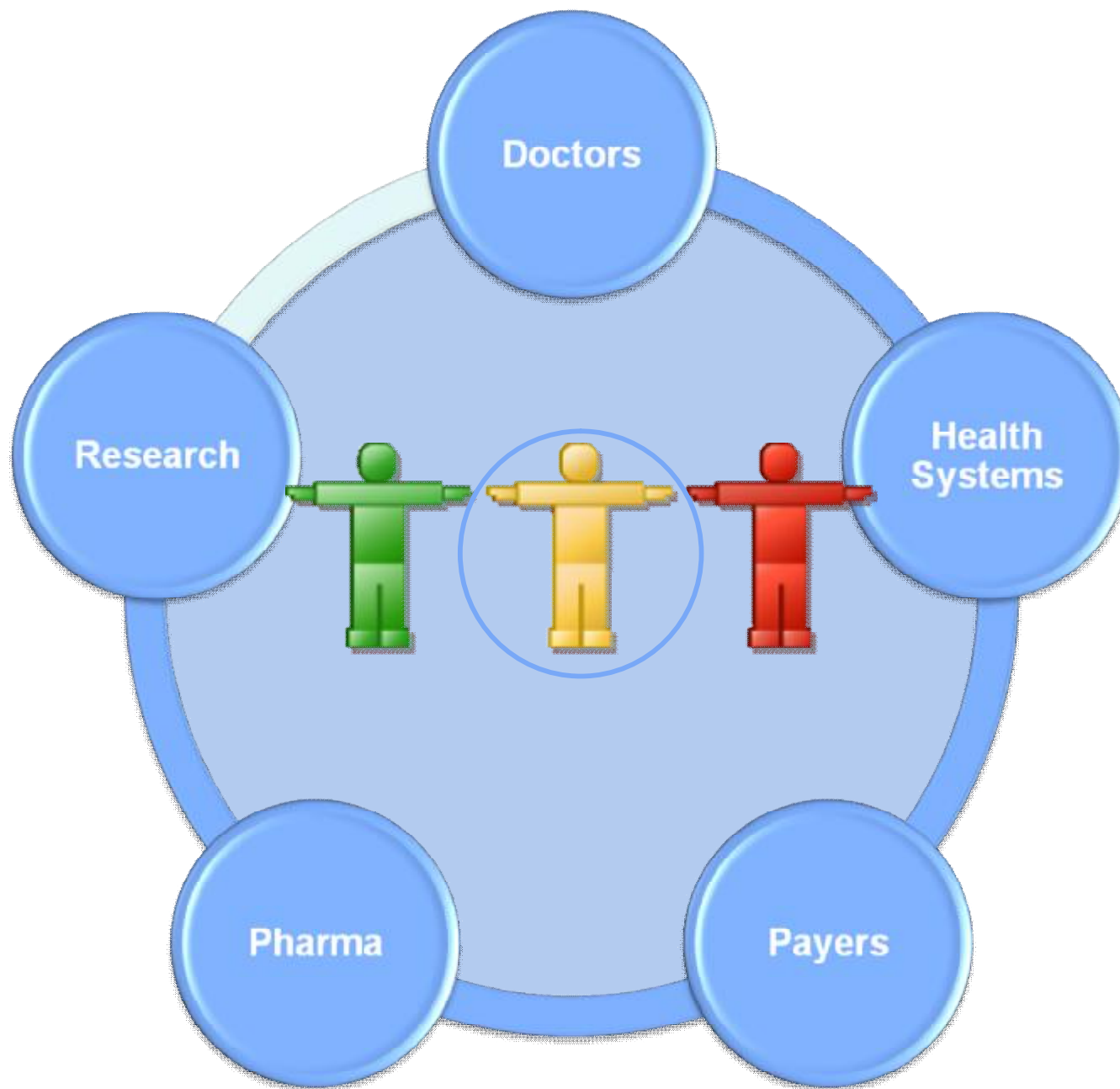




James Allen Heywood

*"All models are wrong, but
some are useful."*

George Edward Pelham Box

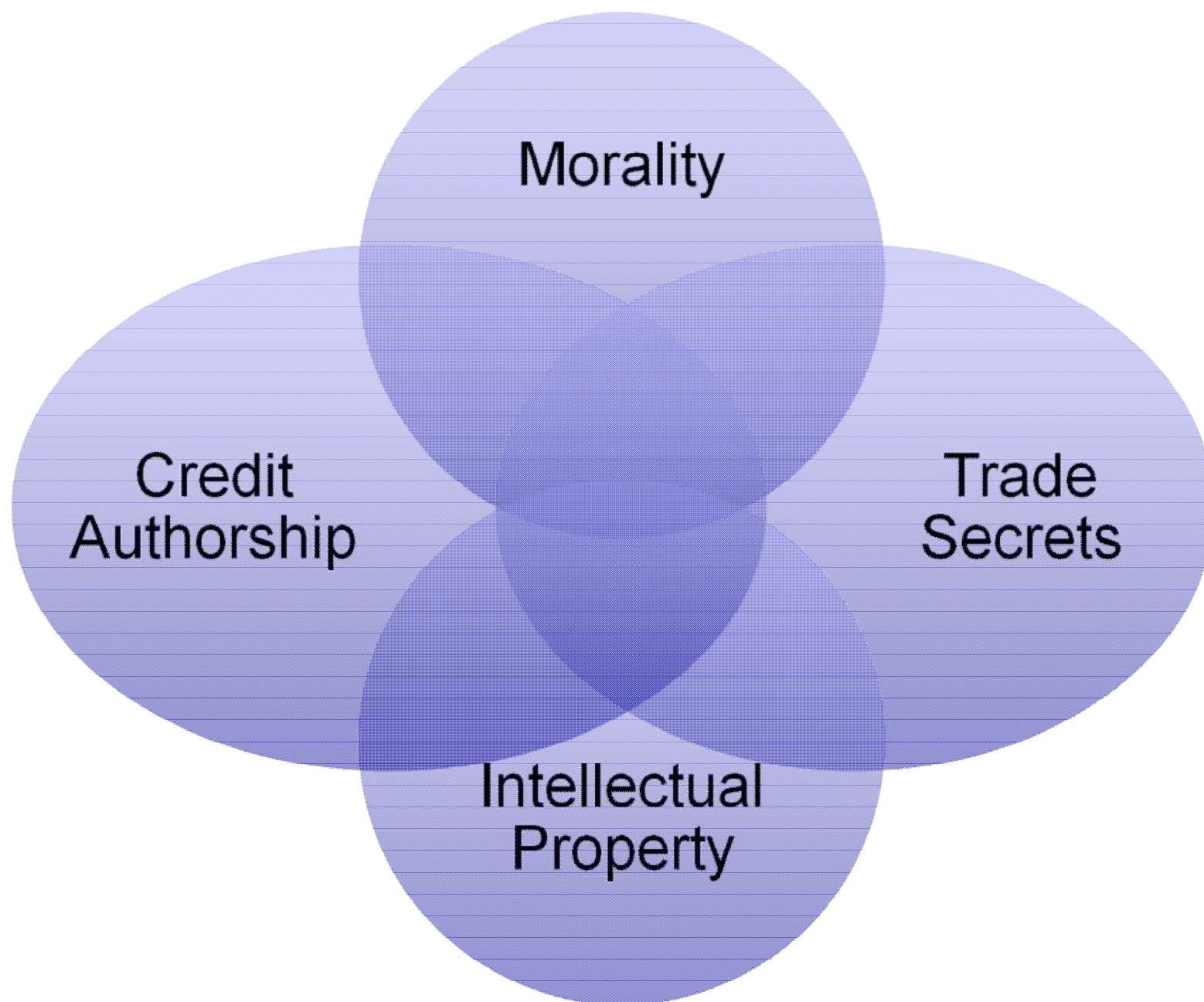


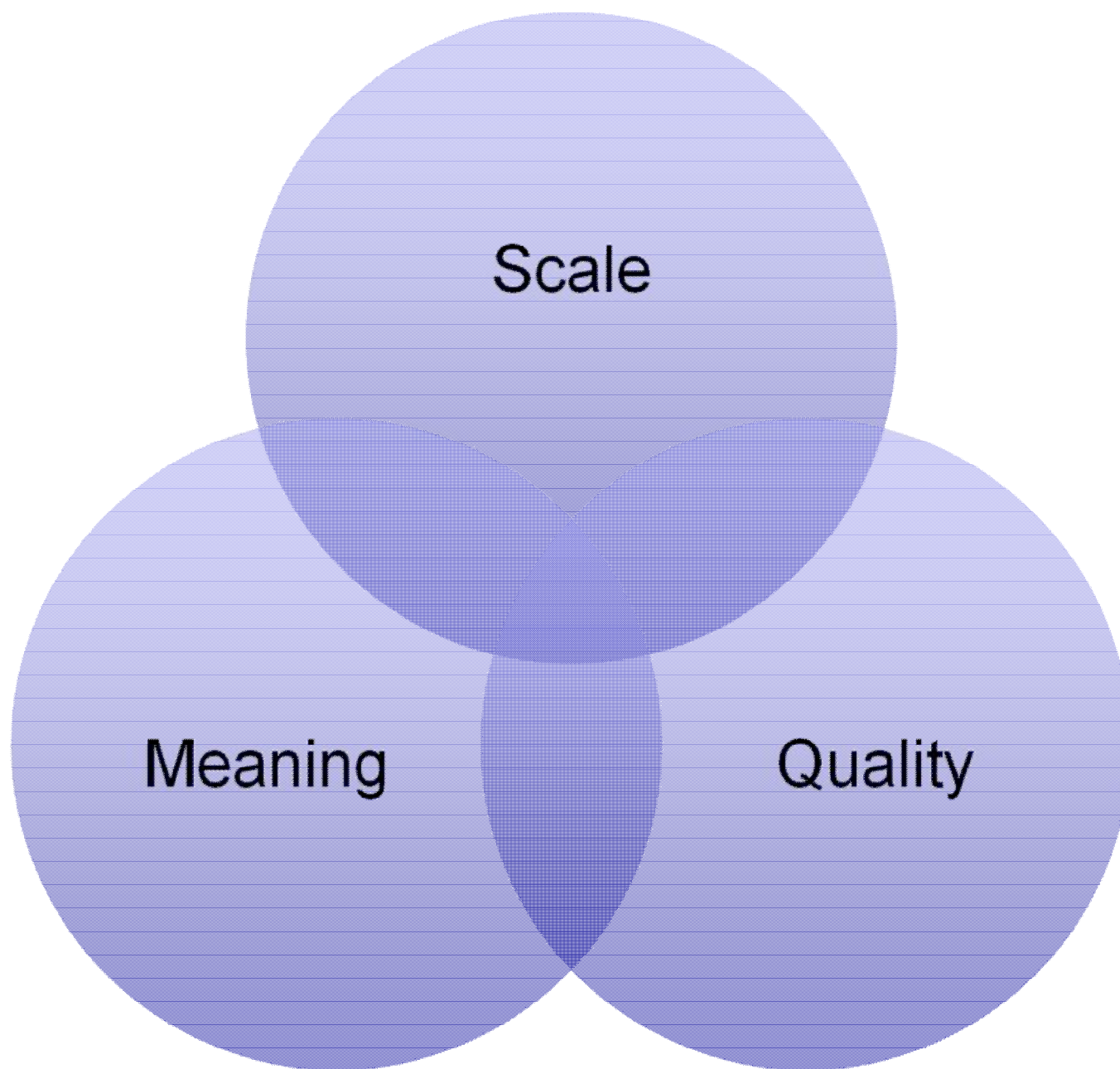
Is Pre-competitive the right model?

