

BRIGHAM AND WOMEN'S HOSPITAL RHEUMATOID ARTHRITIS SEQUENTIAL STUDY (BRASS)

A collaboration of scientific technology and clinical expertise



For further information regarding BRASS, please contact Dr. Nancy Shadick at nshadick@partners.org or visit our website at www.BRASSSTUDY.org



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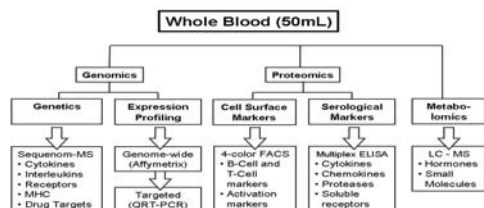
Project Goals

The BRASS registry began recruitment in March 2003 establishing a prospective observational cohort of 1,000 rheumatoid arthritis patients in order to:

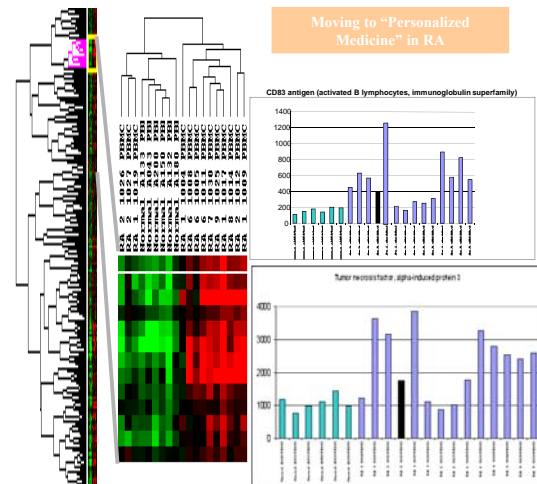
- Determine and validate biomarkers that predict drug response and toxicity in rheumatoid arthritis.
- Determine and validate biomarkers that predict disease activity and prognosis in rheumatoid arthritis.
- Evaluate the natural history of treated rheumatoid arthritis by measuring clinical, functional and economic outcomes

Serological Data whole blood 50ml

Technology Platforms for biomarker discovery Whole blood 50ml



Clustering Diagram Top 200 SNR Genes - PBMCs



Clinical Data

	Questionnaire Timepoints (months)											
	0	6	12	18	24	30	36	42	48	54	60	
PATIENT DOMAINS												
DNA	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Serum	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
RNA	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Whole blood	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Hand Radiographs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Demographics - Age, Gender, Ethnicity												
General Health												
Symptoms	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
List of co-morbidities	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
New conditions	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Surgeries	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Lung	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Coastline function	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Menopause	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pregnancy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Oral Contraceptive Use	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Menstruation history	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Antibiotic use (past 6 mos)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Vaccinations	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Teacher/Healthcare	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Teeth and Gums	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Current Meds												
Arthritis	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pain	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Corticosteroid	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
DM	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Vitamins	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Non-arthritis meds	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Alternative Providers	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Exercise	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Past Meds												
All Arthritis (last 6 mos)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Methotrexate (past 6 mos)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
General Health (function & pain)												
MDHAQ	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
SF-12	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
MH-S	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
PHQ-9	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
EuroQo	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Radii - join man	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Arthritis self-efficacy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pain Q	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
RA Concerns	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Berkman-Syme (social support)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Quality of Life Scale	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
MCS Sleep Scale	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Miscellaneous												
Employ -disability, income	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Health Ins/Medication Ins	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Health Care Resource	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Cohort

N=961	Variable	Values
Female, N (%)		790 (82.2)
Age, mean (SD)		57.05 (14.11)
Disease Duration, mean (SD)		14.18 (12.44)
MDHAQ, median		0.6 (0.0-1.6)
DAS28-CRP, mean (SD)		4.07 (1.52)
RF positive, N (%)		568 (65.6)
CCP positive, N (%)		596 (65.5)

BRASS has the ability to identify biomarkers of disease risk and disease progression

Pilot Study SNP Genotyping Results

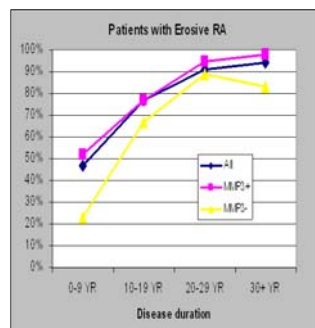
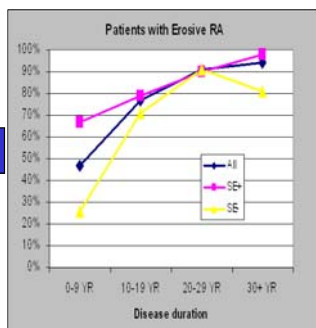
presented at the Keystone Conference 2004

