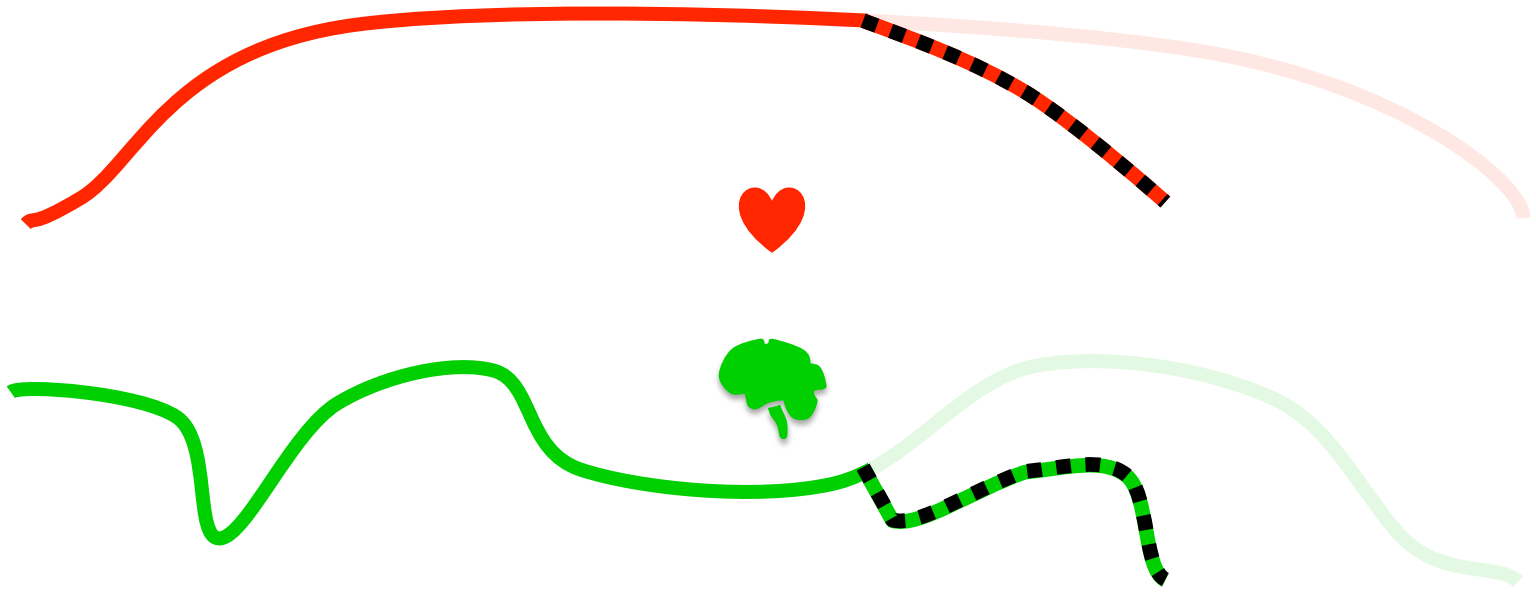
Health



Disease

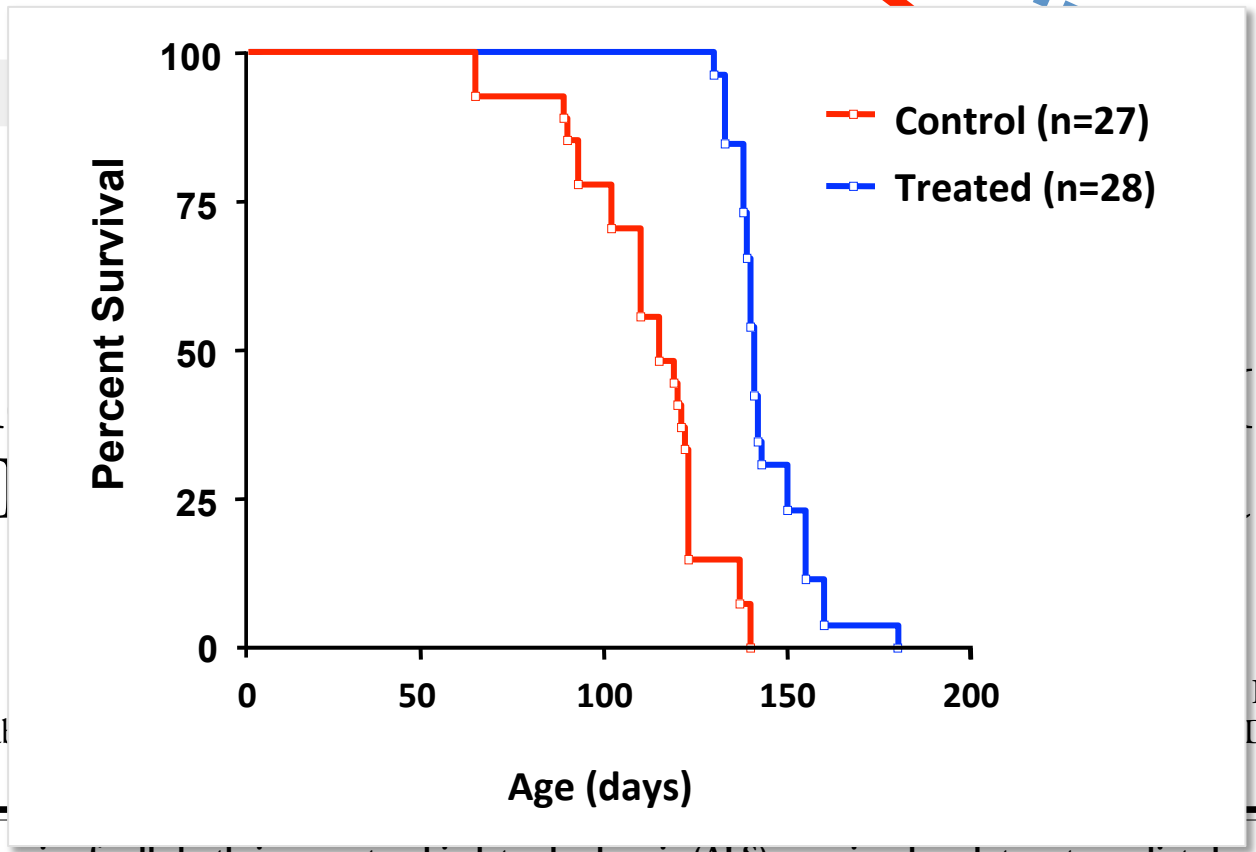
Discovery + Clinical Research + Health Care = Healthspan

Of Mice and Stephen…….