What assumptions does it contain?

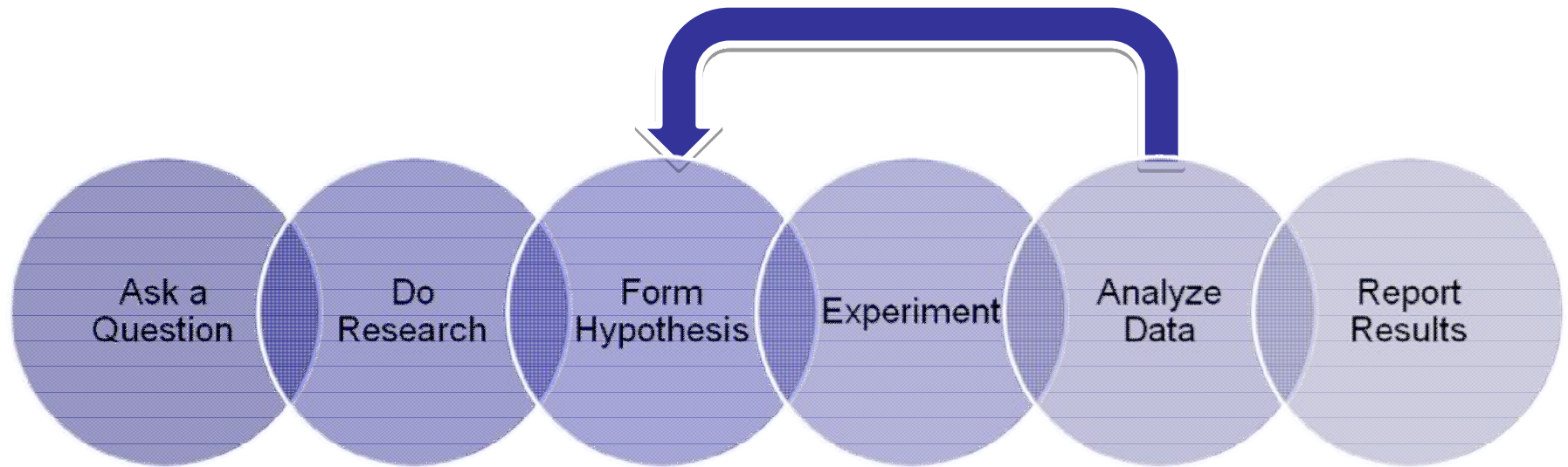
Other models.

- Effectiveness
- Return on Investment
- Industrial/Scale/Quality
- Science vs Engineering

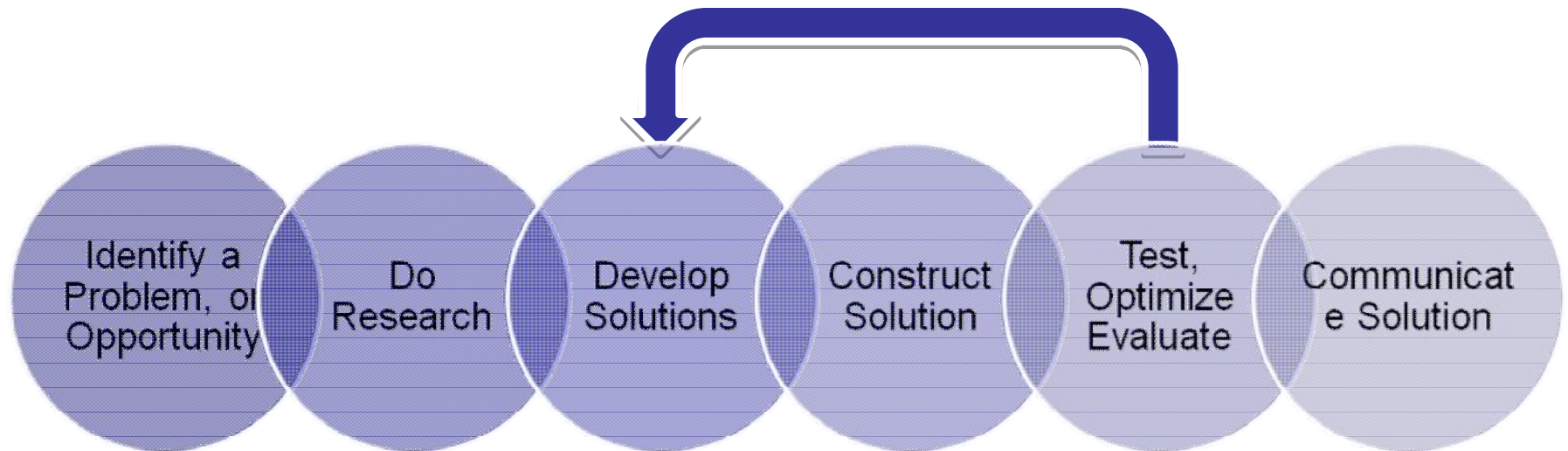


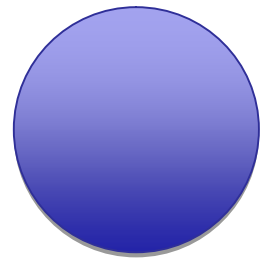


Scientific Method



Engineering Design Process

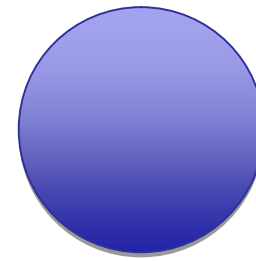




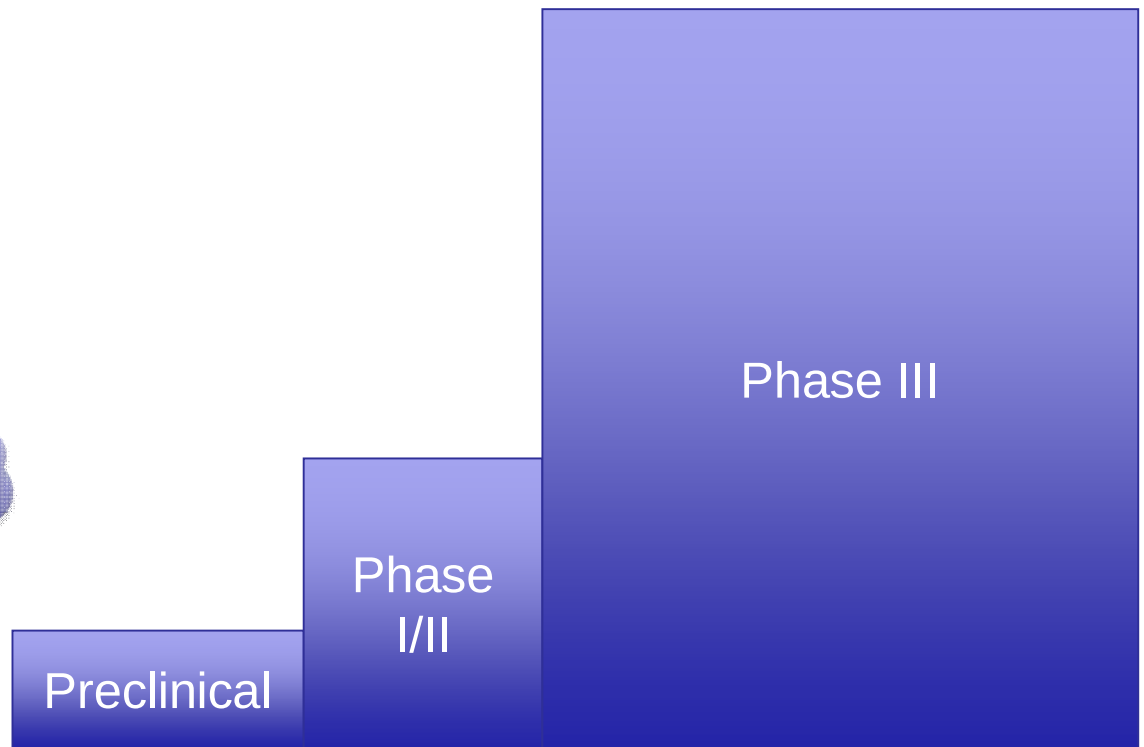
Supply
(Ideas)



vs



Demand
(Specifications)



Industrialize and Systematize

Validation (2001)

- ALS TDI – Mouse Core
- Increased power of model

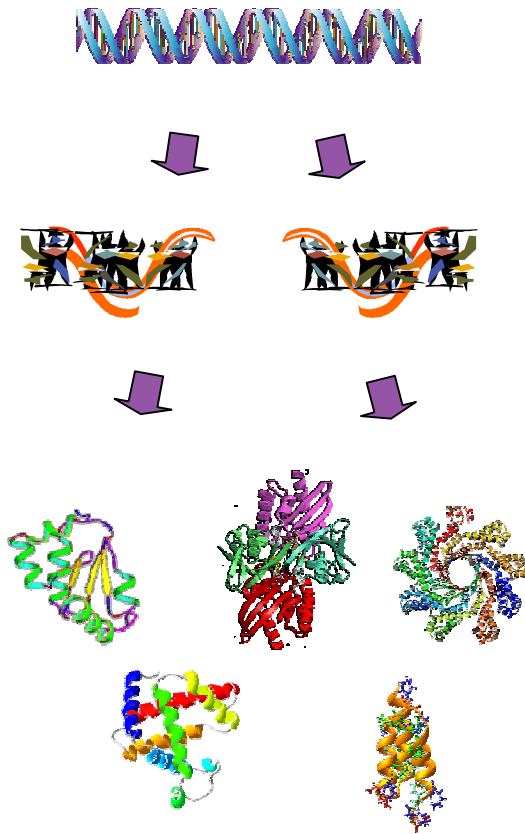
Discovery (2006)

