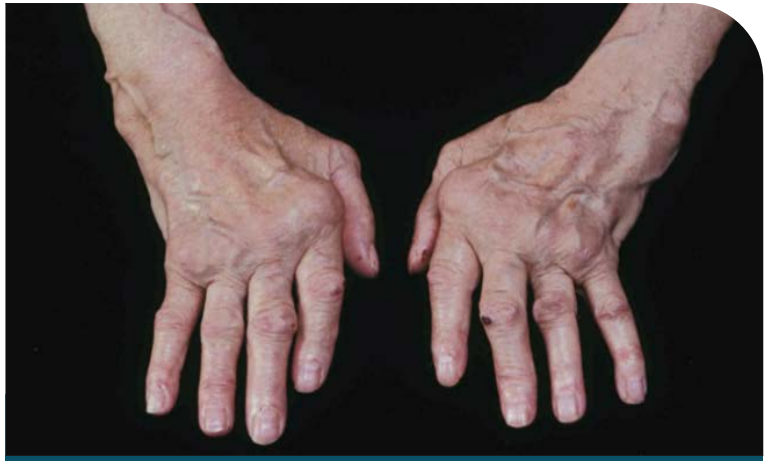
Rheumatoid Arthritis Disease Characteristics

Characteristics of Joint Damage

Rheumatoid Arthritis (RA)



Early-stage



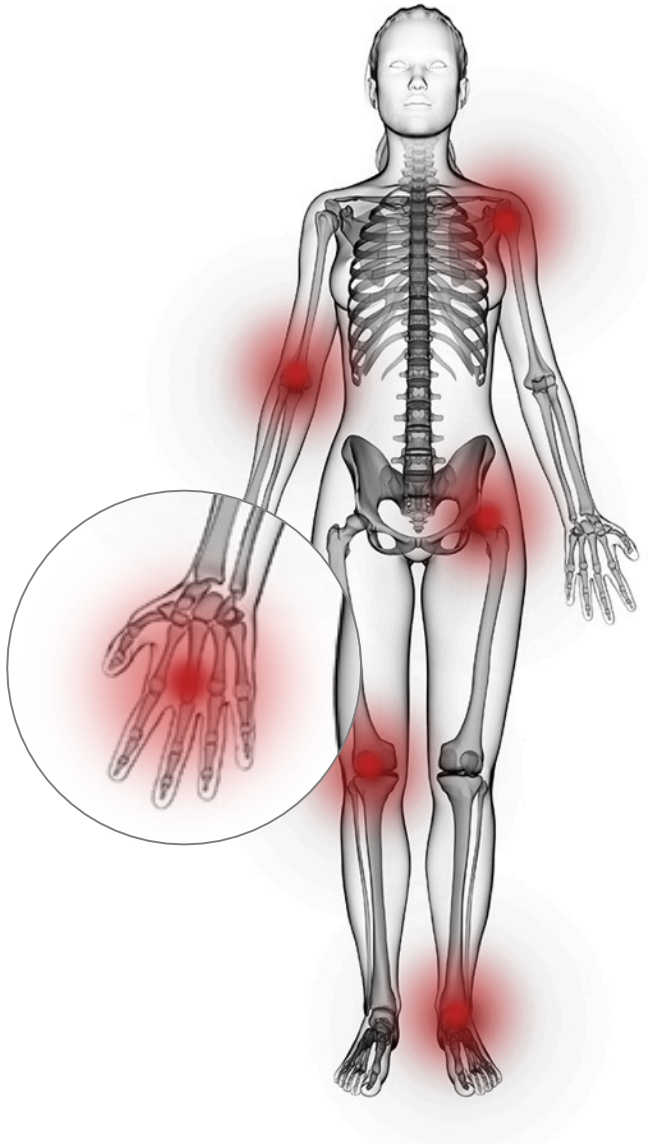
Late-stage

- Early-stage: Very early RA showing swollen and painful PIP joints
- Late-stage: Long-standing RA with typical signs including swollen MCP joints, ulnar deviation of fingers, atrophy of musculli interossei and rheumatoid nodules.
- Affected joints are swollen, tender and warm, and stiffness limits their movement

Herold M. Rheumatoid Arthritis. Ed. Schoenfeld Y, Meroni PL. **The General Practice Guide to Autoimmune Disease.** 2012 Pabst Science Publishers, Lengerich. 63-71.

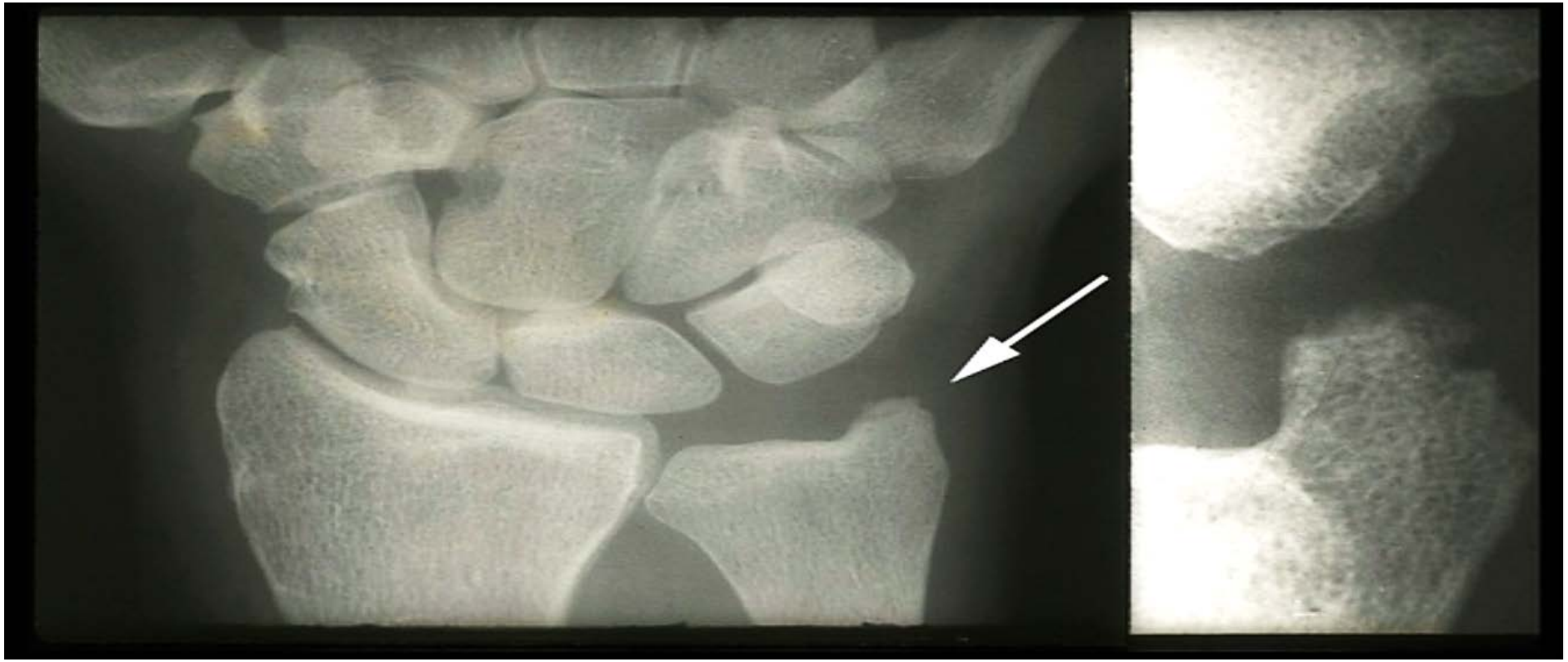
Key Features of Rheumatoid Arthritis (RA)

- Chronicity
- Inflammatory symptoms
- Joint distribution



Characteristics of Radiographic Findings

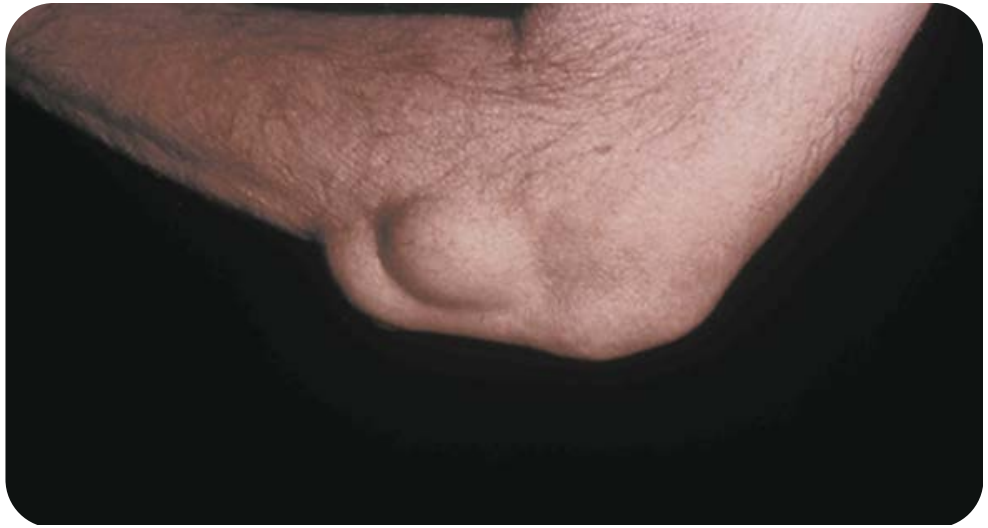
- Marginal erosions and joint space narrowing on x-ray



Adapted from Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arth Rheum.*1988;31:315–324.

Rheumatoid Arthritis (RA): Extra-articular Manifestations[1]

- Nodules occur in about 30 – 40% of patients
  - Positive RF and/or HLA-DR4 positive
  - Males
  - Severe and active disease
- Can occur at any age after onset
- Occasionally systemic manifestations include vasculitis, visceral nodules, Sjögren's syndrome, or pulmonary fibrosis



1 Cojocaru M, Cojocaru IM, Silosi I. Extra-articular Manifestations in Rheumatoid Arthritis. *Maedica* . 2010 Dec; 5(4): 286–291.

Burden of Disease

Burden of Rheumatoid Arthritis (RA)

$19B

annual estimated direct health care costs in the US[1]

9,100

hospitalizations in 2012[2]

~$30,000

Annual direct purchase cost of biologic medications before insurance[1]

$374M

total hospital charges in 2012[2]

2.9M

ambulatory care visits in 2007[3]

1 www.rheumatoidarthritis.org/treatment/costs/ Accessed October 18, 2016.
2 http://www.cdc.gov/arthritis/basics/rheumatoid.htm. Accessed October 18, 2016.
3 https://www.cdc.gov/nchs/data/series/sr_13/sr13_169.pdf Accessed October 18, 2016

Complications of Rheumatoid Arthritis (RA)

The most common comorbidities among people with arthritis in order of prevalence:

1. Cardiovascular Disease[1,2]
2. Infections[1,2]
3. Mental Health Condition[1]
   - Anxiety and depression
4. Malignancies[1]
   - i.e. Lymphoma and Multiple Myeloma
5. Others[2]
   - Osteoporosis
   - Rheumatoid nodules
   - Abnormal body composition (BMI)
   - Lung disease
   - Dry eyes and mouth. (Sjögren's syndrome)
   - Carpal tunnel syndrome

1 http://www.cdc.gov/arthritis/basics/rheumatoid.htm. Accessed October 18, 2016.
2 http://www.mayoclinic.org/diseases-conditions/rheumatoid-arthritis/symptoms-causes/dxc-20197390. Accessed September 5, 2016.