patientslikeme®

Discovery

Death

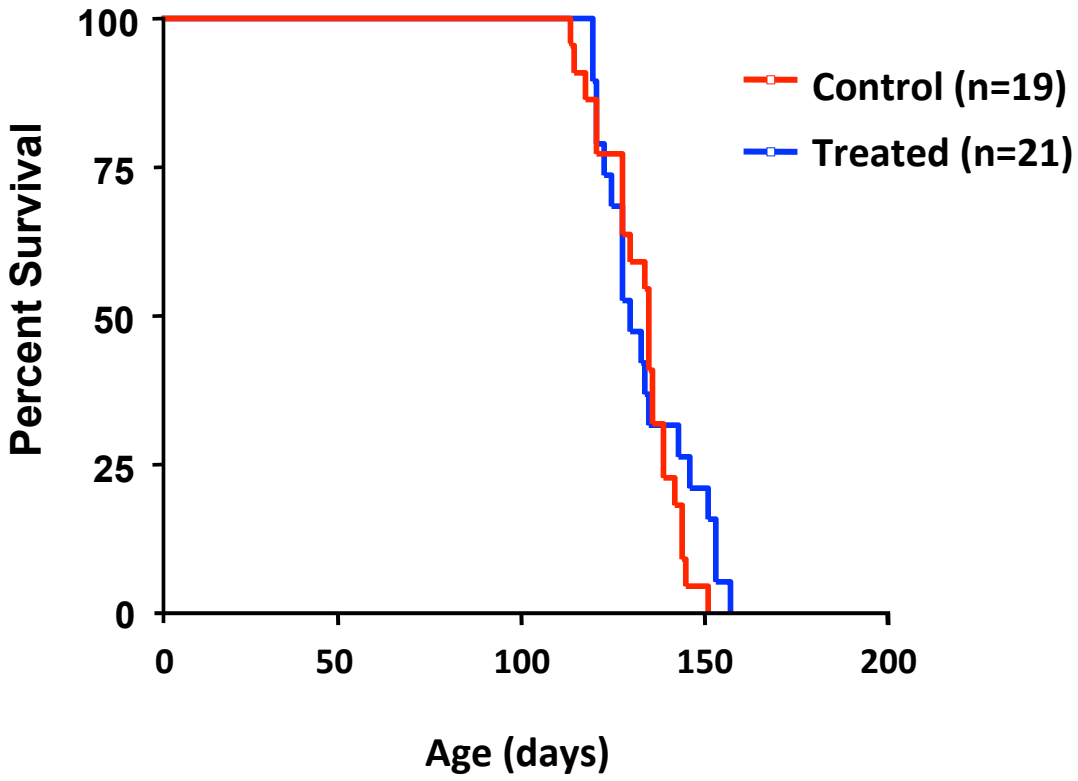


Cycl otor

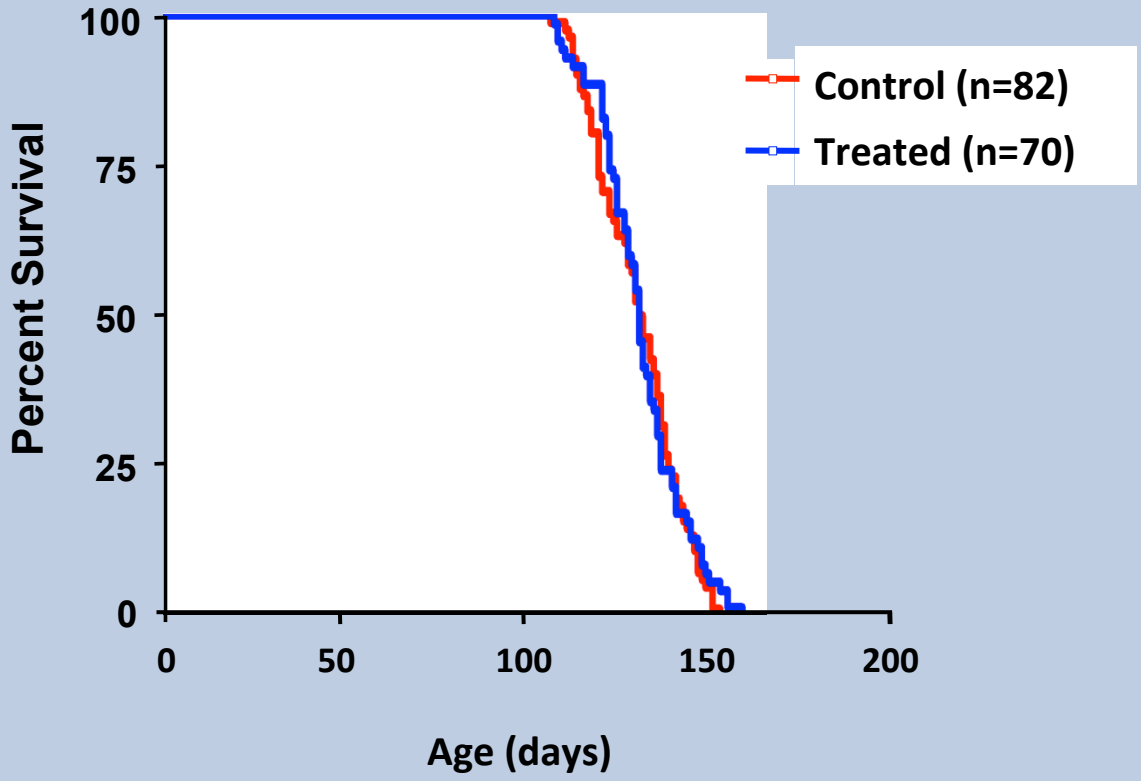
Daniel PhD,[2]
Gal D[1]

The pathogenesis of cell death in amyotrophic lateral sclerosis (ALS) may involve glutamate-mediated excitotoxicity, oxidative damage, and apoptosis. We used a transgenic mouse model of ALS to determine the effect of inhibition of cyclooxygenase-2 in treating the disease. Cyclooxygenase-2, present in spinal neurons and astrocytes, catalyzes the synthesis of prostaglandin E2. Prostaglandin E2 stimulates glutamate release from astrocytes, whereas cyclooxygenase-2 also plays a key role in the production of proinflammatory cytokines, reactive oxygen species, and