- ALS TDI – Discovery Core
- Unbiased discovery of mechanism

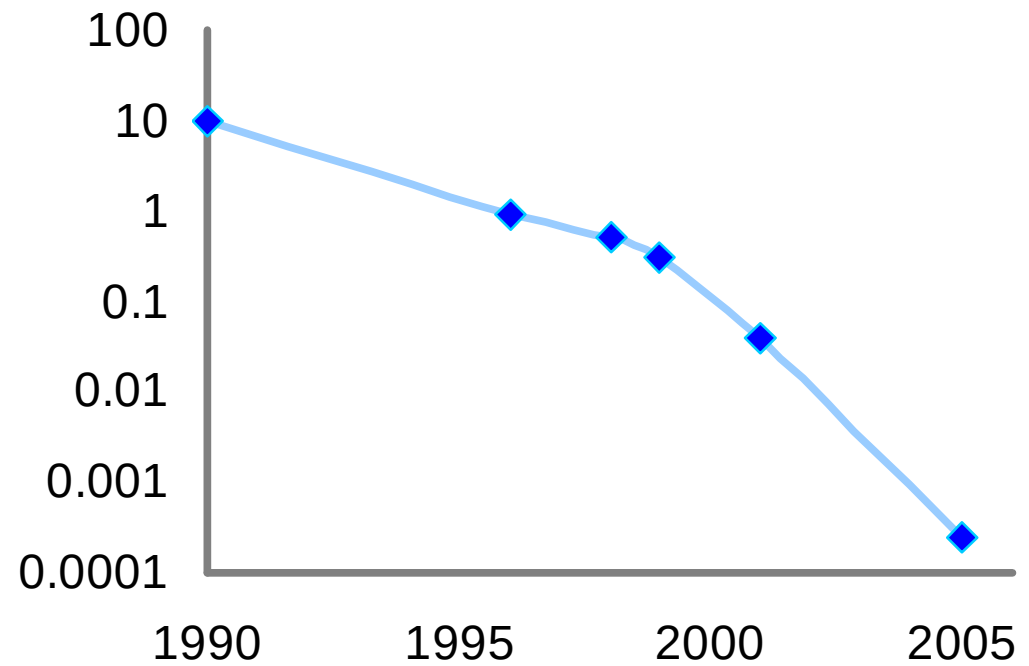
Disease Models (2005)

- PatientsLikeMe
- Advanced Models of Disease

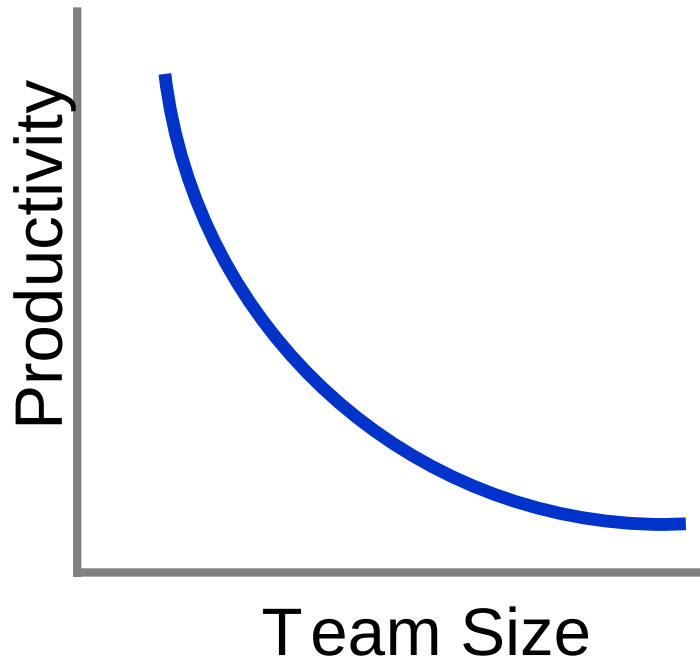
Better, Faster, Cheaper



DNA Sequencing Cost (per base pair)



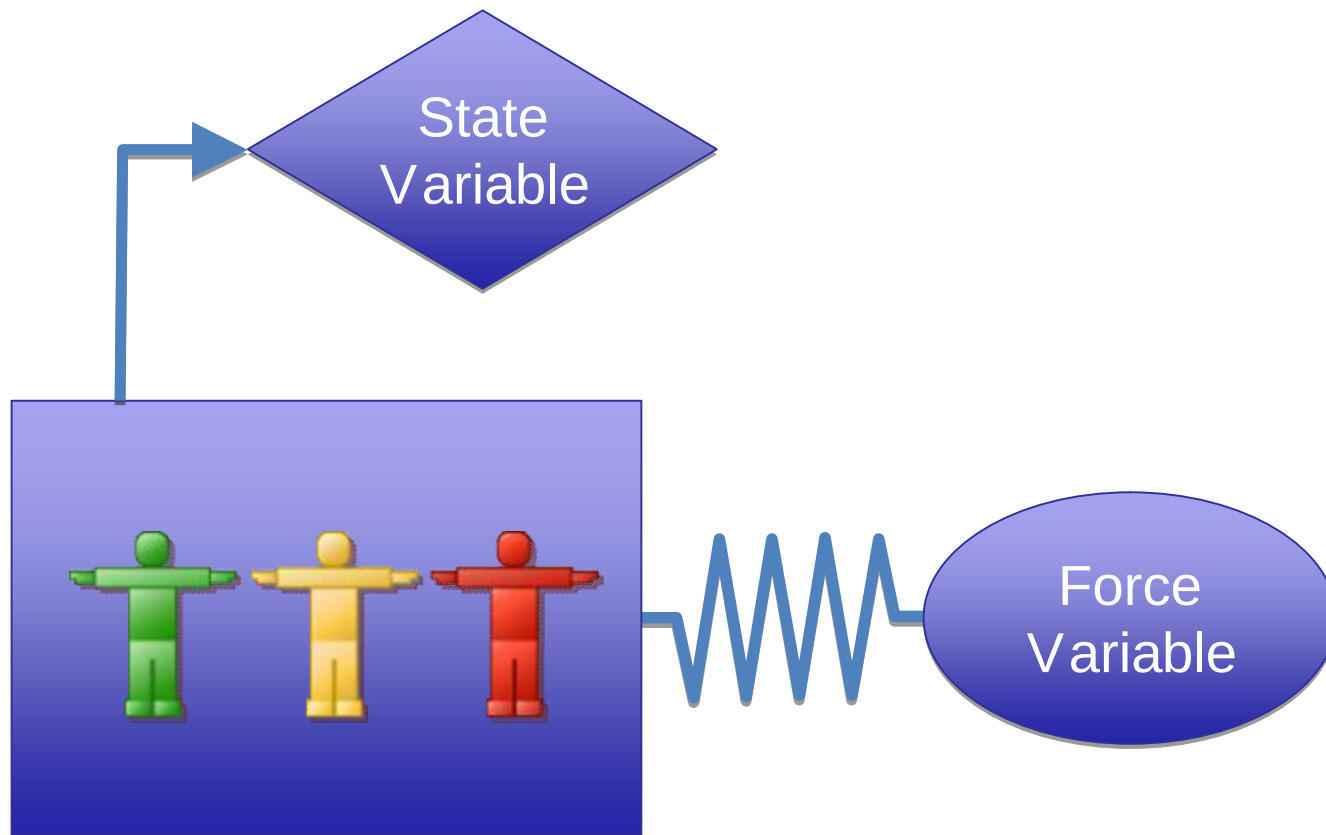
Small can be powerful

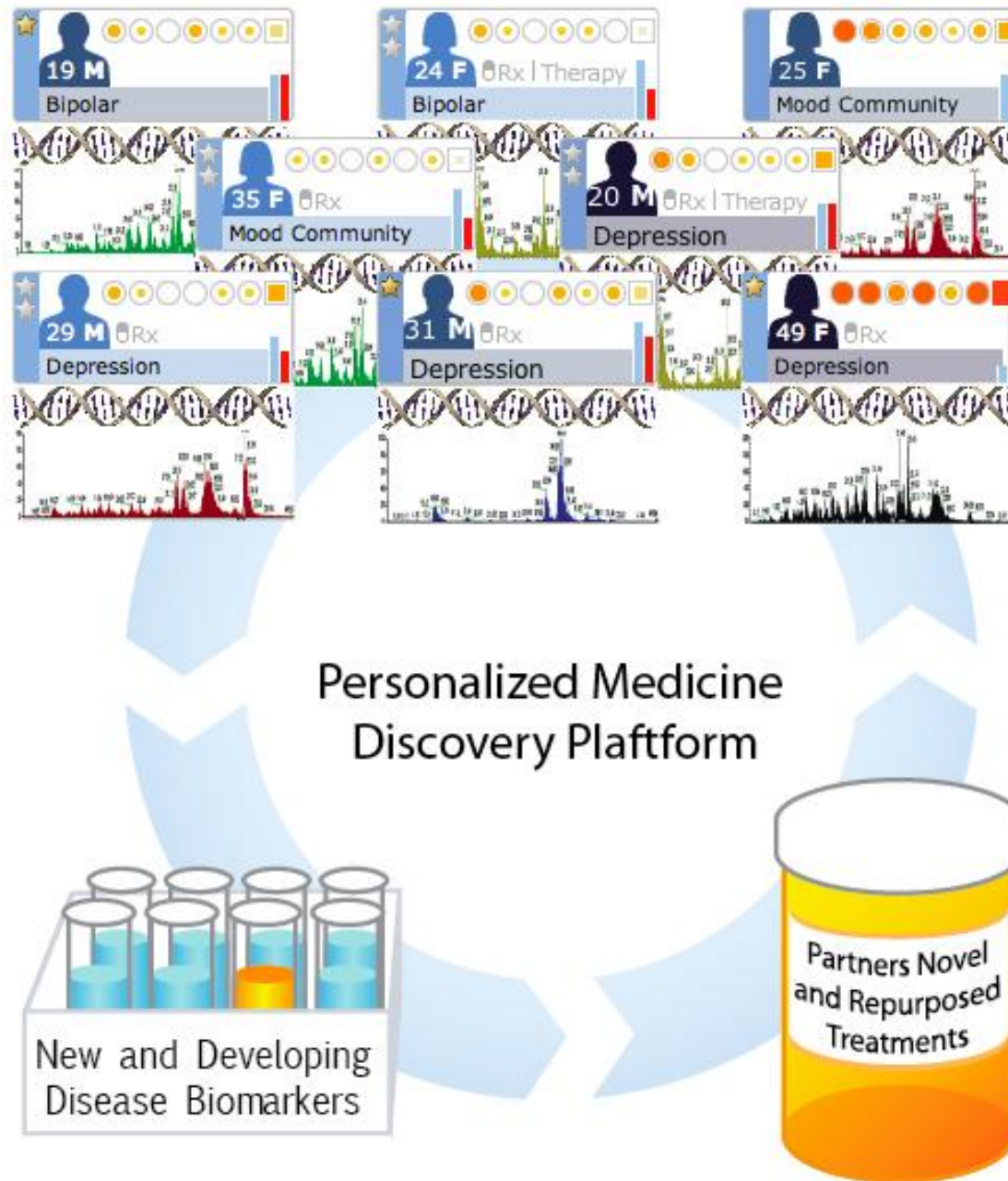


- ü Fast exchange of ideas
- ü Time efficient decisions
- ü Rapid adaptation of new information and possibilities
- ü Low institutional inertia and overhead

“Given my status, what is the best outcome I can hope to achieve, and how do I get there?”

