Brigham and Women's Hospital
Founding Member, Mass General Brigham

Rheumatoid Arthritis

Diagnosis and Management

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	Biomedical Informatics (secondary)

Disclosures

- Merck, UCB, consultant

Objectives

- Explain the definition of rheumatoid arthritis (RA)
- Discuss approaches for diagnosing RA
- Describe considerations surrounding RA treatments
  - What to do prior to starting therapy
  - Major treatment classes and their benefits/risks

Rheumatoid arthritis (RA)

- Most common systemic autoimmune inflammatory joint disease primarily affecting *synovial* joints
- Diagnosed clinically
  - Classification criteria mainly for research
- Inflamed synovium, hallmark of RA
  - “Classic” presentation
    - Bilateral symmetric small joint arthritis
      - Metacarpophalangeal (MCP), proximal interphalangeal (PIP), metatarsophalangeal (MTP)
    - Other than C1/C2, spine usually spared – no synovium

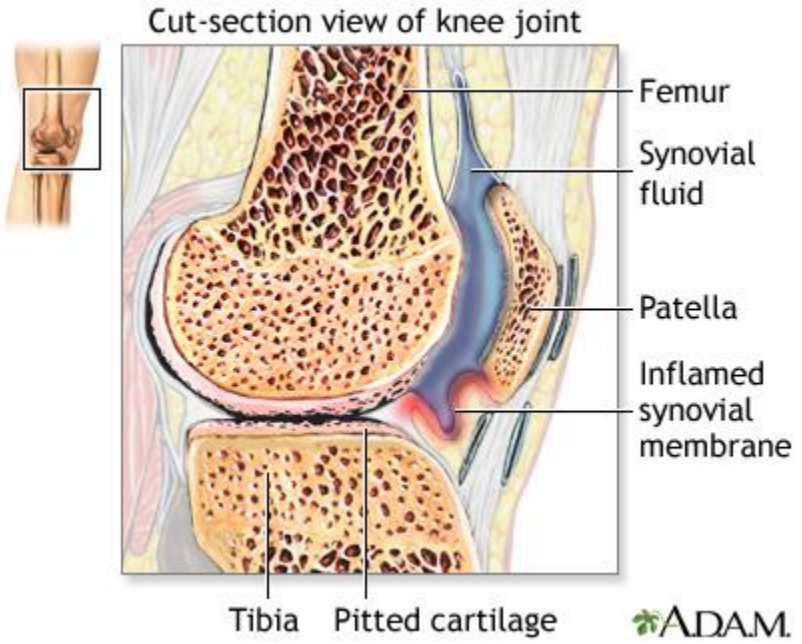
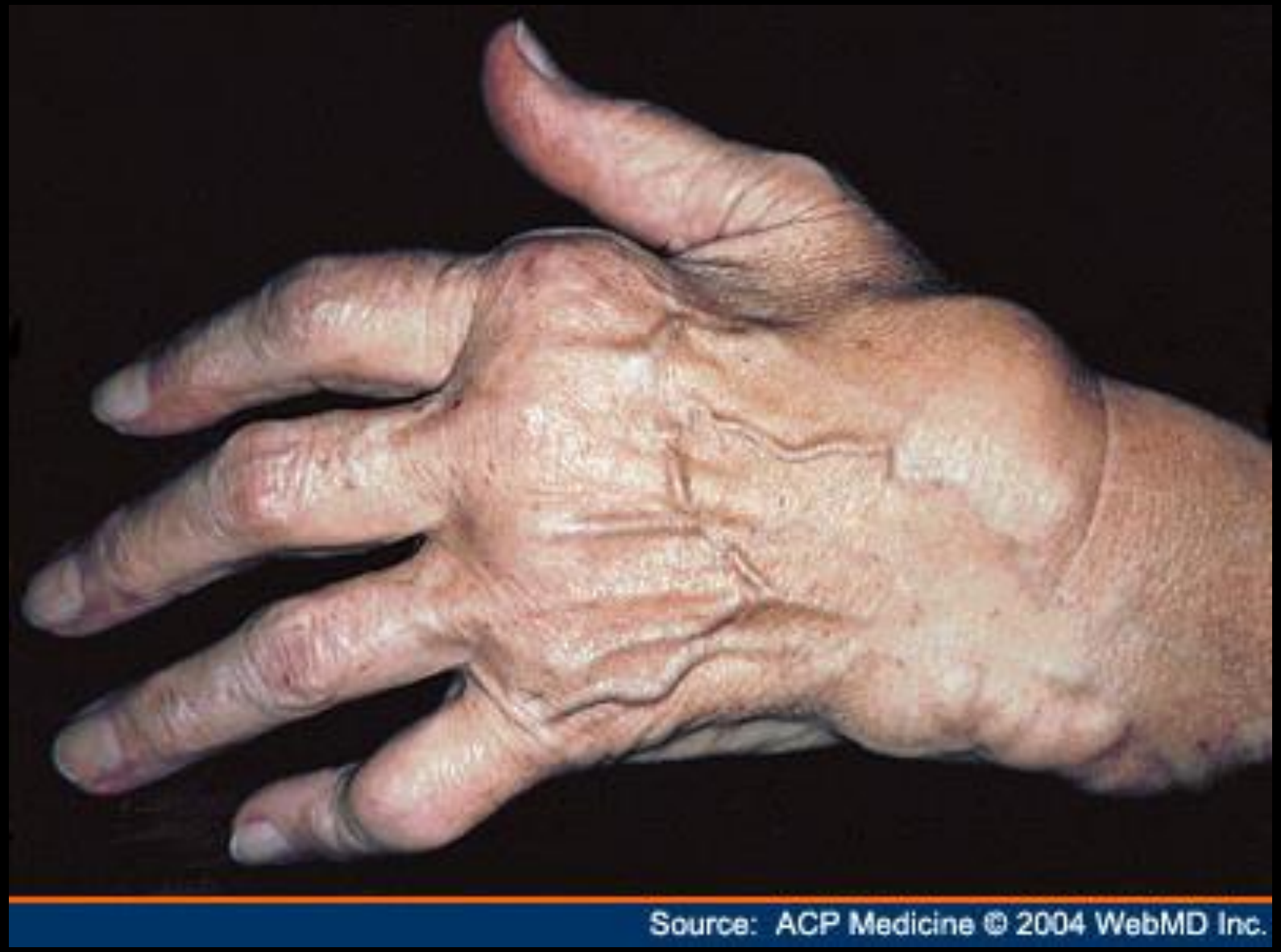


Image: https://medlineplus.gov/ency/article/000431.htm

RA diagnosis & evaluation

- History and exam
- Laboratory tests
- Imaging
- Extra-articular manifestations
- Other considerations
- 2010 ACR/EULAR Classification Criteria for RA



