Brigham and Women's Rheumatoid Arthritis Sequential Study

BRASS

Principal Investigators: Dr. Nancy Shadick and Dr. Michael Weinblatt

BRASS Registry Enrollment Began in March 2003

- Prospective follow-up for 15 years
- 1598 recruited to date
- 30 rheumatologists have contributed patients
- > 90% approached will sign up
- 6 month follow-up (86%)
- 1 year follow-up(>80%)

Original Scientific Aims

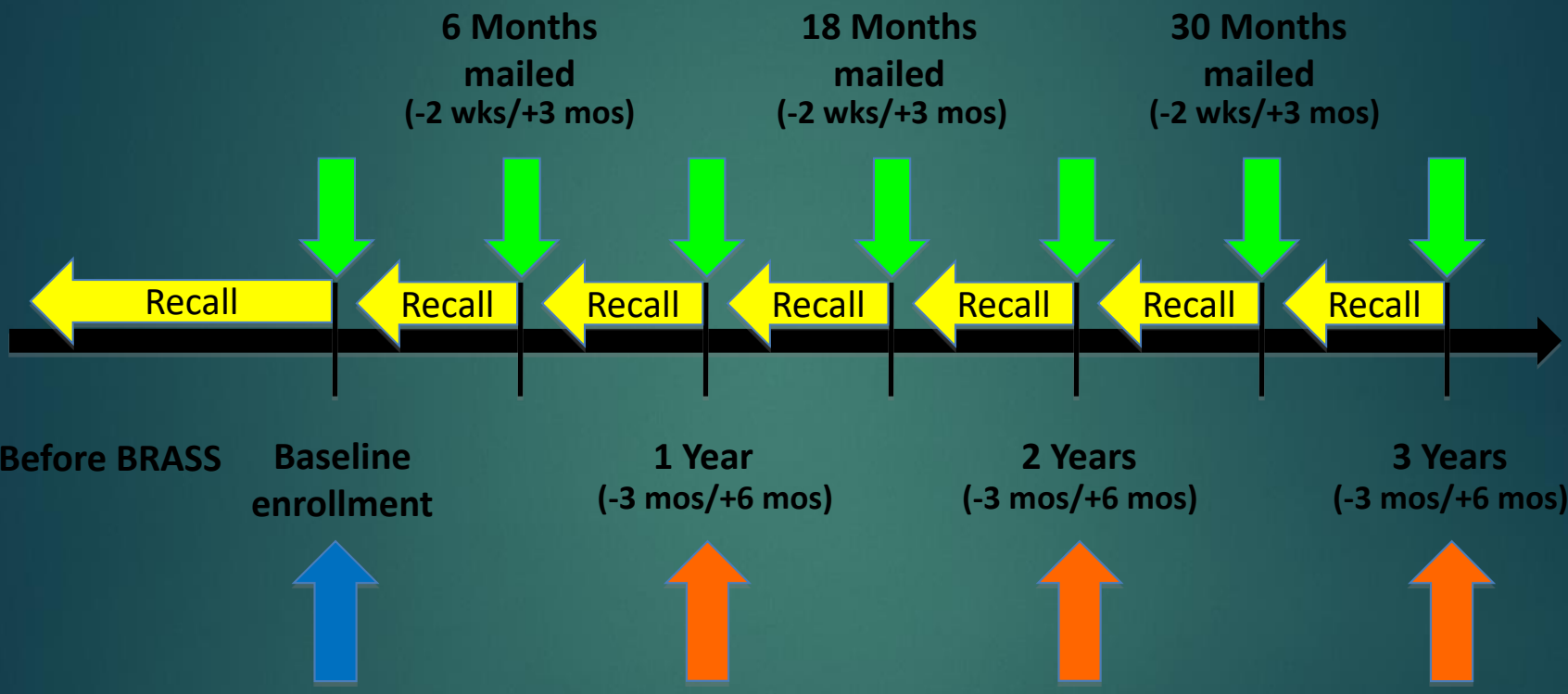
- Identify markers of disease progression and drug response
- Examine pathogenic mechanisms via hypothesis driven experiments
- Broaden our understanding of the epidemiology of RA

Structure of the BRASS Registry

Registry	Structure	Data/Specimens Collected
BRASS	1598 RA patient (15% new onset RA)	Physician data (annually) Patient reported data (6 months) DNA (twice) RNA (annually) Serum (annually) Plasma (annually)

BRASS Protocol

Patient Data Collection Occurs Every 6 months

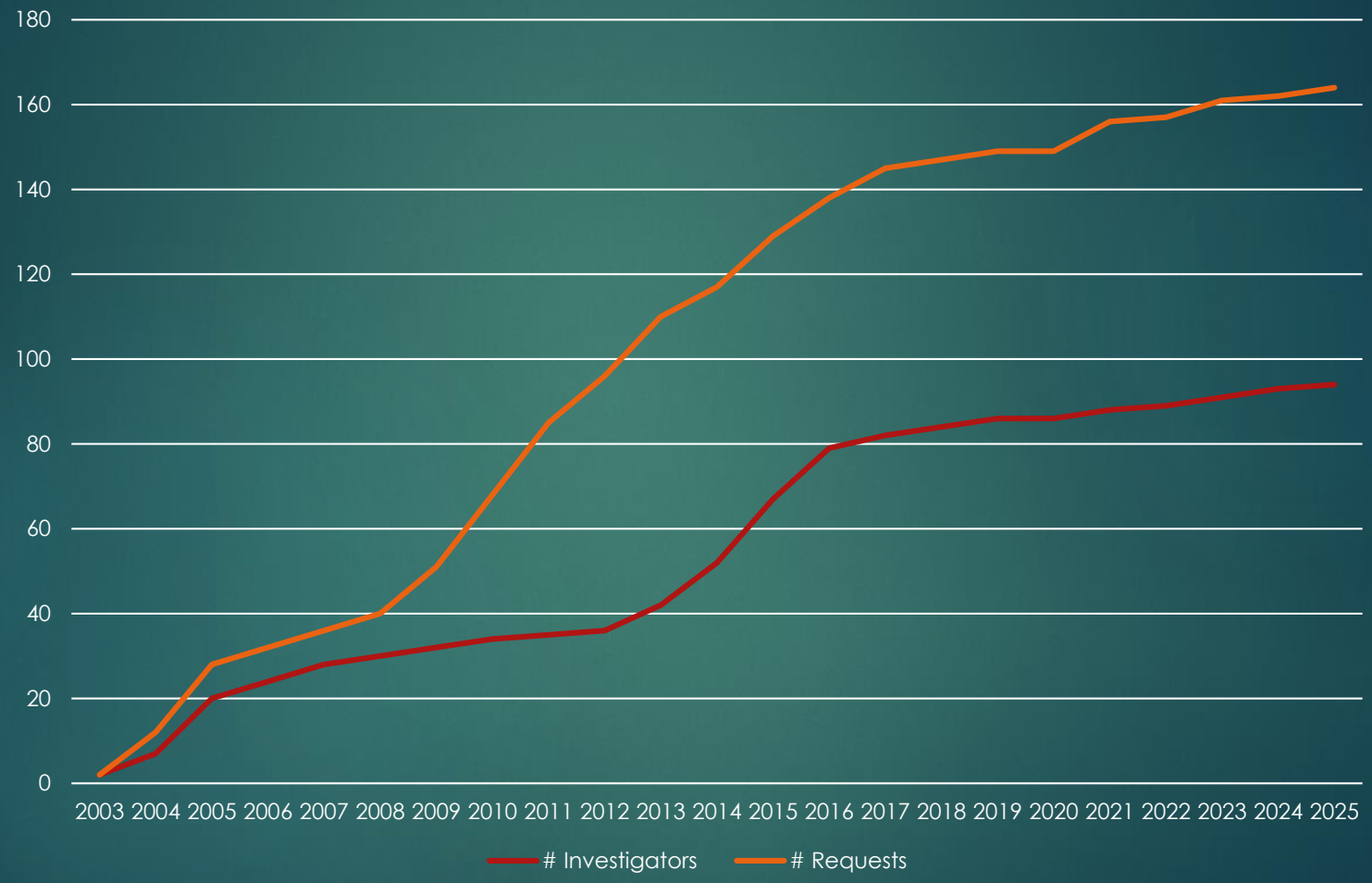


Physician Domains and Labs Measured at Baseline and Yearly

If annual visit and semi-annual mailing will overlap (with-in 2 months), in-person visit takes priority and mailing will not be done.

Hand X-rays done at baseline, 2yr, 5yr, 7yr, 10yr, 12yr, and 15yr (±3 months)

BRASS Registry Usage as of 2025



BRASS Physician Domains

Physician Domains	Baseline	Annual
Inclusion Criteria	✓	
Health & Symptoms		
Morning Stiffness	✓	✓
VAS	✓	✓
Infection/Opportunistic Infections	✓	✓
Extra-Articular Manifestations	✓	✓
Co-morbidities/drug toxicities	✓	✓
28 Joint Count	✓	✓
Medication Changes		
Start	✓	✓
Stop/reason	✓	✓
Change/reason	✓	✓

Data Collection (over 2000 variables)

- Demographics
- General Health
- Current Medications
- Past Medications
- Validated Scales

  MDHAQ, SF-12, MHI-5, PHQ-9, EQ-5D, RADAI, Arthritis Self-Efficacy, for example

The BRASS registry has detailed clinical phenotyping on RA patients

BRASS Currently Enrolled

most recent visits as of 1st Quarter 2025

N=565

Variable	Mean	Std Dev	Min	Max
Age	62.19	13.84	22.00	92.00
Disease Duration	19.75	11.94	0.00	63.00

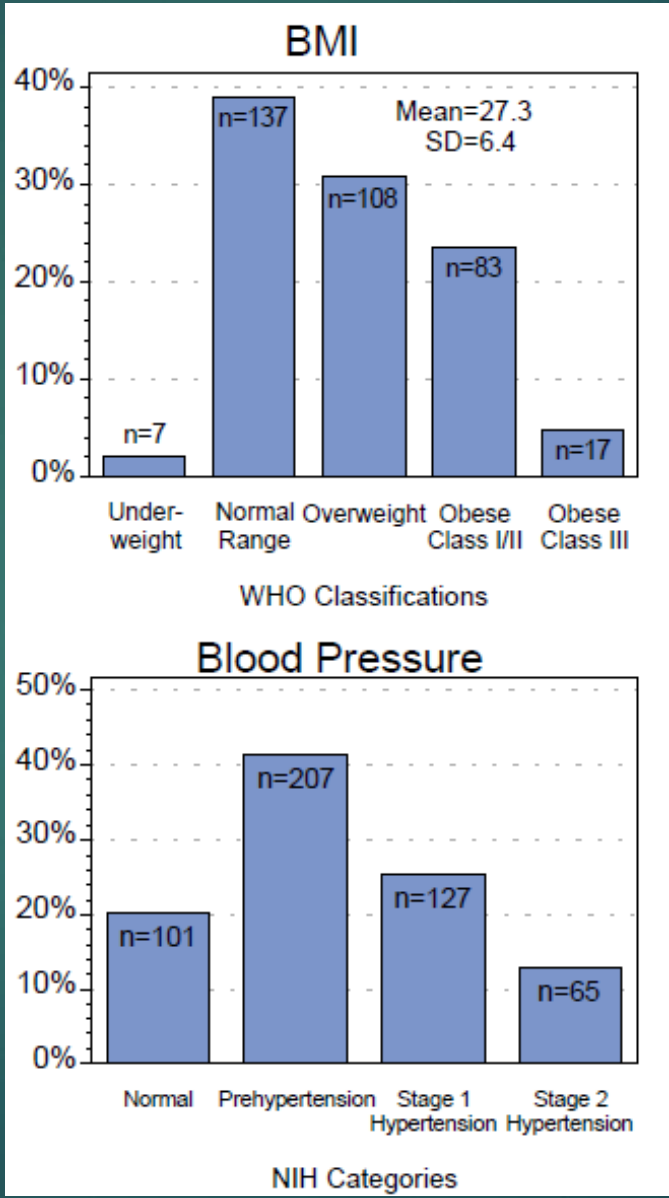
Smoking Status		
Never Smoked	Past Smoker	Current Smoker
62%	35%	3%

