Rheumatoid Arthritis: Biomarkers and Impairments

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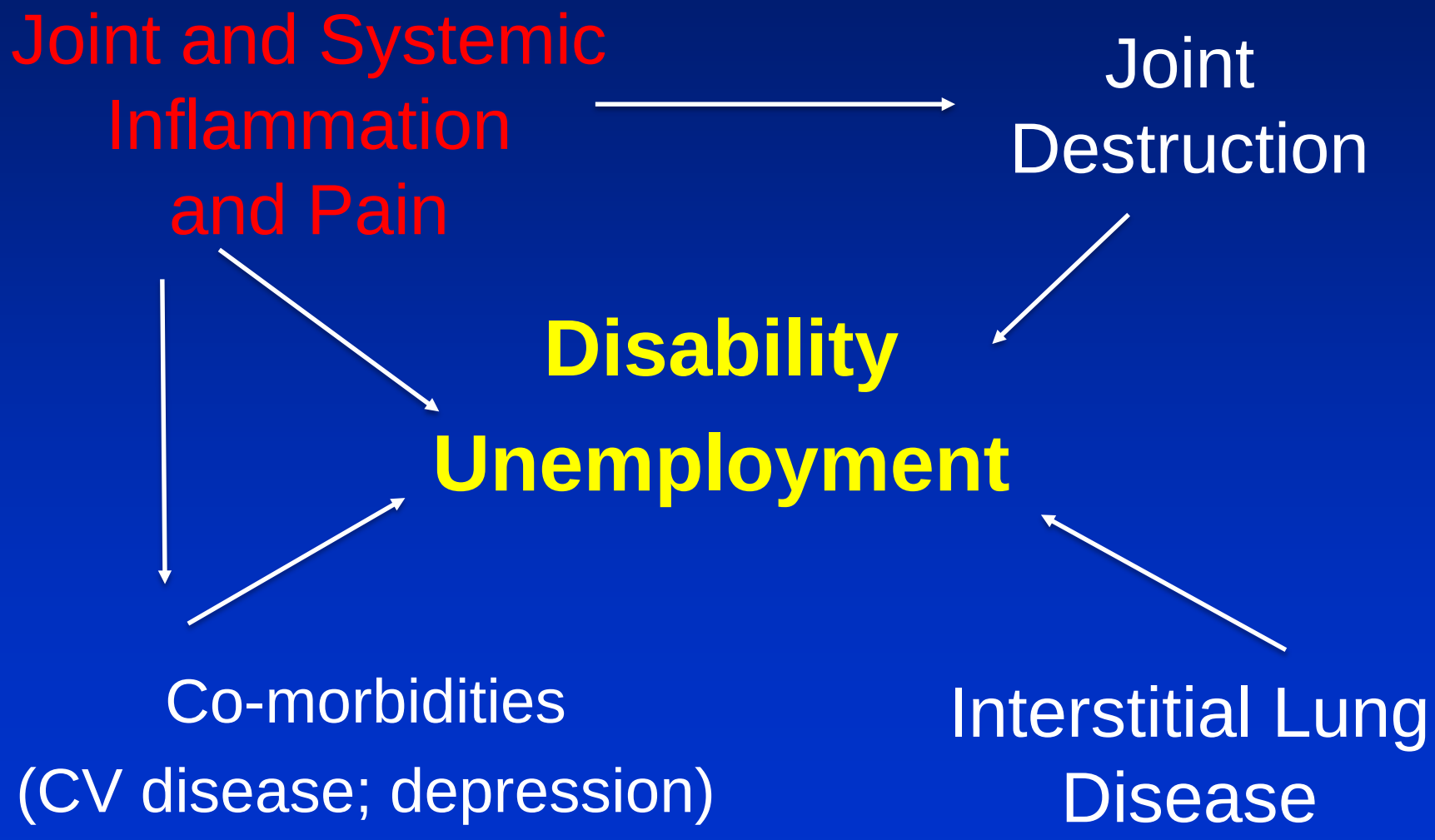
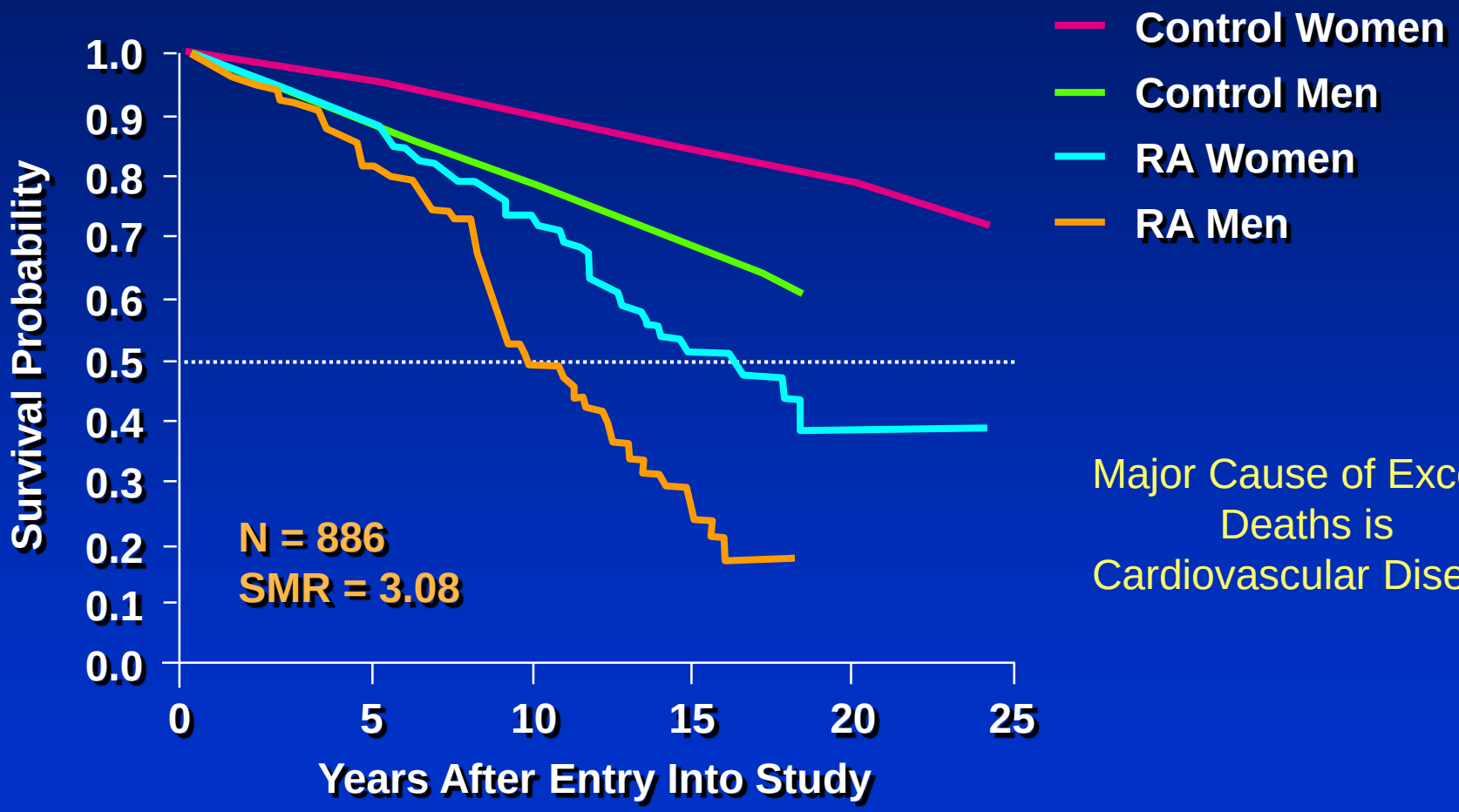
Rheumatoid Arthritis