RA risk: Symptom severity:

Gene	SNP	Allele Freq	P-value (Fisher)	Odds Ratio (0.27-0.77)	Gene	SNP	Allele Freq	P-value (ANOVA)	Symptom
TNFA	308	9.5%	0.0041	0.40	SLC11A1	38	30.5%	0.0016	Swollen Joint Count
Nf-β1L1	80	31.2%	0.025	1.55 (1.02-2.36)	SLC11A1	90	40.6%	0.0078	PGA Score
MMP3	55	49.3%	0.013	0.57 (0.36-0.92)	IL1β	53	21.3%	0.0086	Tender Joint Count
IL4	12	12.2%	0.032	6.73 (0.85-53.1)	IL1β	53	21.3%	0.0294	PGA Score



HLA-SE	Allele Freq	Odds Ratio	OR (<9yrs)
MMP3	83%	2.17	4.90
		2.08	2.86



Abstracts/Publications

2007 BRASS POSTERS/PRESENTATIONS:

- Contemporary Trends in Rheumatoid Arthritis Disease Activity Reduction and Medication Use, 341/POSTER
- Whole Genome Association Study of Quantitative CCP Titer in Rheumatoid Arthritis, 537/POSTER
- Biomarkers of Rheumatoid Arthritis Disease Activity: A Translational Approach, 551/ORAL PRESENTATION
- Association between ATIC, ITPA, AMPD1, MTR and MTRR Polymorphisms and Disease Activity in Rheumatoid Arthritis Patients on Methotrexate, F78/POSTER
- Can Pain Sensitivity SNPs be Replicated in Rheumatoid Arthritis (RA) Patients? 1064/POSTER
- Beyond Fatigue and Pain: Addressing Concerns of Rheumatoid Arthritis Patients Outside of What is Traditionally Covered in the Physician Visit, Workshop, Abstract
- Evaluation of Selected Rheumatoid Arthritis Activity Scores for Office Based Assessment, 1889/POSTER
- Whole Genome Association Study Identifies Rheumatoid Arthritis Risk Locus Near TNFAIP3, 2121/ORAL PRESENTATION
- Rheumatoid Arthritis Outcomes: Focus Groups Emphasize Lifestyle, Social and Self-Image Effects of RA, 2187/ORAL PRESENTATION

PUBLICATIONS:

- Two independent alleles at 6q23 associated with risk of rheumatoid arthritis, Plenge, RM, et al., *Nature Genetics*, 2007 Oct; [Epub ahead of print].
- Peripheral Blood Expression of Nuclear Factor-κB-Regulated Genes Is Associated with Rheumatoid Arthritis Disease Activity and Responds Differentially to Anti-Tumor Necrosis Factor-α versus Methotrexate. Parker A, et al., *J Rheumatol* 2007 Sep;34(9):1817-22
- Associations between HLA, PTPN22, CTLA4 genotypes and RA phenotypes of autoantibody status, age at diagnosis, and erosions in a large cohort study. Karlson EW, et al. *Ann Rheum Dis*. 2007 Jul 31
- Outcomes in rheumatoid arthritis: incorporating the patient perspective. Heller JE, Shadick NA. 2007 Mar;19(2):101-5. Review [Epub ahead of print] *Curr Opin Rheumatol*
- Ongoing effects of the D70 mutation and the shared epitope in HLA-DR4 on disease activity and certain disease phenotypes in rheumatoid arthritis. Shadick NA, et al. *Ann Rheum Dis*. 2007 May 21; [Epub ahead of print].
- Agreement between patient report and medical record review for medications used for rheumatoid arthritis: the accuracy of self-reported medication information in patient registries. Solomon DH, et al. *Arthritis Rheum*. 2007 Mar 15;57(2):234-9.
- Principal components analysis corrects for stratification in genome-wide association studies. Price AL, et al. *Nature Genetics*. 38(8):904-9, 2006 Aug.
- The validity of a rheumatoid arthritis medical records-based index of severity compared with the DAS28. Sato M, et al. *Arthritis Research & Therapy*. 8(3):R57, 2006.
- Agreement between patient report and medical record review for medications used for rheumatoid arthritis: the accuracy of self-reported medication information in patient registries. Solomon DH, et al. *Arthritis Care Research*, in press.
- Dietary Caffeine Does Not Affect Methotrexate Efficacy in Rheumatoid Arthritis Patients. Elizabeth Benito-Garcia, et al., *Journal of Rheumatology* 2006;33:1275-81.

Collaborators

- Broad Institute, Cambridge, MA
- University of Alabama
- UCLA, School of Medicine
- National Institute of Environmental Health Sciences
- Bristol Myers Squibb Foundation