Variable	Values, N(%)
Female	466 (82.6)
Caucasian	524 (92.9)
Early RA (< 2yrs)	87 (15.4)
Seropositive	321 (67.7)
RF Positive	267 (57.8)
Anti-CCP Positive	282 (59.7)

BRASS Currently Enrolled

most recent visits as of 1st Quarter 2025

N=565



BRASS Currently Enrolled

most recent visits as of 1st Quarter 2025

N=565

Disease Characteristics

Variable	N	Mean	Std Dev	Min	Max
MDHAQ Score	518	0.46	0.49	0.00	2.80
Modified RADAI	488	2.60	2.09	0.00	9.22
Pain VAS	513	28.54	26.24	0.00	100.00
Patient Global	526	29.08	24.58	0.00	100.00
Physician Global	560	17.34	16.88	0.00	90.00
FSMHI5 Scale	411	78.19	16.22	15.00	100.00
Self Efficacy Score	89	78.39	17.36	20.00	100.00
DAS 28-CRP4S	111	2.57	1.26	0.99	6.21
Total Swollen Joints	564	1.80	3.94	0.00	22.00
Total Painful Joints	564	1.16	2.81	0.00	21.00

Current Medicines at Last Visit

Variable	Values, N(%)
Methotrexate	247 (43.7)
Only MTX (not including NSAIDs or Steroids)	93 (16.5)
Anti-TNF	217 (38.4)
Anti-TNF and MTX	103 (18.2)
Plaquenil	87 (15.4)
NSAIDs	218 (38.6)
Any DMARD	505 (89.4)
Biologic DMARD	295 (52.2)
Non-Biologic DMARD	332 (58.8)
Non-Bio DMARD, not including MTX or Plaquenil	37 (6.5)
Steroid	116 (20.5)
Narcotic	31 (5.5)
Other Pain Med (non-narcotic)	165 (29.2)

BRASS Currently Enrolled

most recent visits as of 1st Quarter 2025

N=565

Medicines Ever Taken

Variable	Values, N(%)
Methotrexate	505 (89.4)
Anti-TNF	414 (73.3)
Plaquenil	363 (64.2)
Biologic DMARD	431 (76.3)
Non-Biologic DMARD	559 (98.9)
Non-Bio DMARD, not including MTX or Plaquenil	272 (48.1)
Steroid	505 (89.4)

Current Supplements at Last Visit

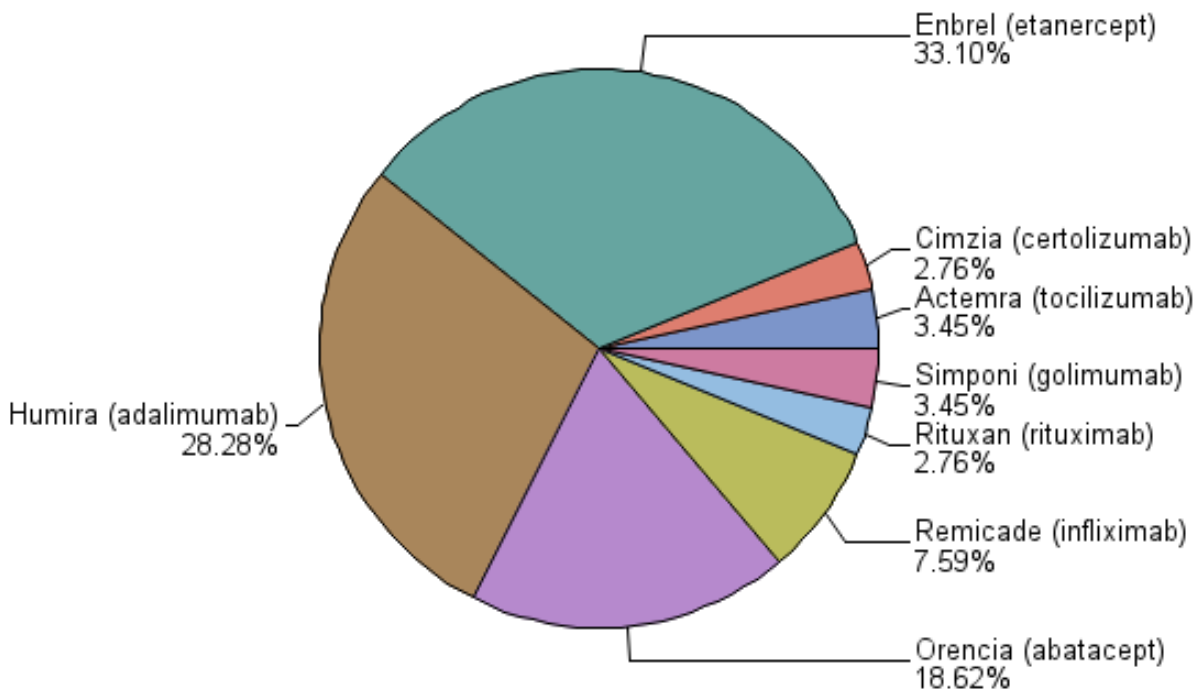
Vitamins/Minerals

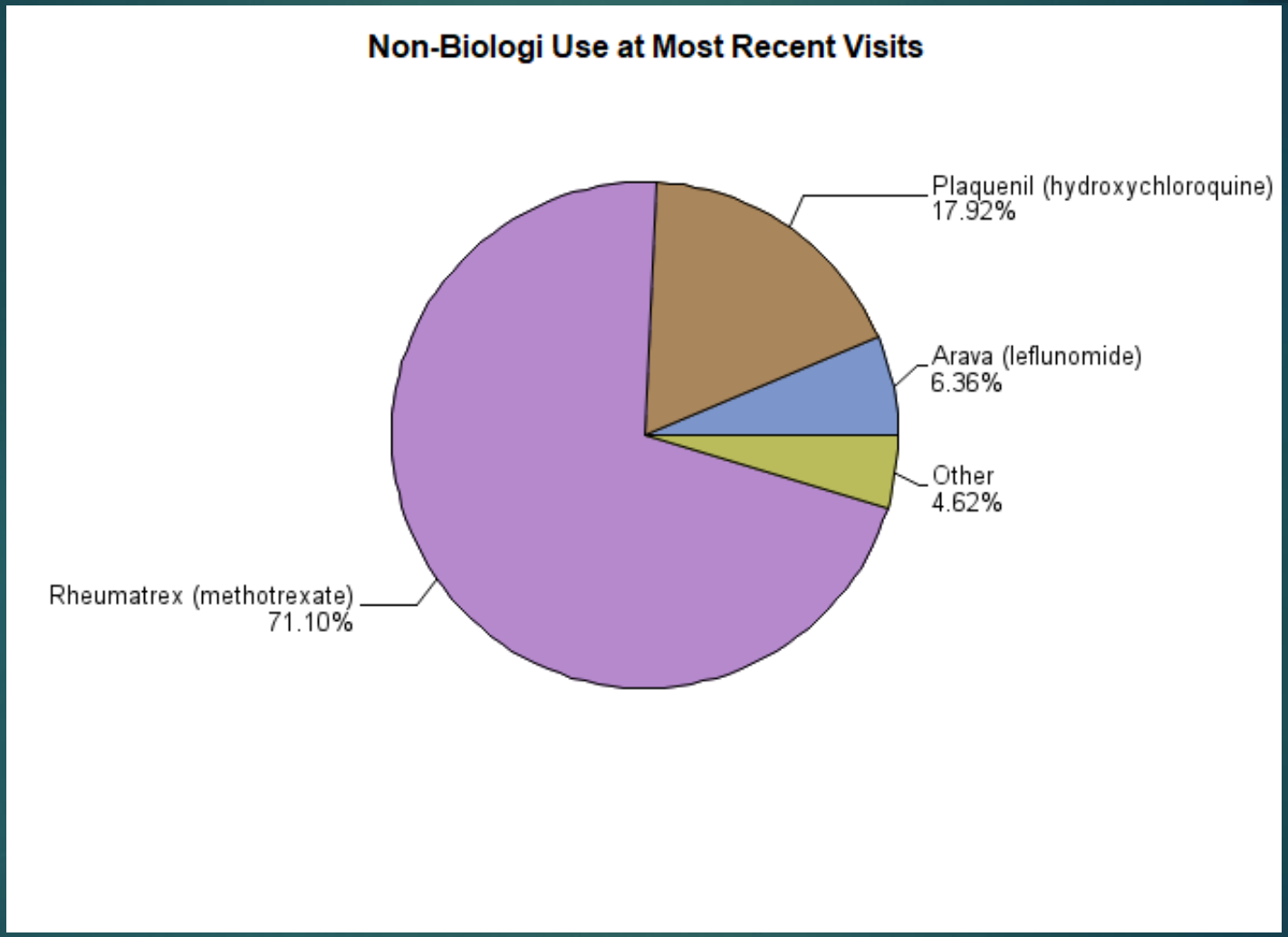
Variable	Values, N(%)
Vitamin B	39 (7)
Vitamin B6	7 (1.3)
Vitamin B12	59 (10.6)
Vitamin C	64 (11.5)
Vitamin D	306 (54.8)
Vitamin E	11 (2)
Calcium	152 (27.2)
Folic Acid	191 (34.2)
Iron	30 (5.4)
Magnesium	52 (9.3)
Multivitamin	231 (41.4)