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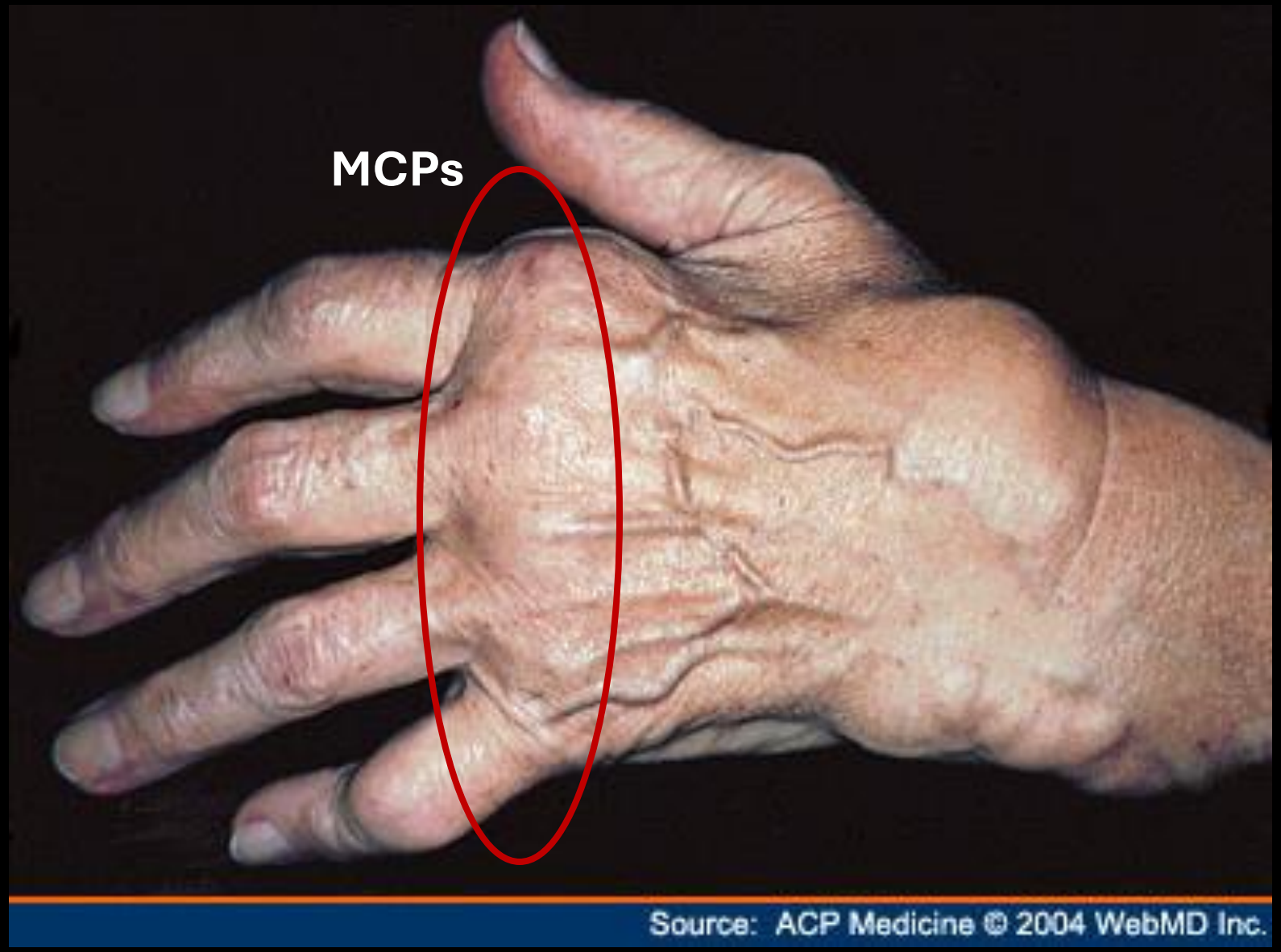
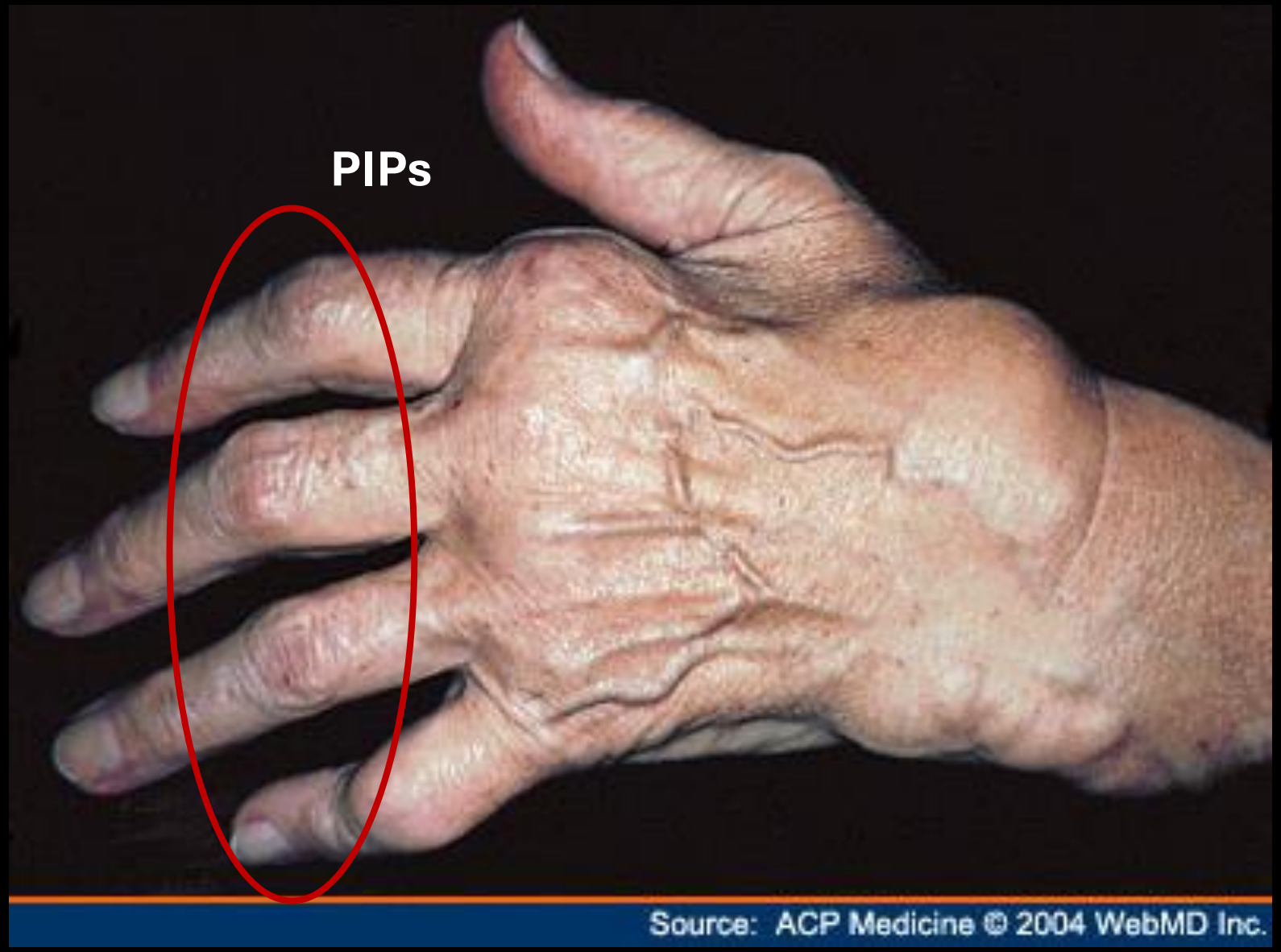

MCPs
Source: ACP Medicine © 2004 WebMD Inc.