Mortality

- Increased mortality compared to general population
- Lymphoma, atherosclerosis / myocardial Infarction

Men lose
4 years

Women lose
10 years

Pincus T, Callahan LF. What is the natural history of rheumatoid arthritis? *Rheum Dis Clin North Am*. 1993;19:123–151.

Impact on Quality of Life

- People with Rheumatoid Arthritis (RA) have lower functional status than those with osteoarthritis, and those without arthritis[1]
- One quality of life study compared those with RA (self-reported) and those without RA, and people with RA were[1]:

40%
more likely to report fair or poor general health

30%
more likely to need help with personal care

2x
as likely to have a health-related activity limitation

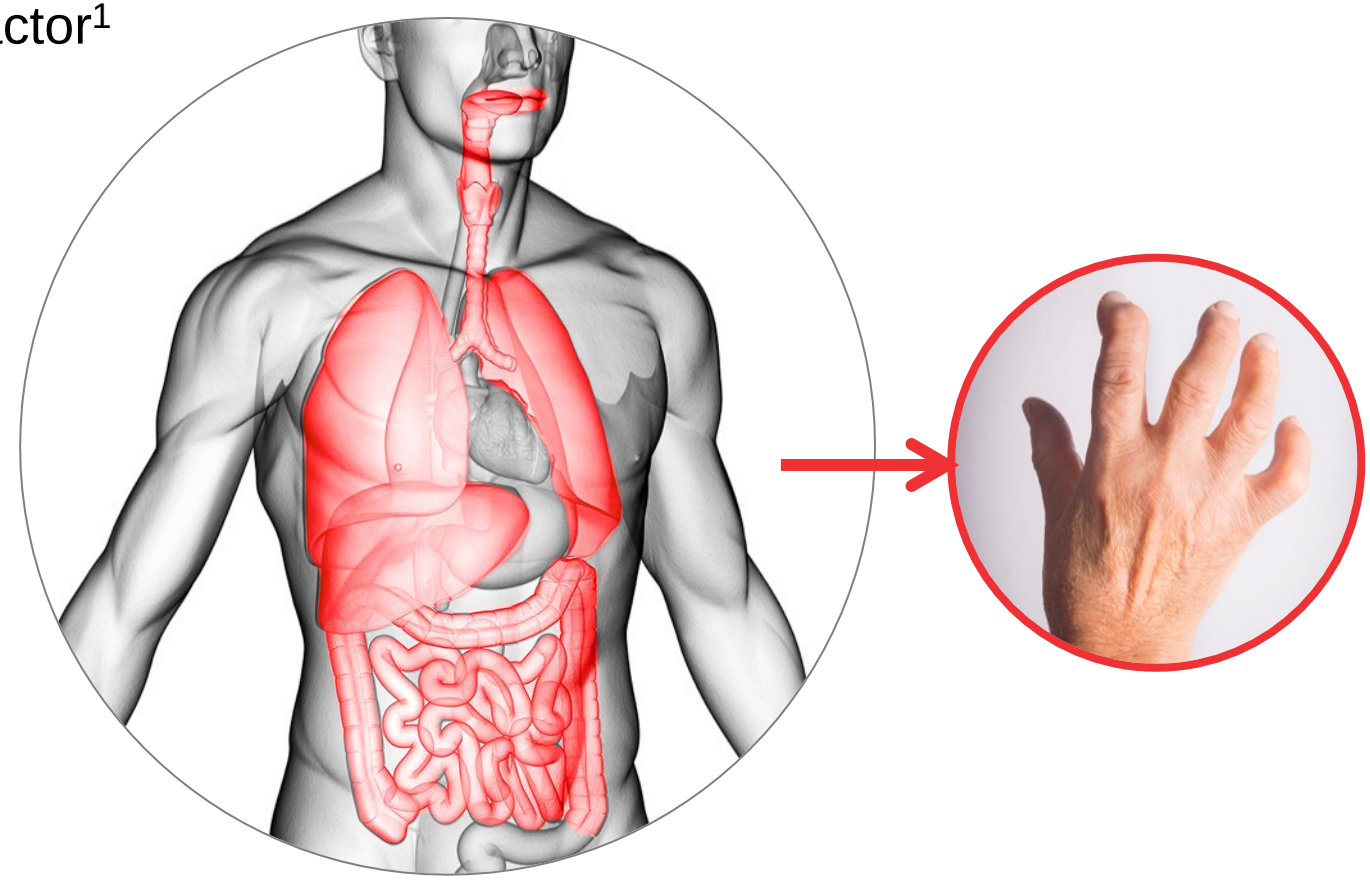
1 http://www.cdc.gov/arthritis/basics/rheumatoid.htm Accessed October 18, 2016.

Pathogenesis / Causal Factors

Mucosal Sites and Smoking as a Trigger in Rheumatoid Arthritis (RA) Development

Growing evidence suggests RA initiates outside the joint

- Smoking is the primary environmental risk factor[1]
- Association between RA and mucosal sites (lung, oral cavity and gut)[2]
  - Increases in gut bacteria *Prevotella copri*, a gram-negative anaerobe



1 Scott DL, Wolfe F, Huizinga TW. Rheumatoid Arthritis. *Lancet.* 2010 Sep 25;376(9746):1094–1108.
2 Brusca SB, Abramson SB, Scher JU. Emerging data implicates the microbiome in RA pathogenesis. Mucosal sites exposed to a high load of bacterial antigens - such as the periodontium, lung, and gut – may represent the initial site of autoimmune generation. *Curr Opin Rheumatol*. 2014 January;26(1):101–107.

Genetics and Risk of Rheumatoid Arthritis (RA) Development

RA Susceptibility Loci

- Expression of two HLA-DRB1*04 alleles – causes an elevated risk for nodular disease, major organ involvement and surgery related to joint destruction[2]

50%

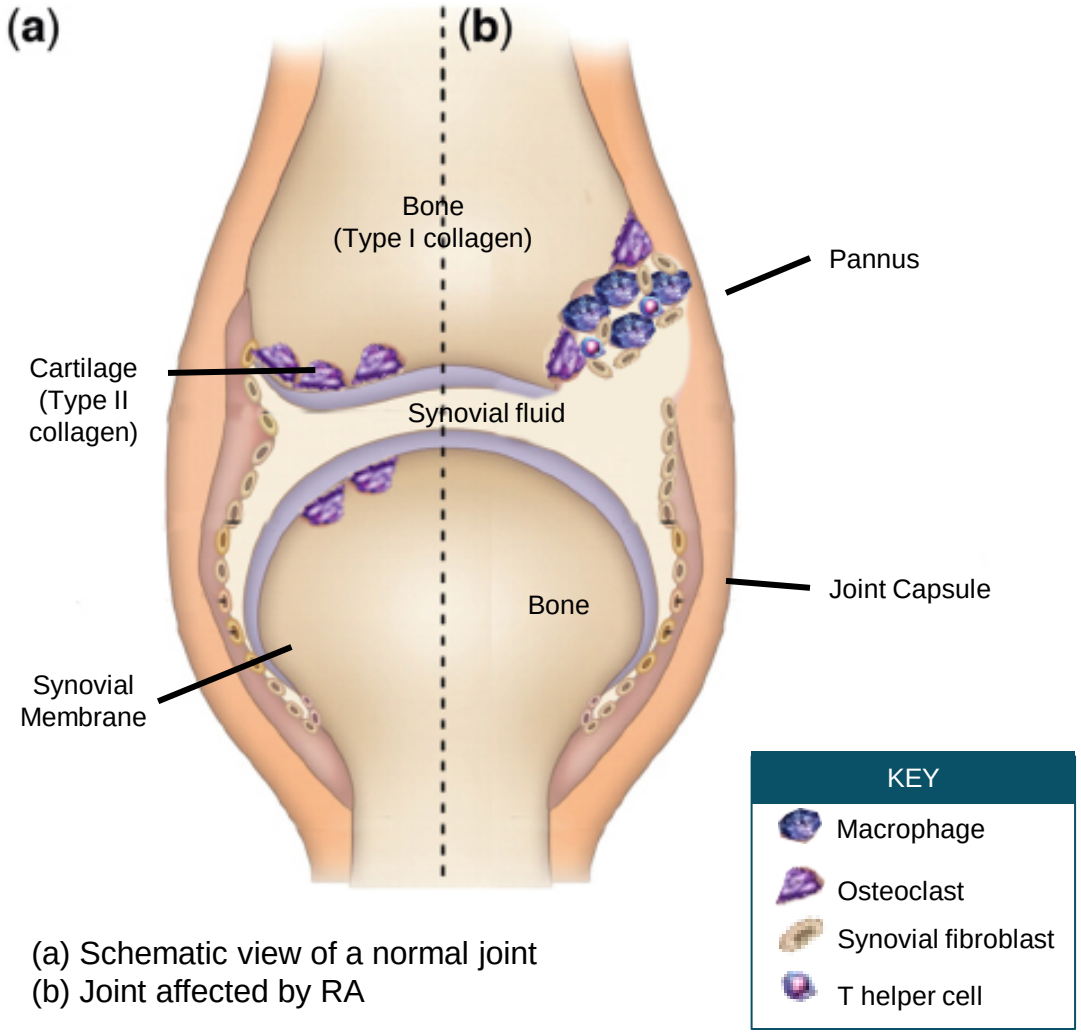
of the risk for development of RA is attributable to genetic factors[1]

>80%

of patients carry the epitope of the HLA-DRB1*04 cluster[2]

1 Scott DL, Wolfe F, Huizinga TW. Rheumatoid Arthritis. Lancet. 2010 Sep 25;376(9746):1094–108. doi: 10.1016/S0140–6736(10)60826–4.
2 Choy E. Understanding the dynamics: pathways involved in the pathogenesis of rheumatoid arthritis. *Rheumatology.* 2012; 51,(suppl 5):v3-v11.