Premature Mortality in Patients with RA



Major Cause of Excess Deaths is Cardiovascular Disease

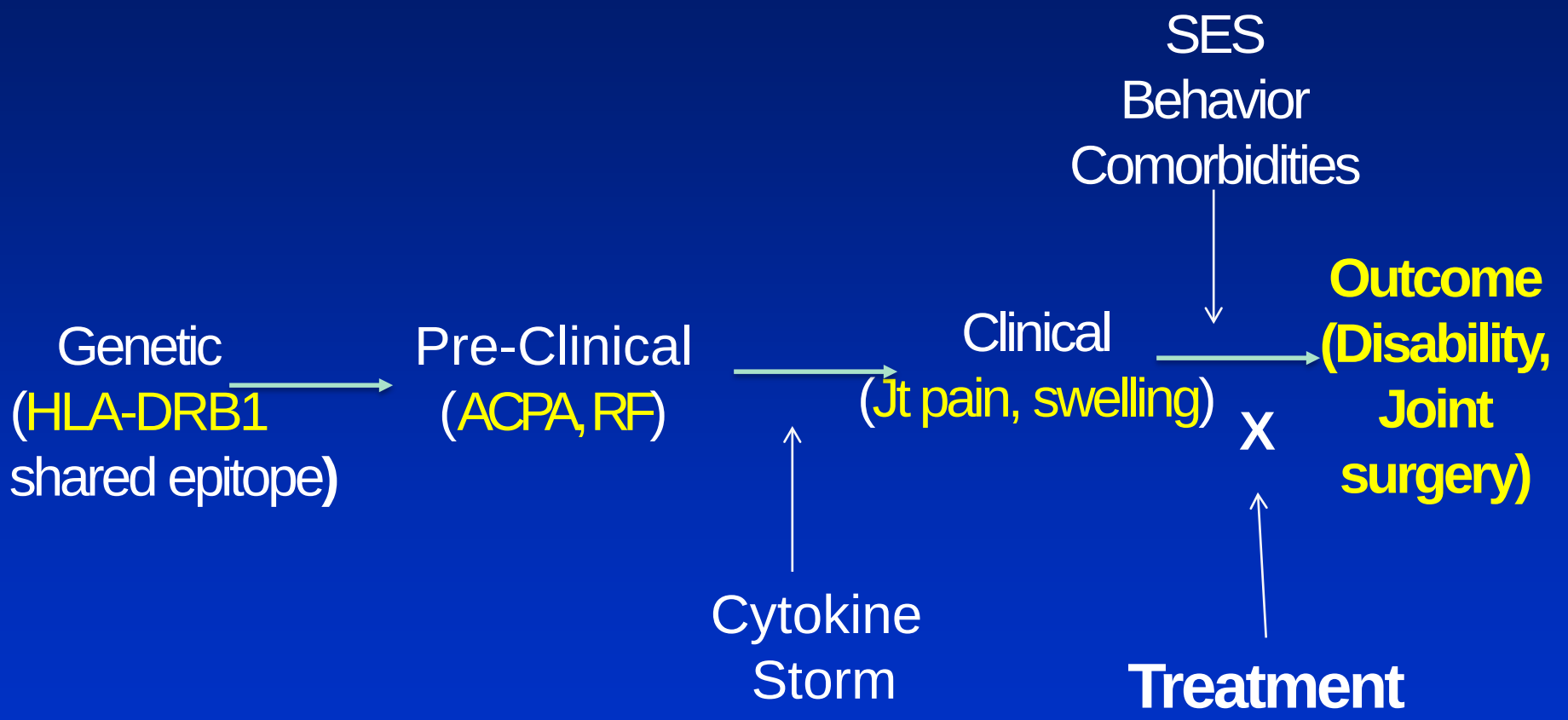
SMR = standardized mortality ratio for patients with RA compared with non-RA controls.

Wolfe F, et al. *Arthritis Rheum*. 1994;37:481-494.

Current State of the Art of Biomarkers in RA

- Limited in number (but not for lack of investigation)
- In general, laboratory biomarkers in RA are not independently adequate for diagnosis, prognosis, response to treatment
- Require coupling with measures from exam and patient questionnaires → Composite Measures

RA: Natural History



RA: Diagnostic Biomarkers

RA: Diagnostic Biomarkers

- There are no defined clinical criteria for diagnosis of RA, only classification criteria
  - Due to slow evolution, different patterns, can mimic other types of inflammatory arthritis
- Nonetheless, 2 antibodies very helpful for diagnosis
  - Anti-citrullinated peptide Ab (anti-CCP or ACPA)
  - Rheumatoid factor (RF)
- ACPA is more specific than RF for diagnosis of RA
- But a positive Ab can precede symptoms by up to 10 years !

Anti Citrullinated Peptide Antibodies (ACPA; anti-CCP)

- High specificity for RA[1,2]
- Highly associated with HLA-DR SE+
- High positive predictive value for RA[3]
- Detectable earlier than RF[4]
- Found in up to 40% of patients who are RF negative especially early in disease[5]
- Predictive of erosive disease and joint damage[6]
- But also not 100% specific for RA

1. Schellekens GA et al. *Arthritis Rheum* 2000; 43: 155-63. 2. Lee DM Schur PH. *Ann Rheum Dis* 2003; 62: 870-4. 3. Jansen LMA et al. *J Rheumatol* 2002; 29: 2074-6. 4. Nielen MMJ et al. *Arthritis Rheum* 2004; 50: 380-6. 5. Vallbracht I, *et al*. *Ann Rheum Dis* 2004; 63: 1079-84. 5. van Gaalen FA et al. *Ann Rheum Dis*. 2005 Mar 30; [Epub ahead of print]