Herbal/Health Foods

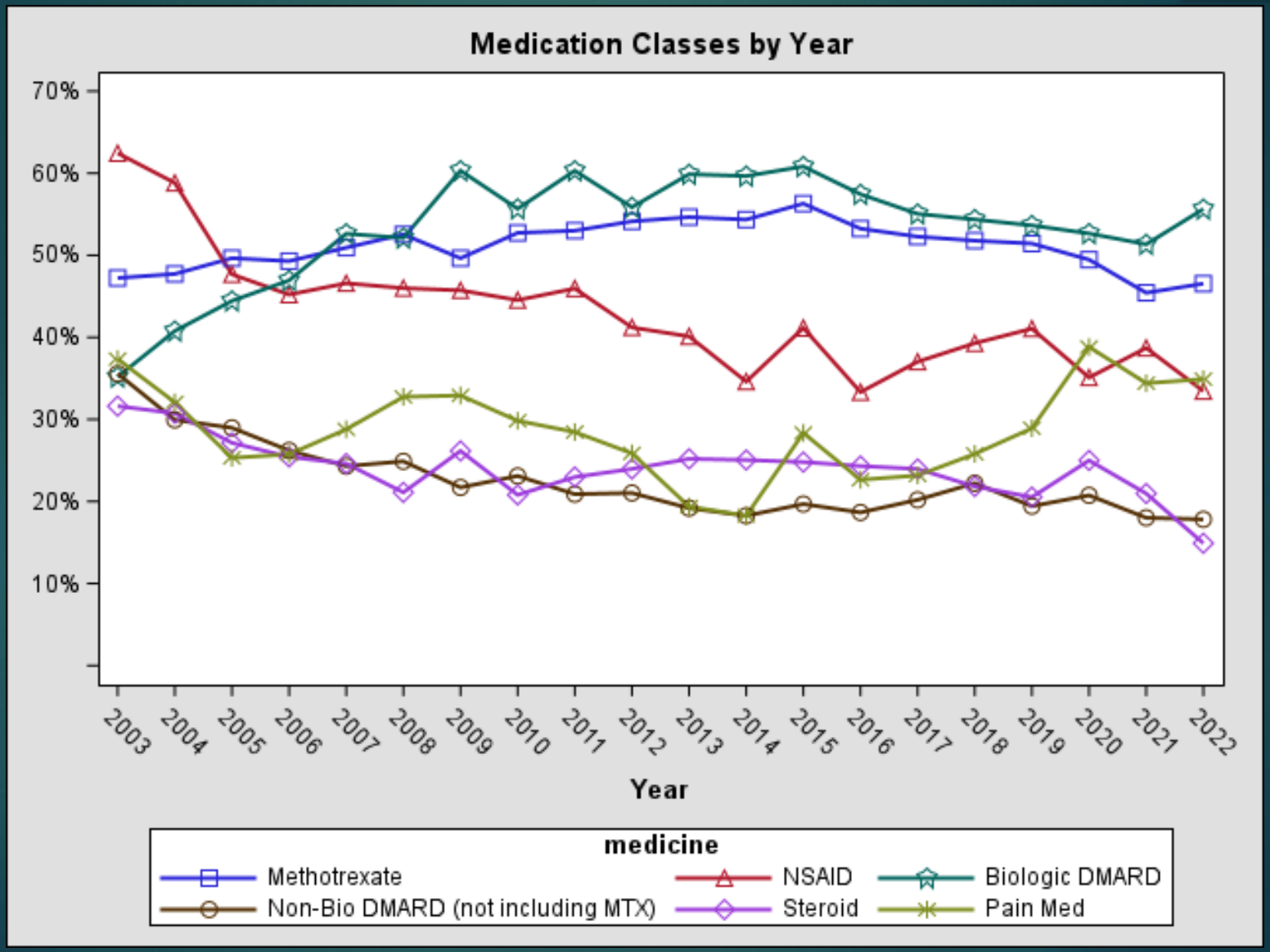
Variable	Values, N(%)
Borage Seed Oil	2 (0.4)
Capsaicin	1 (0.2)
Evening Primrose Oil	1 (0.2)
Fish Oil	91 (16.3)
Glucosamine/Chondroitin	12 (2.1)
Other	104 (18.6)

Biologic Use at Most Recent Visits



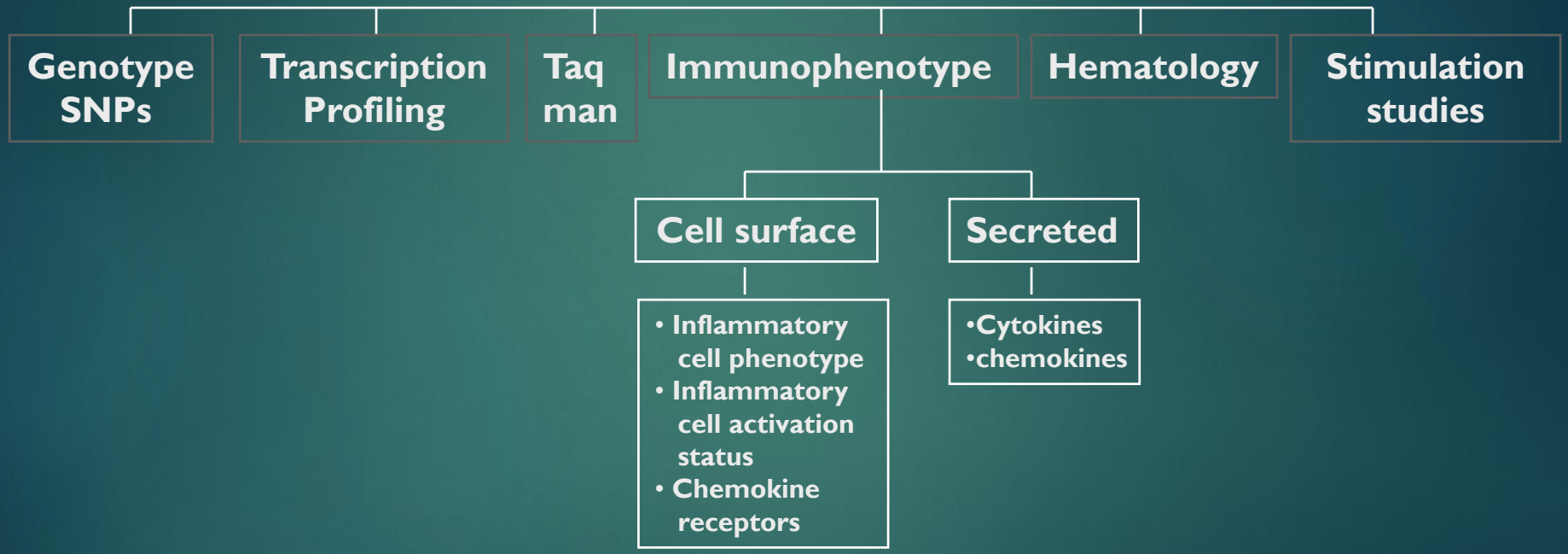

Non-Biologi Use at Most Recent Visits
Plaquenil (hydroxychloroquine)
17.92%
Arava (leflunomide)
6.36%
Other
4.62%
Rheumatrex (methotrexate)
71.10%

Medication Classes by Year



Technology Platforms for biomarker discovery

Whole Blood (50ml)



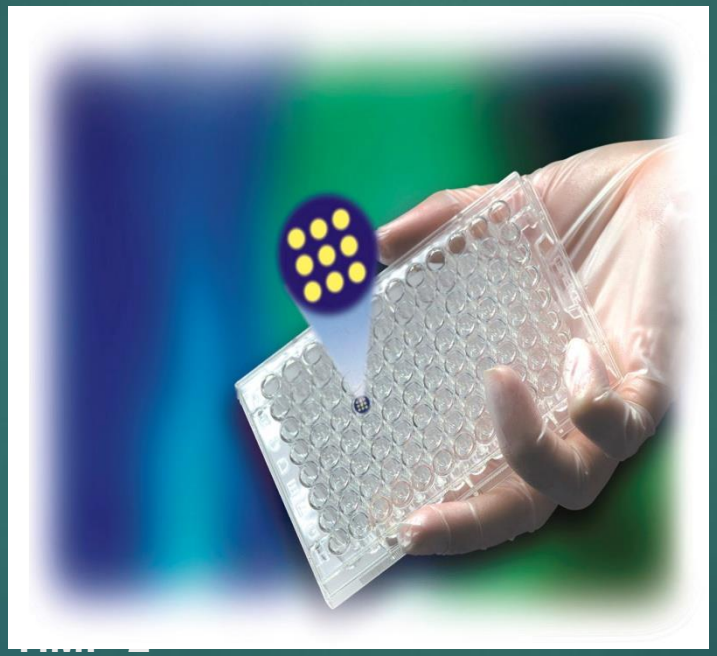
Biomarkers of Disease Activity

Panel I

TNF-a
IFN-g
IL-1b
IL-4
IL-6
IL-7
IL-8
IL-10
IL-12 p70
IL-12 p40
IL-18
MCP-1
MIP-1a
MIP-3a
MMP-10
MMP-13

Panel II

MadCAM



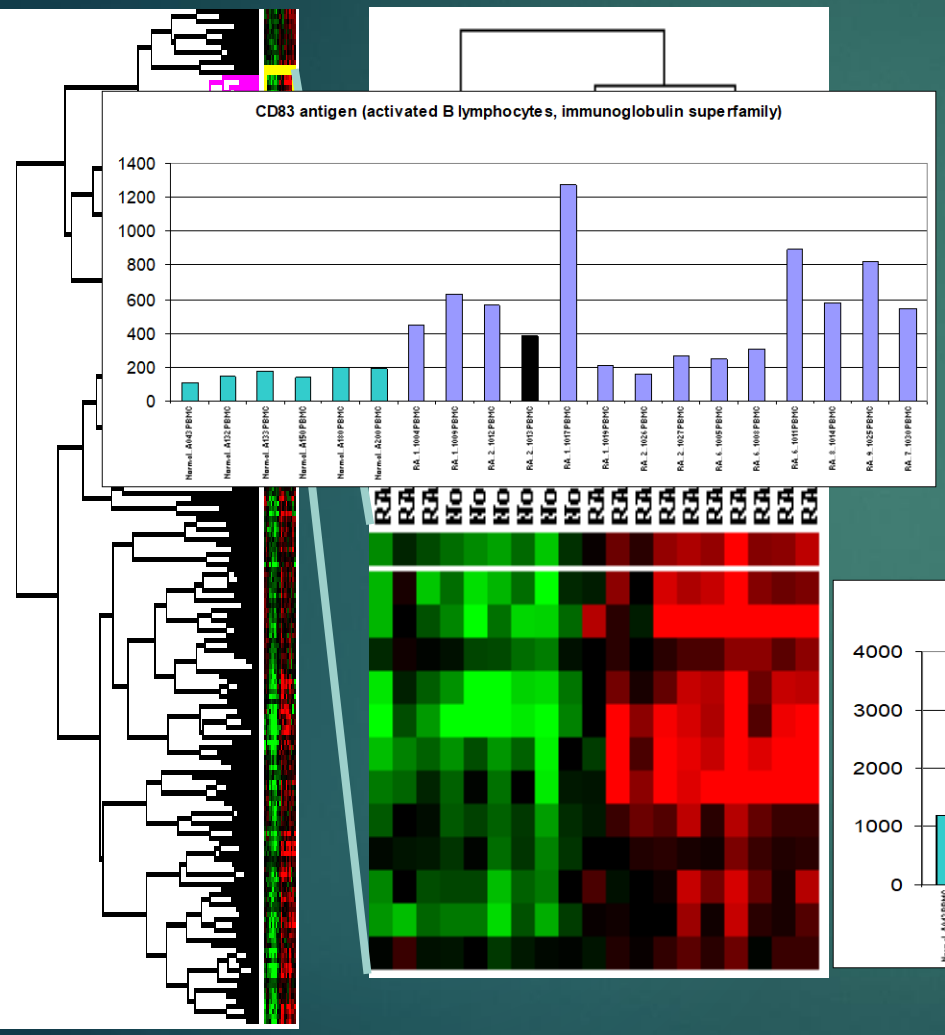
TNFR55
TNFR75

SearchLight™ Proteome Array (PerBio)