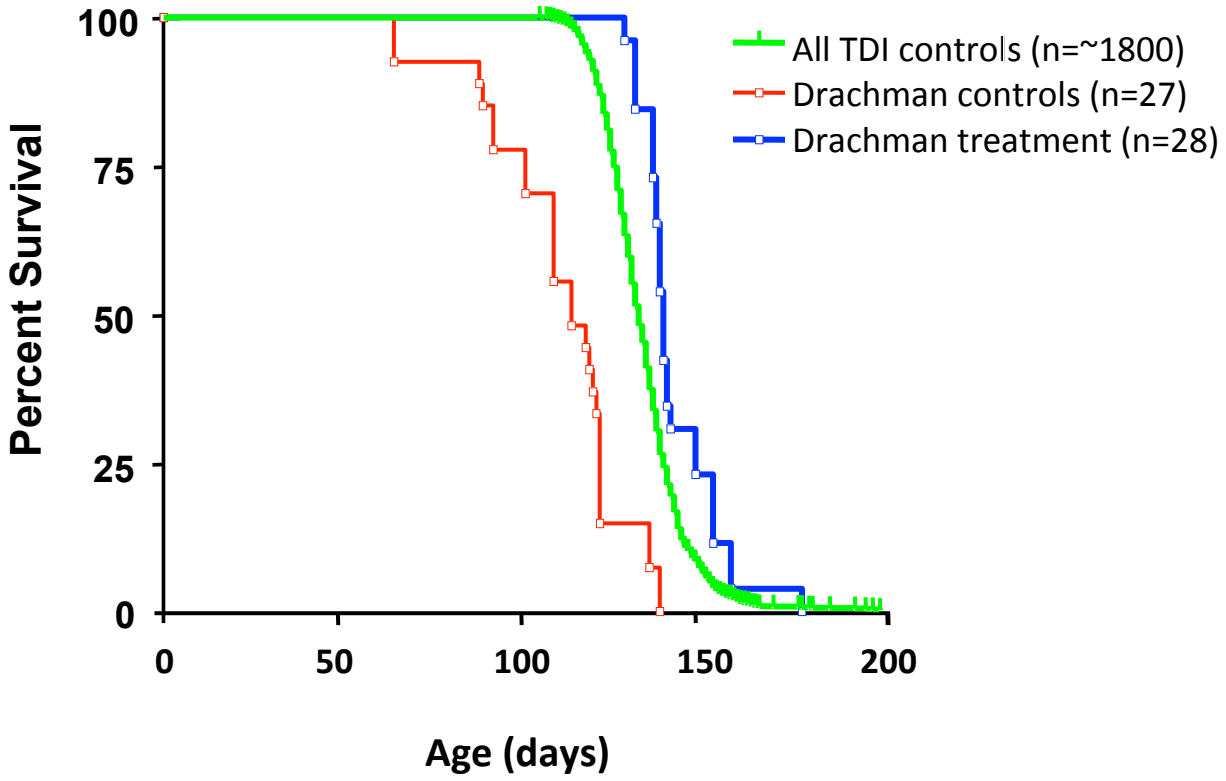
"Trust but verify"



“Trust but verify”



"Trust but verify"



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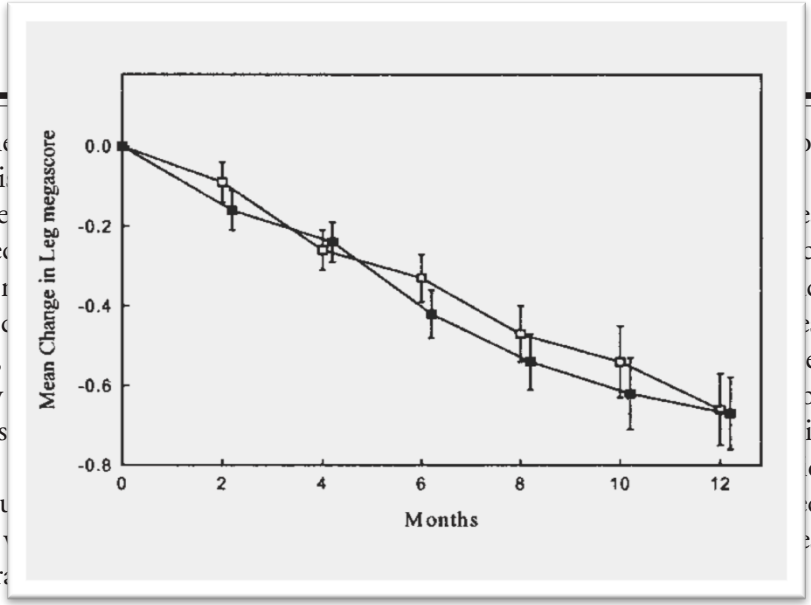
Now in patients…

ANNALS of Neurology

ORIGINAL ARTICLES

Trial of Celecoxib in Amyotrophic Lateral Sclerosis

Merit E. Cudkowicz, MD, MSc,[1,2] Jeremy M. Shefner, MD, PhD,[3] David A. Schoenfeld, PhD,[4] Hui Zhang, MSc,[5] Katrin I. Andreasson, MD,[3] Jeffrey D. Rothstein, MD, PhD,[5] Daniel B. Drachman, MD,[5]



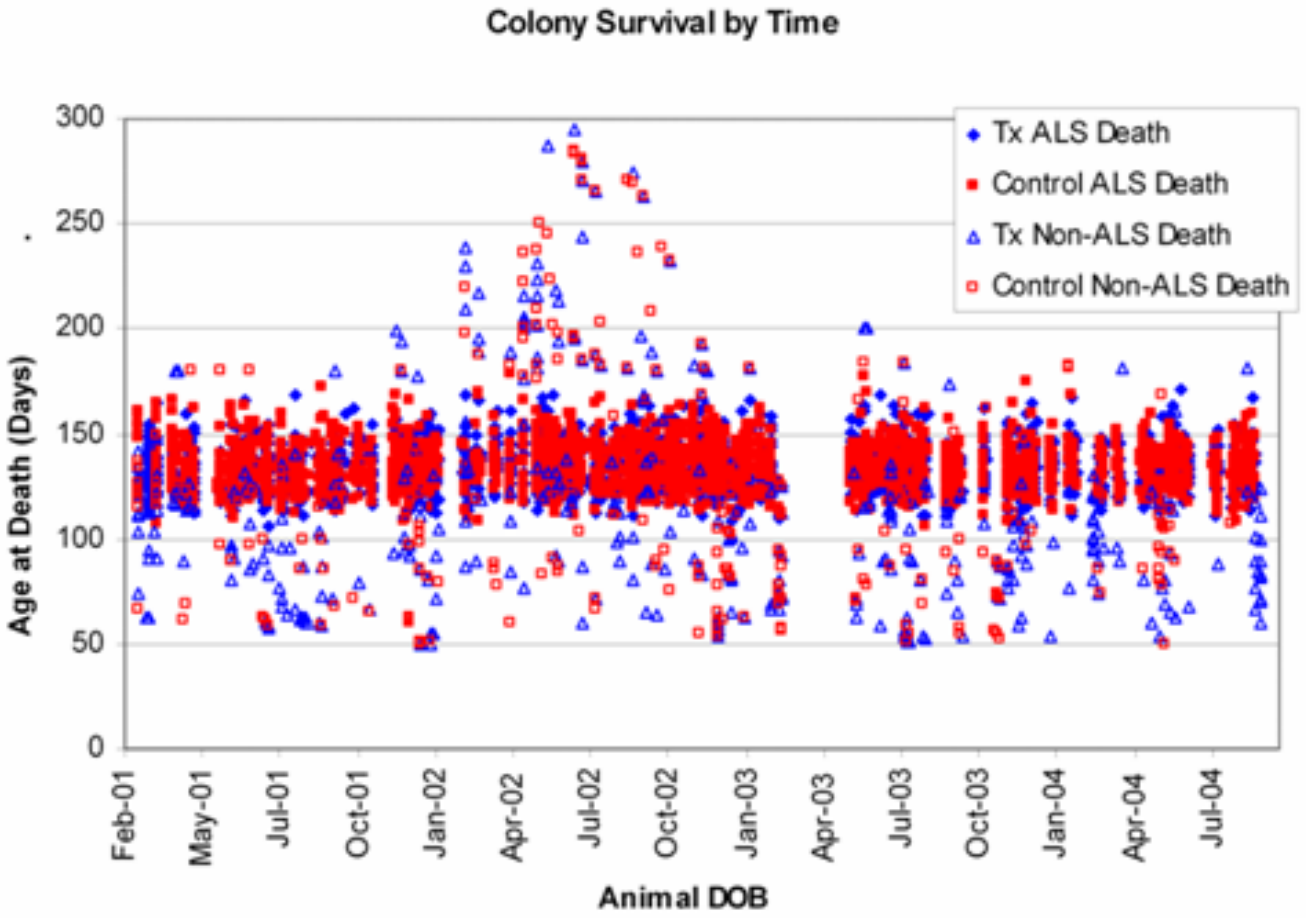
Objective: To determine whethe…or that has been shown to be beneficial in preclinical testing, i…
Methods: A double-blind, place…earch subjects with ALS were randomized (2:1) to receive celec…come measure was the rate of change in upper extremity motor…ction strength. Secondary end points included safety, survival, …s in the rate of decline of leg and grip strength, vital capacity, …estimates.
Results: Celecoxib did not slow…per estimates, ALS Functional Rating Scale-Revised, or affect s…ith an increased frequency of adverse events. Prostaglandin E_2…d not decline with treatment.
Interpretation: At the dosage stu…cts with ALS, and it was safe. A biological effect of celecoxib …s of celecoxib at a dosage of 800mg/day in ALS are not warra…