PIPs
Source: ACP Medicine © 2004 WebMD Inc.

Source: ACP Medicine © 2004 WebMD Inc.

Characteristic history and exam

- Symmetric small joint pain and swelling
- AM stiffness >20 min

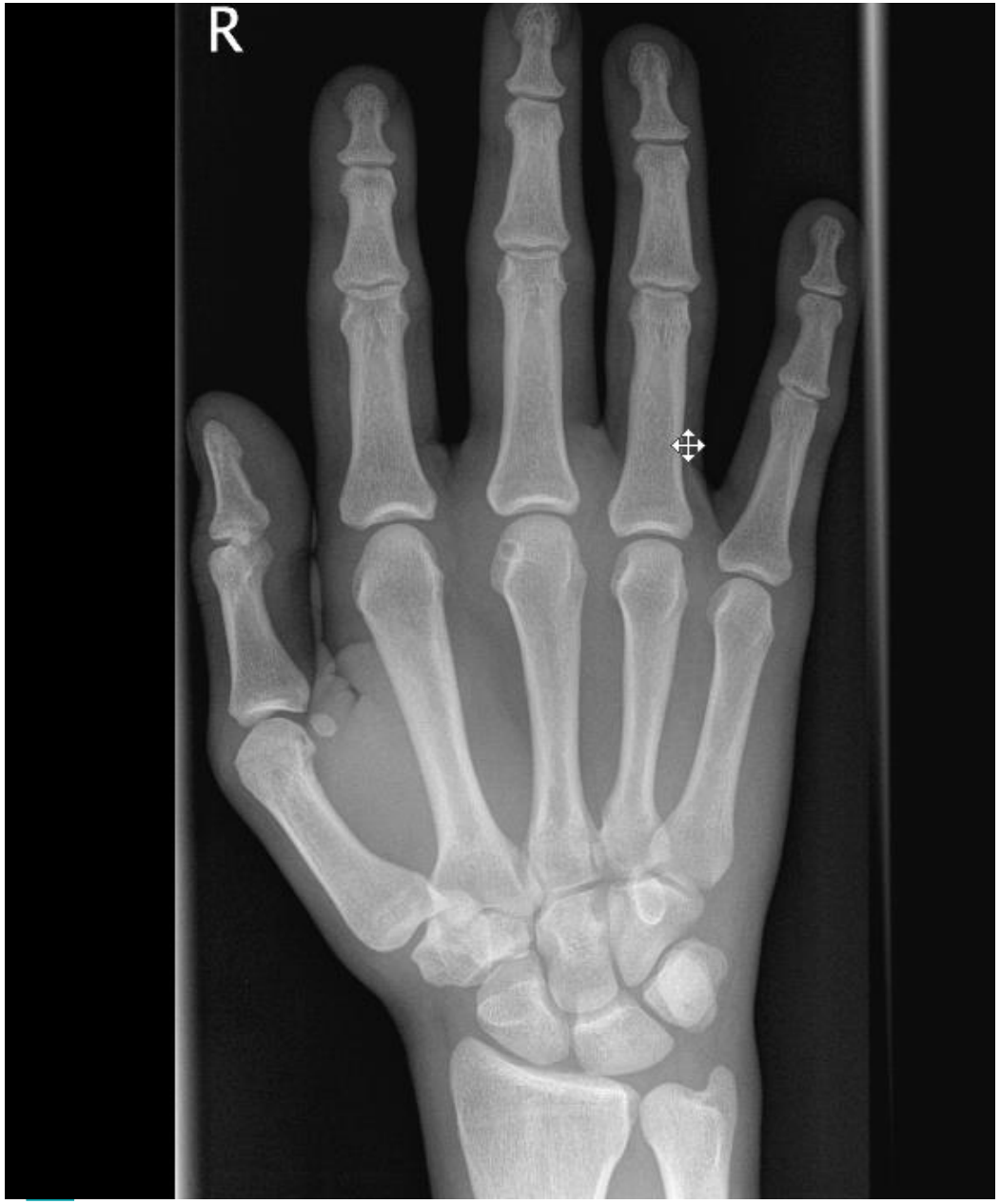
- Symmetric synovitis
  - Small joint involvement is most common
  - Joints generally spared
    - Distal interphalangeal joints (DIPs)
      - Synovial joint
    - Thoracic and lumbosacral spine
      - Cartilaginous joint; no synovium