Tissue Reaction and Matrix Remodeling in Advanced Rheumatoid Arthritis

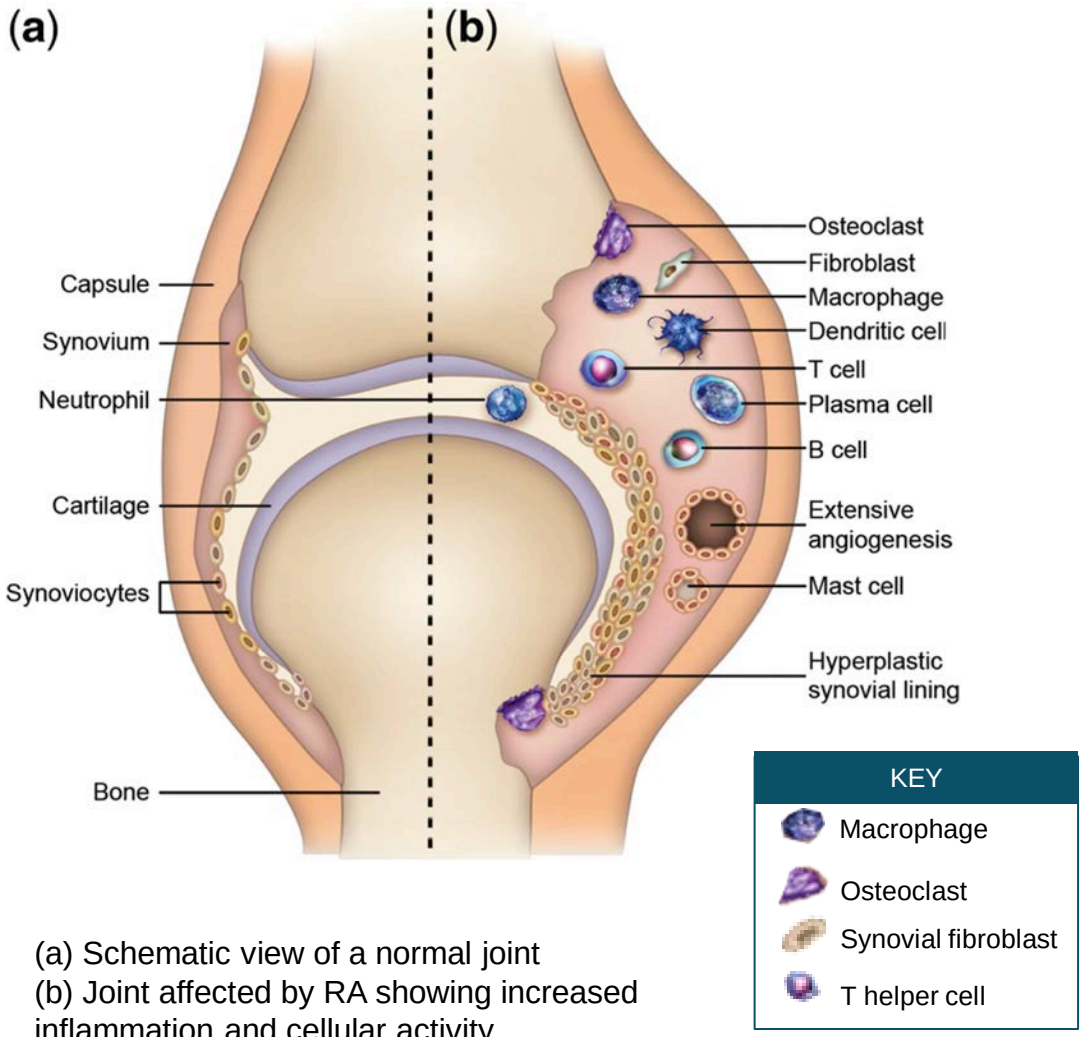


(a) Schematic view of a normal joint
(b) Joint affected by RA

- Arthritic synovial fibroblasts
  - Main source of destructive proteinases (e.g. matrix metalloproteinase and cathepsins)
  - Mediate pannus invasion of bone and articular cartilage
- Pannus-infiltrating macrophages contribute to joint degradation after their activation by increased cytokine and protease expression

1 Schurigt U. Role of Cysteine Cathepsins in Joint Inflammation and Destruction in Human Rheumatoid Arthritis and Associated Animal Models, 2013. *Innovative Rheumatology*, Dr. Hiroaki Matsuno (Ed.), InTech.

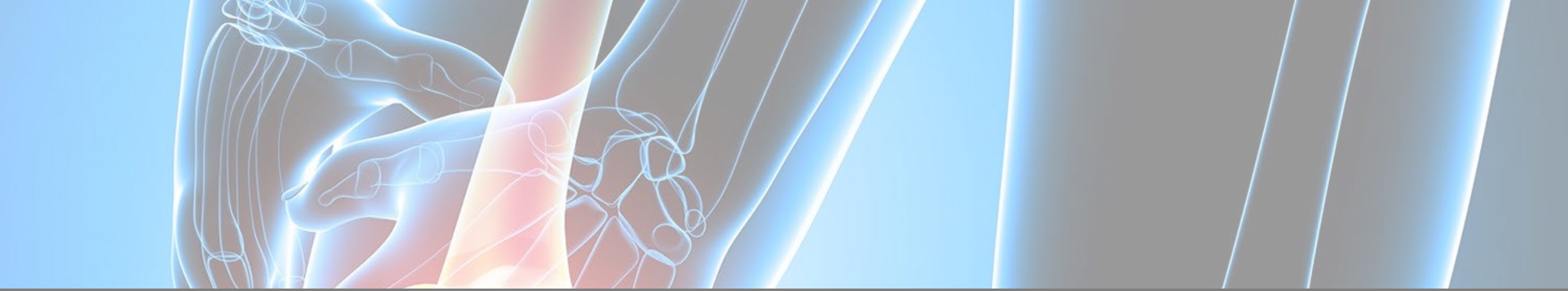
Pathophysiology – Inflammation and Cellular Activity in Rheumatoid Arthritis



(a) Schematic view of a normal joint
(b) Joint affected by RA showing increased inflammation and cellular activity

- Complex interaction of immune modulators
  - Cytokines and effector cells) and signaling pathways
  - Responsible for joint damage that begins at the synovial membrane and covers most IA structures
- Synovitis
  - T cells, B cells, plasma cells, dendritic cells, macrophages and mast cells) influx and/or local activation of mononuclear cells; and by angiogenesis
- Synovial lining becomes hyperplastic, and the synovial membrane expands and forms villi.
- Osteoclast-rich portion of the synovial membrane, or pannus, destroys bone, whereas enzymes secreted by neutrophils, synoviocytes and chondrocytes degrade cartilage

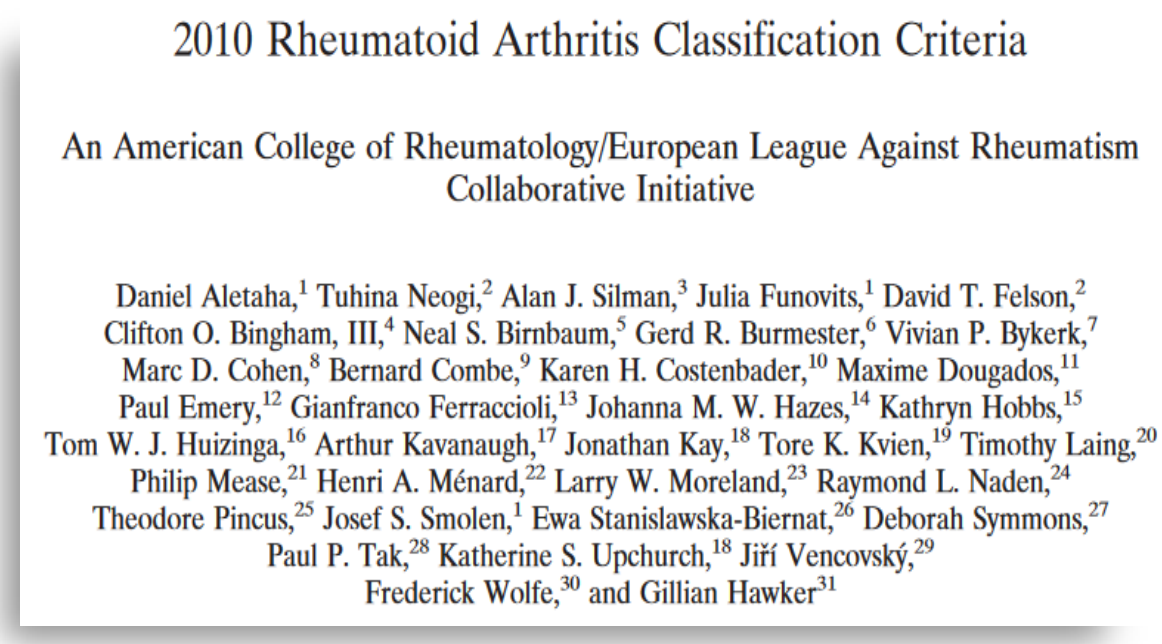
1 Choy E. Understanding the dynamics: pathways involved in the pathogenesis of rheumatoid arthritis. *Rheumatology.* 2012;51,(suppl 5):v3–v11.



Guidance Criteria for Diagnosis

Classification Criteria Update – An American and European Collaborative Initiative

American College of Rheumatology (ACR)

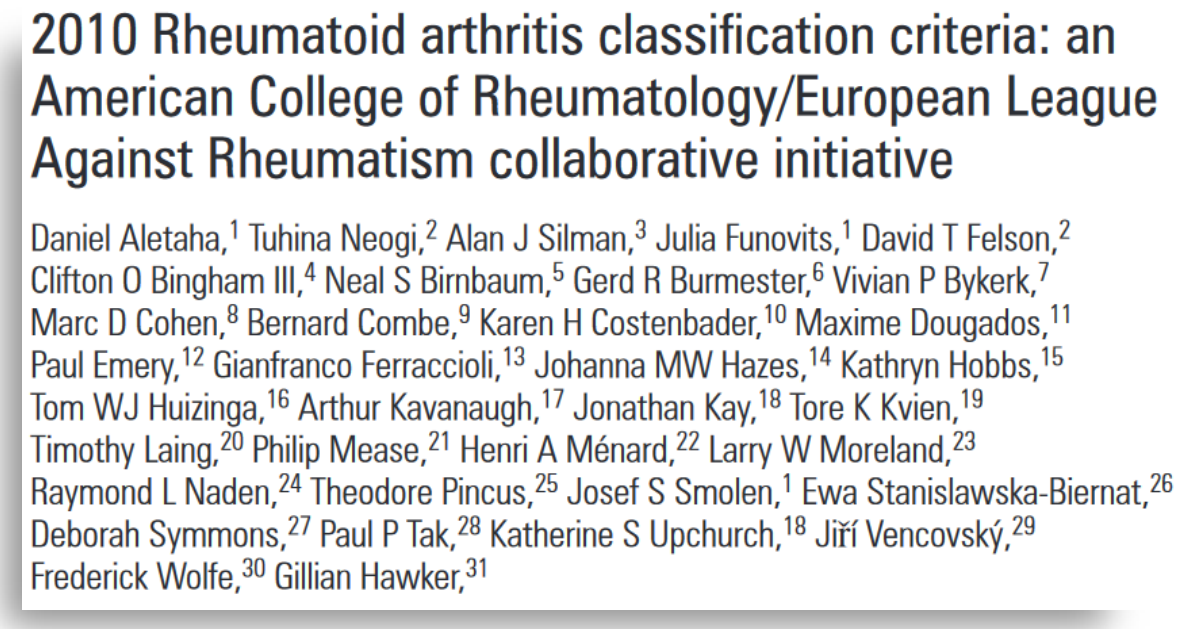


2010 Rheumatoid Arthritis Classification Criteria

An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative

Daniel Aletaha,[1] Tuhina Neogi,[2] Alan J. Silman,[3] Julia Funovits,[1] David T. Felson,[2] Clifton O. Bingham, III,[4] Neal S. Birnbaum,[5] Gerd R. Burmester,[6] Vivian P. Bykerk,[7] Marc D. Cohen,[8] Bernard Combe,[9] Karen H. Costenbader,[10] Maxime Dougados,[11] Paul Emery,[12] Gianfranco Ferraccioli,[13] Johanna M. W. Hazes,[14] Kathryn Hobbs,[15] Tom W. J. Huizinga,[16] Arthur Kavanaugh,[17] Jonathan Kay,[18] Tore K. Kvien,[19] Timothy Laing,[20] Philip Mease,[21] Henri A. Ménard,[22] Larry W. Moreland,[23] Raymond L. Naden,[24] Theodore Pincus,[25] Josef S. Smolen,[1] Ewa Stanislawska-Biernat,[26] Deborah Symmons,[27] Paul P. Tak,[28] Katherine S. Upchurch,[18] Jiří Vencovský,[29] Frederick Wolfe,[30] and Gillian Hawker[31]

European League Against Rheumatism (EULAR)



2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative

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1 Aletah D, Neogi T, Silman AJ, et. al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*. 2010; Sep;62(9):2569–2581.
2 Aletah D, Neogi T, Silman AJ, et. al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative .*Ann Rheum Dis* 2010; 69 :1580–1588.