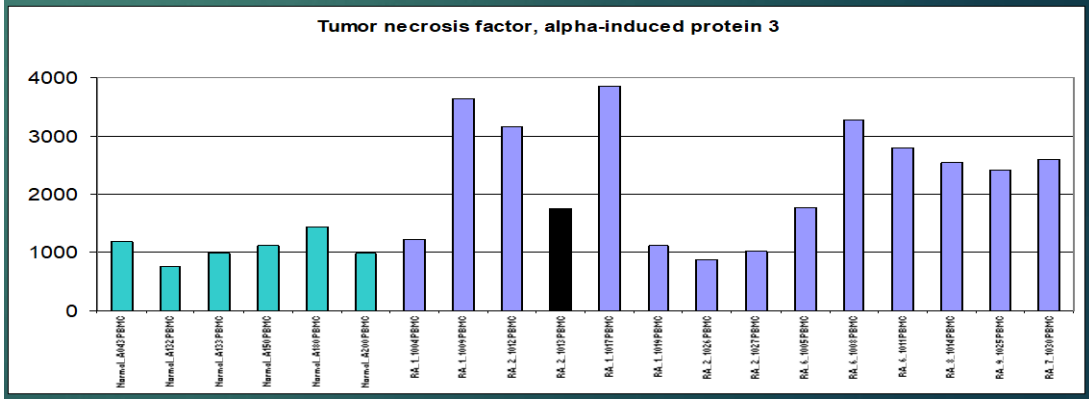
AVAILABLE BIOMARKERS

Adiponectin
AGER
ALB
Alkaline Phosphatase
Apolipoprotein A-I
Apolipoprotein A-II
Apolipoprotein B
Apolipoprotein C-II
Apolipoprotein C-III
Apolipoprotein E
APRIL
Basic FGF (basic fibroblast growth factor)
C2C
Calprotectin
Cartilage Glycoprotein-39 (YKL-40)
CCL2
CCL3
CCL4
CCL5
CCL11
CCL13
CCL17
CCL18
CCL20
CCL22
CCL26
CD30
CD40 Ligand
COMP (cartilage oligomeric matrix protein)
Complement Factor D (adipsin)
CRP
CXCL5
CXCL10
CXCL11
EGF
EGFR
GP130
Haptoglobin
Hepatocyte Growth Factor
Hyaluronan
ICAM1
IL1B
IL2
IL2RA
IL4R
IL5
IL6
IL6R
IL8
IL10
Interleukin 1 Receptor Antagonist
Interleukin 1 Receptor, Type I
Interleukin 1 Receptor, Type II
Kappa Free Light Chains
Leptin
MCSF
MMP1
MMP2
MMP3
MMP7
MMP8
MMP9
MMP12
MMP13
Osteocalcin
Osteonectin
Osteopontin
Osteoprotegerin
RANKL (TNFSF11)
Resistin
SAA1
Sclerostin
Selectin E
Selectin L
Selectin P
SERPINE1
sFLT1
sFLT4
sKDR
Thrombomodulin
Thyroid Peroxidase
TIMP1
TIMP2
TIMP3
TIMP4
TNF-alpha
TNFRSF1A
TNFRSF1B
VCAM1
VEGFA

Clustering Diagram Top 200 SNR Genes - PBMCs



(p-value: 0.01)



Pharmacoeconomic data in BRASS

- Health care resource use
- Diagnostic tests and visits
- Employment status
- Data on income, job change, disability
- EUROQOL data used in cost effectiveness analyses

Extensive data collection for future studies

- Originally collected information….only now being used.
  - Dyspnea questionnaire
  - Cognitive function questionnaire
  - Social support questionnaire
  - Flare questions
  - Exercise(Mets)
  - CAM
  - MOS Sleep
  - Periodontal disease questions….

Genome-wide association studies

From vision…

How to test the role of *common variants* in complex disease such as RA

…**to reality**:

Practical with whole genome marker sets

Impact of BRASS

- More than 150 articles published to date
- Specifically:
  - Expanded genetic information on risk of RA and treatment response.
  - Utilized for quality measures analyses
  - Utilized as a gold standard comparisons for disease activity in NLP and Claims.
  - Gave birth to patient centered care studies
  - Provided knowledge in fields outside of RA…model of inflammation

BRASS Collaborations

Title	Collaborator
TARGET- Improving Cardiovascular Risk Assessment in Rheumatoid Arthritis	Dan Solomon
IMIRA- Inflammation, subclinical myocardial injury, and CV risk in RA	Kat Liao
MUC5B - Improving risk-stratification of patients with rheumatoid arthritis (RA) for preclinical interstitial lung disease (ILD)	Jeff Sparks+Philippe Dieudé +Dr. Tracy Doyle
Rheum_CARD- Immunologic and Clinical Sequelae After COVID-19 in Patients with Systemic Autoimmune Rheumatic Diseases	Jeff Sparks+ Zachary Wallace
SAIL RA- Study of Inflammatory Arthritis and Interstitial Lung Disease in Early Rheumatoid Arthritis	Jeff Sparks
Understanding high patient global assessments when joint counts are low	David Felson(BU)
The Relative Frequency of Erosions in Specific Joints of the Hand in Rheumatoid Arthritis	Ron Anderson
Evaluation of Difficult to treat RA	Misti Paudel

Examples of impact of BRASS: Original investigations

The Association between Changes in Inflammation and HDL Cholesterol Efflux Capacity in RA

LIAO KP, PLAYFORD MP, FRITS M, COBLYN JS, IANNACCONE C, WEINBLATT ME, SHADICK NA, MEHTA NN.

J AM HEART ASSOC 2015

Lipids in RA

- RA patients appear to have a "better" lipid profile than non-RA

		RA cases		NHANES* (general population)		
Lipid	**Time period**	**N**	**Mean (SD), mg/dL**	**N**	**Mean (SD), mg/dL**	**P-value**
Tchol	2007-2010	290	**186 (20)**	4486	**200 (64)**	0.0002
LDL	2007-2010	297	**105 (18)**	2027	**118 (69)**	0.0010
HDL	2007-2010	295	**58 (10)**	4486	**59 (30)**	0.40

*National Health and Nutrition Examination Survery (NHANES)
Note: Data above for women only, age >20, not on statins

Liao, et al., Arthritis Care & Research 2013; Carroll et al., *JAMA* 2010

Efflux capacity and CVD

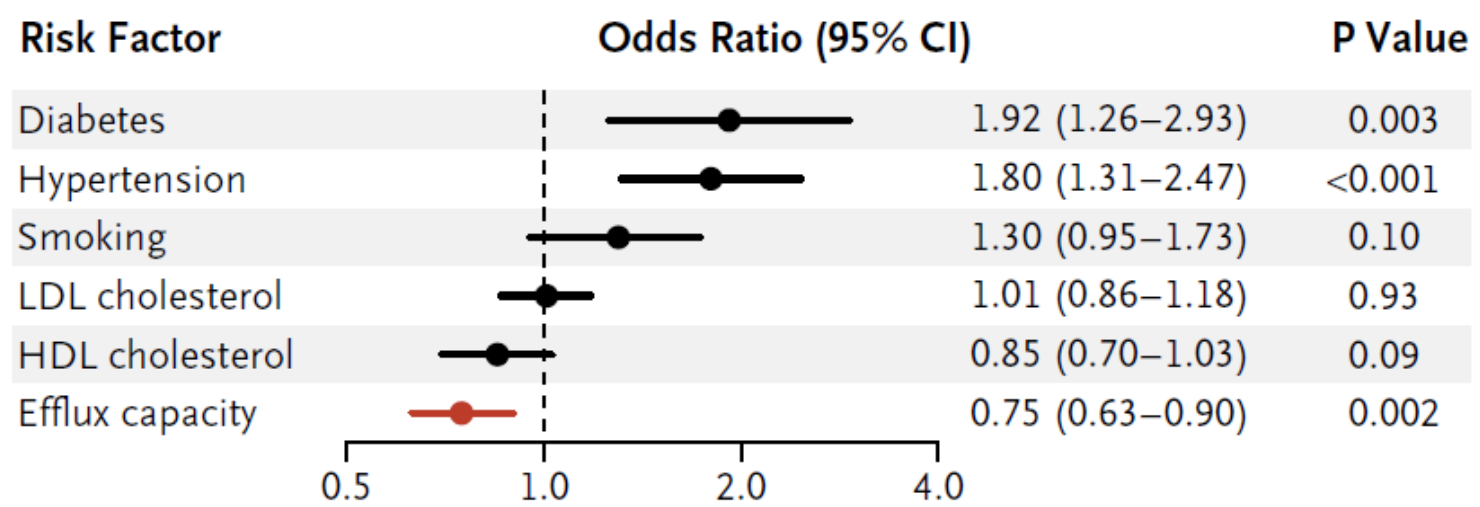
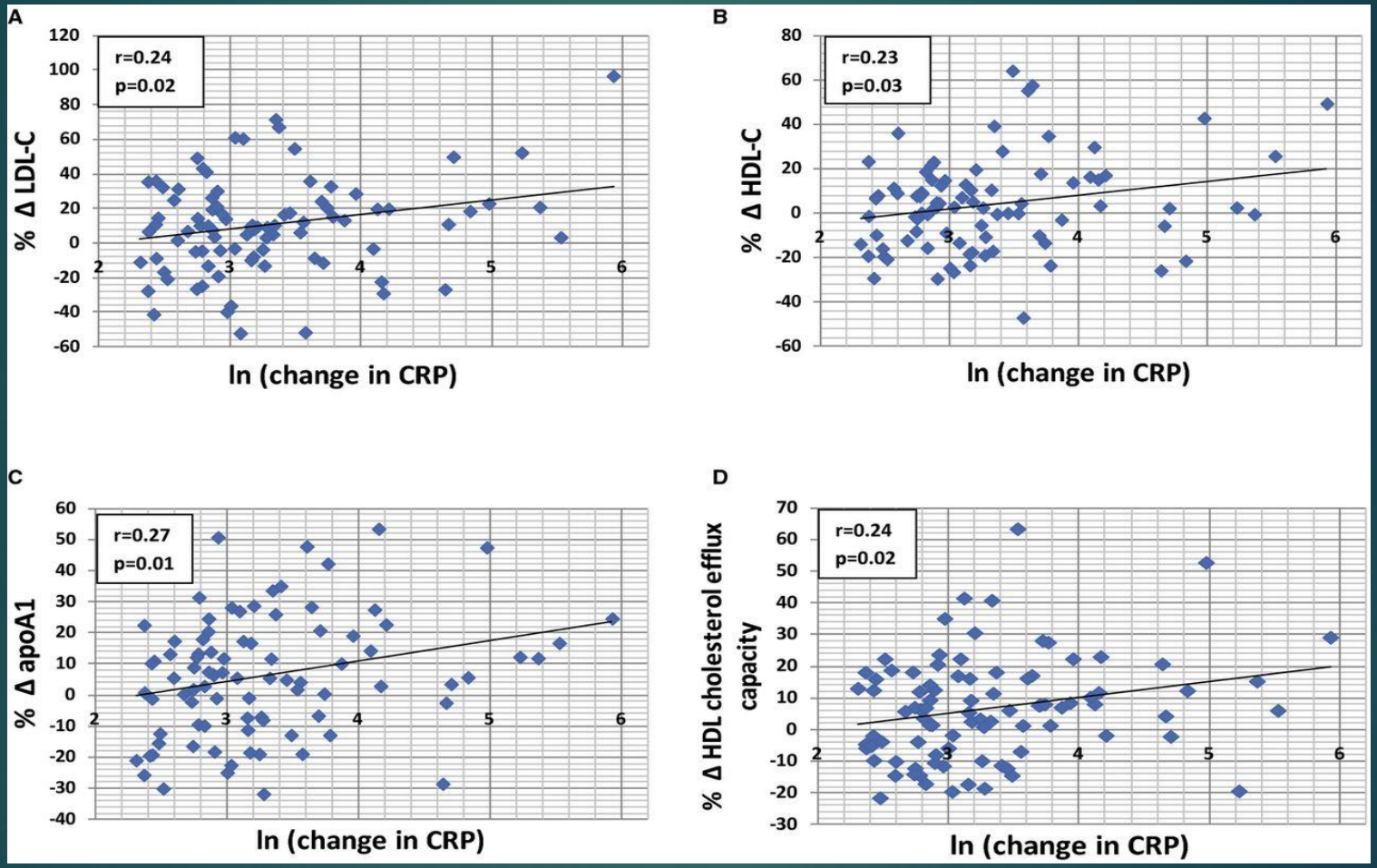