Classification Criteria for RA Includes Autoantibody

Category	Sub-category	Points
Joint Involvement	1 large joint	0
	2-10 large joints	1
	1-3 small joints	2
	4-10 small joints	3
	> 10 joints (≥ 1 small)	5
Serology	Neg RF and neg anti-CCP	0
	Low-pos RF ***or*** low pos anti-CCP	2
	High pos RF *or* high pos anti-CCP	**3**
Acute phase reactants	Normal CRP ***and*** normal ESR	0
	Abnormal CRP ***or*** abnormal ESR	1
Duration of symptoms	< 6 weeks	0
	≥ 6 weeks	1

"Definite" RA
≥ 6/10 points

RA: Disease Activity Biomarkers

Individual Reversible Core 'Biomarkers' of Disease Activity*

- Tender joint count (28 vs 44 vs 68 joints)
- Swollen joint count (28 vs 44 vs 68 joints)
- Patient global assessment of disease activity
- Physician global assessment of disease activity
- Level of C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)

***Assessed at a Single Time Point ("State")**

Composite Scores Incorporate Core Biomarkers

- Disease activity score (DAS/DAS28)
- Simplified Disease Activity Index (CDAI)
- Clinical Disease Activity Index (SDAI)

Limitations:

  - Poor reproducibility between physician joint examinations
  - Complex calculation (DAS)
- Strengths:
  - Can be done in the clinic at no additional cost
  - Responsive; nothing better as of yet

Can a Laboratory Biomarker(s) Substitute for Composite Disease Activity Scores?

- CRP, ESR alone are poor substitutes
- Interleukin-6 (IL-6) alone likely inadequate
- Multi-biomarker of Disease Activity (MBDA; Vectra-DA™)1
  - 12 proteins; algorithmic calculation of score
  - Commercially available

1Eastman PS et al, J Pharm Biomed Anal 2012:70:415

MBDA; Vectra-DA™

- Validated against DAS but DAS cheaper
- Is it a better predictor than DAS of poor outcomes – e.g., progression of radiographic damage ?

Study	Number Studied	Result
CAMERA	120	No
DRESS	171	No
SweFot	235	Yes

Bakker et al, *Ann Rheum Dis* 2012; Bouman et al, *Rheumatology* 2017; Hambardzumyan et al, *Ann Rheum Dis* 2015

RA: Treatment Response Biomarkers

Response to RA Therapies : Current State of the Art (Used in Clinical Trials)

Clinical (Disease Activity) Outcomes

- ACR-20, -50, and -70
  - Uses ACR core measures
  - Change score only
- EULAR response
  - State plus change scores

Radiographic Outcome (Damage)

- Modified total Sharp scores
  - Erosion scores
  - Joint space narrowing (JSN)

HRQoL/Patient-Reported Outcomes

- Short Form-36 (SF-36)
- Health Assessment Quest (HAQ)

Felson DT, et al. *Arthritis Rheum*. 1995;38:727–735; Felson DT, et al. *Arthritis Rheum*. 1993;36:729–740; Tugwell P, Boers M. *J Rheumatol*. 1993;20:528–530; Van Riel PL, van de Putte LB. *Curr Opin Rheumatol*. 1994;6:132–139; Prevoo ML, et al. *Arthritis Rheum*. 1995;38:44–48.

RA Remission Criteria use same biomarkers w/cut-offs

Meet and sustain remission criteria

Better Surrogate Outcomes
- Lower HAQ
- Absent/reduced radiographic progression

?  ?

Lower disability rates
Lower unemployment rates
Reduced mortality

Validity of Index Remission Definitions: Predicting a Good Outcome for X-ray and HAQ

	Percent in Remission with Good Outcome	Percent NOT in Remission with Good Outcome	Positive Likelihood Ratio	P Value
TJC28, SJC28, CRP, PtGA ≤1	66%	17%	7.2	<.0001
I N D E X E S				
DAS28<2.6	38%	18%	2.2	0.01
DAS28<2.0	56%	20%	4.5	0.01
SDAI≤3.3	56%	17%	4.8	<.0001

RA: Biomarkers of Poor Prognosis

RA: Biomarkers for Poor Prognosis (Assessed At or Near Time of Diagnosis)