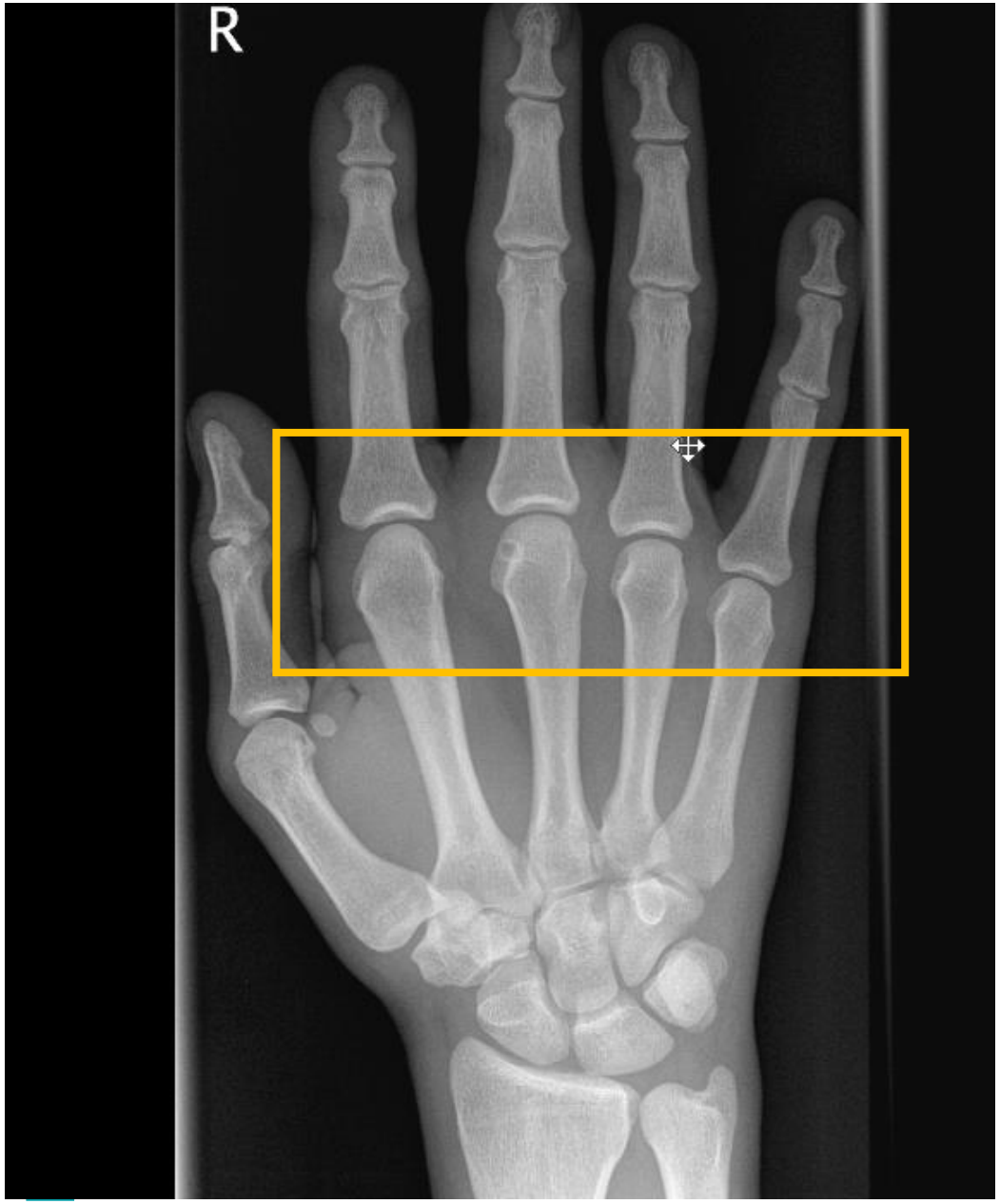
RA diagnosis: Laboratory studies

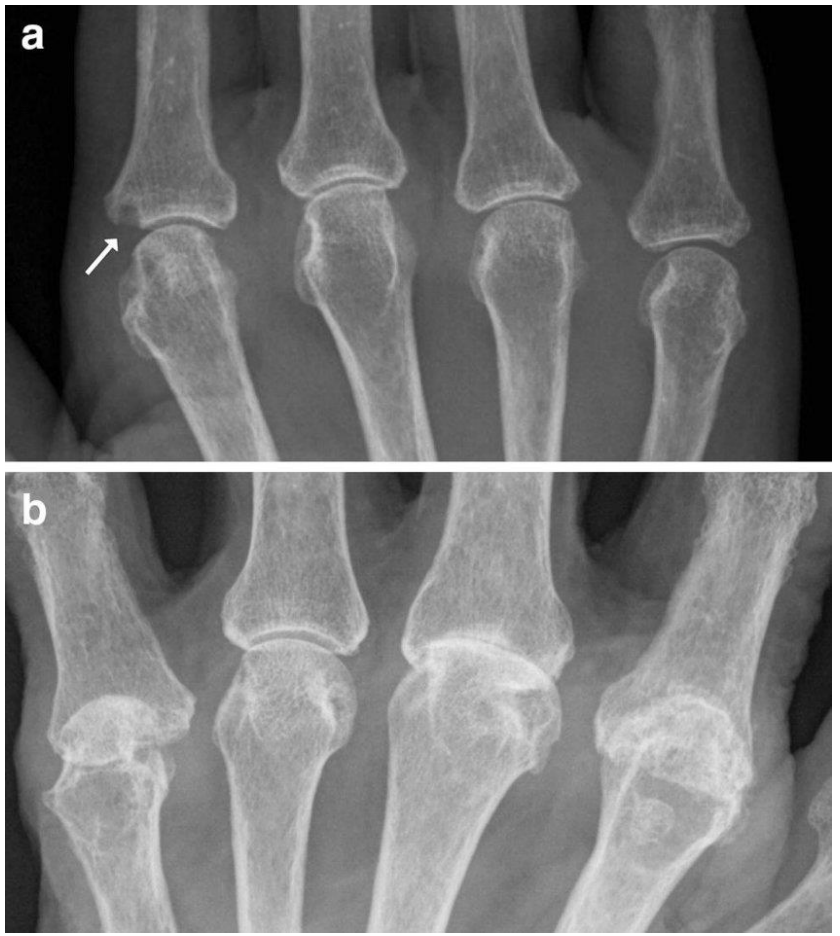
- Elevated inflammatory markers
  - Erythrocyte sedimentation rate (ESR)
  - C-reactive protein (CRP)
- Positive serologies
  - Rheumatoid factor (RF)
    - Positive in 70-80% of RA patients
  - Antibodies to cyclic citrullinated peptides (anti-CCP) a type of anti-citrullinated peptide antibodies (ACPA)
    - High specificity
- Complete blood count (CBC)
  - Anemia, leukocytosis, thrombocytosis
- If joint is aspirated, inflammatory fluid (>2000 WBC)

RA diagnosis: Imaging

- X-ray
  - Peri-articular osteopenia, erosions
  - Changes not generally seen for at least 3 months
  - Useful for diagnosis and staging
- Ultrasound and MRI more commonly used
  - Synovitis, tenosynovitis
  - Useful for confirmation of synovitis if not evident on exam


R





Drosos et al., Rheum Int 2019

2010 ACR/EULAR Classification Criteria for RA

Pt must have ≥1 joint with synovitis
Synovitis not better explained by another disease
≥6 out 10 considered RA

Joint involvement	Score
1 med-large	0
2-10 med-large	1
1-3 small	2
4-10 small	3
>10 (≥1 small)	5

Serology	Score
RF & ACPA neg	0
Low RF or ACPA pos	2
High RF or ACPA pos	3

Acute phase reactants	Score
Normal ESR & CRP	0
Abnormal ESR or CRP	1

Duration of sx	Score
<6 wk	0
≥6 wk	1

- Those with erosions typical of RA with history compatible with fulfilment of the 2010 criteria should be classified as RA
- Choose highest number from each category for total score
- Low positive serology <3x ULN