Systems Model of Disease





ALS King101

Lithium delays progression of amyotrophic lateral sclerosis

Proceedings of the National Academy of Sciences of the United States of America

Francesco Fornai^{1,2}, Patrizia Longone³, Luisa Cafaro¹, Olga Kastsiuchenka¹, Michela Ferrucci¹, Maria Laura Manca³, Gloria Lazzeri¹, Alida Spalloni³, Natascia Bellio¹, Paola Lenzi¹, Nicola Modugno¹, Gabriele Siciliano³, Ciro Isidoro¹, Luigi Murri³, Stefano Ruggieri¹, and Antonio Paparelli¹

¹Department of Human Morphology and Applied Biology, and ²Department of Neuroscience, Clinical Neurology, University of Rome Tor Vergata, 00133 Rome, Italy; ³Istituto Neurologico Mediterraneo, Istituto Di Ricovero e Cura a Carattere Scientifico Neuromed, 86077 Pozzilli (IS), Italy; Santa Lucia Foundation, 00179 Rome, Italy; and ⁴Department of Medical Sciences, University of Novara, 28100 Novara, Italy

Edited by Thomas C. Südhof, University of Texas Southwestern Medical Center, Dallas, TX, and approved December 21, 2006 (received August 24, 2007)

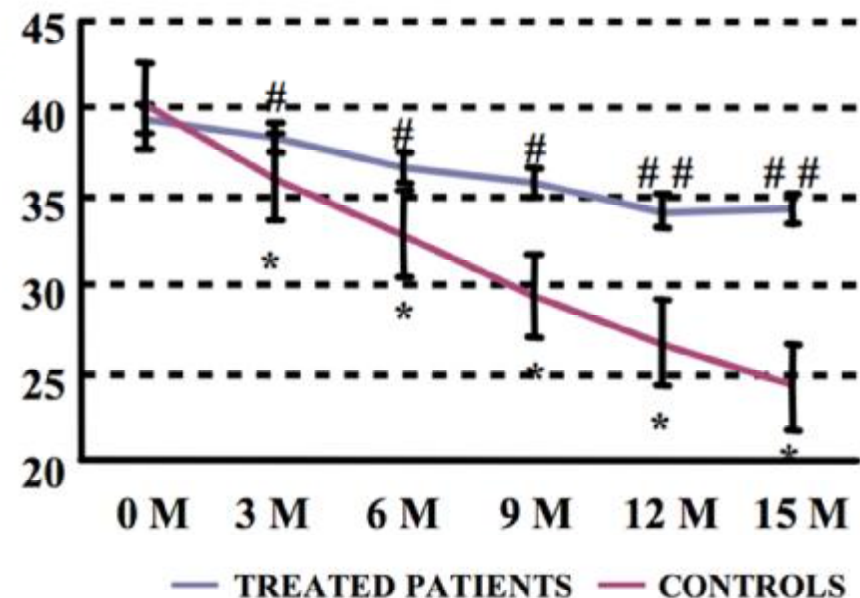
ALS is a devastating neurodegenerative disorder with no effective treatment. In the present study, we found that daily doses of lithium, leading to plasma levels ranging from 0.4 to 0.8 mEq/liter, delay disease progression in human patients affected by ALS. None of the patients treated with lithium died during the 15 months of the follow-up, and disease progression was markedly attenuated when compared with age-, disease duration-, and sex-matched control patients treated with riluzole for the same amount of time. In a parallel study on a genetic ALS animal model, the G93A mouse, we found a marked neuroprotection by lithium, which delayed disease onset and duration and augmented the life span. These effects were concomitant with activation of autophagy and an increase in the number of the mitochondria in motor neurons and

G93A ALS mouse model. Based on these results, we propose that lithium treatment should be considered as a potential therapeutic approach for ALS.

Results

Effects of Lithium on Disease Duration in G93A Mice. G93A male mice were treated daily with 10 mEq/kg, i.p., starting at 75 days of age. This treatment prolonged the mean survival time to 148 ± 4.3 (n = 20, ~36% of the 1a; $P < 0.001$) and, most important, (from a mean of 9 days to >38 day compared with the G93A mice treated with vehicle).

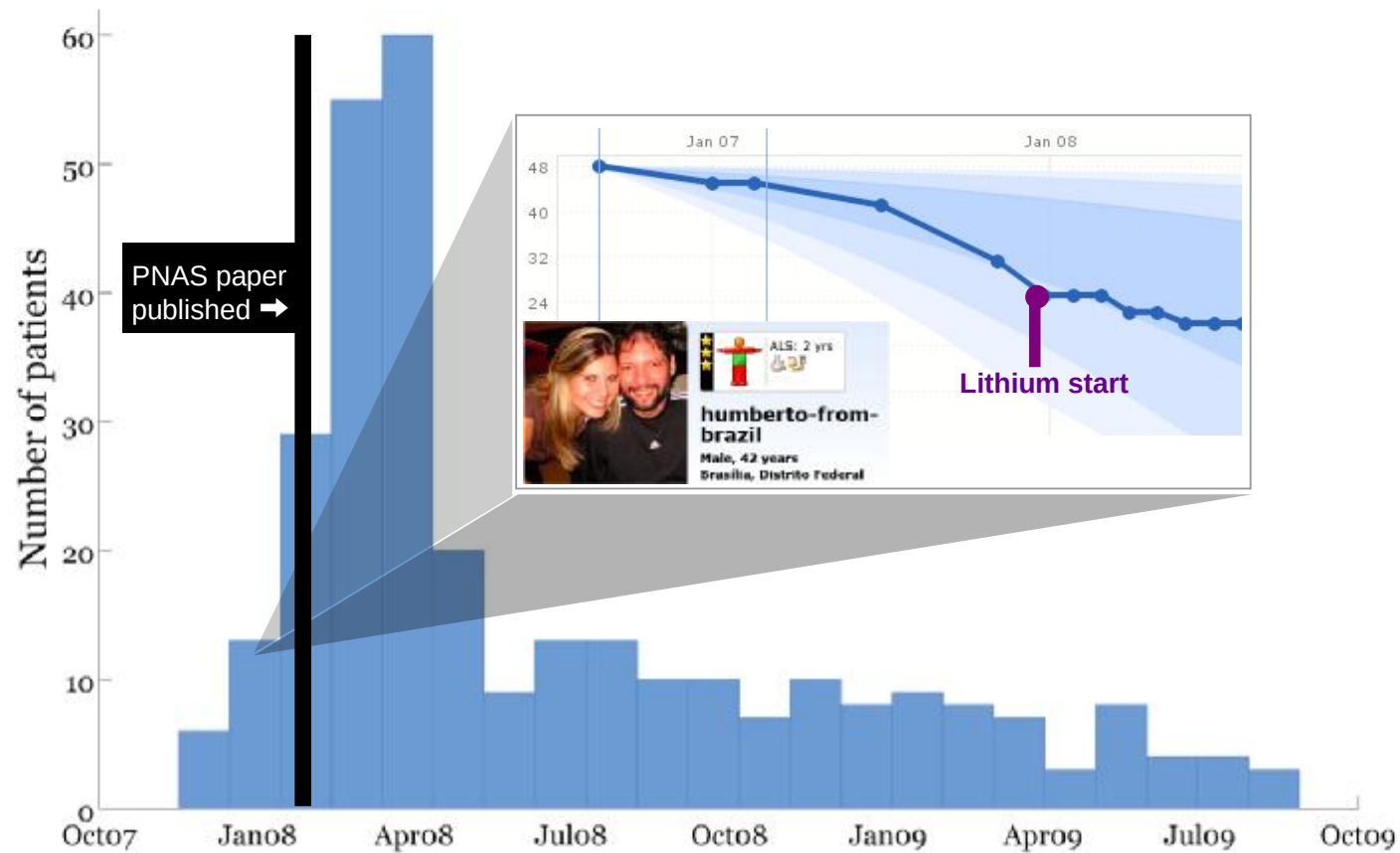
ALSFRS-R (raw data)



Methods - Observational study to compare those treated with lithium vs. controls

- Of those providing demographic info:
 - 3481 users
 - 3069 patients
 - 370 took lithium; 2699 control
 - 137 treated meet study criteria
 - 1368 control meet study criteria
- Employ novel algorithm to match pre-treatment disease profiles, reducing bias
- Two treatment cohorts followed:
 - Intent-to-treat [>2 mo lithium]
 - Full course [>12 mo lithium]

Distribution of Lithium Start Dates



Patient	Profile Star						Current Star		History Star		# of FRS scores		# of data points in months before and after Lithium start												
	Onset Date	Diagnosis Date	Type	Sex	Age						Onset to Start	Start to Today	-1	0	1	2	3	4	5	6					
● humberto-from-brazil	✓	✓	✓	✓	✓		✓	✓			4	12	0	1	1	1	1	1	1	1					



humberto-from-brazil
Male, 43 years
Onset: Arms

On Rilutek

Side Effects

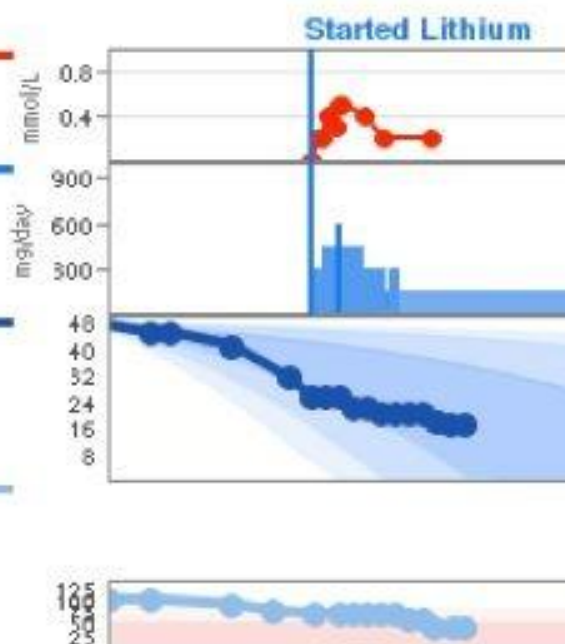
■ Constipation ■ Slurred speech ■ Excessive saliva
 ■ Weight gain or loss ■ Depression ■ Muscle weakness, stiffness, twitching, or tightness ■ Joint or muscle pain ■ Tiredness