- Antibodies
  - High titer of APCA and/or RF
- Inflammatory markers
  - High levels of CRP and/or ESR
  - ??Interleukin-6 (IL-6) or (Vectra DA™)??
- Exam
  - High number of swollen and tender joints
- Imaging
  - Erosive joint damage on xray at baseline

+

APCA, RF

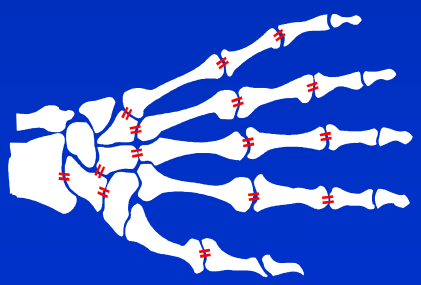
+

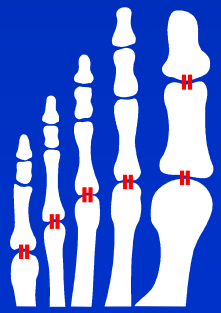
CRP, ESR

RA: Surrogates of Outcomes

Imaging as a Surrogate Outcome

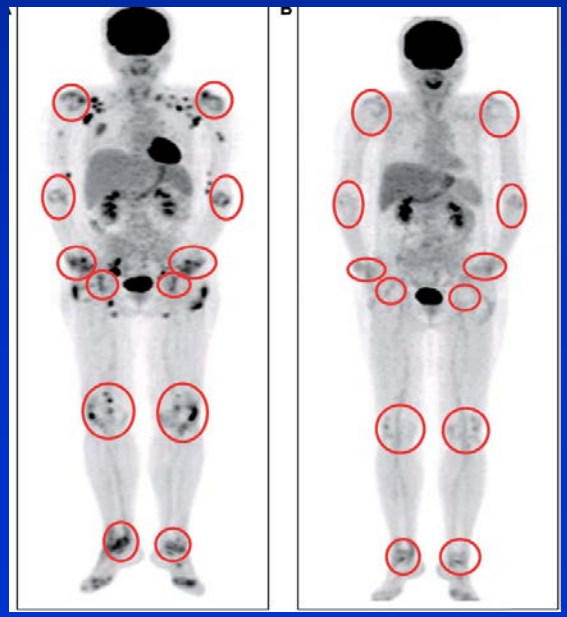
- Goal of treatment
  - Rapidly attain and sustain remission
  - Thereby preventing functional impairments
- Progression of joint damage = common surrogate
  - Xrays reflect permanent damage
    - But, extent of damage doesn't necessarily correlate with patient reported disability





RA: Other Imaging Biomarkers

- MRI: expensive, 1-2 joints only
- Ultrasound: time intensive in clinic
  - doesn't improve remission when added to traditional clinical composite measures
- PET/CT with FDG uptake
  - all joints assessed simultaneously
  - not validated yet
  - radiation



Health Assessment Questionnaire (HAQ) Another Surrogate for RA Outcome

Widely accepted, validated, rheumatology-specific instrument to assess physical function in RA

- Gold standard of OMERACT/FDA
- 20 questions covering eight types of activities
  - Dressing and grooming, arising, eating, walking, hygiene, reaching, gripping, activities of daily living
  - A **mean decrease of at least 0.22** in HAQ score is considered a minimum clinically important difference

HAQ Disability Index (HAQ-DI)

- Scores the worst items within each of the eight scales
- Based on use of aids and devices

Buchbinder R, et al. *Arthritis Rheum*. 1995;38:1568–1580; Sullivan FM, et al. *Ann Rheum Dis*. 1987;46:598–600; Kosinski M, et al. *Arthritis Rheum*. 2000;43:1478–1487.

Health Assessment Questionnaire (HAQ)

HAQ has been proven to be predictive of RA disease progression[1,2]

- An increase of 1 point per year in HAQ-DI scores during the first 2 years of disease results in 90% greater disability and 87% greater costs over the next 3 years