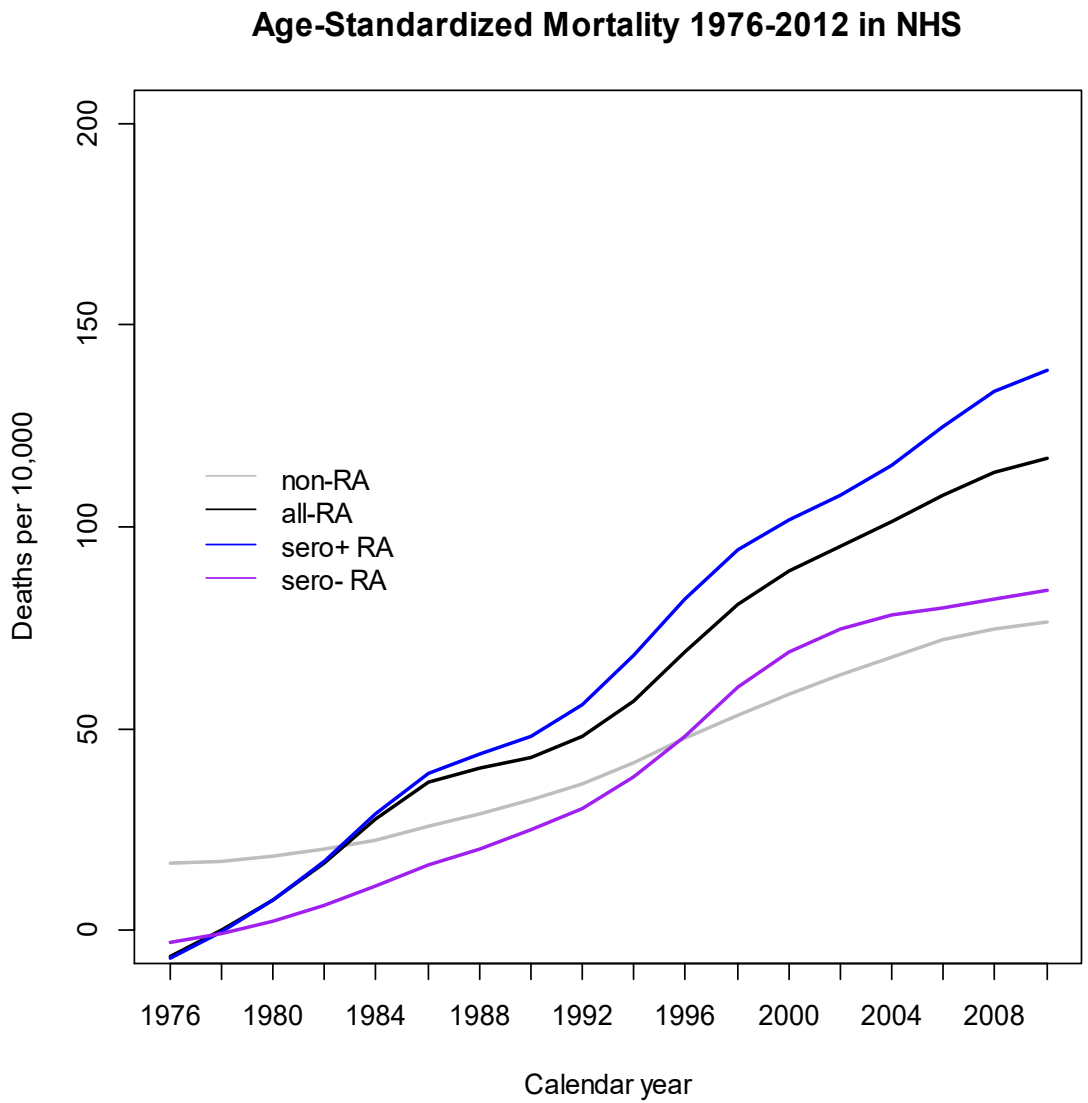
Aletaha, et al. , Arth & Rheum 2010

When to initiate RA treatment

- As soon as you make the diagnosis
  - Early treatment has been linked to better outcomes for patients
    - Reduced surgeries
    - Reduced evidence of joint damage on imaging
    - Better chance of remission
  - Early aggressive RA treatment may improve life expectancy
    - Refer early

- Disease modifying anti-rheumatic drugs (DMARDs)
  - Slow or halt progression of RA
  - Contrast to acute therapies, e.g., glucocorticoids, non-steroidal anti-inflammatory (NSAIDs)

Decreased life expectancy in RA



- Driven by increased risk of cardiovascular disease
- Treatment may substantially improve life expectancy

Sparks et al, Arthritis Care Res 2016
Avina-Zubieta et al, Arth Care Res 2008
Wasko et al, Arth Rheum 2014
Westlake et al, Rheumatology 2010
Chiu et al, Arth Rheum 2021

Comparison for top 3 specific causes of death in RA across cohort studies

Cohort	Ontario, n=11,778	Veterans Affairs, n=1,652	Nurses Health Study, n=964
Study period	2000-2013	2003-2013	1976-2012
Female, %	70	0	100
Cardiovascular disease, %	29	32	26
Cancer/malignancy, %	26	23	23
Respiratory, %	12	15	14

Widdifield et al., Arth Care & Res 2018; Sparks, et al., Arth Care & Res 2016; England et al., Arth Care & Res 2015

Extraarticular involvement

- Lung
  - Interstitial lung disease
- Cardiovascular
  - Coronary artery disease
  - Heart failure
  - Vasculitis
  - Pericarditis
- Skin
  - Rheumatoid nodules

Types of DMARDs

- Conventional synthetic DMARD (csDMARD)
- Biologic DMARD (bDMARD)
- Targeted synthetic DMARD (tsDMARD)

Steroids as disease modifying therapy?

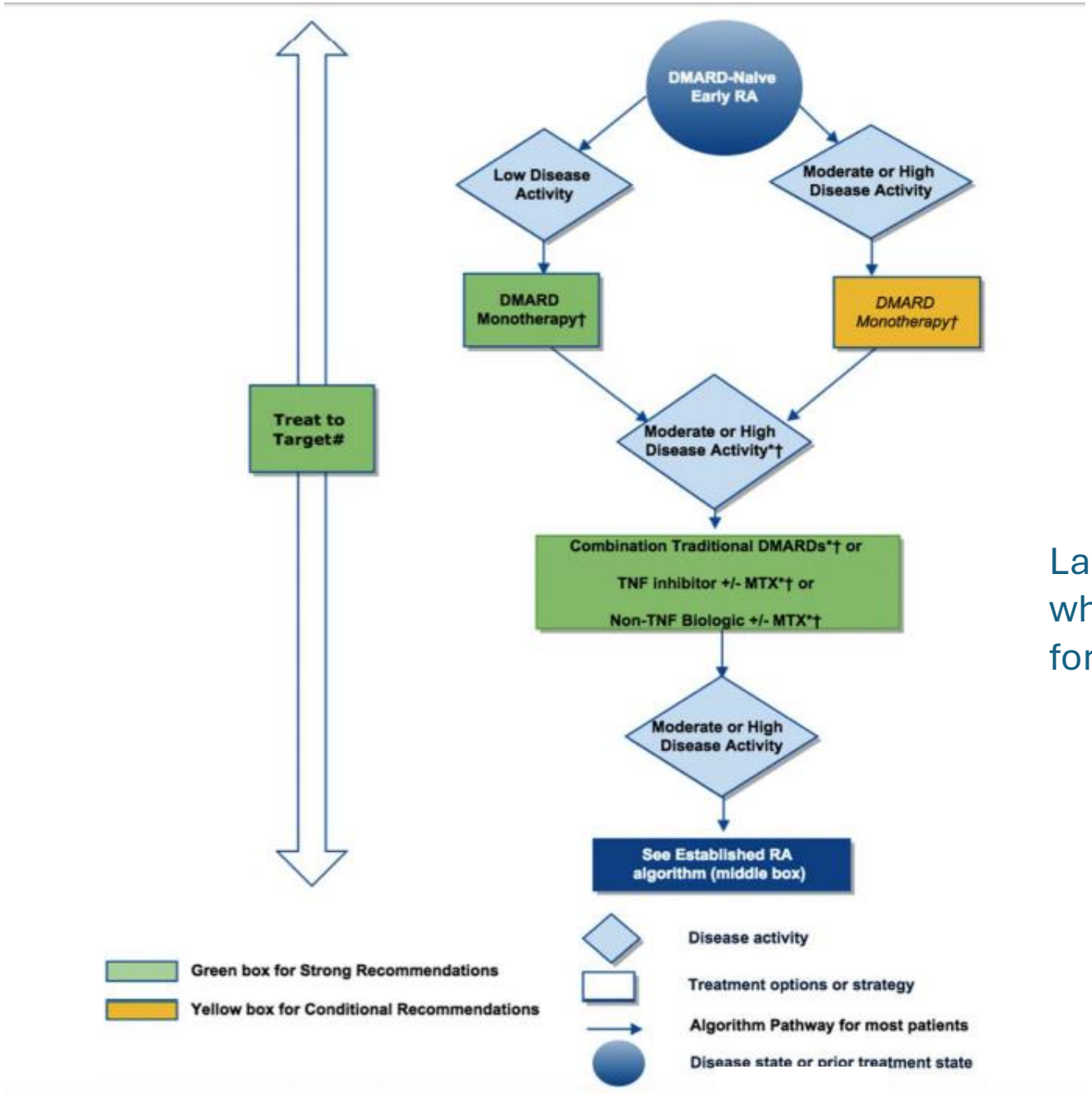
- Helps to quickly decrease inflammation are not DMARDs- do not halt progression of disease