Classification Criteria ≠ Diagnostic Criteria in Rheumatic Diseases

- Criteria are labeled as “classification” criteria NOT diagnostic criteria
  - Influenced by age, gender, population, etc.
  - Includes many more aspects than can be included in formal criteria
  - May help clinical diagnosis by a rheumatologist
- For the purpose of classification, radiographs should only be performed
- Need to precisely define erosions (size, site, number)
- No exhaustive list of exclusions is defined
- Limits false positive classification

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Aletah D, Neogi T, Silman AJ, et. al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*. 2010;Sep;62(9):2569–2581.

2010 ACR / EULAR Classification Criteria for Rheumatoid Arthritis (RA)

JOINT DISTRIBUTION (0 – 5 points)	Points
1 large joint	0
2 – 10 large joints	1
1 – 3 small joints (large joints not counted)	2
4 – 10 small joints (large joints not counted)	3
>10 joints (at least one small joint)	5
SEROLOGY (0 – 3 points)	**Points**
RF IgM (–) AND ACPA (–)	0
RF IgM (low positive) OR ACPA (low positive)	2
RF IgM (high positive) OR ACPA (high positive)	3
SYMPTOM DURATION (0 – 1 points)	**Points**
< 6 weeks	0
≥ 6 weeks	1
ACUTE PHASE REACTANTS (0 – 1 points)	**Points**
Normal CRP AND normal ESR	0
Abnormal CRP OR abnormal ESR	1

Interpretation of "SEROLOGY"

Negative: ≤ULN (for the respective lab)

Low positive: >ULN but ≤3xULN

High positive: >3xULN

www.rheumatology.org/Portals/0/Files/ra_class_slides.pdf

Biomarkers for Assessing Rheumatoid Arthritis

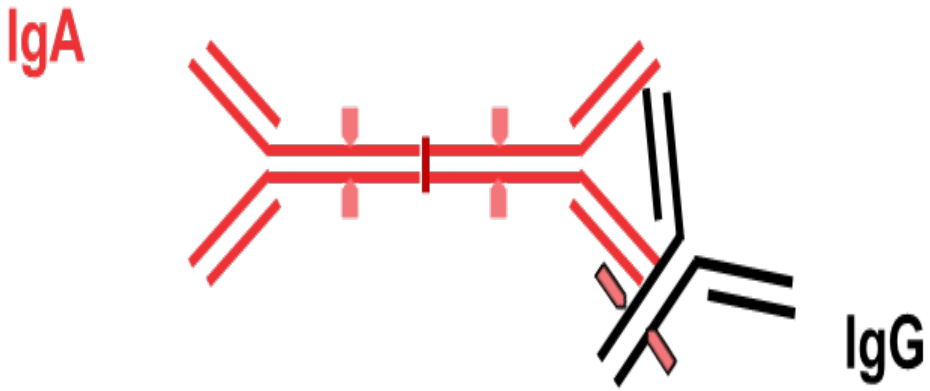
Rheumatoid Factor (RF), the original Rheumatoid Arthritis Biomarker

- Introduced in the 1940's[1]
- Sensitivity 50 - 90%[1]
- Low specificity[1]
  - Present in other inflammatory diseases[1]
  - Present in up to 25% of healthy individuals[1]
- RF activity can be found in IgM, IgA, IgG, IgD, & IgE

RF IgA Antibodies appear

3.2 years

before symptoms[2]



1 https://en.wikipedia.org/wiki/Rheumatoid_factor#cite_ref–1. Last accessed September 20, 2016

2 Taylor P, Gartemann J, Hsieh J., et al. A Systematic Review of Serum Biomarkers Anti-Cyclic Citrullinated Peptide and Rheumatoid Factor as Tests for Rheumatoid Arthritis. *Autoimmune Diseases*, 2011, Article ID 815038, 18 pages.

Rheumatoid Factor (RF) Assays Differ in Performance

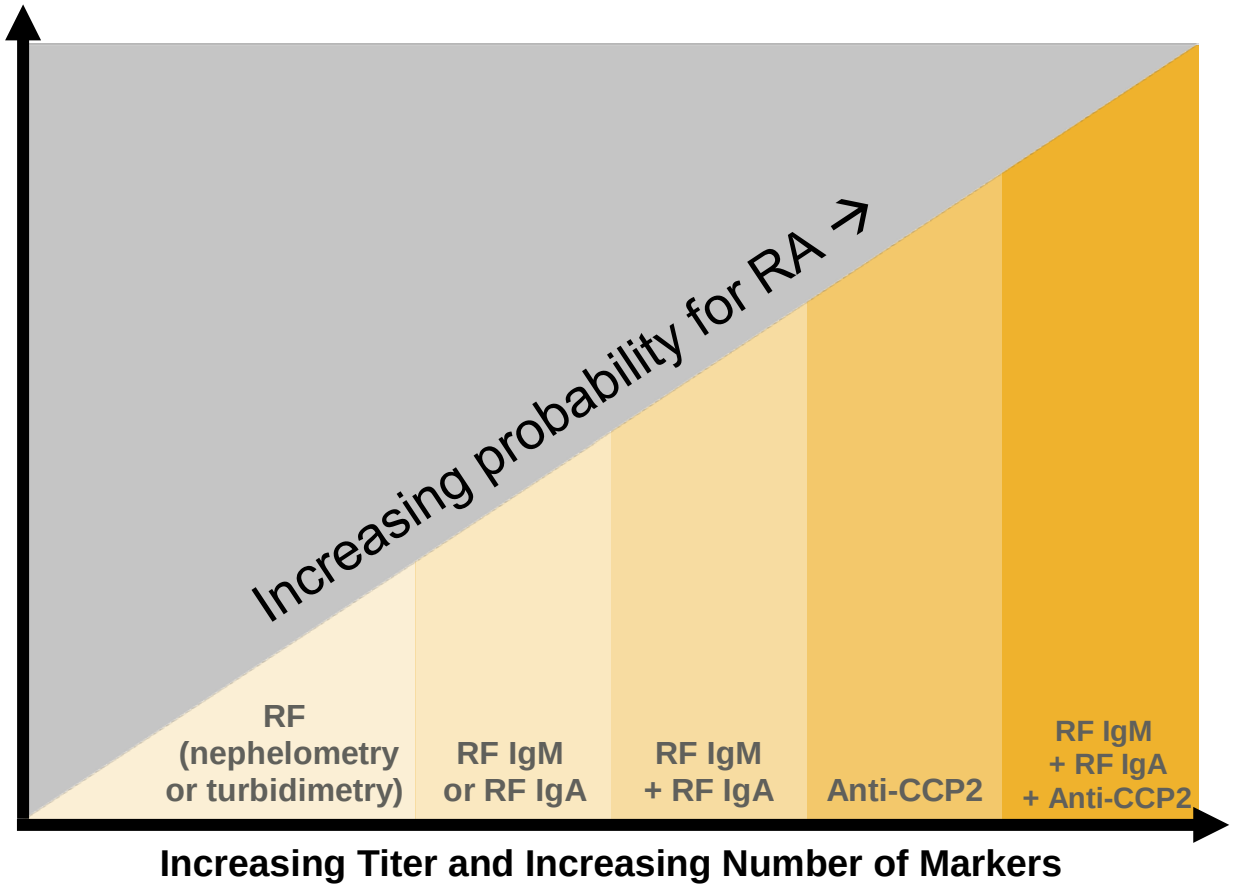
Method	Manufacturer	RF Isotype Detected	Average Sensitivity[1]	Average Specificity[1]	Average Positive Likelihood Ratio[2]
Latex Agglutination	various	IgM	61.7%	84.0%	9.9
Nephelometry	Beckman Immage 800, Siemens Vista	IgM, IgG, IgA*	72.9%	78.8%	6.7
EliA RF IgM	Thermo Fisher Scientific	IgM	63%	88.6%	10.3
Turbidimetric	Roche, Abbott, Siemens, and Beckman automated platforms	IgM, IgG, IgA*	86%	82%	High false positive rate because RF IgG is common in healthy individuals and other diseases

* Nephelometric and turbidimetric assays cannot differentiate the individual RF isotypes[2]

1 Nishimura, K; Sugiyama, D; Kogata, Y, et. al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. *Annals of Internal Medicine.* 5 June 2007;146 (11):797–808.
2 Jaskowski TD, Hill HR, Russo KL, et al. Relationship Between Rheumatoid Factor Isotypes and IgG Anti-Cyclic Citrullinated Peptide Antibodies. *J Rheumatol* 2010;37:1582–1588.
3 Likelihood Ratios Part 1: Introduction, http://omerad.msu.edu/ebm/diagnosis/diagnosis6.html. Last accessed on September 4, 2016.

Serologic Testing – Positivity Combinations Tie to Higher Risk of Rheumatoid Arthritis

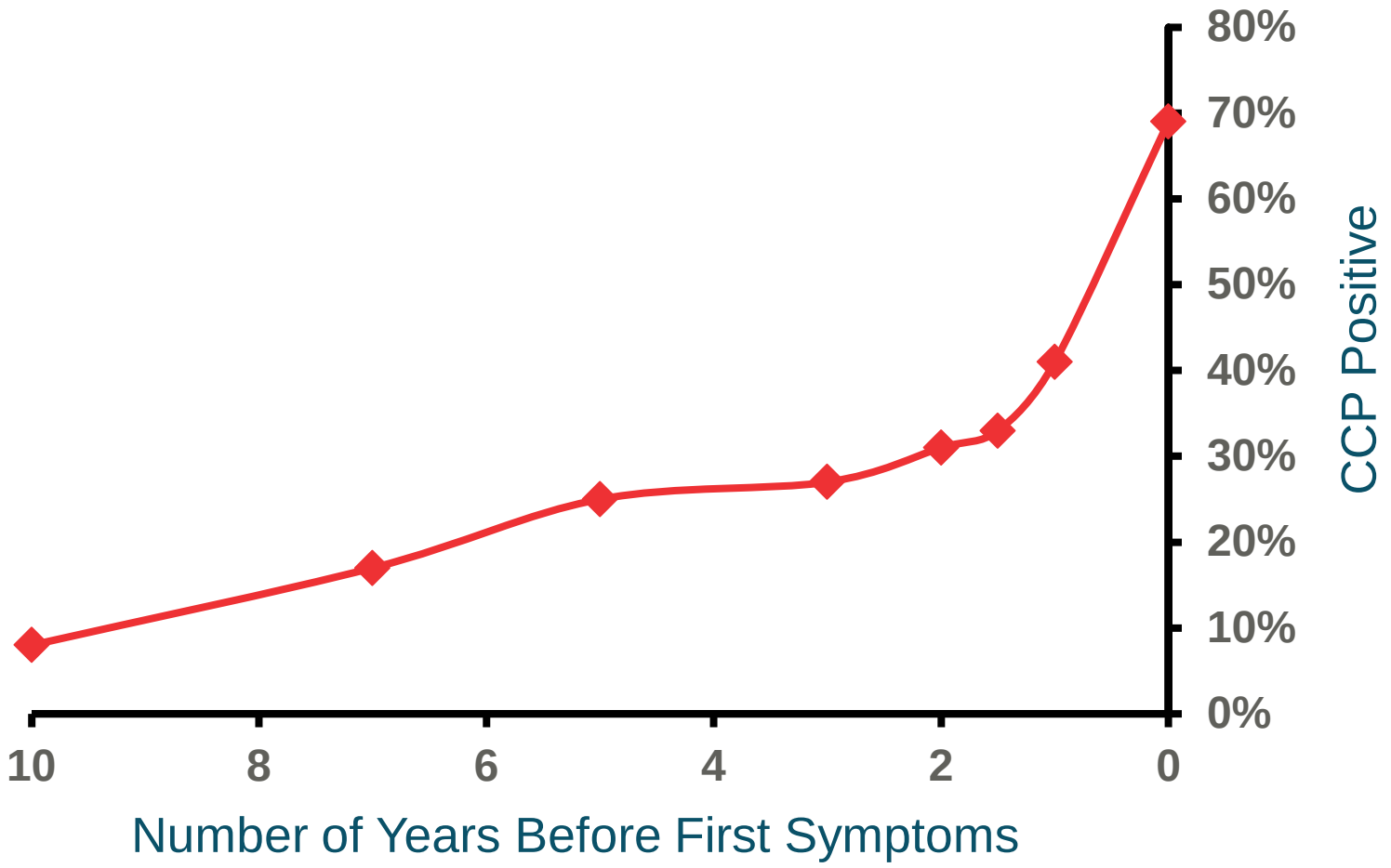
- 2010 Criteria includes both RF IgM and CCP as equal options for serologic workup[1]
- In contrast to a combined elevation of IgM and IgA RF, elevation of only one RF isotype may not be a significant risk factor for the development of RA[2]
- Positivity of RF IgM and CCP correlates with a higher risk of RA[3,4]