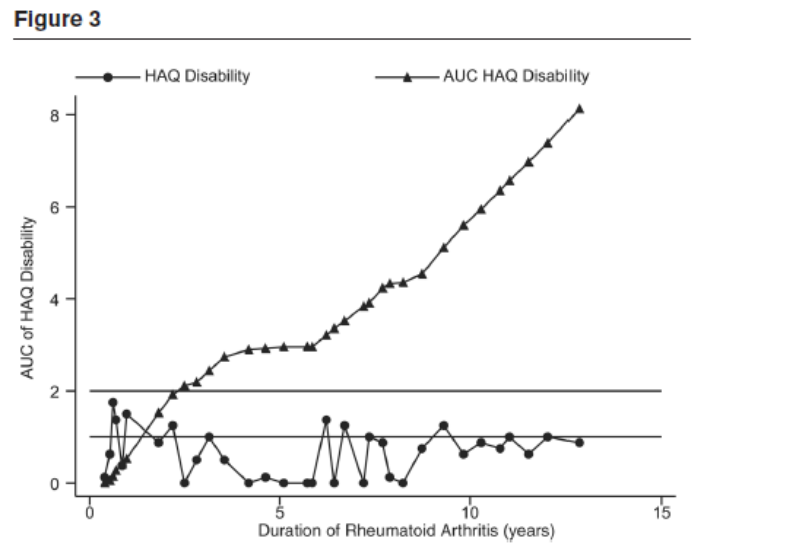
HAQ scores predict:

- Functional status[3,4]
- Work disability[5,6]
- Costs of treatment[7]
- Joint replacement surgery[8]
- Death[1,3,9]

1. Pincus T, et al. *Ann Intern Med*. 1994;120:26–34; 2. Fries JF, et al. *Arthritis Rheum*. 1996;39:616–622; 3. Pincus T, et al. *Arthritis Rheum*. 1984;27:864–872; 4. Wolfe F, et al. *J Rheumatol*. 1991;18:1298–1306; 5. Callahan LF, et al. *J Clin Epidemiol*. 1992;45:127–138; 6. Wolfe F, et al. *J Rheumatol*. 1998;25:2108–2117; 7. Lubeck DP, et al. *Arthritis Rheum*. 1986;29:488–493; 8. Wolfe F, et al. *Arthritis Rheum*. 1998;41:1072–1082; 9. Wolfe F, et al. *Arthritis Rheum*. 1994;37:481–494.

HAQ

- Advantage: Patient reported measure
- Also a measure of disease activity
- Varies considerably from visit to visit
- AUC over time may be better measure of disability



Wolfe F. Arthritis Res 2002

Other Usually Unmeasured Factors that Affect Outcomes in RA

GOOD OUTCOME

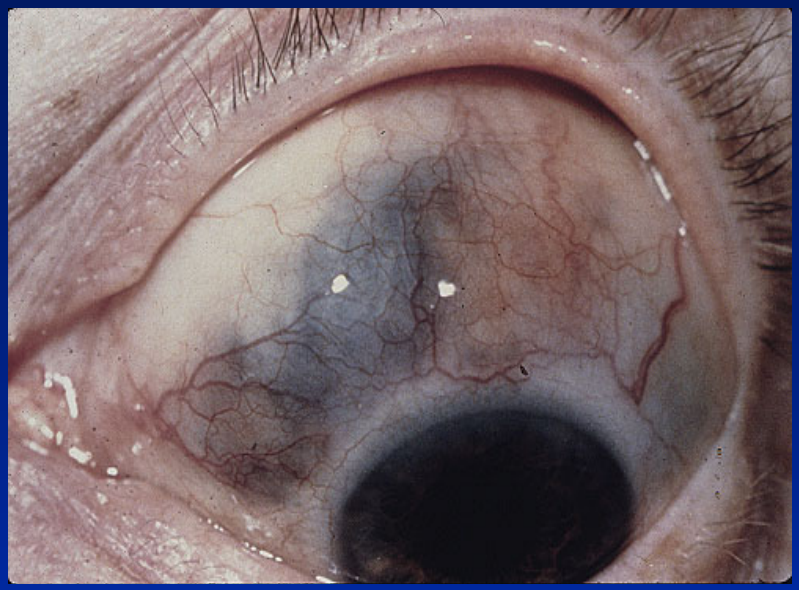
- Early treatment
- Demographics:
  - ↑ SES status
- Health behaviors
  - Adherence to medications
  - Weight management
  - Exercise
- No co-morbid illness

POORER OUTCOME

- Delayed treatment
- Demographics:
  - ↓ SES status
- Affective: depression
- Poor health behaviors
- Co-morbid illnesses
  - Cardiovascular dz

Muscle Atrophy and Osteoporosis in RA

Rheumatoid Scleritis and Vasculitis



Rheumatoid Nodules: Subcutaneous, Pulmonary