Blood Level
0.2 mmol/L

Lithicarb
150 mg/day

FRS
17

FVC
40

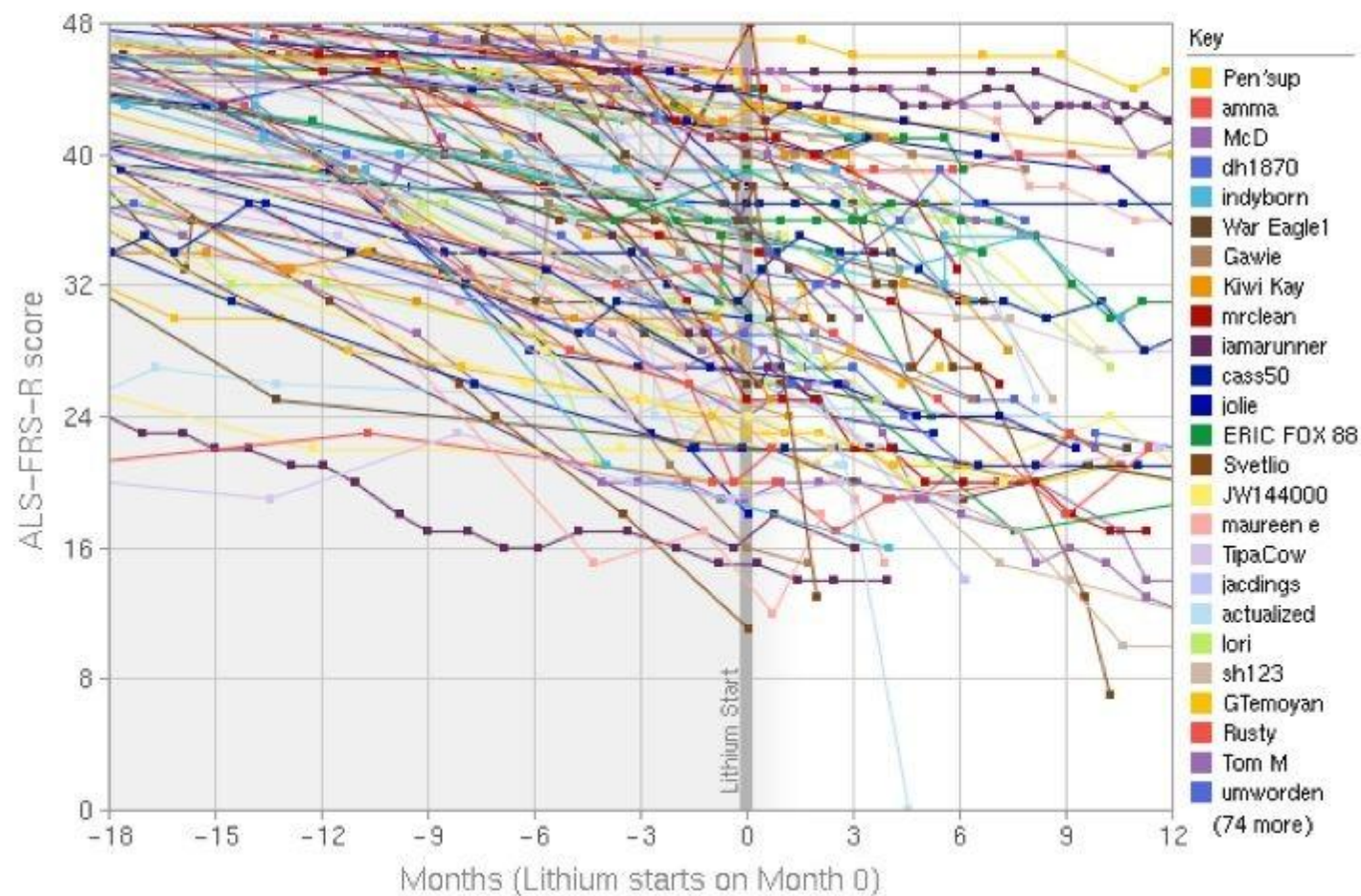


Timeframe		Limit Patients to	
18	months before lithium	3	FRS points before lithium
12	months after lithium	1	FRS points after lithium

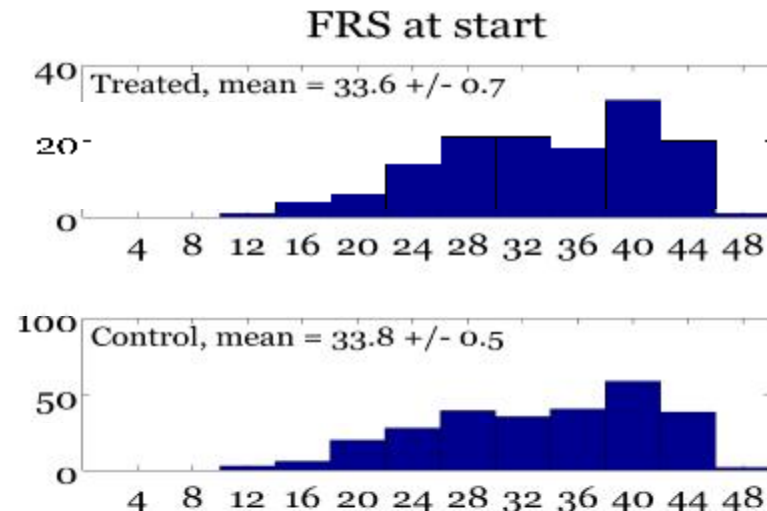
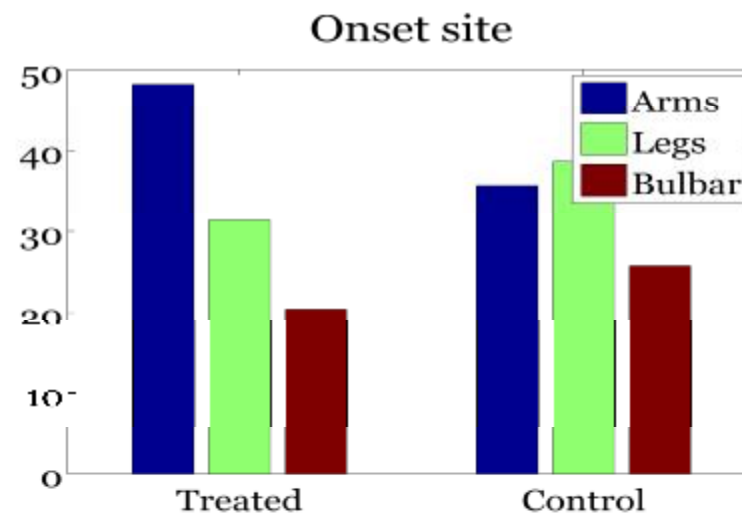
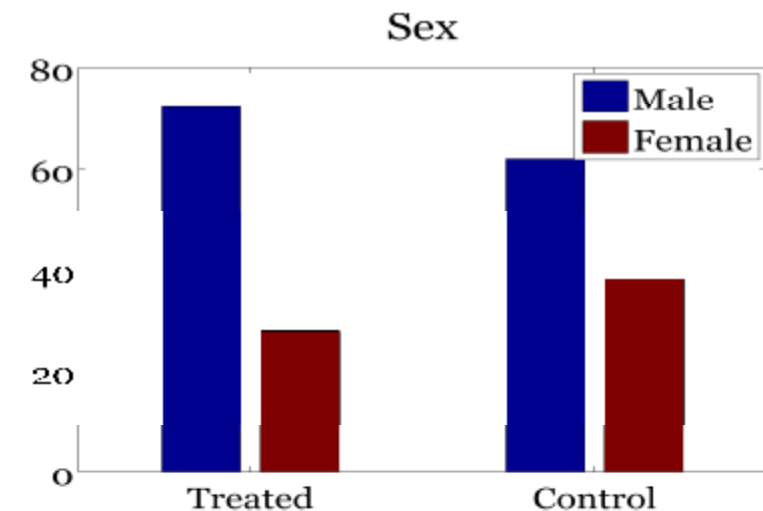
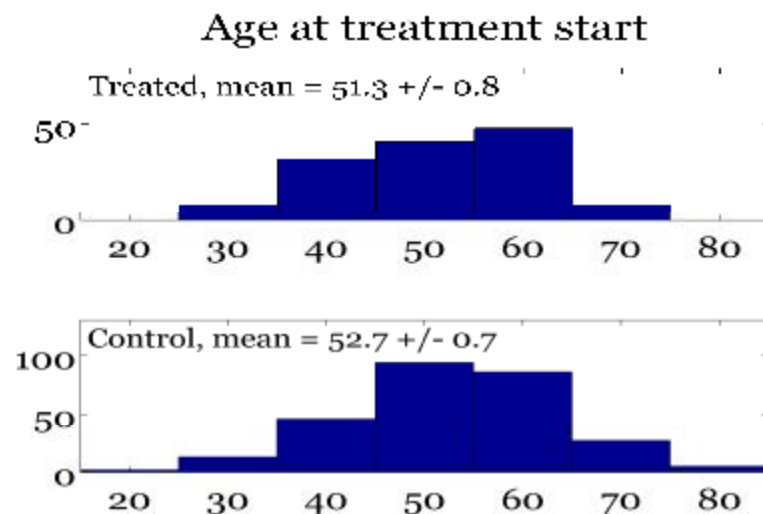
[Update Graph](#)