1 Aletaha D et al. Rheumatoid Arthritis Classification Criteria. An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. *Arthritis Rheum* 2010;62:2569–2581.
2 Jonsson T et al. Elevation of only one rheumatoid factor isotype is not associated with increased prevalence of rheumatoid arthritis: a population based study. *Scand J Rheumatol* 2000;29:190–191.
3 Jaskowski TD, Hill HR, Russo, KL, et al. Relationship Between Rheumatoid Factor Isotypes and IgG Anti-Cyclic Citrullinated Peptide Antibodies. *J Rheumatol* 2010;37:1582–1588.
4 Taylor P, Gartemann J, Hsieh J., et al. A Systematic Review of Serum Biomarkers Anti-Cyclic Citrullinated Peptide and Rheumatoid Factor as Tests for Rheumatoid Arthritis. *Autoimmune Diseases*, 2011, Article ID 815038, 18 pages.

Anti-Citrullinated Protein Antibodies (ACPA)

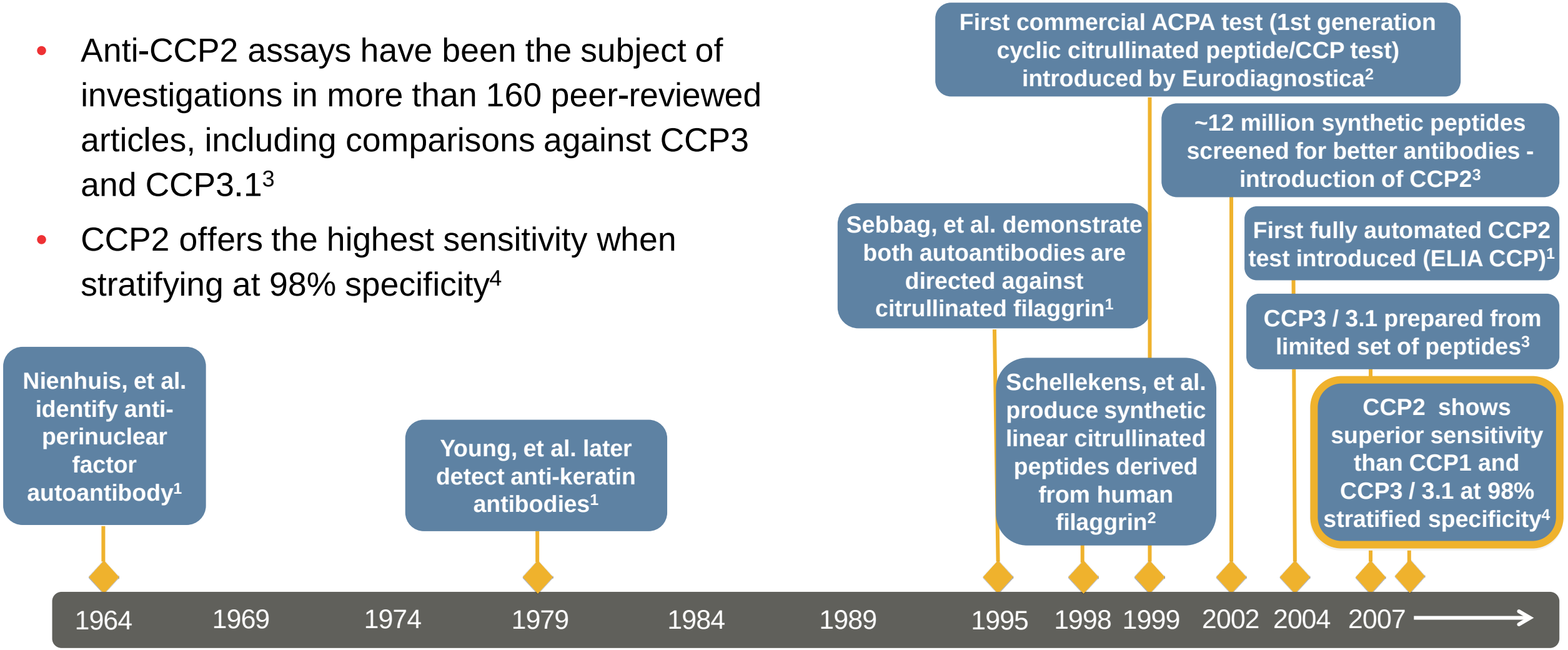
- CCP antibodies appear in early stage rheumatoid disease
- Early diagnosis allows earlier treatment – early therapy slows disease progression[1]
- Anti-CCP antibody and RFs of all isotypes predated the onset of RA by several years[1]



Adapted from Figure 2. Rantapää-Dahlqvist et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. *Arthritis Rheum.* 2003;48:2741–2749.

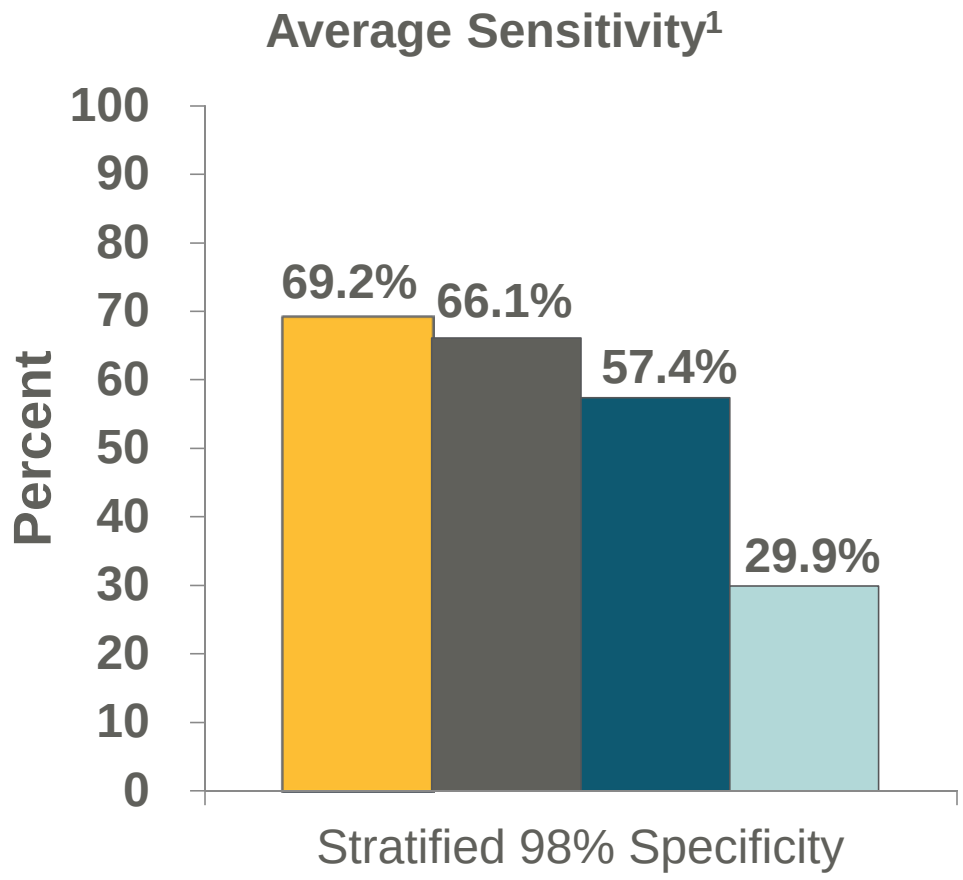
History of ACPA Assays

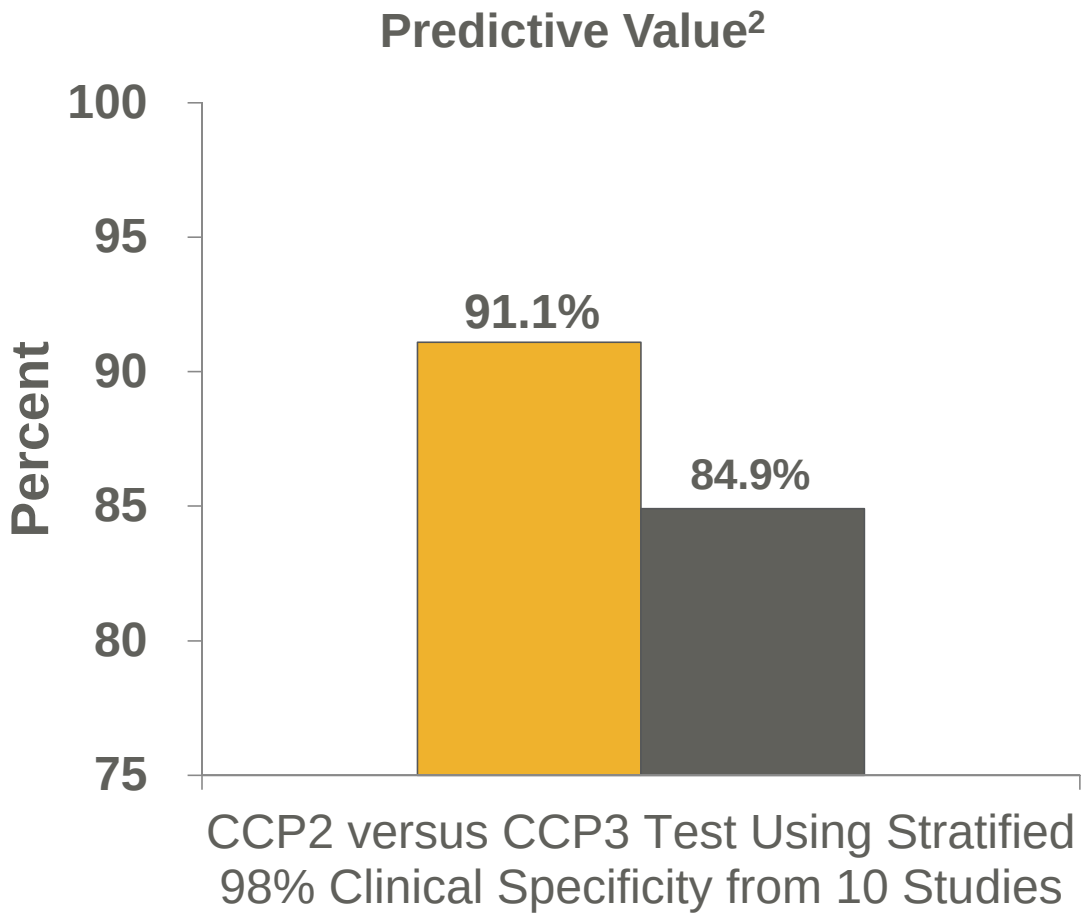
- Anti-CCP2 assays have been the subject of investigations in more than 160 peer-reviewed articles, including comparisons against CCP3 and CCP3.1[3]
- CCP2 offers the highest sensitivity when stratifying at 98% specificity[4]



1 Herold M, Boeser V, Russe E, et al. Anti-CCP: history and its usefulness. *Clinical and Developmental Immunology*. 2005;12(2):131–135.
2 Aggarwal R, Liao K, Nair R, et al. Anti-Citrullinated Peptide Antibody (ACPA) Assays and their Role in the Diagnosis of Rheumatoid Arthritis. *Arthritis Rheum*. 2009 November 15; 61(11):1472–1483.
3 Van Venrooij, W J, van Beers JJBC, and Pruijn GJM. Anti-CCP antibodies: the past, the present and the future. *Nat. Rev. Rheumatol*.2011;7,391–398.
4 Bizzaro N, Tonutti E, Tozzoli R, et al. Analytical and Diagnostic Characteristics of 11 2nd- and 3rd-Generation Immunoenzymatic Methods for the Detection of Antibodies to Citrullinated Proteins. *Clinical Chemistry*. 2007;53:8,1527–1533.