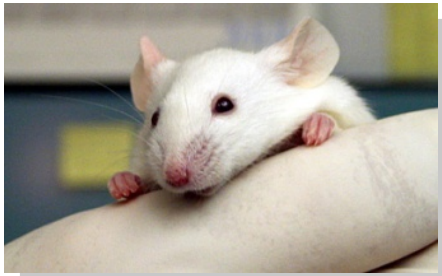
Ann Neurol 2006;60:22–31

patientslikeme®

Of mice and Stephen…….

ALSTDI
ALS Therapy Development Institute





20,000+ mice

130+ drugs

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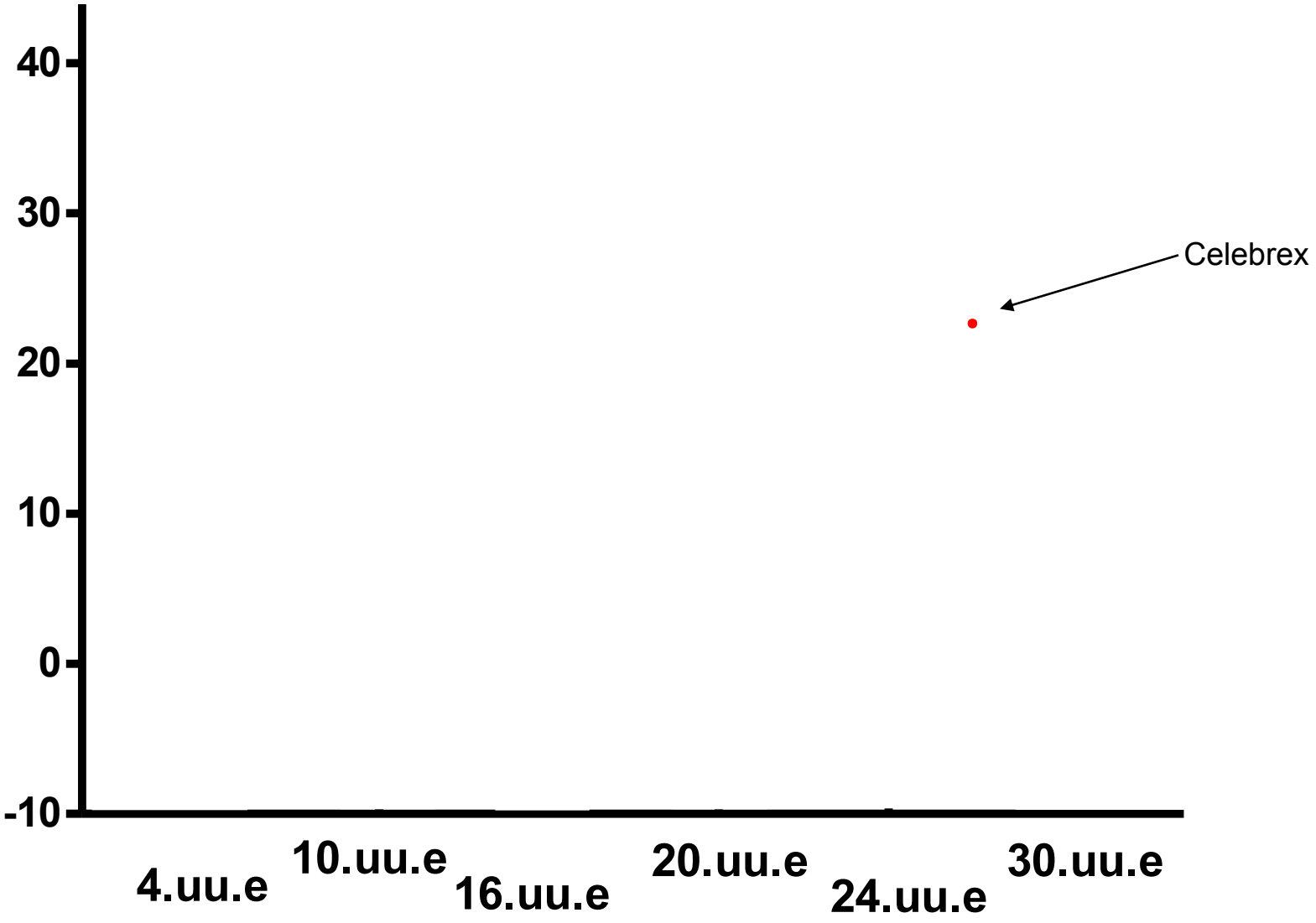
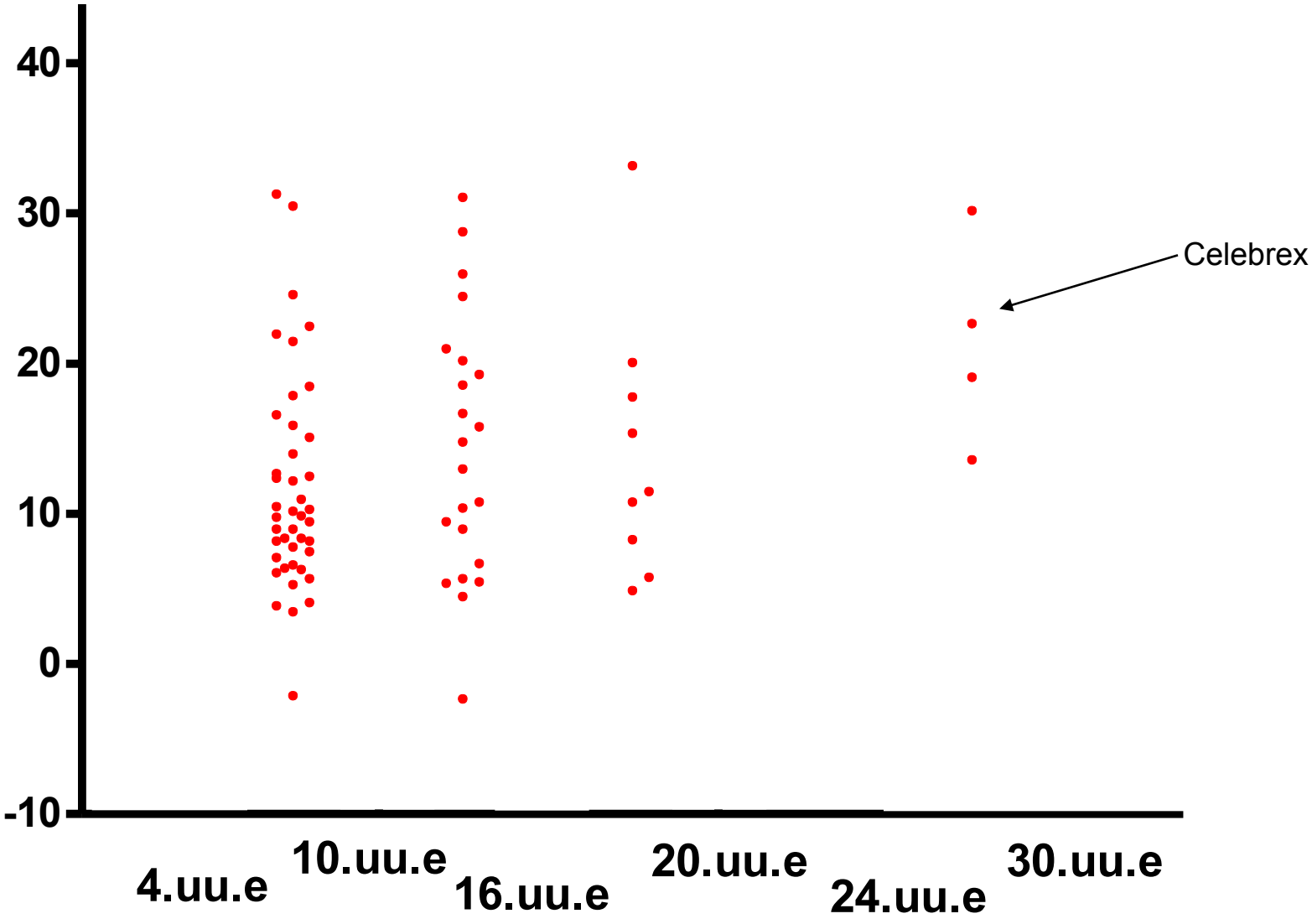
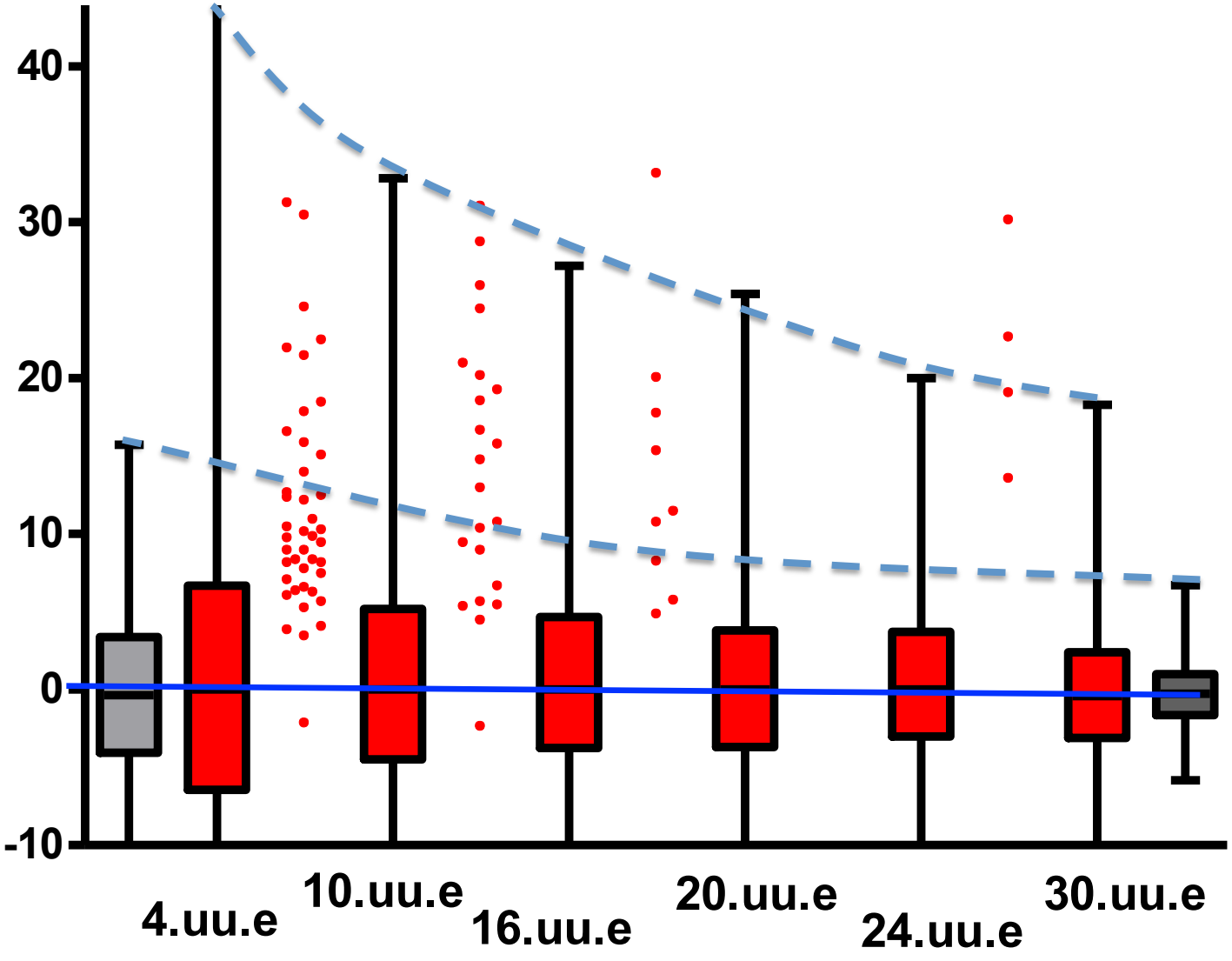
Of mice and Stephen