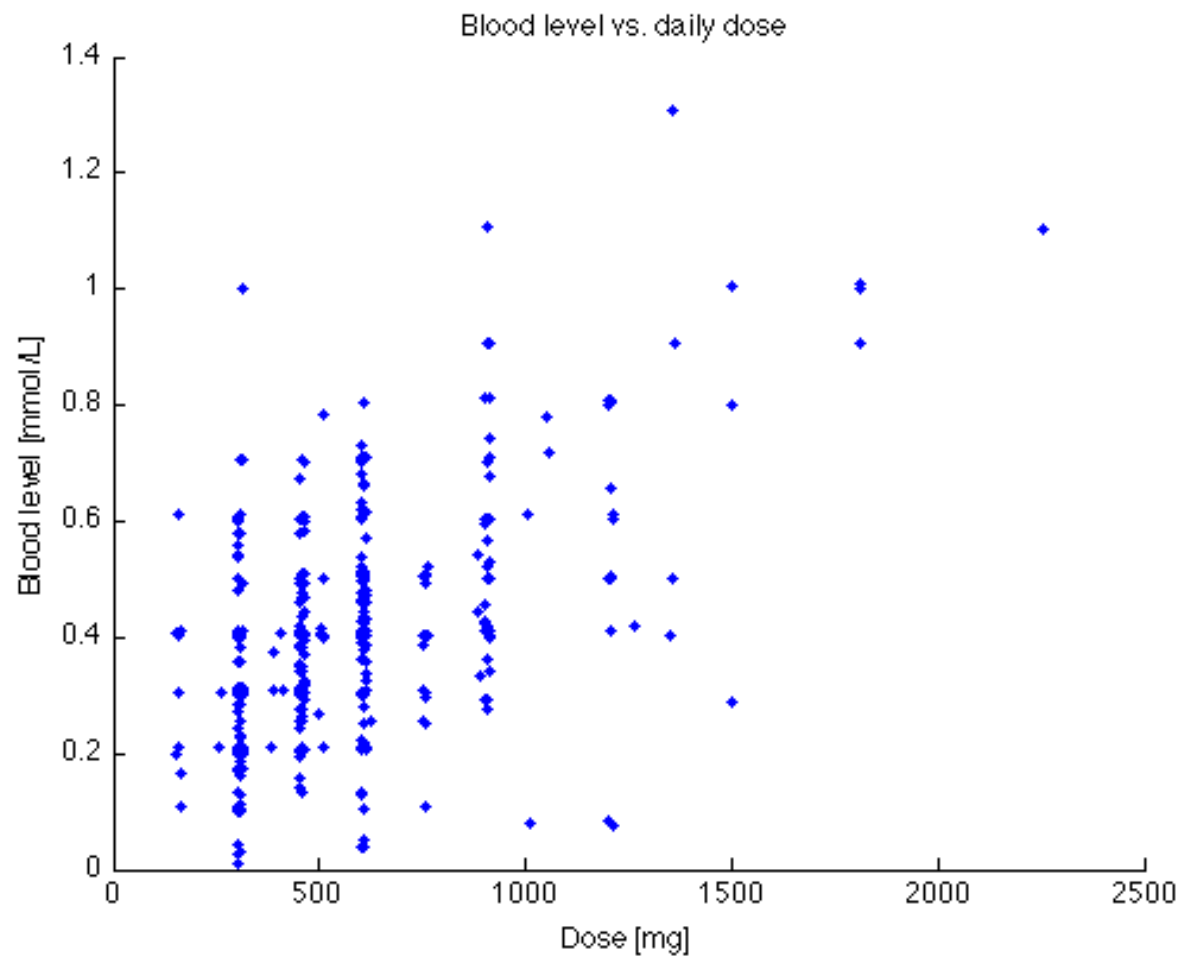
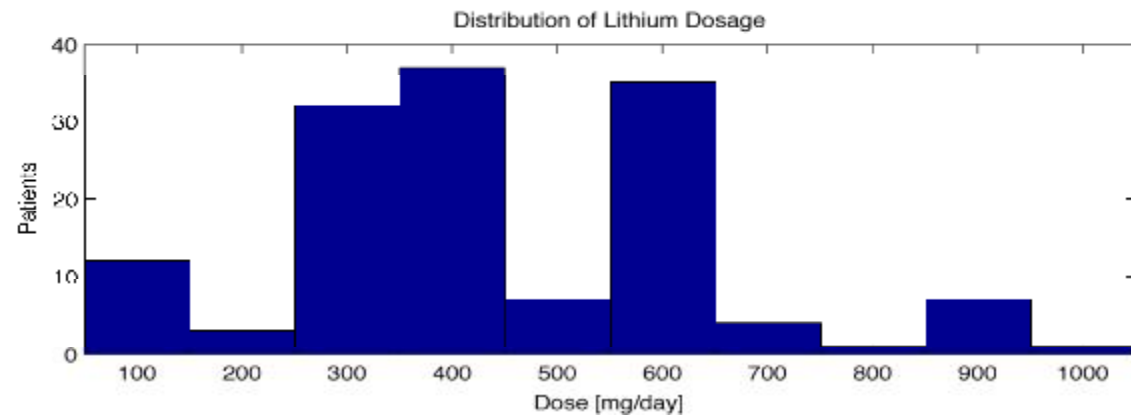
[Printable Version](#) [Print a copy of this graph.](#)

ALSFRS-R Scores of Patients on Lithium



Demographics





Mood / Mental

Severity reports — all patients

	None	Mild	Moderate	Severe
Confusion	236	29	2	3
Depression	212	60	17	6
Giddiness	232	24	11	1
Hallucinations (seeing things or hearing voices that do not exist)	245	7	2	1
Restlessness	223	48	10	3

Mouth

Severity reports — all patients

	None	Mild	Moderate	Severe
Change in the ability to taste food	225	47	12	4
Dry mouth	202	75	25	7
Excessive saliva	176	87	37	9
Swollen lips	240	22	1	1
Tongue pain	243	11	3	1

Eating / Appetite / Gastro-Intestinal / Urinary

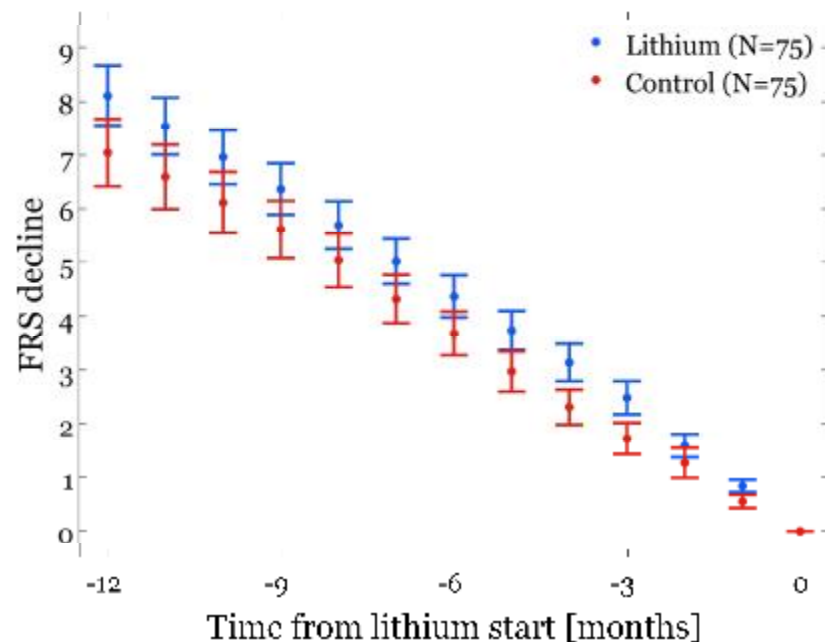
Severity reports — all patients

	None	Mild	Moderate	Severe
Constipation	185	80	38	16
Diarrhea	233	33	7	3
Excessive thirst	198	82	24	5
Frequent urination	170	99	42	12
Gas	202	70	17	2
Indigestion	221	37	10	3
Loss of appetite	214	65	16	4
Stomach pain or bloating	225	37	7	3
Vomiting	247	7	1	1