- Risks of long-term side effects of steroid-only therapy for RA likely outweigh benefit for most
  - Osteoporosis
  - Increased cardiovascular risk
  - Elevated blood glucose

Van Everdingen et al, Ann Intern Med, 2002
Boers, Ann Rheum Dis, 2022

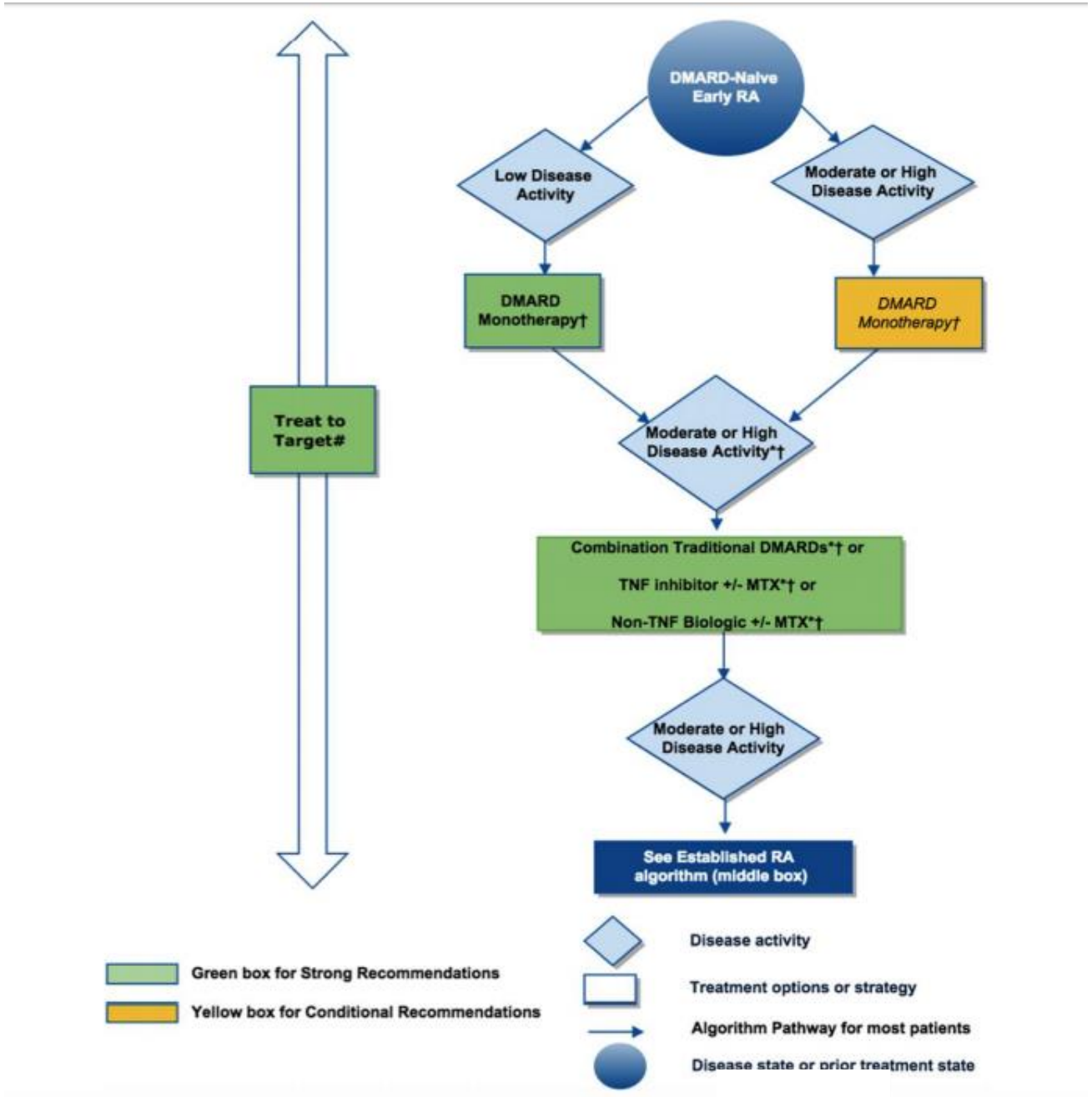
What to ensure your patient has before starting DMARD therapy

- Lab baseline
  - CBC, creatinine, liver function tests
- Screening for underlying infections
  - T spot/quantiferon gold, hepatitis panel
- Vaccines
  - Influenza, Pneumonia (PCV21), COVID-19 vaccines, and non-live recombinant shingles (Shingrix)
  - Most live vaccines are CONTRAINDICATED on immunosuppressive therapy
- CXR
  - Optional but would consider in older patient or smokers



Lack of definitive data to guide which treatment would work better for which patient at which time point

Fraenkel et al., Arth Care & Res. 2021; Singh et al., Arth Rheumatol. 2015



Fraenkel et al., Arth Care & Res. 2021; Singh et al., Arth Rheumatol. 2015

Brief overview of DMARDs

And what to know

What changed the face of RA treatment…

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE ARCHIVE

Efficacy of Low-Dose Methotrexate in Rheumatoid Arthritis

Michael E. Weinblatt, M.D., Jonathan S. Coblyn, M.D., David A. Fox, M.D., Patricia A. Fraser, M.D., Donald E. Holdsworth, M.D., David N. Glass, M.B., Ch.B., and David E. Trentham, M.D.

N Engl J Med 1985; 312:818-822 | March 28, 1985 | DOI: 10.1056/NEJM198503283121303

csDMARD: Methotrexate (MTX)

- First line therapy for RA
- Changed natural history of RA
- Decrease extra-articular manifestations
- Increase quality of life and potentially survival

csDMARD: Methotrexate

- Dosed weekly and taken with folic acid
- Potential side effects
  - Gastrointestinal discomfort (most common)
  - Liver and hematologic abnormalities
  - Opportunistic infections
  - Cannot be taken when trying to conceive
  - Rare complications:
    - Methotrexate lung injury/pneumonitis
      - Typically occurs in first year of therapy
      - Separate from RA-ILD, for which methotrexate is NOT thought to be a culprit
    - Nephrotoxicity at high doses (not used for RA)

Juge, Eur Respir J, 2021

csDMARDs: hydroxychloroquine, sulfasalazine

- Hydroxychloroquine
  - Generally well-tolerated
  - Potential side effects
    - Common: Gastrointestinal discomfort, rash
    - Screen: visual field testing recommended every 6-12 months for retinal pigmentation
    - Rare: Myopathies, cardiac conduction abnormalities, ocular toxicity

- Sulfasalazine
  - Generally used as part of “triple therapy” regimen in RA
  - Potential side effects
    - Gastrointestinal toxicity
    - Hematologic toxicity
    - Hypersensitivity reactions

csDMARD: Leflunomide

- Similar to methotrexate
  - Simpler dosing schedule- daily vs weekly w/ methotrexate
  - Quicker onset of action
  - Similar side effect profile as methotrexate
    - Teratogenic with long half-life
      - Avoid in women of child-bearing age

What if a csDMARD is not enough?