Of mice and Stephen

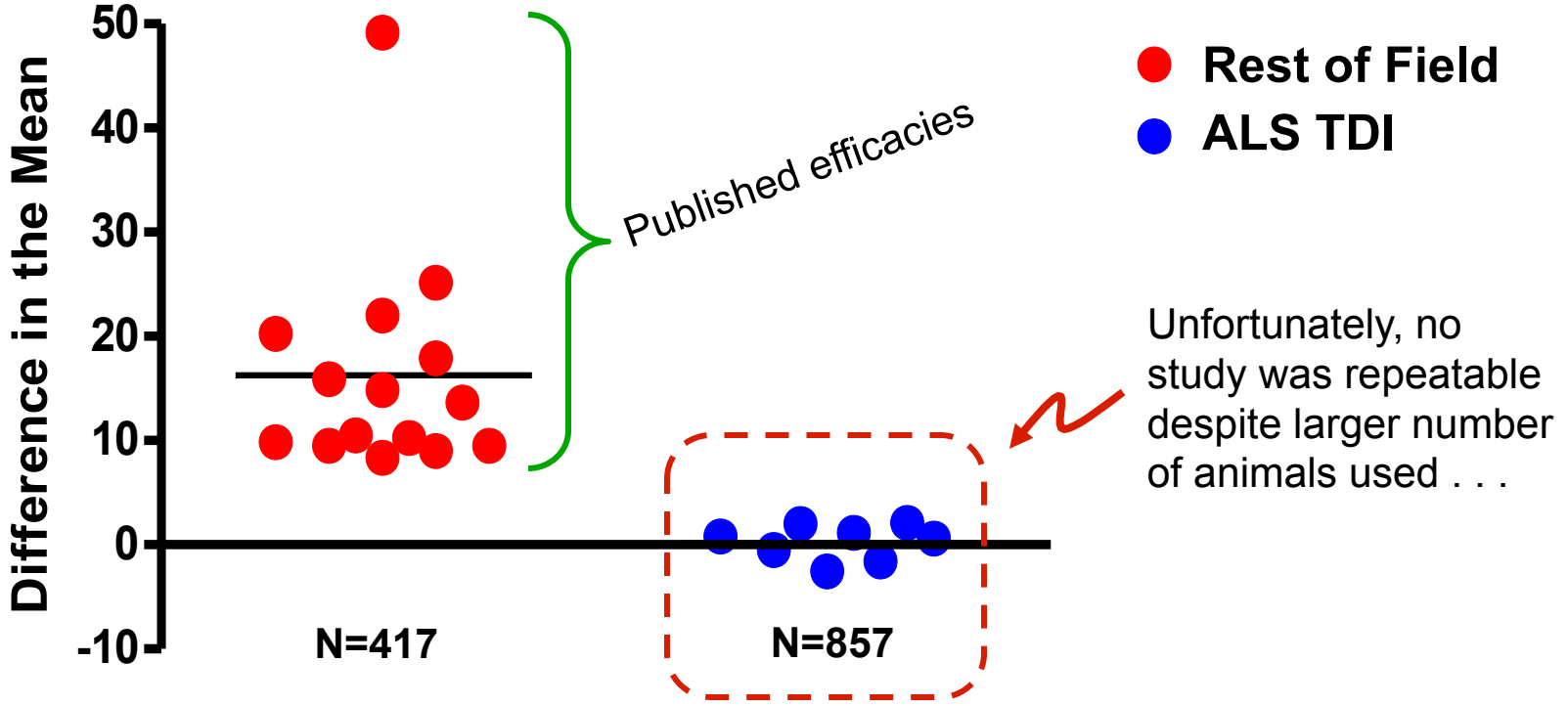


Of mice and Stephen



ALSTDI
ALS Therapy Development Institute

Published v. TDI Retest



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nature
journal of science

CORRESPONDENCE

LINK TO ORIGINAL ARTICLE

Believe it or not: how much can we rely on published data on potential drug targets?

Florian Prinz, Thomas Schlange and Khusru Asadullah

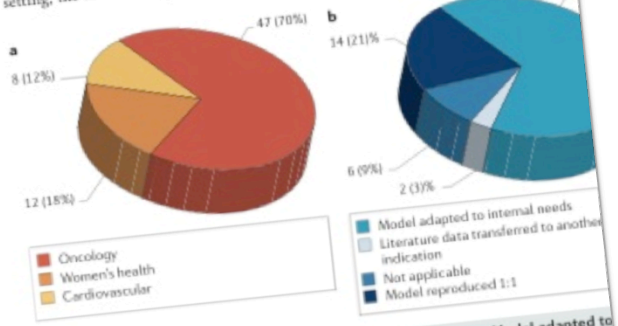
A recent report by Arrowsmith noted that the success rates for new development projects in Phase II trials have fallen from 28% to 18% in recent years, with insufficient efficacy being the most frequent reason for failure (Phase II failures: 2008–2010. *Nature Rev. Drug Discov.* **10**, 328–329 (2011))[1]. This indicates the limitations of the predictivity of disease models and also that the validity of the targets being investigated is frequently questionable, which is a crucial issue to address if success rates in clinical trials are to be improved.

Candidate drug targets in industry are derived from various sources, including in-house target identification campaigns, in-licensing and public sourcing, in particular based on reports published in the literature and presented at conferences. During the transfer of projects from an academic to a company setting, the focus changes from 'interesting'

results that are published are hard to reproduce. However, there is an imbalance between

to 'feasible/marketable', and the financi
of pursuing a full-blown drug discov
development programme for a partic
get could ultimately be hundreds of mil
Euros. Even in the earlier stages, inves
in activities such as high-throughput
ing programmes are substantial, and t
validity of published data on potential
is crucial for companies when deciding
novel projects.