Control matching

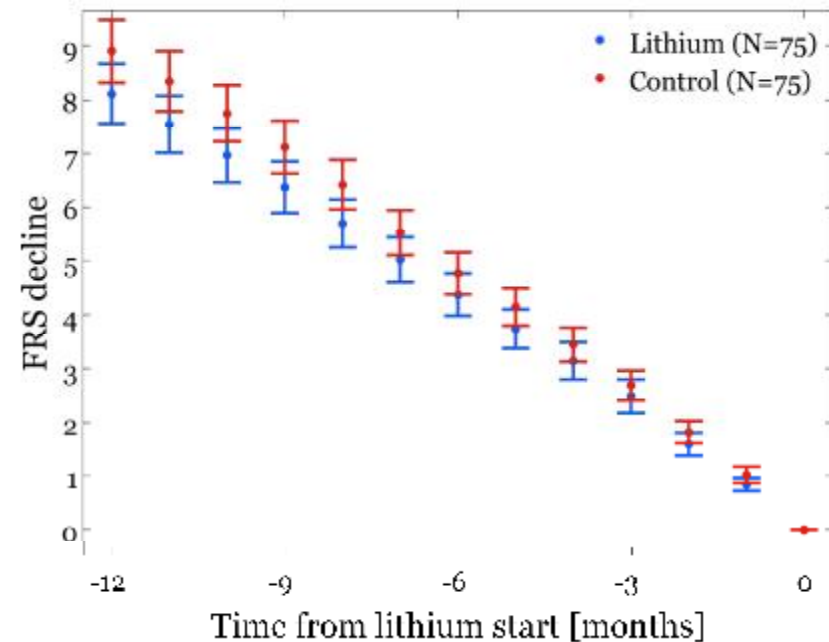
Random

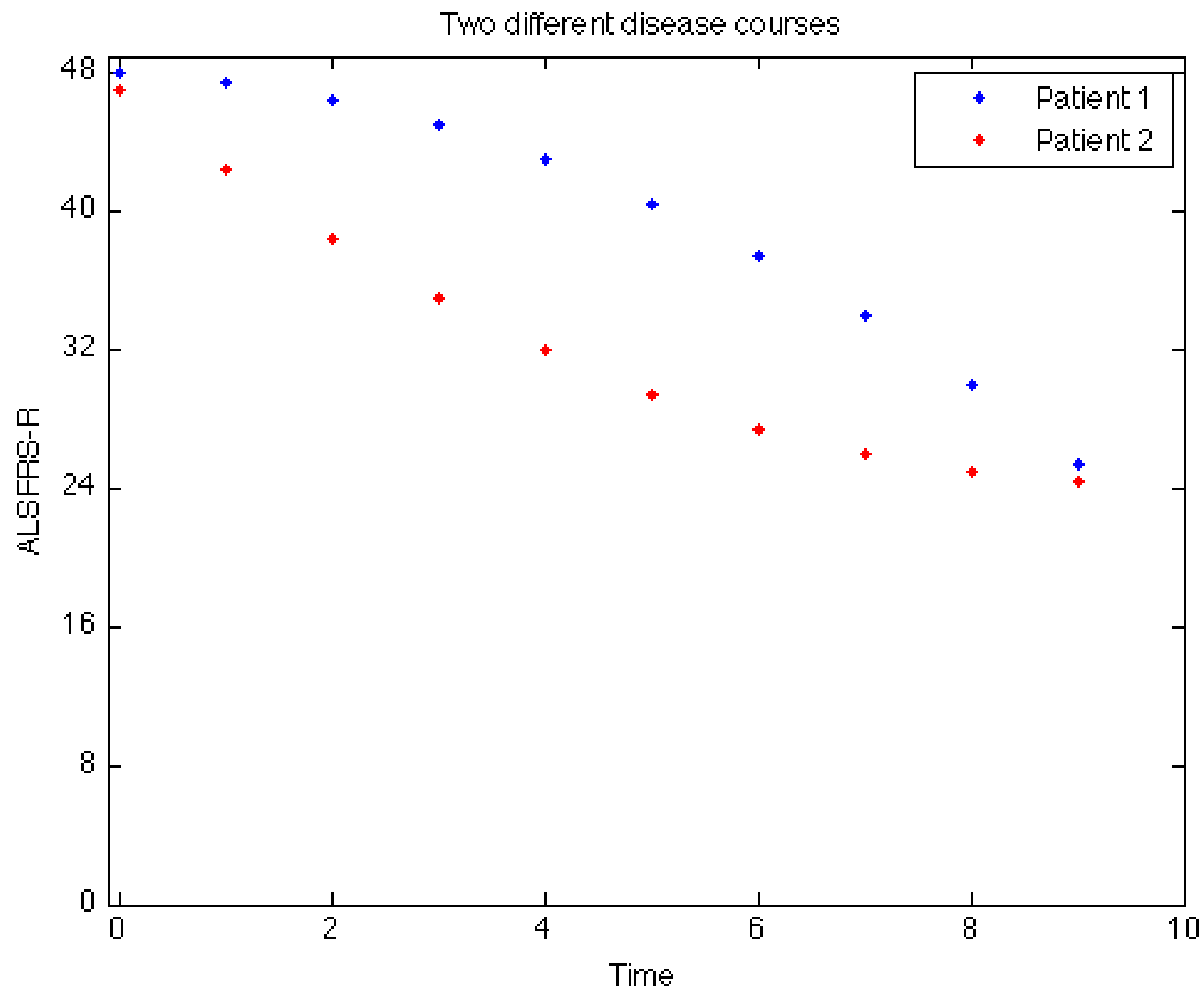
Mean decline in FRS over time

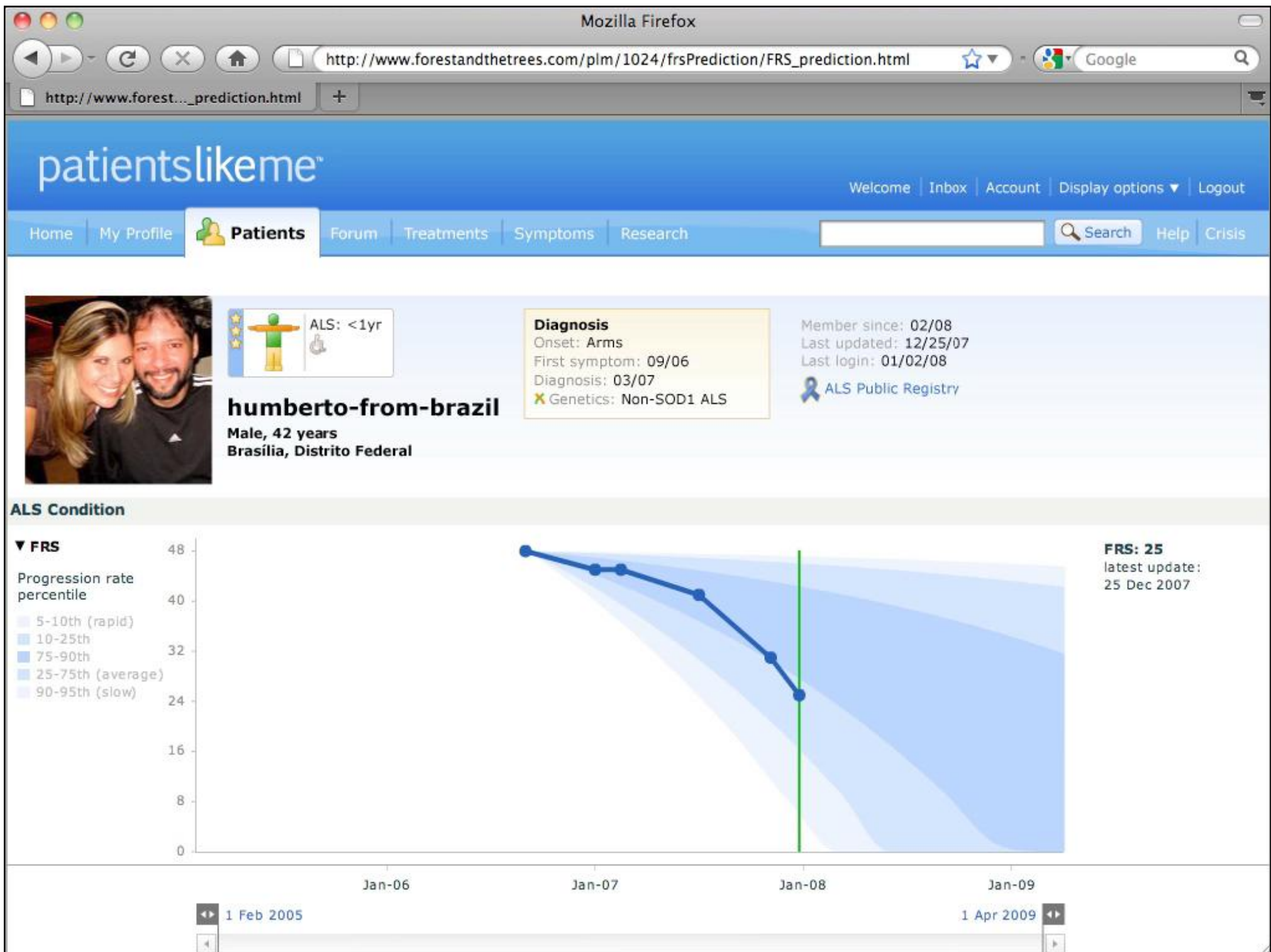


Traditional

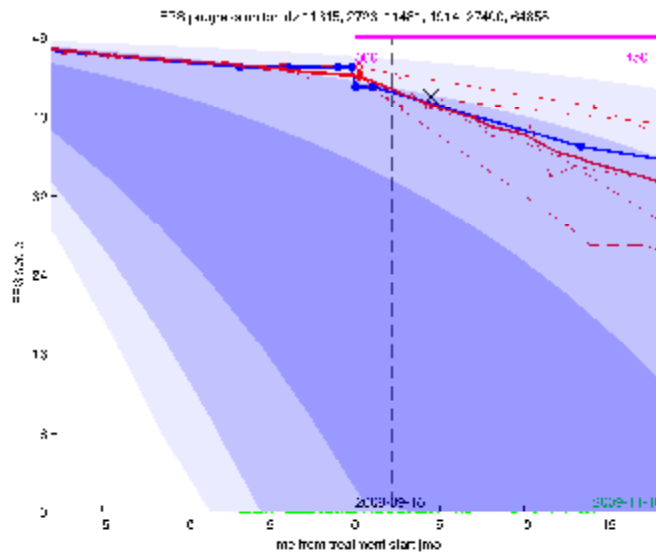
Mean decline in FRS over time