Figure 1. Odds Ratios for Coronary Artery Disease According to Efflux Capacity and Selected Risk Factors.

The logistic-regression model was also adjusted for age and sex. Odds ratios for continuous variables are per 1-SD increase.

Correlations between magnitude of reduction in CRP (natural log transformed) and the percentage change in (A) LDL-C, (B) HDL-C, (C) apoA1, and (D) HDL cholesterol efflux capacity between baseline and 1-year follow-up.



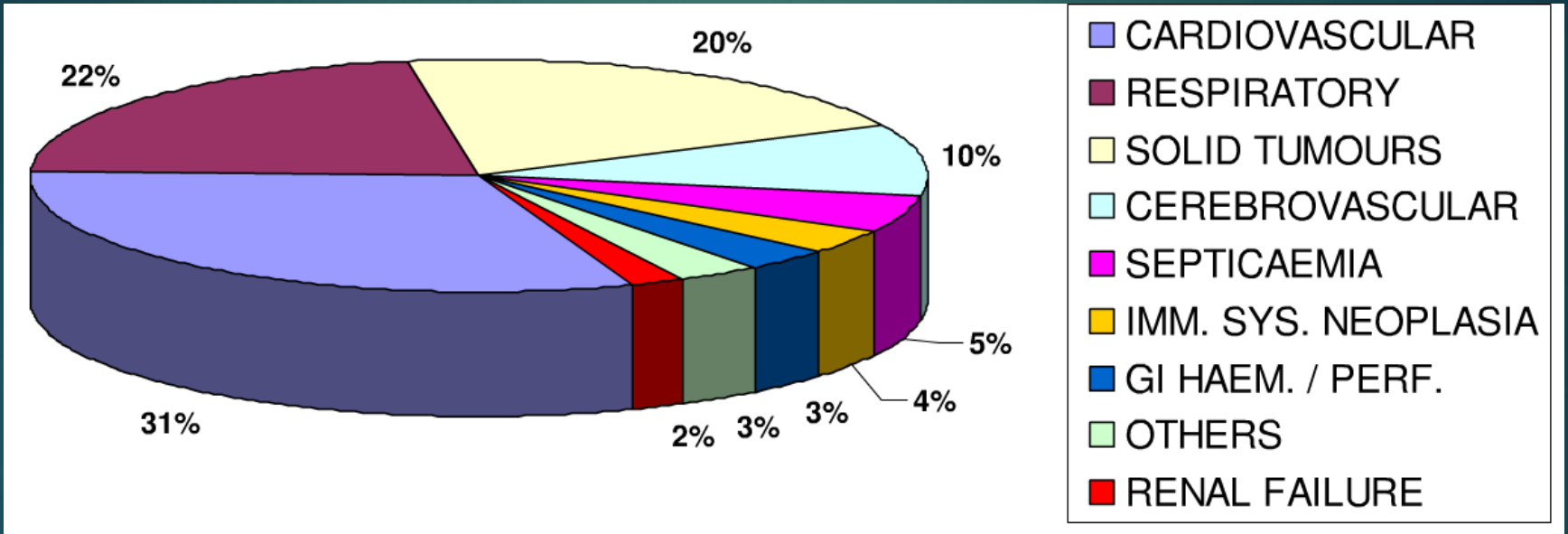
Katherine P. Liao et al. J Am Heart Assoc 2015;4:e001588

Detection of Rheumatoid Arthritis-Interstitial Lung Disease is enhanced by Serum Biomarkers

DOYLE TJ,…. DELLARIPA PF, FRITS ML, IANNACCONE CK,….,WEINBLATT ME, SHADICK NA, ROSAS IO.

AMERICAN J OF RESP AND CCM.2015

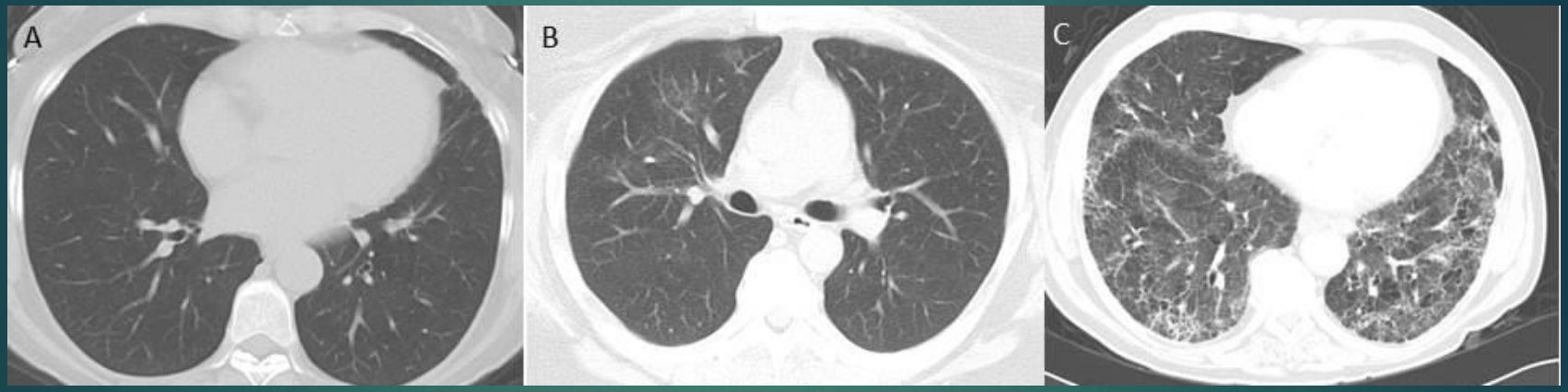
Main Causes of Death in RA Patients



Young Rheumatology 2007

Spectrum of RA-ILD

No RA-ILD | Subclinical RA-ILD | Clinically-evident RA-ILD



40% of individuals with rheumatoid arthritis (RA) have a spectrum of interstitial lung disease (ILD), yet RA-ILD is poorly understood and under-recognized.

Doyle Chest 2014

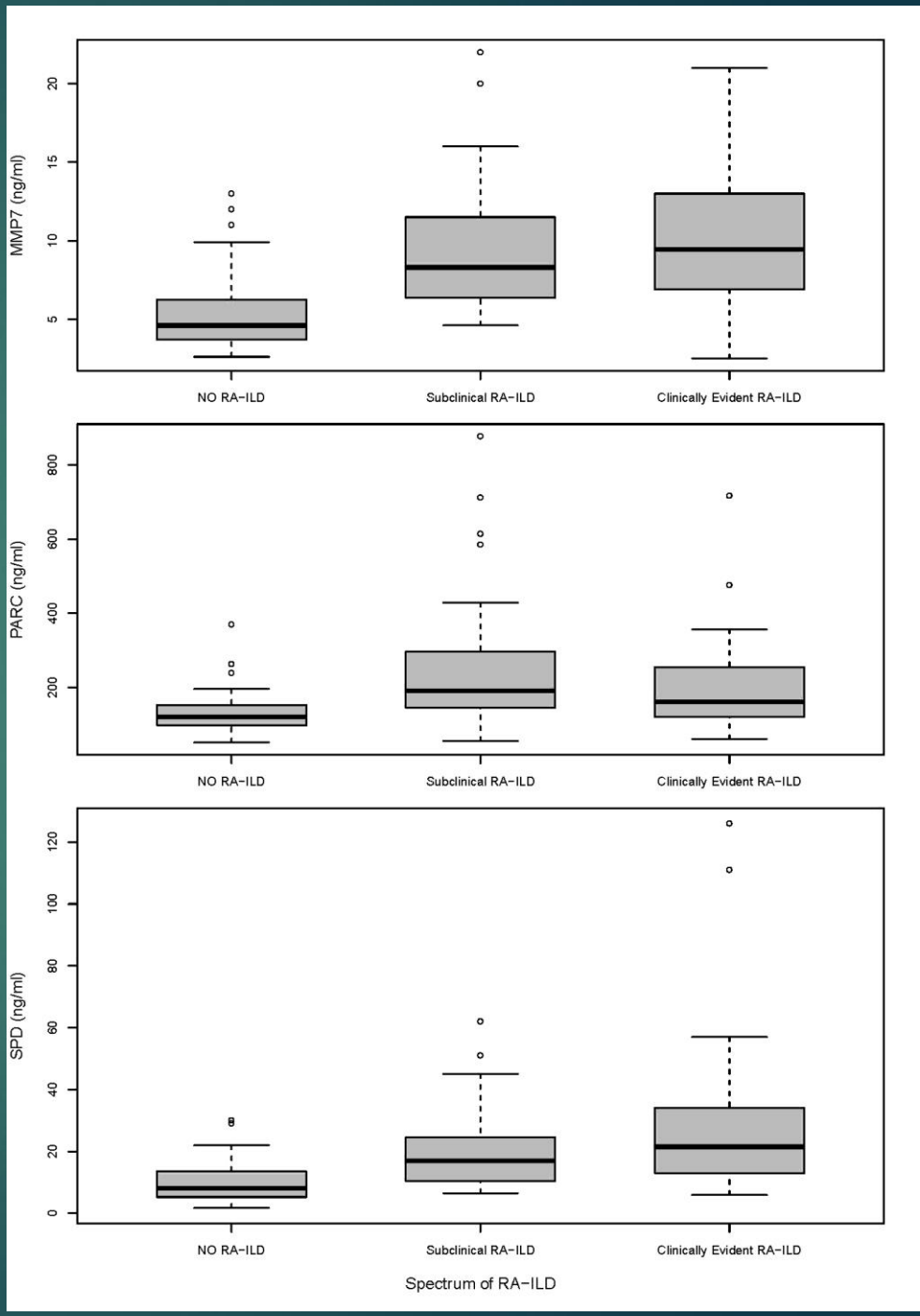
Biomarker Levels

	BRASS Cohort		
	No RA-ILD (n=29)	**Subclinical RA-ILD (n=29)**	**Clinically-evident RA-ILD (n=17)**
MMP7	5.7 ± 2.5	9.1 ± 3.3*	10.4 ± 3.2*
PARC	132 ± 63	277 ± 183*	169 ± 72*
SP-D	11.9 ± 7.9	20.6 ± 12.0*	27.5 ± 28.7*