Comparing Sensitivity & Predictive Value of Rheumatoid Arthritis Serology Tests



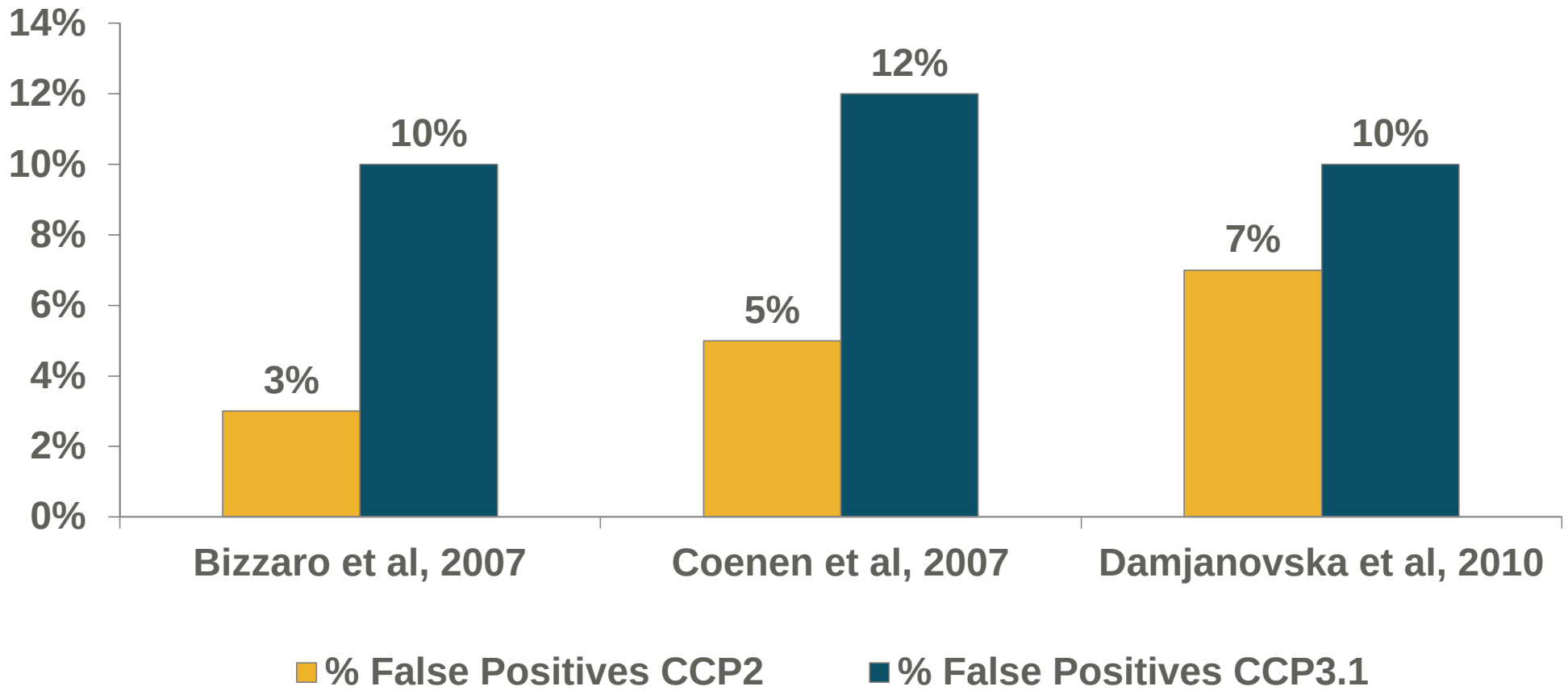


EliA CCP2 | CCP 3.0 | CCP 3.1 | RF

1 Adapted from Pruijn GJM, Wiik A, van Venrooij WJ. The use of citrullinated peptides and proteins for the diagnosis of rheumatoid arthritis *Arthritis Research & Therapy* 2010;12:203.
2 Wiik AS, et al, All you wanted to know about anti-CCP but were afraid to ask. *Autoimmun Rev* (2010), doi:10.1016/j.autrev.2010.08.009.

ACPA Test Performance… When a Name is Only a Name

- CCP2 across studies continues to be the better performing APCA test[1]



1 Grenmyr E, Sommarin Y. Anti-CCP2 is the anti-citrullinated protein antibody (ACPA) test with highest diagnostic value in rheumatoid arthritis. Poster no. 32, 11th Dresden Symposium on Autoantibodies, September 2013

Large Laboratory – Population, Prevalence, Specificity and Sample Source Still Impact Accuracy

Primary Care Source

Prevalence	1.0%	1.0%
	CCP2 (EliA)	CCP3.1
Sensitivity[1]	74.0%	74.0%
Specificity[1]	98.6%	89.6%
Population Size	500,000	500,000

Evaluation Summary	CCP2 (EliA)	CCP3.1
PPV	33.3%	6.7%
NPV	99.7%	99.7%
False +	7,425	51,480
False –	1,300	1,300

CCP2 = 44,055 fewer false positives

1 Bizzaro N, Tonutti E, Tozzoli R, et al. Analytical and Diagnostic Characteristics of 11 2nd- and 3rd-Generation Immunoenzymatic Methods for the Detection of Antibodies to Citrullinated Proteins. *Clinical Chemistry*. 2007;53:8,1527–1533.
** Rheumatology Advisor to Thermo Fisher Scientific.

Large Laboratory – Population, Prevalence, Specificity and Sample Source Still Impact Accuracy

Specialty Practice Source

Prevalence	50.0%	50.0%
	CCP2 (EliA)	CCP3.1
Sensitivity[1]	74.0%	74.0%
Specificity[1]	98.6%	89.6%
Population Size	500,000	500,000

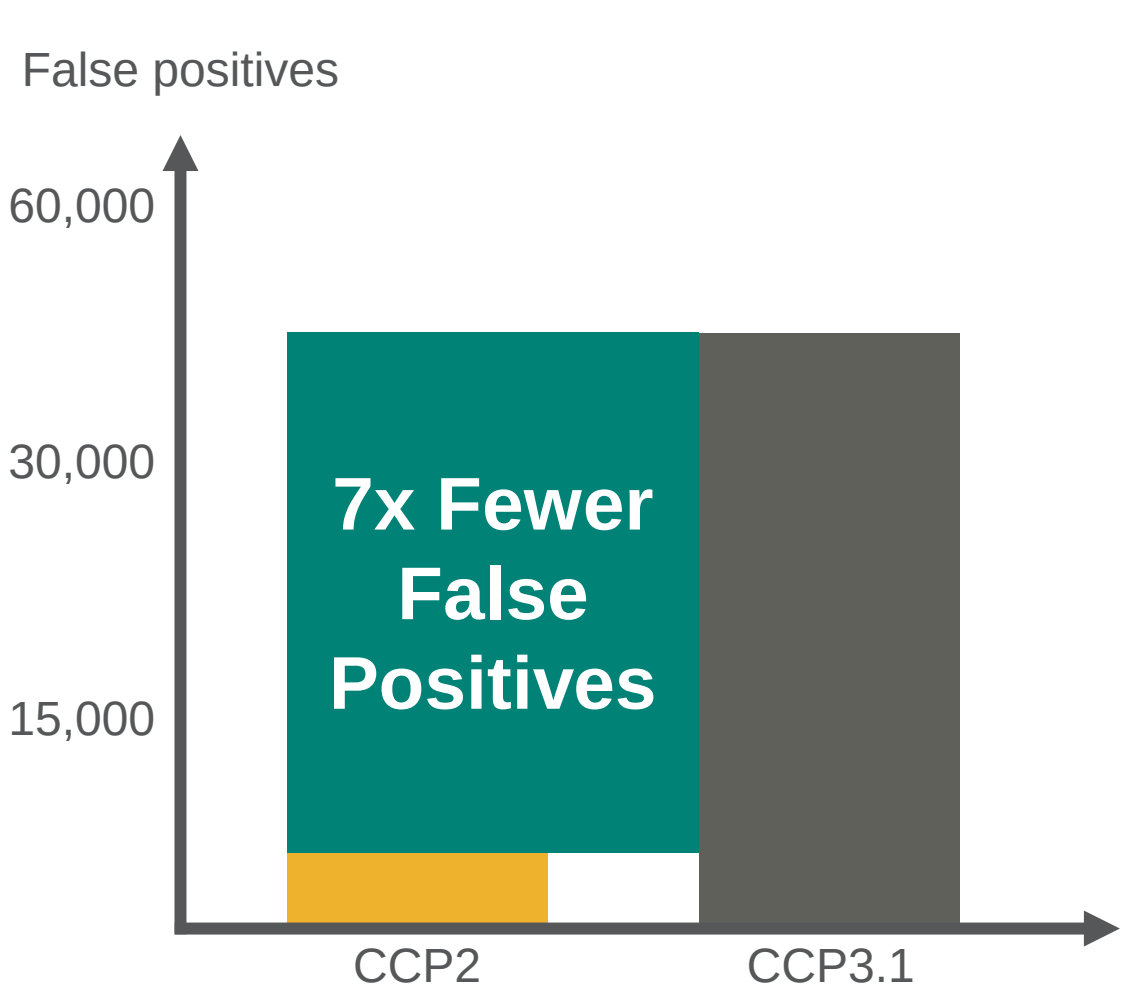
Evaluation Summary	CCP2 (EliA)	CCP3.1
PPV	98.0%	87.7%
NPV	79.1%	77.5%
False +	3,750	26,000
False –	65,000	65,000