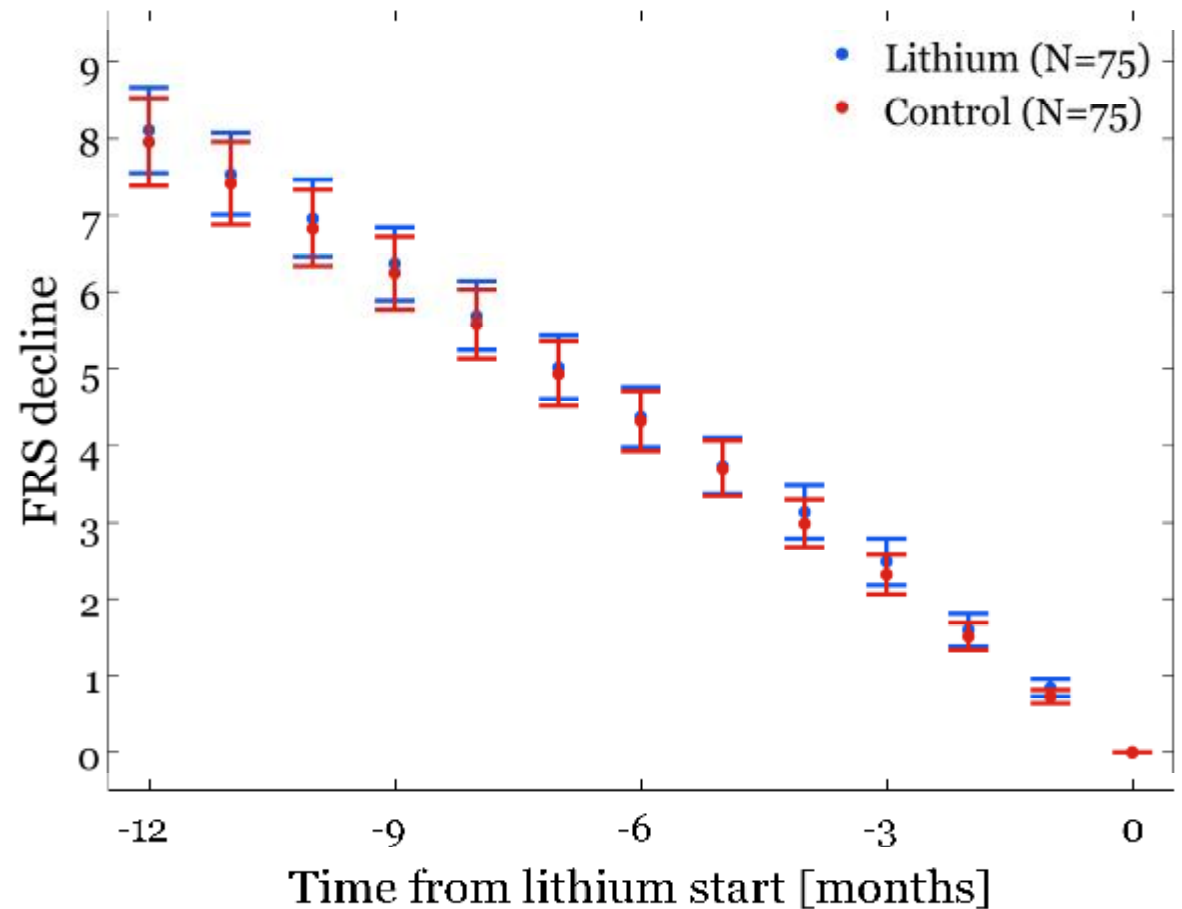


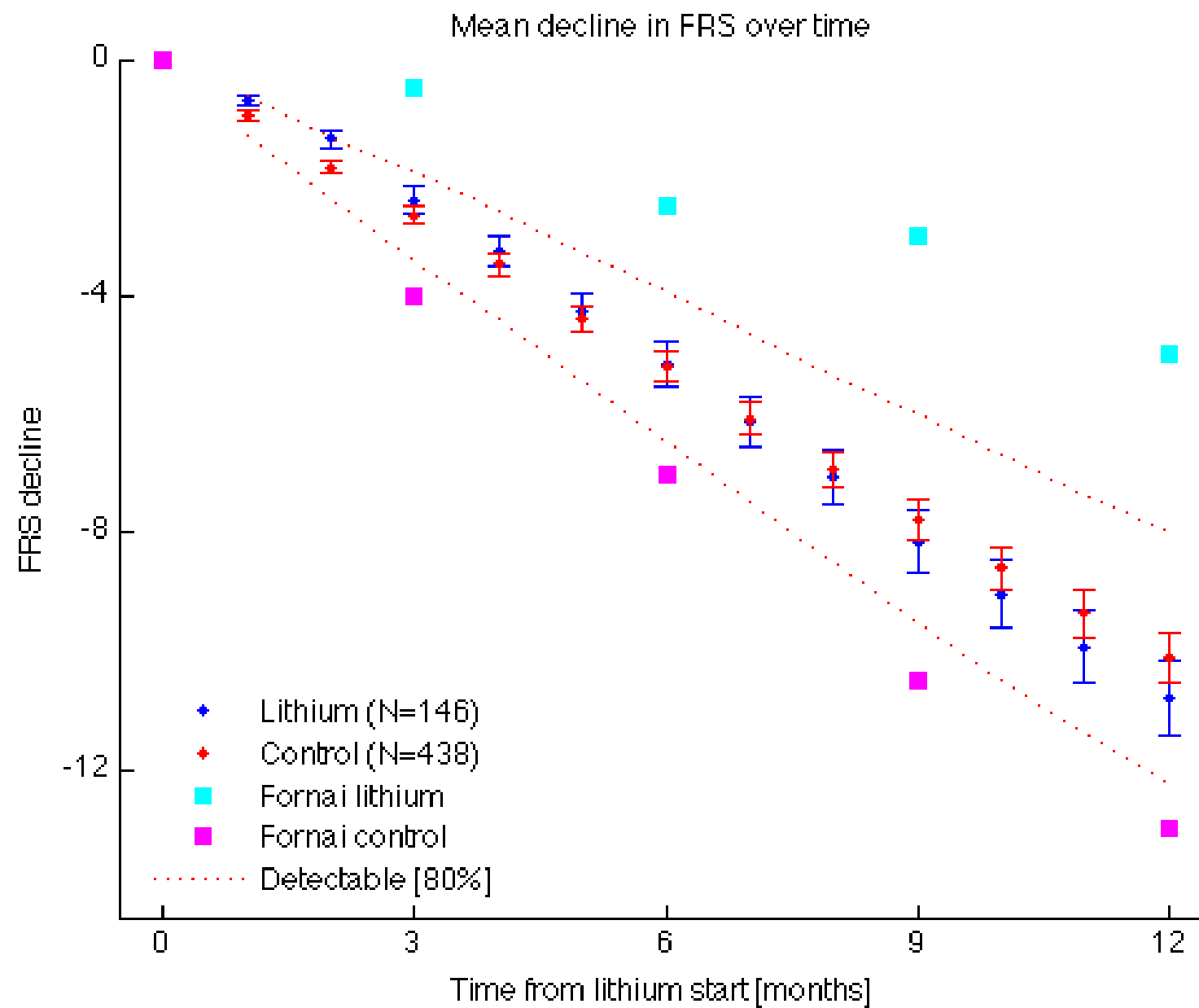


Algorithmic matching

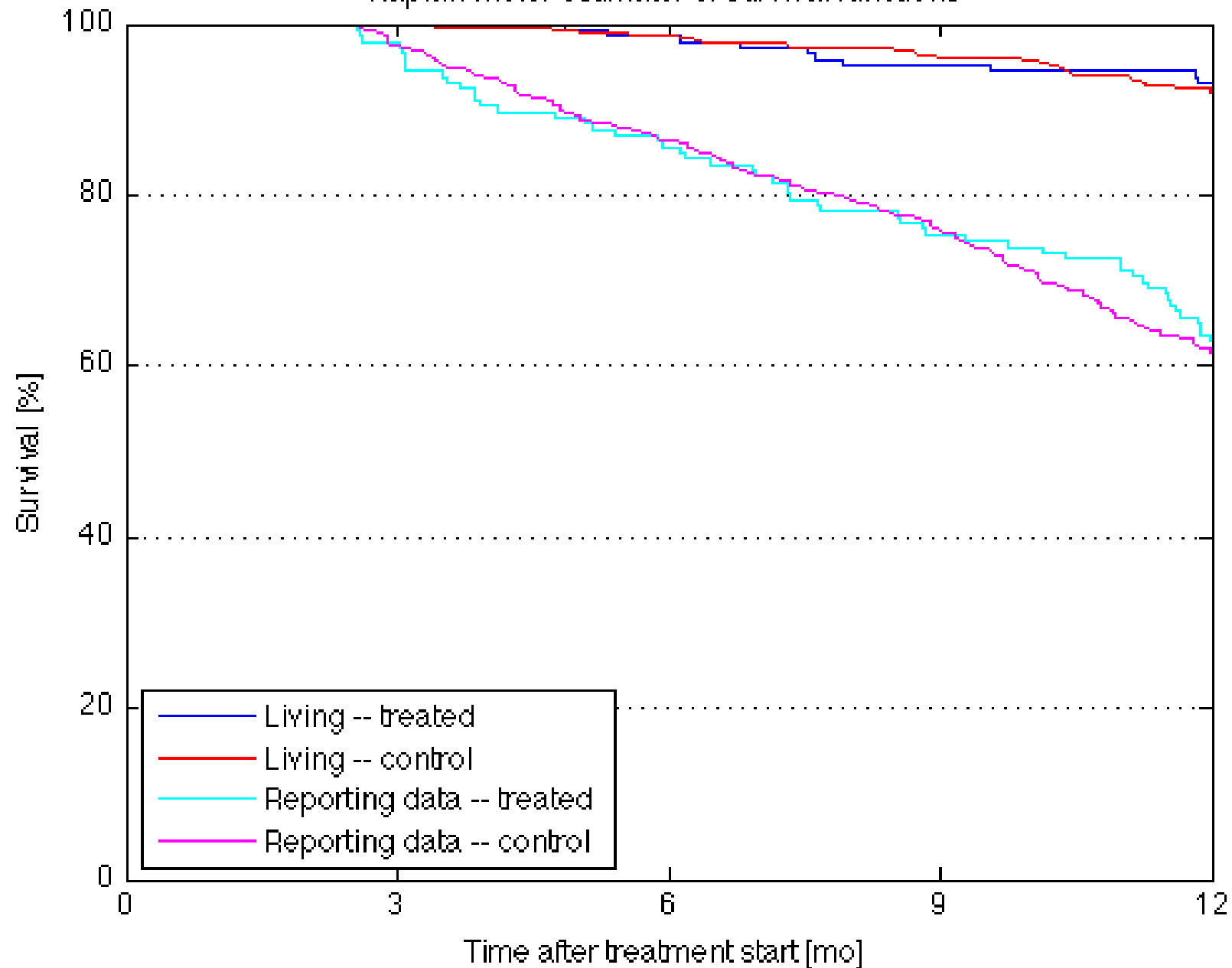


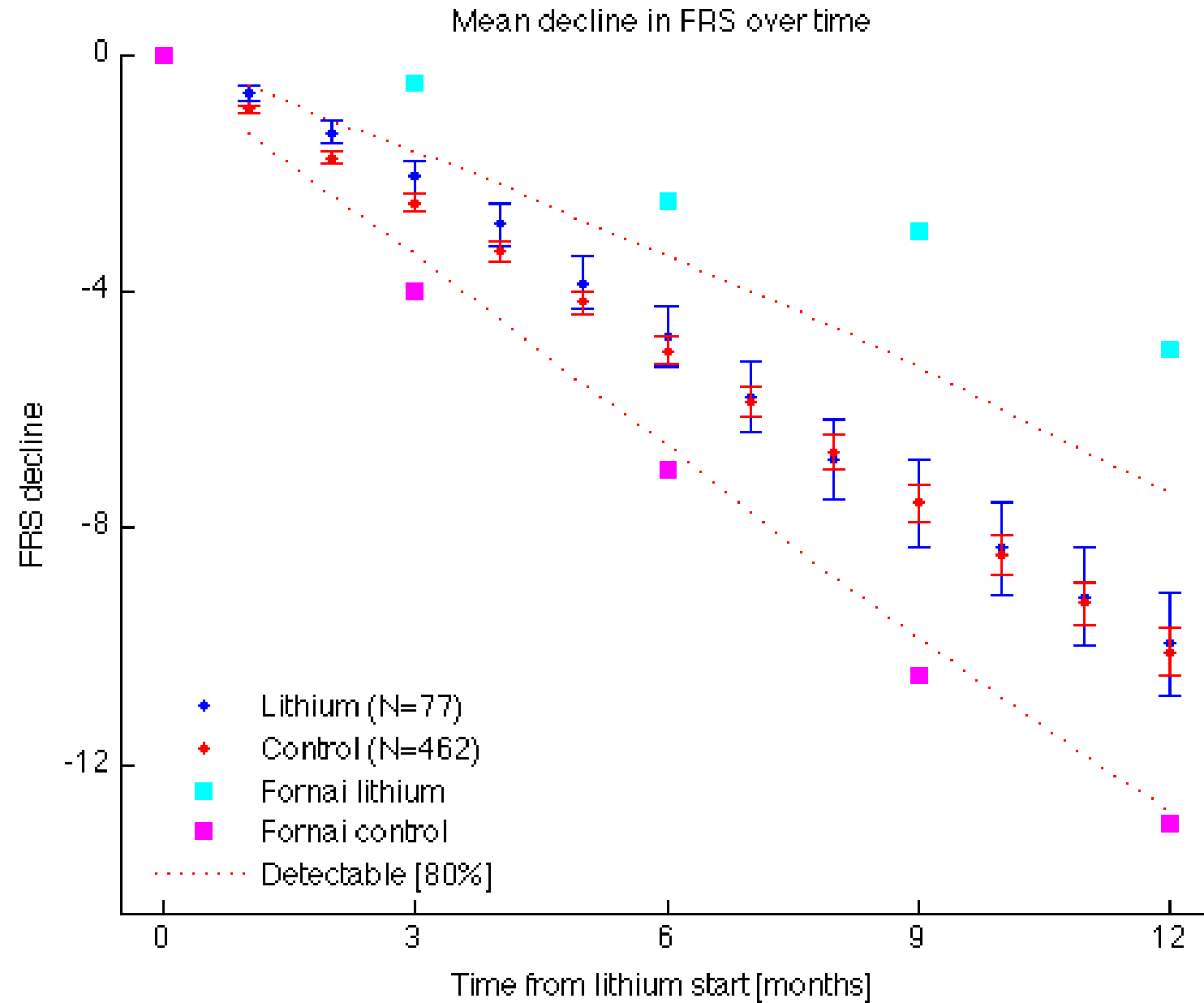
Mean decline in FRS over time





Kaplan-Meier estimator of survival functions







James Allen Heywood