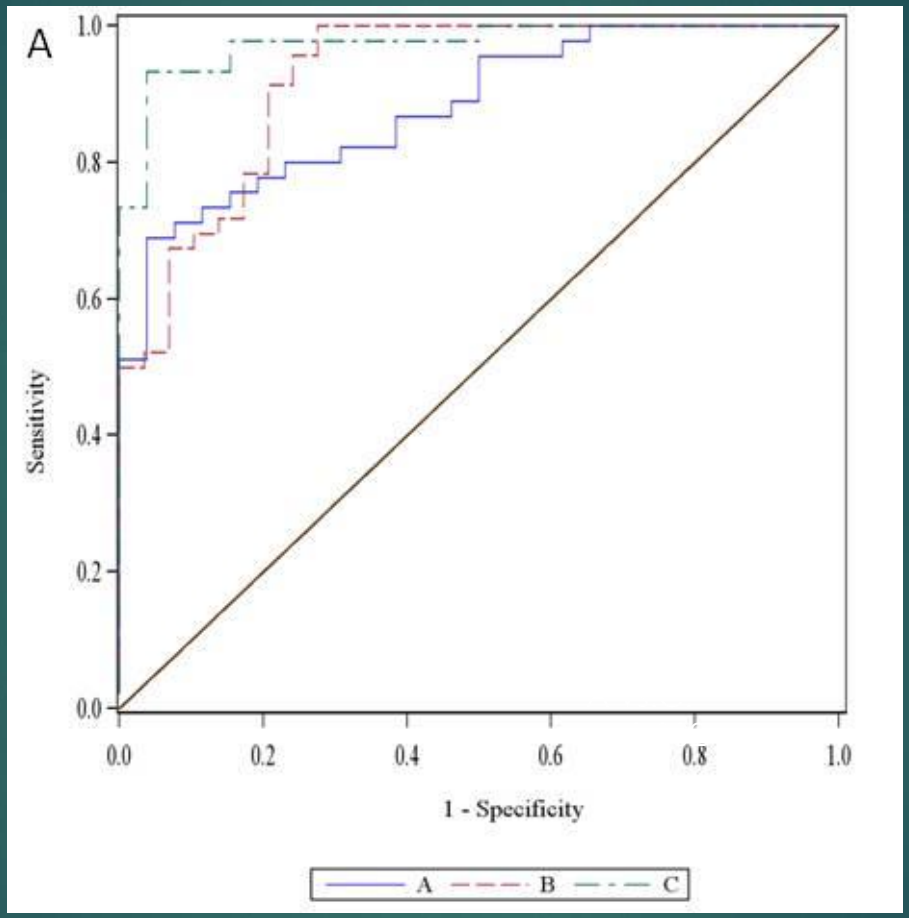
MMP7

PARC

SP-D



ROC curves for the Spectrum of RA-ILD



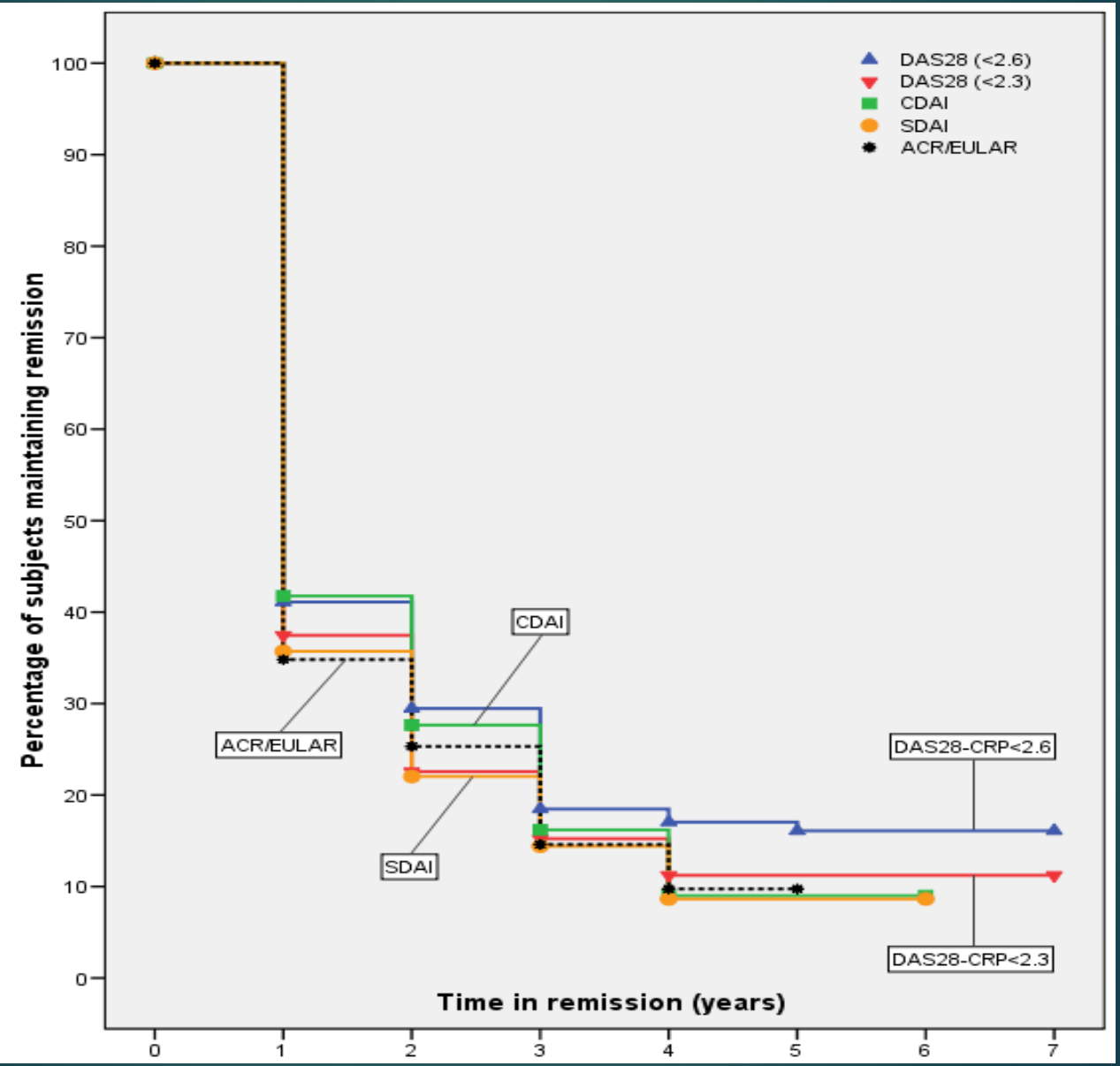
A: Age, gender, ever smoker, RF, CCP
B: MMP7, PARC, SP-D
C: Age, gender, ever smoker, RF, CCP, MMP7, PARC, SP-D

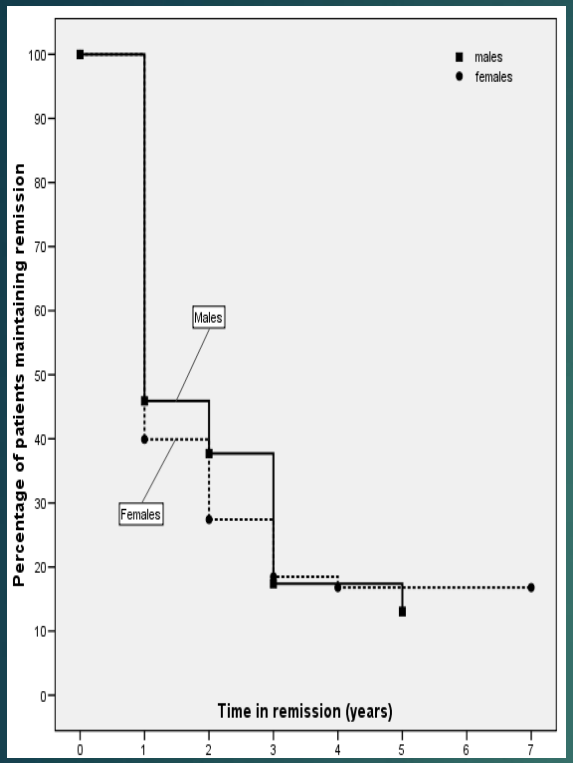
- Similar trends seen in both subclinical and clinically-evident RA-ILD

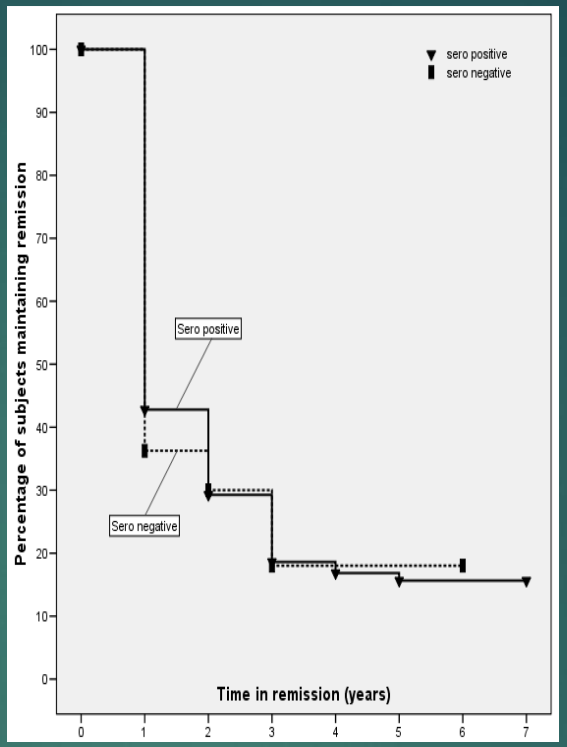
Sustained rheumatoid arthritis remission is uncommon in clinical practice

PRINCE FM, BYKERK V, SHADICK N, LU B, CUI J, FRITS M, IANNACCONE C, WEINBLATT M, SOLOMON D. ARTHRITIS RES THER. 2012 MAR 19;14(2):68.

Figure 2. Kaplan-Meier survival curves for subjects maintaining remission according to various remission definitions, demonstrating the Kaplan-Meier survival curves for the percentage of subjects maintaining remission over time.