- Options
  - Triple therapy: methotrexate, sulfasalazine, hydroxychloroquine
  - Biologic DMARD (bDMARD)

- How to decide
  - Both have equal efficacy
    - Disease progression is similar
      - Possibly less radiographic progression with biologics
      - Possibly quicker time to effect with biologics
  - Consideration of side effects, patient adherence, and cost

Moreland et al, Arth Rheum 2012; O'Dell et al, NEJM 2013

Biologic and targeted synthetic DMARDs in 2026

- **Biologic DMARD**
  - Anti-tumor necrosis factor (anti-TNF): adalimumab, certolizumab, etanercept, golimumab, infliximab
  - IL-6 receptor inhibitor: Tocilizumab, sarilumab
  - T-cell costimulatory blocker/CTLA4Ig: abatacept
  - Anti-CD20/B-cell depletion: rituximab
  - Il-1 receptor inhibitor: anakinra
- **Targeted synthetic DMARD**
  - Janus kinase inhibitor (JAKi)
    - Baricitinib, tofacitinib, upadacitinib

Anti-TNF Therapy

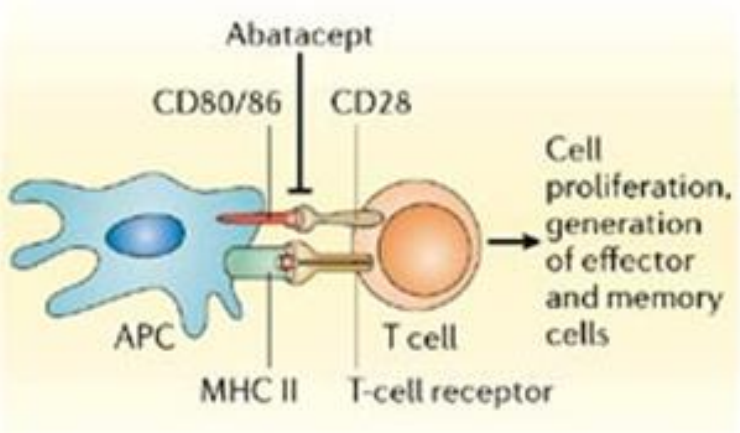
- All have similar effects—response rate ~60-70%
- Works in early disease and late disease
  - Clinical outcomes better in early disease
- Stabilize radiographic progression
- Decreased NSAIDS, steroids and methotrexate doses
- Remission in some studies upon withdrawal

Anti-TNF Therapy – adverse events

- Cutaneous
  - Injection site reactions
  - Diffuse rashes
- Infectious
  - Sepsis, septic joints, pneumococcal infections
  - Tuberculosis
- Cardiac
  - FDA warning for class III-IV heart failure
- Neurologic
  - Demyelination
- Oncologic
  - Initial concern for increased lymphoma risk, not borne out in f/u studies
  - Possible increased risk of skin cancers

Brown et al, Arth Rheum 2002; Solomon et al, Sem Arth Rheum 2014

Abatacept



- Blocks T-cell co-activation pathway
- Similar risks to anti-TNF but less TB risk
- May be used with or without methotrexate
- Usually after TNF “failure”—response rate 50%
- Onset 4-16 weeks

Rituximab

- B cell depletion (anti-CD20)
- For use mainly in seropositive patients
- Adverse side effects
  - Infections including PML, Hepatitis B
    - Ensure Hepatitis panel is checked prior to starting rituximab
  - Rashes including psoriasis
  - Low cell counts (WBC)
  - Low IgG for long durations

IL-6 Inhibition

- Tocilizumab
  - Monoclonal antibody that blocks IL-6R
  - Works quickly - onset 2-12 weeks
  - Impressive improvements in CRP, QOL, fatigue
  - Adverse events:
    - Infections
    - ? GI perforation - avoid in patients with history of diverticulitis
    - Lipid, leukocyte and liver test abnormalities
- Sarilumab
  - Monoclonal antibody that binds both soluble and membrane-bound IL-6 receptors

JAK inhibitor

- Types
  - Tofacitinib
    - First oral agent that targets a biologic pathway
  - Baricitinib
  - Upadacitinib
- Potential complications
  - Infections
    - Increased risk for zoster- Important to consider vaccination before starting
  - Abnormal lab findings
    - Lipid and LFT abnormalities, neutropenia, anemia

JAK inhibitors may be associated with increased risk of thrombosis (2019)

FDA approves Boxed Warning about increased risk of blood clots and death with higher dose of arthritis and ulcerative colitis medicine tofacitinib (Xeljanz, Xeljanz XR)

FDA Drug Safety Communication

US FDA communication, February and July 2019

JAK inhibitors may be associated with increased risk of cardiovascular events and lung cancer

Initial safety trial results find increased risk of serious heart-related problems and cancer with arthritis and ulcerative colitis medicine Xeljanz, Xeljanz XR (tofacitinib)

FDA will evaluate the trial results

US FDA communication, February 2021

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis

Steven R. Ytterberg, M.D., Deepak L. Bhatt, M.D., M.P.H., Ted R. Mikuls, M.D., M.S.P.H., Gary G. Koch, Ph.D., Roy Fleischmann, M.D., Jose L. Rivas, M.D., Rebecca Germino, Ph.D., Sujatha Menon, Ph.D., Yanhui Sun, Ph.D., Cunshan Wang, Ph.D., Andrea B. Shapiro, M.D., Keith S. Kanik, M.D., and Carol A. Connell, R.N., Ph.D., for the ORAL Surveillance Investigators*

Patient with RA on therapy calls with a fever…

- Stop DMARD potentially with exception of hydroxychloroquine
- Have patient come into clinic to be assessed
- Consider further work-up and treatment (ie CXR, antibiotics) sooner than you would with an otherwise healthy patient

RA patients and vaccines

- Non-live vaccines are safe and strongly recommended
  - Speak to rheumatologist before administering any live vaccines, which are often contraindicated
  - Immunosuppression can decrease efficacy of vaccines
    - If stable RA, consider holding immunosuppressives around the time of vaccines as this can increase efficacy