To mitigate some of the risks of such
ments ultimately being wasted, mos
maceutical companies run in-house
validation programmes. However, val
projects that were started in our co
based on exciting published data hav
resulted in disillusionment when k
could not be reproduced. Talking to
tists, both in academia and in industr
seems to be a general impression tha



d	Model reproduced 1:1	Model adapted to needs (cell line, a
In-house data in line with published results	1 (7%)	12 (86%)
Inconsistencies that led to project termination	11 (26%)	26 (60%)

Figure 1 | **Analysis of the reproducibility of published data in 67 in-house projects. a** | This figure illustrates the distribution of projects within women's health and cardiovascular indications that were ana- used to reproduce the pub- of each of the with published the most releva sistencies that that were almo

COMMENT


S. GSCHMEISSNER/SPL

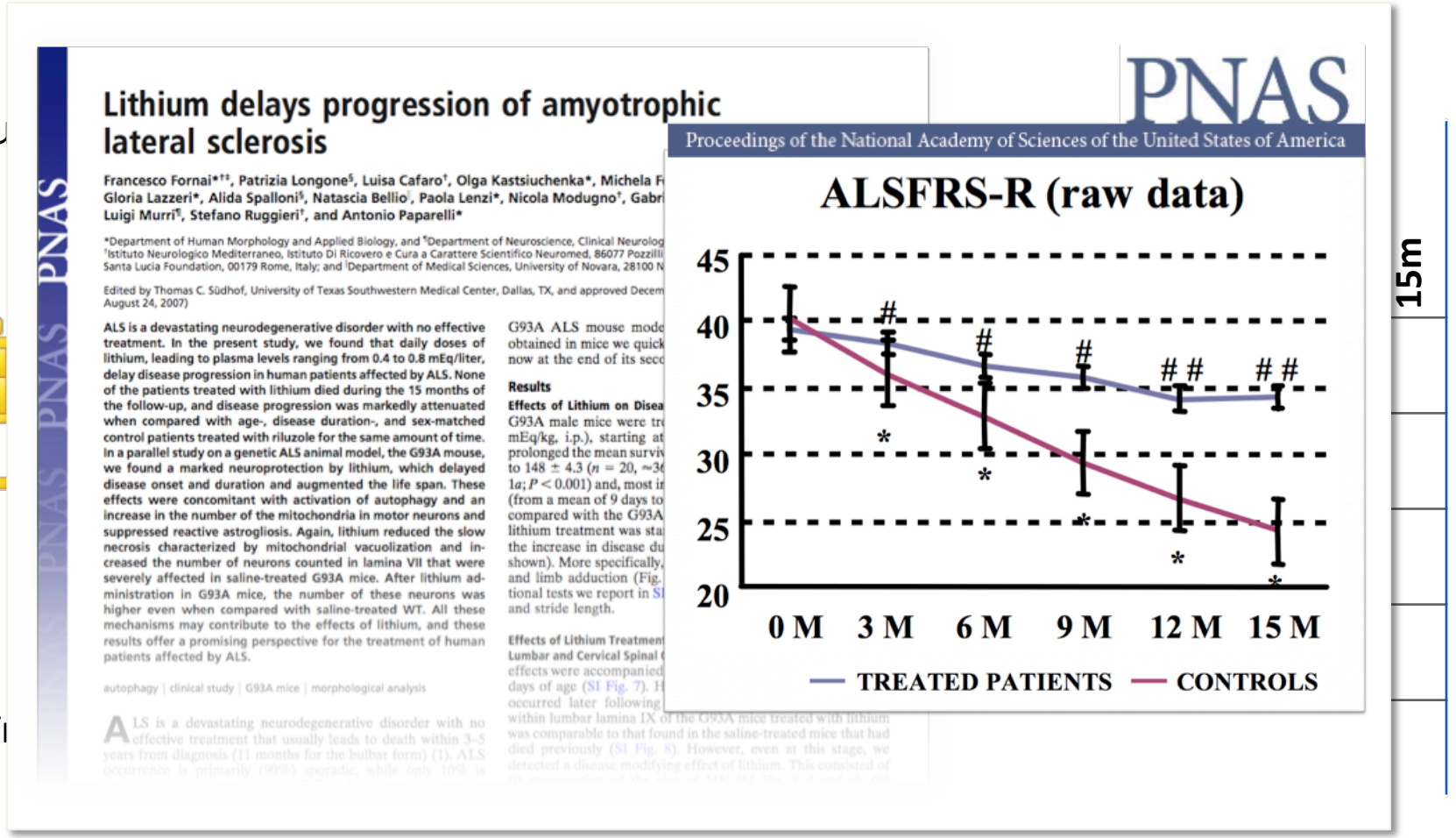
Many landmark findings in preclinical oncology research are not reproducible, in part because of inadequate cell lines and animal models.

Raise standards for preclinical cancer research

C. Glenn Begley and **Lee M. Ellis** propose how methods, publications and tives must change if patients are to benefit.

Clinical Research

Lithiu



PNAS

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

Lithium delays progression of amyotrophic lateral sclerosis

Francesco Fornai*†‡, Patrizia Longone§, Luisa Cafaro†, Olga Kastsiuchenka*, Michela F
Gloria Lazzeri*, Alida Spalloni§, Natascia Bellio, Paola Lenzi*, Nicola Modugno†, Gabri
Luigi Murri¶, Stefano Ruggieri†, and Antonio Paparelli*

*Department of Human Morphology and Applied Biology, and †Department of Neuroscience, Clinical Neurolog
‡Istituto Neurologico Mediterraneo, Istituto Di Ricovero e Cura a Carattere Scientifico Neuromed, 86077 Pozzilli
Santa Lucia Foundation, 00179 Rome, Italy; and ¶Department of Medical Sciences, University of Novara, 28100 N

Edited by Thomas C. Südhof, University of Texas Southwestern Medical Center, Dallas, TX, and approved Decem
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 suppressed reactive astrogliosis. Again, lithium reduced the slow necrosis characterized by mitochondrial vacuolization and increased the number of neurons counted in lamina VII that were severely affected in saline-treated G93A mice. After lithium administration in G93A mice, the number of these neurons was higher even when compared with saline-treated WT. All these mechanisms may contribute to the effects of lithium, and these results offer a promising perspective for the treatment of human patients affected by ALS.

autophagy | clinical study | G93A mice | morphological analysis

ALS is a devastating neurodegenerative disorder with no effective treatment that usually leads to death within 3–5 years from diagnosis (11 months for the bulbar form) (1). ALS occurrence is primarily (90%) sporadic, while only 10% is

G93A ALS mouse mode
obtained in mice we quick
now at the end of its seco

Results

Effects of Lithium on Disea

G93A male mice were tr
mEq/kg, i.p.), starting at
prolonged the mean surviv
to 148 ± 4.3 (n = 20, ~36
1a; $P < 0.001$) and, most ir
(from a mean of 9 days to
compared with the G93A
lithium treatment was sta
the increase in disease du
shown). More specifically,
and limb adduction (Fig.
tional tests we report in SI
and stride length.

**Effects of Lithium Treatment
Lumbar and Cervical Spinal**

effects were accompanied
days of age (SI Fig. 7). H
occurred later following
within lumbar lamina IX of the G93A mice treated with lithium
was comparable to that found in the saline-treated mice that had
died previously (SI Fig. 8). However, even at this stage, we
detected a disease modifying effect of lithium. This consisted of

ALSFRS-R (raw data)

15m

Tr

patientslikeme®

THE LANCET Neur

Safety and e
for treatmen
double-blind,

Swati P Aggarwal*, Lorne Zinma
David Schoenfeld, Jeremy Shefne

Summary

Background In a pilot study
to confirm or disprove thes
patients with ALS.