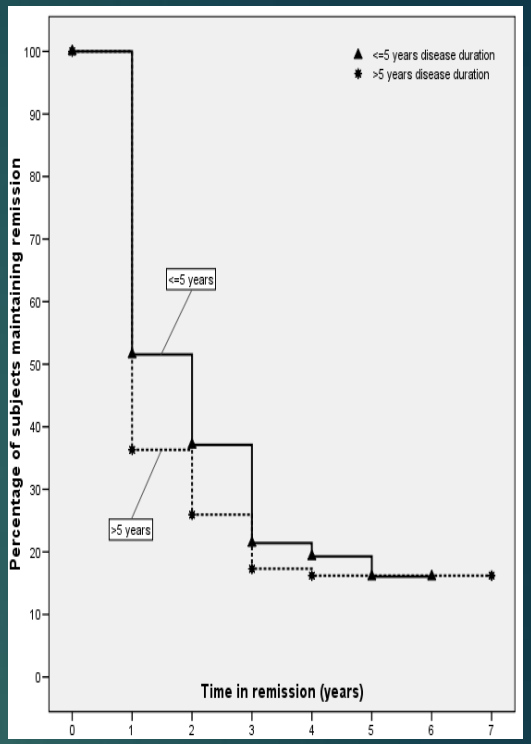
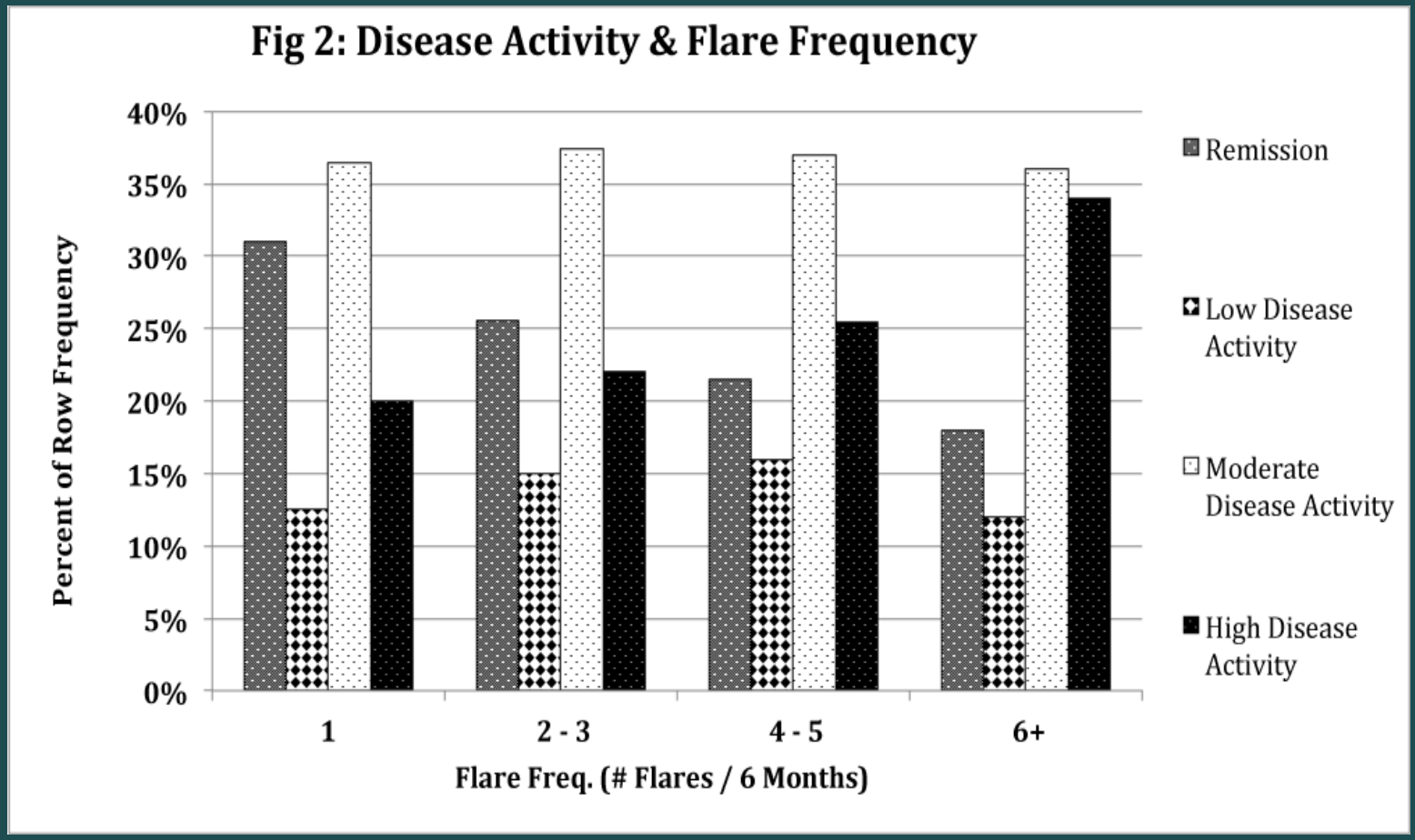


Figure 3. Kaplan-Meier survival curves for subjects maintaining DAS28-CRP < 2.6 remission, stratified according to (a) gender, (b) serologic status, (c) disease duration. We demonstrate the Kaplan-Meier survival curve for the percentage of patients maintaining DAS28-CRP< 2.6 remission over time. Patients are stratified according to different patient and disease characteristics.

Flares in Rheumatoid Arthritis: Frequency and Management. A Report from the BRASS Registry

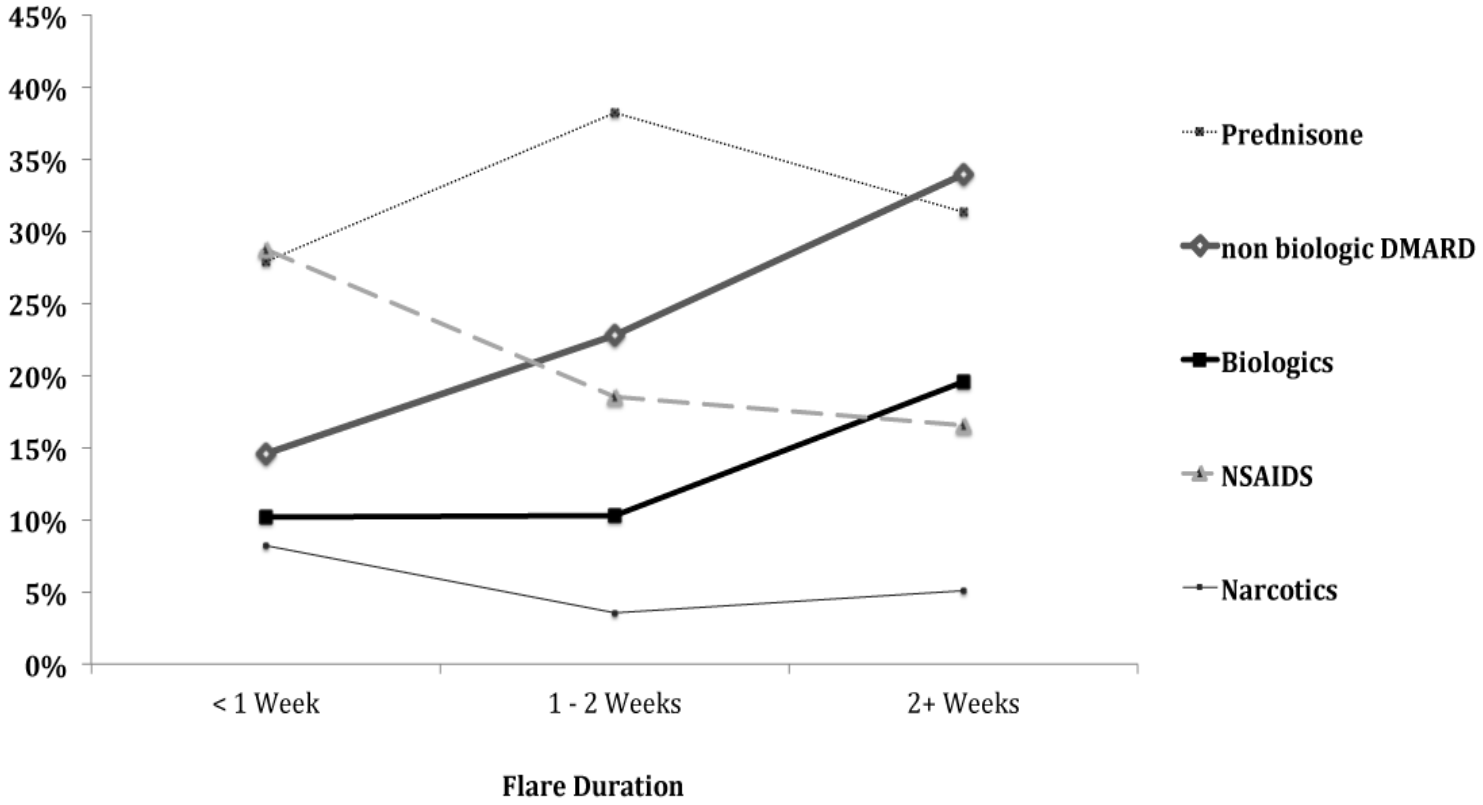
BYKERK V, SHADICK N, FRITS M, BINGHAM C, JEFFERY I, IANNACCONE C, WEINBLATT M, SOLOMON DH. J RHEUM 2013

Figure 2: Flares are reported more often in patients with higher disease activity, however even patients in remission report they have had flares



A chi-square test examining the relationship between disease activity (measured with DAS28-CRP) and flare frequency was statistically significant (p=0.0003) indicating that the relationship between the two categories is not independent.

Fig 4: New & Increased Medication by Flare Duration



Of 57% of patients whose flare lasted < 1week, more patients used prednisone and NSAIDs, whereas in the 30% of patients with flares ≥ 2 weeks more patients used DMARDs and Biologic therapies. The kinds of medication employed for flare management varied depending on the duration of flare (p=<. 0001 based on a chi-square test)

Conclusions

- Patients frequently report flares in RA at a variety of disease activity levels
- These data provide insight into aspects of RA flare including patient reported management strategies of flares.
- There is a need to consider both duration of flare and these strategies in the development of a standardized composite measure of flare.

The Longitudinal Impact of Biologic Use on Disability Within a Rheumatoid Arthritis Registry

Shadick N[1], Gerlanc N[2], Frits M[1], Stolshek B[3], Brady B[2], Iannaccone C[1], Collier D[3], Cui J[1], Mutebi A[3], Weinblatt M[1]

[1]Brigham and Women's Hospital, Boston, MA; [2]Health Analytics, LLC, Columbia, MD; [3]Amgen Inc., Thousand Oaks, CA

Objectives

- To assess the longitudinal impact of the cumulative time taking biologics on changes in disease activity and disability in patients with RA enrolled in the BRASS registry.

Methods: Modeling Methodology

- Linear mixed repeated measures regression was used to model the impact of biologic exposure on changes in disability (Modified Health Assessment Questionnaire [mHAQ]) and disease activity (Disease Activity Score 28-joint count with C-reactive protein (4) [DAS28-CRP4]) and Rapid 3.