Park et al, BMJ 2017

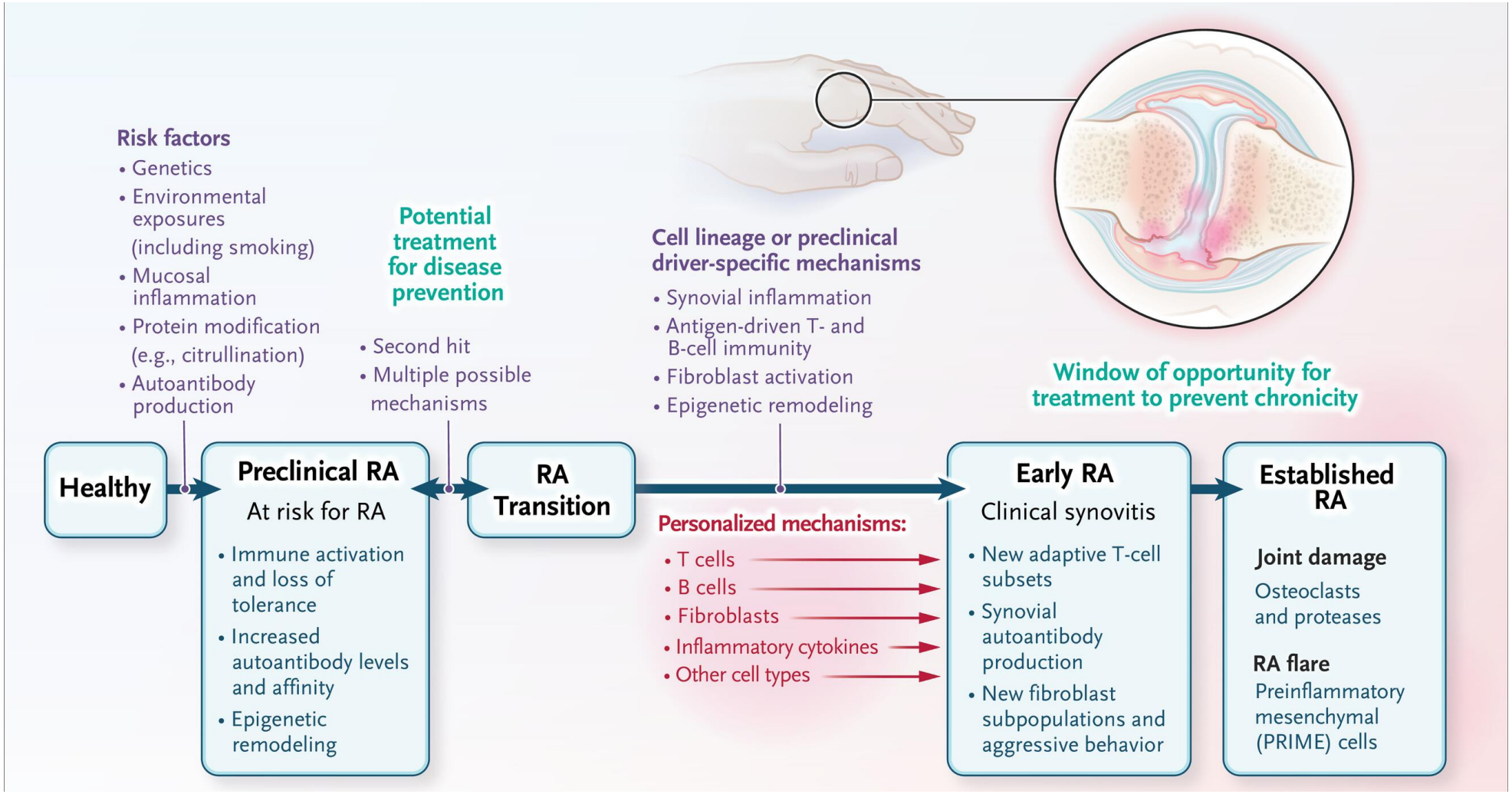
COVID vaccination and RA medications

Medication	Timing Considerations for Immunomodulatory Therapy and Vaccination (applies to both primary vaccination and supplemental [booster] dosing)	Level of Task Force Consensus
Abatacept IV	Time vaccination so that it occurs one week prior to the next dose of IV abatacept	Moderate
Abatacept SQ	Hold for one to two weeks (as disease activity allows) after each COVID vaccine dose	Moderate
Acetaminophen, NSAIDs	Assuming that disease is stable, hold for 24 hours prior to vaccination. No restrictions on use post vaccination once symptoms develop.	Moderate
Belimumab SQ	Hold for one to two weeks (as disease activity allows) after each COVID vaccine dose	Moderate
TNFi, IL-6R, IL-1R, IL-17, IL12/23, IL-23, and other cytokine inhibitors[†]	The Task Force failed to reach consensus on whether or not to temporarily interrupt these following each COVID vaccine dose, including both primary vaccination and supplemental (booster) dosing	Moderate
Cyclophosphamide IV	Time CYC administration so that it will occur approximately 1 week after each vaccine dose, when feasible	Moderate
Hydroxychloroquine, **IVIG**	**No modifications to either immunomodulatory therapy or vaccination timing**	Strong (HCQ), **Moderate (IVIG)**
Rituximab or other anti-CD20 B-cell depleting agents	Discuss the optimal timing of dosing and vaccination with the rheumatology provider before proceeding[‡]	Moderate
All other conventional and targeted immunomodulatory or immunosuppressive medications (e.g., JAKi, MMF) except those listed above[§]	Hold for one to two weeks (as disease activity allows) after each COVID vaccine dose	Moderate

Note: individual medications that were specifically voted on by the task force are listed on separate rows and were not collapsed, even if the resulting recommendation was similar to others.

COVID -19 Vaccine Clinical Guidance Summary for Patients with Rheumatic and Musculoskeletal Diseases. Updated 2022, American College of Rheumatology

RA pathogenesis



Gravallese et al., NEJM 2023

MOC Take Home Summary

- Risk of RA stems from a combination of genetics and environmental exposures
- Early diagnosis followed by early aggressive treatment can alter the natural history of the disease
  - Less joint replacements and improved morbidity and mortality
- Many treatment options, however lack of data to guide which drug is better for which patient
- Ensure patient is up to date with monitoring and vaccines while on therapy
  - Counsel patients on certain immunosuppressives that vaccines may not be as effective
  - Consider holding immunosuppressives around the time of vaccine

Question 1

- A 58-year-old male presents with polyarticular pain that has lasted for 6 weeks. He has had fevers and weight loss and has a history of traveling to Cape Cod and Martha's Vineyard. He has morning stiffness, as well as shoulder, hip and MCP pain. Physical exam is normal except for MCP tenderness upon palpation and a small right knee effusion.

Question 1

- All should be a part of the initial diagnostic work-up *EXCEPT*:
  - A. CXR and hand and feet films
  - B. Lyme titer and ANA
  - C. Rheumatoid factor and anti-CCP
  - D. Aspiration of the knee
  - E. ESR and CRP

Question 1: Answer A

- **A: CXR and hand/foot films**
  - While it is not wrong to obtain a CXR (and in fact may be done when deciding drug therapy) it is not essential for diagnosis.
  - Hand and foot films are unlikely to reveal anything significant after only 6 weeks of symptoms.

Question 2

A 48-year-old man presents with rheumatoid arthritis. He is deciding what DMARDs to take. He has erosive disease, and has a history of travel to Russia and Peru, and has a vague sulfa allergy. His labs are unremarkable, except for a creatinine of 1.7 and an AST of 58.

Question 2

All tests should be done before deciding the next therapy *EXCEPT*:

a. CXR
b. T-SPOT
c. Pneumonia vaccination
d. HCV and HBsAg and HBcAg
e. ACE level and SPEP

Question 2: Answer E

- **ACE level and SPEP**
  - An ACE level would not be helpful in the diagnosis of rheumatoid arthritis and an SPEP, while always interesting, is not needed at this juncture.

References

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Thank you

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BWH/MGB Rheumatology

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