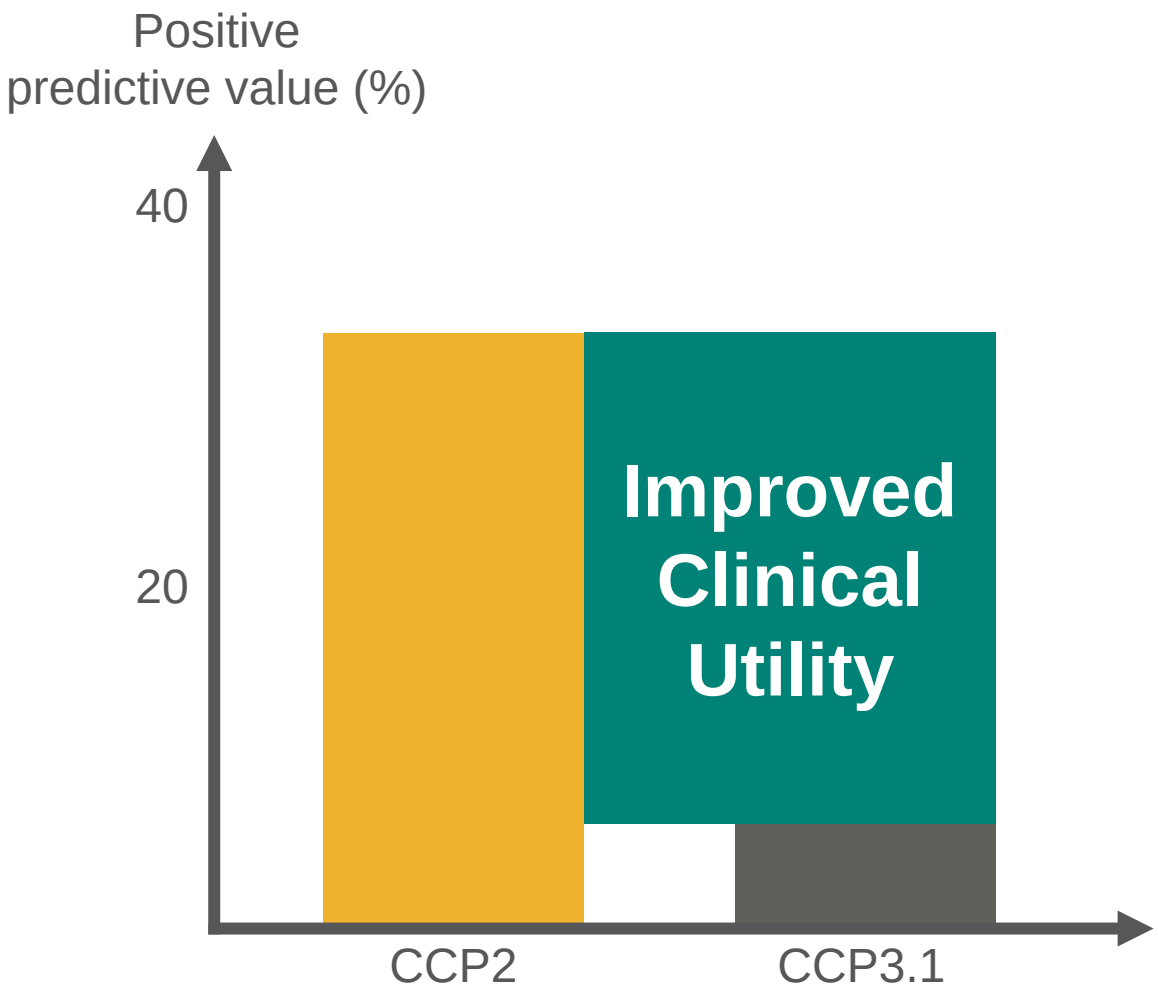
CCP2 = 22,750 fewer false positives

1 Bizzaro N, Tonutti E, Tozzoli R, et al. Analytical and Diagnostic Characteristics of 11 2nd- and 3rd-Generation Immunoenzymatic Methods for the Detection of Antibodies to Citrullinated Proteins. *Clinical Chemistry*. 2007;53:8,1527–1533.
** Rheumatology Advisor to Thermo Fisher Scientific.

Effect of Prevalence and Specificity on Clinical Utility: Rheumatoid Arthritis

1% Prevalence Primary Care Population





1 Bizzaro N, Tonutti E, Tozzoli R, et al. Analytical and Diagnostic Characteristics of 11 2nd- and 3rd-Generation Immunoenzymatic Methods for the Detection of Antibodies to Citrullinated Proteins. *Clinical Chemistry*. 2007;53:8,1527–1533.

98% Stratified Specificity[1]

Why Does Clinical Accuracy Matter?

Missed diagnosis	Unnecessary referrals	Over and misdiagnosis
Untreated disease	Additional lab testing	Emotional trauma
Deterioration	Higher healthcare utilization and costs	Inappropriate therapy

Example / Simple Referral Guide – Serologic Algorithm for Rheumatoid Arthritis (RA)

1. Clinical Suspicion	Symptoms of early Arthritis (one or more Joints) (assess joint distribution and assign points)					
	↓				↓	
2. Lab Diagnostics	**SEROLOGY** CCP + RF IgM + RF IgA				**ACUTE PHASE REACTANTS** Inflammatory Markers (ESR, CRP)	
	↓					
3. Differential Diagnosis	CCP (+) RF IgM (+) RF IgA (+)	CCP (-) RF IgM (+) RF IgA (+)	CCP (-) RF IgM (+) RF IgA (-)	CCP (-) RF IgM (-) RF IgA (-)	Normal CRP + Normal ESR	Abnormal CRP or Abnormal ESR
	↓				↓	
	RA Very Likely	RA Very Likely	Possible RA	RA Less Likely	Active RA Less Likely	Active RA Possible (non-specific)
	↓				↓	
4. Re-evaluation / Treatment	Referral or appropriate treatment				Re-evaluate clinical symptoms, imaging and other serologic markers	

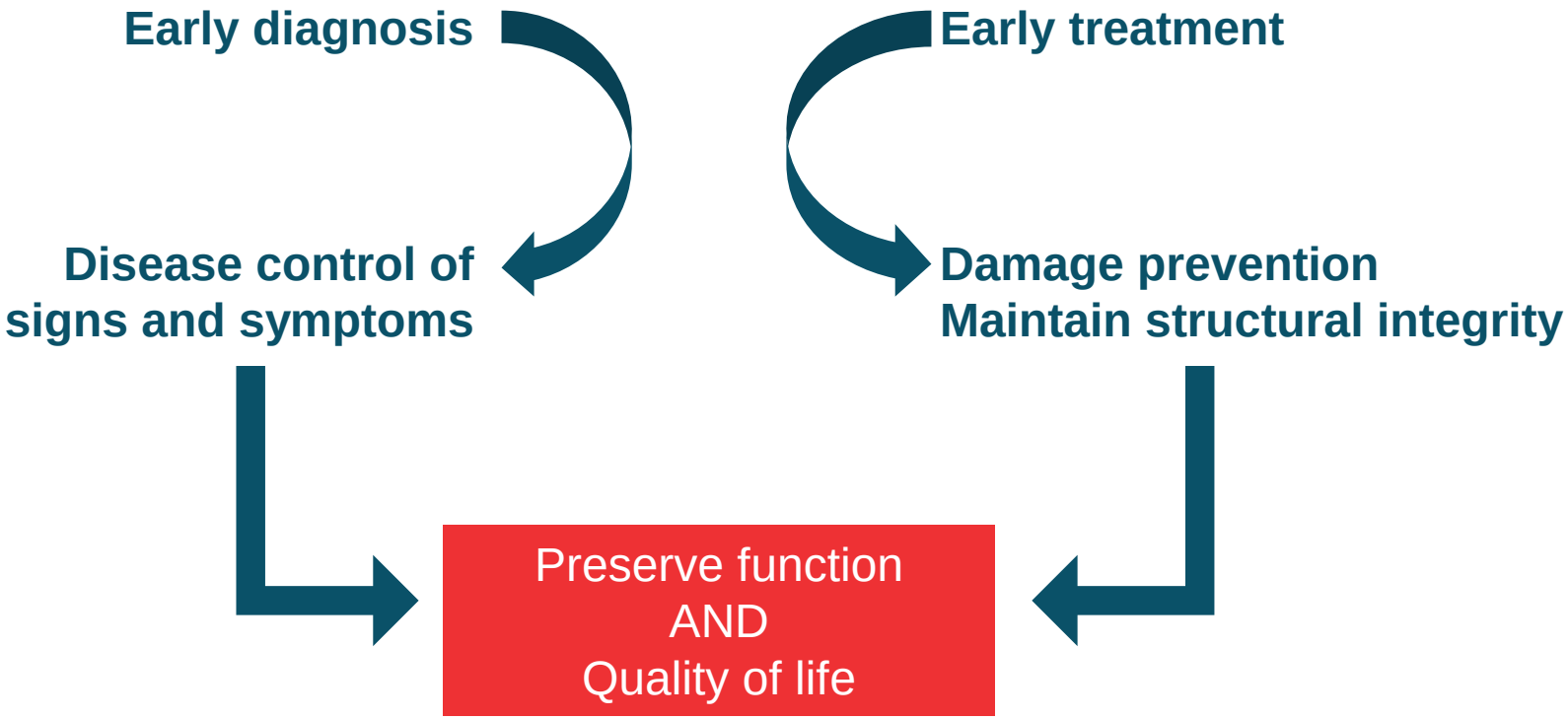
Adapted from Jaskowski TD, Hill HR, Russo, KL, et al. Relationship Between Rheumatoid Factor Isotypes and IgG Anti-Cyclic Citrullinated Peptide Antibodies. *J Rheumatol.* 2010;37:1582–1588.

Rheumatoid Arthritis (RA) Treatment

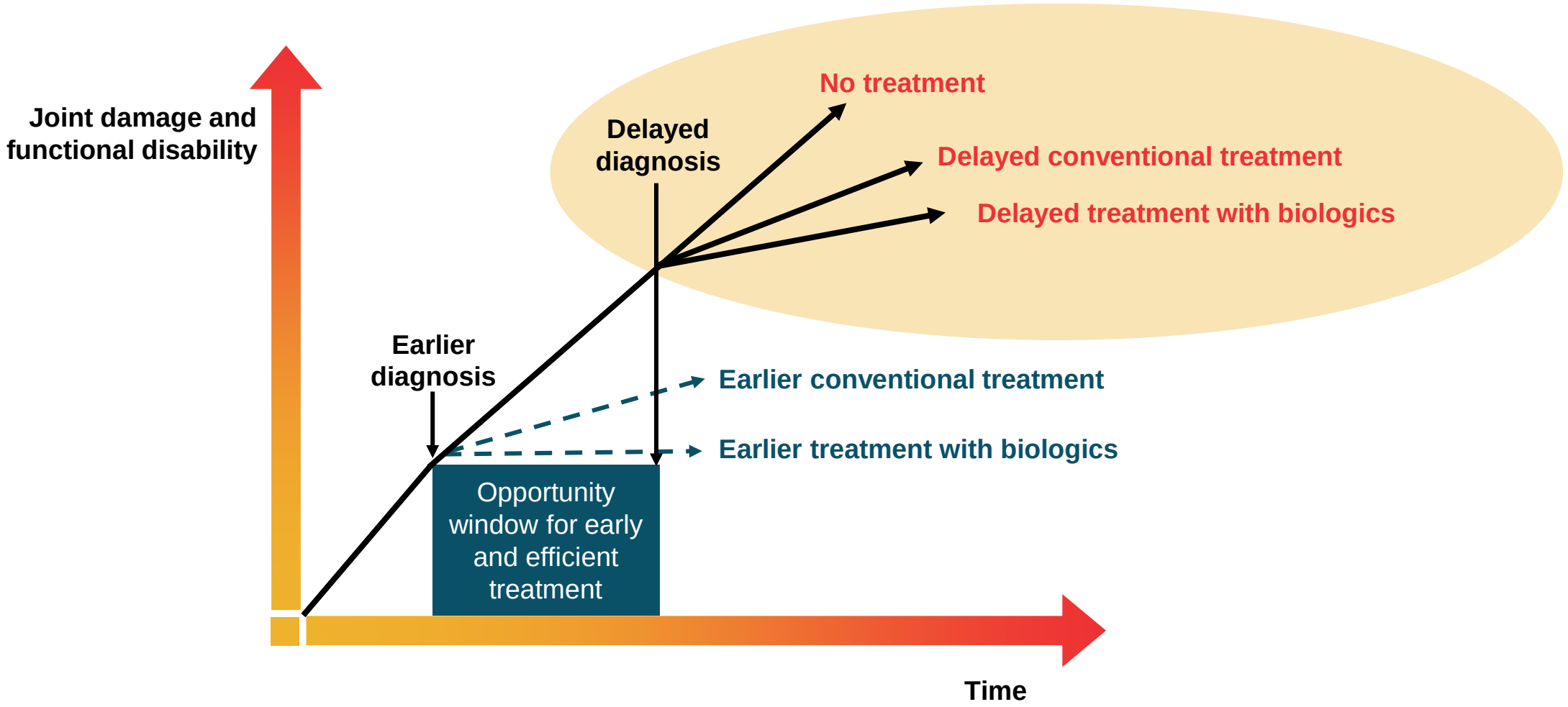
Paradigm shift: DMARD + biologic therapy for Rheumatoid Arthritis