- Cumulative biologic exposure,or the mean biologic exposure ratio, the primary independent variable, was quantified at each follow-up as the ratio of a patient's time on a biologic relative to their time participating in the cohort.

Decreased Disease Activity Over Time With Increased Biologic Exposure. Each data point represents the mean annual value ± standard error.

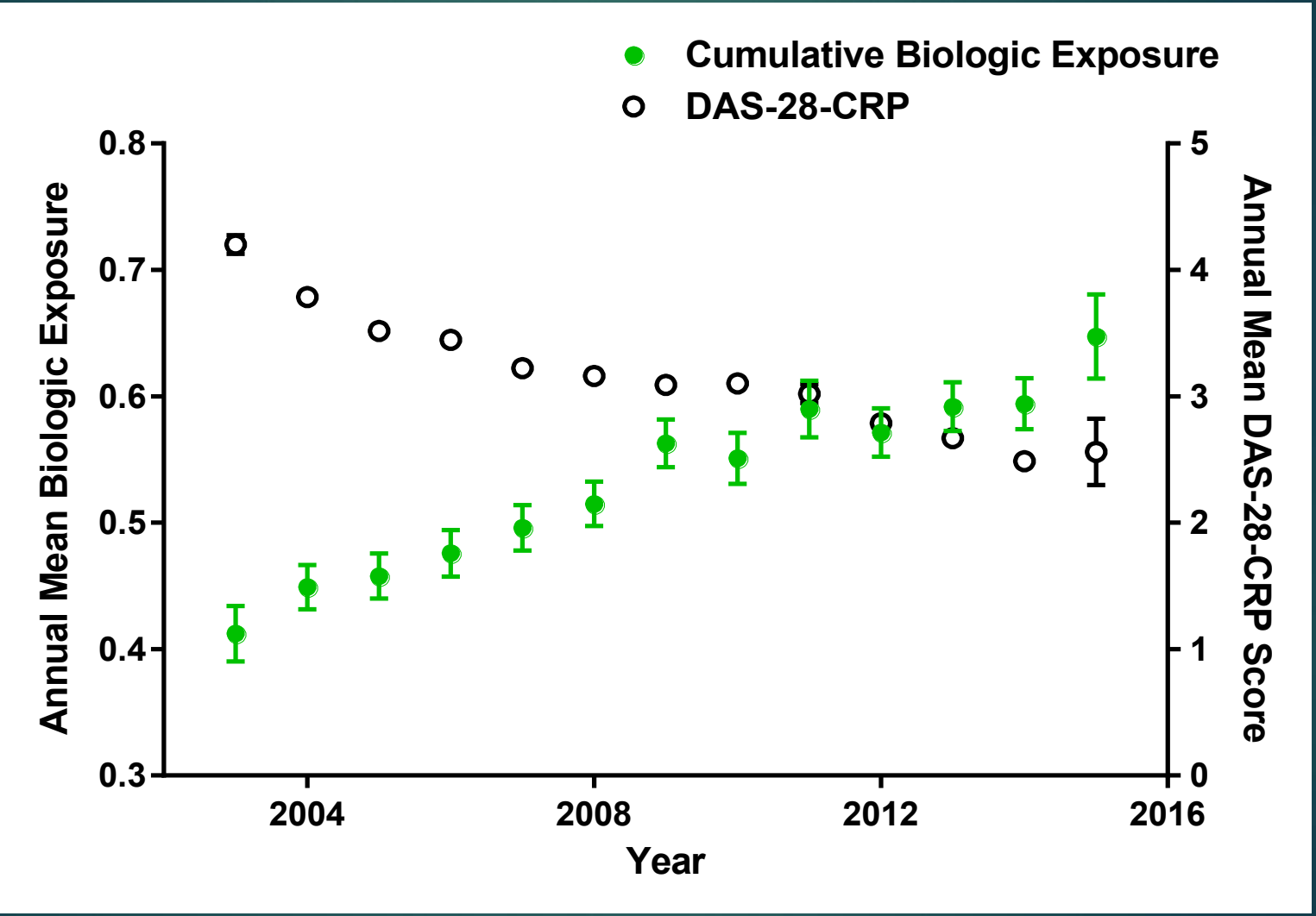


Table 3. Disease Activity: DAS28-CRP4 Repeated Measures Regression Model Omnibus Results			
Effect	Estimate	P-value	t-value
Intercept	0.571	0.014	2.45
Cumulative biologic exposure	-0.673	<0.001	-8.29
On methotrexate	-0.139	<0.001	-3.59
Smoking status	0.081	0.028	2.20
Education at baseline	-0.031	0.014	-2.47
Disease duration	0.008	<0.001	4.27
Baseline mHAQ	0.147	0.013	2.50
Baseline DAS28-CRP4	0.552	<0.001	32.70
Biologic use prior to enrollment	0.352	<0.001	5.47
Biologic use at baseline	0.598	<0.001	7.85
2003	1.295	<0.001	5.80
2004	0.994	<0.001	4.49
2005	0.731	0.001	3.31
2006	0.728	0.001	3.29
2007	0.517	0.019	2.34
2008	0.564	0.010	2.57
2009	0.417	0.058	1.90
2010	0.471	0.032	2.14
2011	0.412	0.062	1.87
2012	0.304	0.165	1.39
2013	0.137	0.533	0.62
2014	-0.023	0.916	-0.11

Results: DAS28-CRP4

- DAS28-CRP4 scores consistently decreased over time and longer biologic exposure was associated with a significant reduction in annual population means for disease activity (*$P < 0.001$; Figure 2)*.
- Longer mean biologic exposure ratio was associated with decreased disease activity as measured by DAS28-CRP4 (Table 3).
- The strongest predictor of increased disease activity was baseline DAS28-CRP4 score, followed by biologic use at baseline, biologic use prior to enrollment, disease duration, baseline mHAQ, and smoking status (Table 3).
- Both use of methotrexate and an increased level of education were predictors of decreased disease activity (Table 3).

Decreased Disability Over Time With Increased Biologic Exposure. Each data point represents the mean annual value ± standard error. See Table 2 for annual sample sizes.

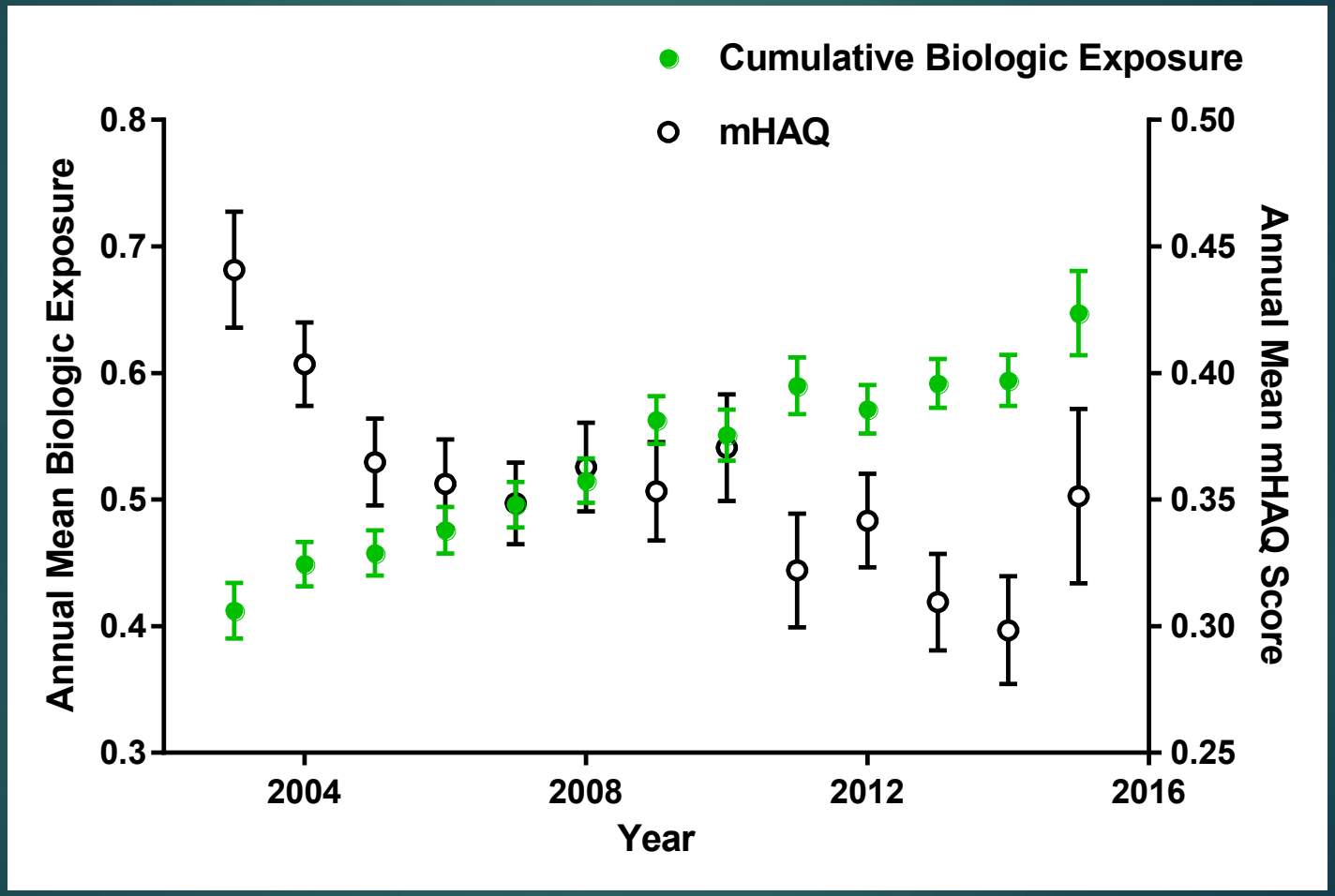


Table 4. Disability: mHAQ Repeated Measures Regression Model Omnibus Results			
Scale/Effect	Estimate	P-value	T-value
Intercept	0.059	0.002	3.05
Cumulative biologic exposure	-0.101	<0.001	-5.28
On methotrexate	-0.036	<0.001	-3.70
Smoking status	0.019	0.048	1.98
Education at baseline	-0.004	0.213	-1.25
Disease duration	0.003	<0.001	6.80
Baseline mHAQ	0.741	<0.001	53.54
Biologic use at baseline	0.102	<0.001	5.33

Results: Disability (mHAQ)

- mHAQ scores generally decreased over time, indicating a reduction in disability over time (Figure 3).
- Baseline mHAQ score was the strongest predictor of disability during follow-up, disease duration was the second strongest predictor of disability, and biologic use at baseline and being a current or previous smoker were also significant predictors of disability (Table 4).
- Both longer cumulative biologic exposure and methotrexate use were predictors of reduced disability.

Conclusions

- Longer biologic exposure was associated with reduced disease activity and disability in this longitudinal population of RA patients.
- Although biologic use improved the functional status of the population, patient RA status at enrollment remained the most significant predictor of disability.
- The results of the longitudinal models developed here suggest that use of biologics may help to reduce long-term disease activity and disability in the RA population.