2010 Treat to Target Recommendations

- Based on systematic literature review (19 full papers, 5 abstracts)



Rheumatoid Arthritis Goal: Gain Time for Treatments to Mitigate or Minimize Irreversible Destruction



1 Bukhari MAS, Wiles NJ, Lunt BJ, Scott DGI, Symmons DPM, Silman AJ. Influence of disease modifying therapy on radiographic progression in inflammatory polyarthritis at five years. *Arthritis Rheum* 2003;48:46–53.

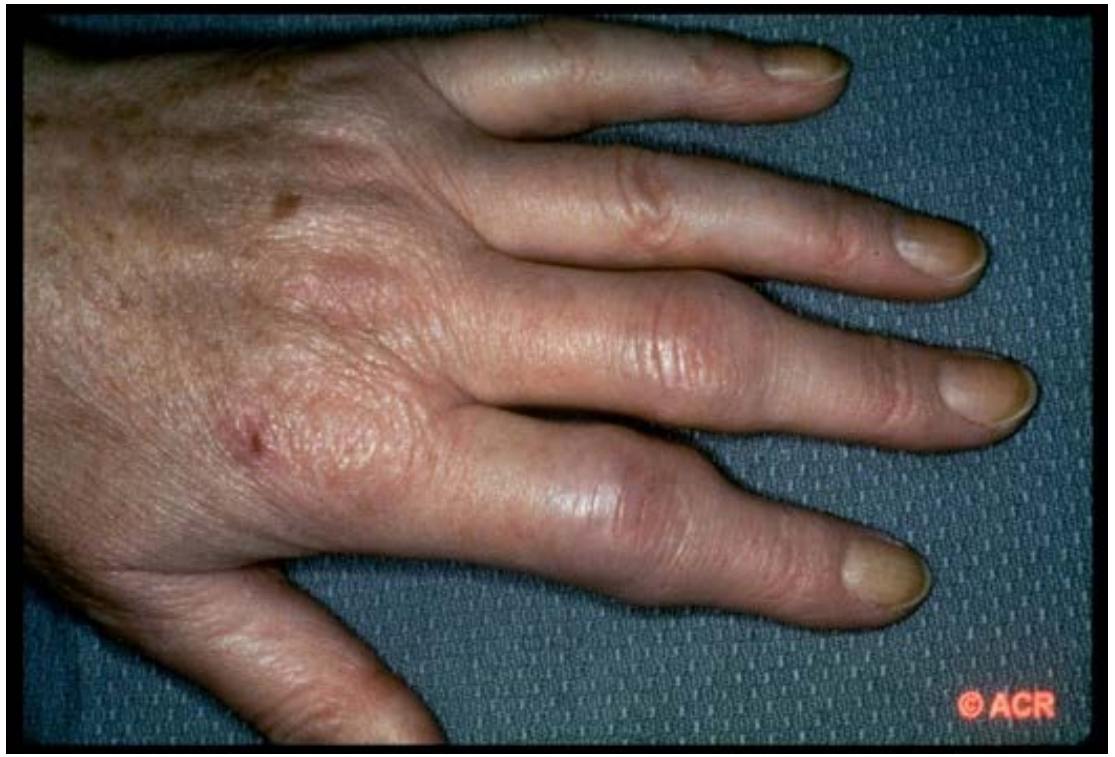
Case Study

Rheumatoid Arthritis Case

- The patient is a 32 year old female school teacher
- Chief complaint: hand pain, neck stiffness, and worsening fatigue over the last 3 months
- History
  - No recent infections, trauma, or travel
  - Pain is localized to knuckles of hand and pads of feet
  - Mother has unknown form of crippling arthritis
  - Ibuprofen helps some, and acetaminophen does not
  - No rash, nodules, oral ulcers, alopecia, or chest pain
  - Monogamous, no IV drug use
- Differential Diagnosis
  - Inflammatory arthritis (seronegative, psoriatic, rheumatoid, lupus)
  - Chronic infectious arthritis (Lyme, GC, hepatitis)
  - Fibromyalgia

Case Continued – Physical Findings

- Normal complete physical examination with the exception of the hands*, which were tender when palpated over the 2nd and 3rd proximal interphalangeal joints

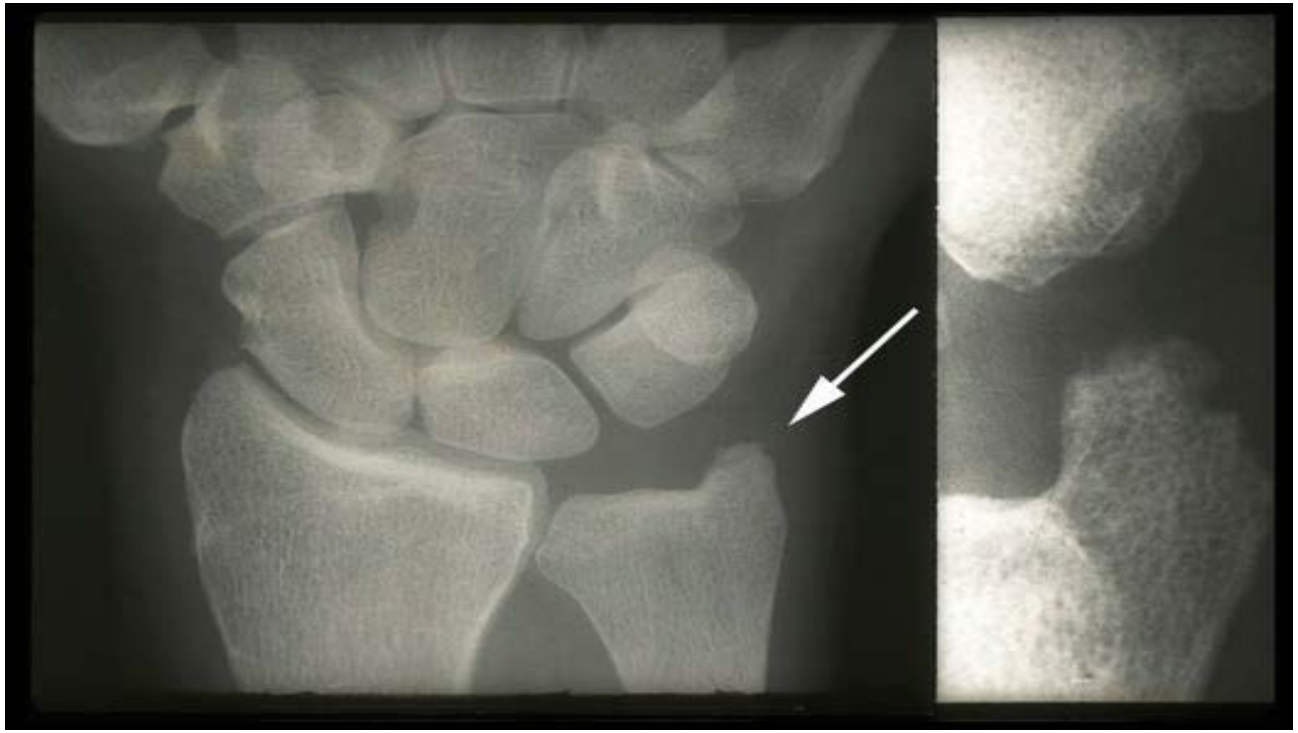


* representative

American College of Rheumatology Image bank

Case Continued – Diagnostic work up

- Imaging* – Marginal erosions were detected on radiographs
- Labs
  - CBC, Chem7, LFTs, urinalysis normal
  - ANA – Positive
  - Anti-dsDNA – Negative
  - Anti-CCP2 – Positive
  - RF IgM – Positive



* representative

Case – Wrap up

- Diagnosis
  - Inflammatory arthritis, rheumatoid
- Treatment
  - Steroids and methotrexate initially
  - Biologics or triple therapy if inadequate response
- Follow-up
  - Every 8-12 weeks in the beginning to assess therapies and monitor methotrexate labs
  - Physician visits may extend to every 3-6 months if well controlled

Summary

Take Home Points – Rheumatoid Arthritis (RA) Management

Disease and Disease Management

- RA is the second most common autoimmune disease
- It is a chronic, systemic inflammatory disorder affecting approximately 1.3 to 2.6M adults, and 294,000 children in the US[1]
- The cause of RA is unknown and there is no cure
- New criteria are geared for diagnosing RA early for aggressive intervention with a goal of remission
- Early treatment can help prevent irreversible joint damage, premature death, disability, and improve quality of life[2]
- Treatment costs are a burden, supporting the need to correctly identify patients

1 Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum*. 2008 Jan;58(1):15-25. doi: 10.1002/art.23177.
2 Herold M. Rheumatoid Arthritis. In: Shoenfeld Y and Meroni PL, ed. The General Practice Guide To Autoimmune Diseases. Lengerich, Germany: Pabst Science Publishers; 2012.63–71.

Take Home Points – Rheumatoid Arthritis (RA) Management (cont'd)

Serologic Markers and Test Selection

- In adults anti-CCP may be present 12-14 years prior to onset of overt clinical symptoms[1]
- In children, detection occurs closer to disease onset[1]
- In combination with other clinical measures, testing for anti-CCP and RF isotypes produces a positive predictive value (PPV) near 100%, greater than the PPV of each test
- *Not all CCP tests perform the same*.
  - At a stratified specificity of 98%, the sensitivity of anti-CCP2 tests is superior to all other CCP tests (anti-CCP1, anti-CCP3 and 3.1 assays)[2,3]
- The higher CCP2 test specificity produces fewer false positive results[2], which can reduce inappropriate referrals, inappropriate treatments, and the associated costs

1 Taylor P. et al. Systematic Review of CCP and RF. *Autoimmune Diseases*. 2011, Article ID 815038, 18 pages. doi:10.4061/2011/815038
2 Grenmyr E, Sommarin Y. Anti-CCP2 is the anti-citrullinated protein antibody (ACPA) test with highest diagnostic value in rheumatoid arthritis.Poster no 32, 11th Dresden Symposium on Autoantibodies, September 2013.
3 Bizzaro N, Tonutti E, Tozzoli R, et al. Analytical and Diagnostic Characteristics of 11 2nd- and 3rd-Generation Immunoenzymatic Methods for the Detection of Antibodies to Citrullinated Proteins. Clinical Chemistry. 2007;53:8,1527–1533.

Q&A