Methods We did a double-bli
patients with ALS who were
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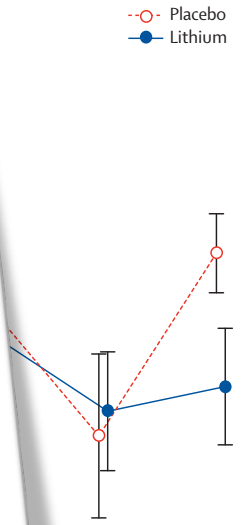


Published onl
NEUROLOGY 2010;

Lithium carbo

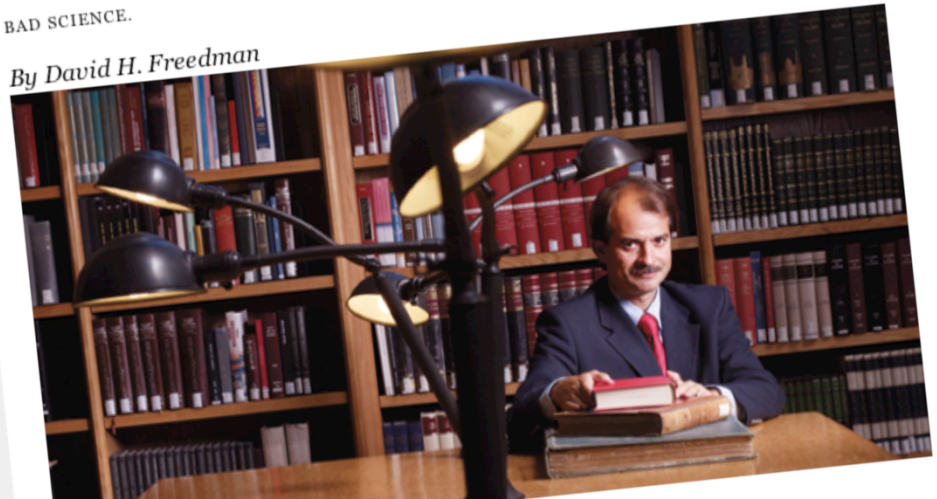
Lack of efficacy in a

the Atlantic
November 2010

Lies, Damned Lies, and Medical Science

MUCH OF WHAT MEDICAL RESEARCHERS CONCLUDE IN THEIR STUDIES IS MISLEADING, EXAGGERATED, OR FLAT-OUT WRONG. SO WHY ARE DOCTORS—TO A STRIKING EXTENT—STILL DRAWING UPON MISINFORMATION IN THEIR EVERYDAY PRACTICE? DR. JOHN IOANNIDIS HAS SPENT HIS CAREER CHALLENGING HIS PEERS BY EXPOSING THEIR BAD SCIENCE.

By David H. Freedman



Clinical Research

"It is simply no longer possible to believe much of the clinical research that is published, or to rely on the judgment of trusted physicians or authoritative medical guidelines.
I take no pleasure in this conclusion, which I reached slowly and reluctantly over my two decades as an editor of The New England Journal of Medicine."

Marcia Angell, MD

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

BMJ

Abstract

Objectives To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.
Design Systematic review of randomised controlled trials.
Data sources: Medline, Web of Science, Embase, and the Cochrane Library databases; appropriate internet sites and citation lists.
Study selection: Studies showing the effects of using a parachute during free fall.
Main outcome measure Death or major trauma, defined as an injury severity score >15.
Results We were unable to identify any randomised controlled trials of parachute intervention.
Conclusions As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence

accepted intervention was a fabric device, secured by strings release fall wit exclud

Defini The m trauma 15.[6]

Meta-a Our st chute a the pre We ch geneity fixed e causes assess tests to

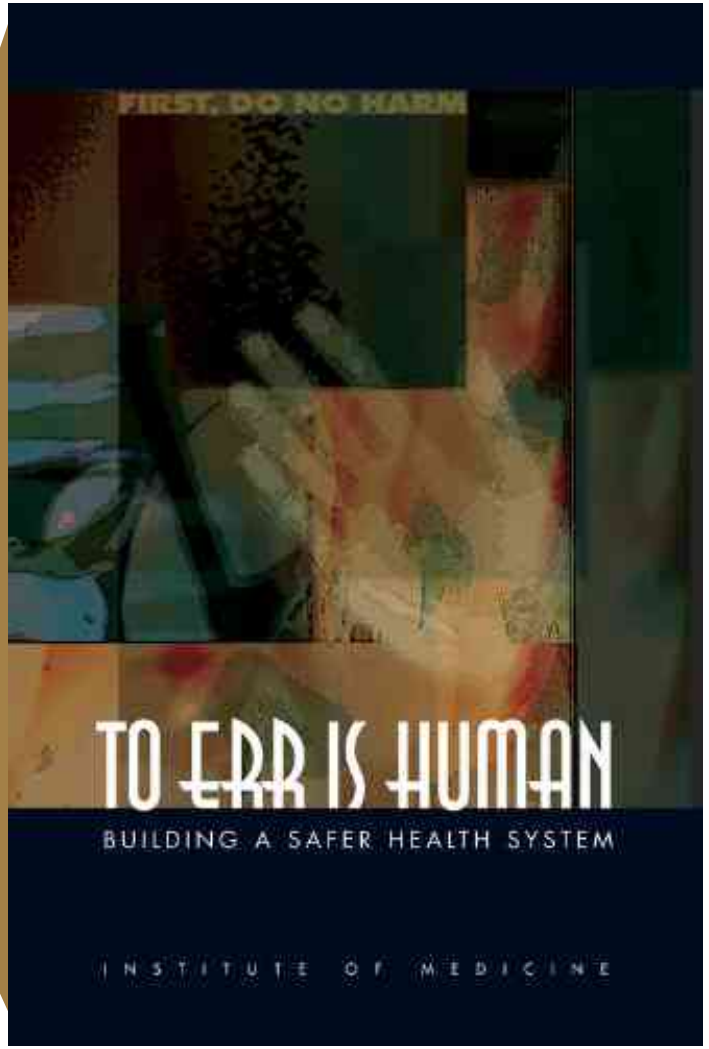
Department of

HULTON/GETTY

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Leading Cause of Death in the United States*		
1	Heart Disease	652,091
2	Cancer	559,312
3	Stroke	143,579
4	Chronic Lower Respiratory Disease	130,933
5	Accidents (unintentional injuries)	117,809
	Preventable Medical Errors**	**98,000**
6	Diabetes	75,119
7	Alzheimer's Disease	71,599
8	Influenza/Pneumonia	63,001
9	Nephritis/Nephrosis	43,901
10	Septicemia	34,136



A New, Evidence-based Estimate of Patient Harms Associated with Hospital Care

John T. James, PhD

the best estimate from combining these 4 studies is

34,400,000 x 0.69 x 0.0089 = ***210,000***

preventable adverse events per year that contribute to the death of hospitalized patients

TABLE 2. Recent Studies of Preventable Adverse Events

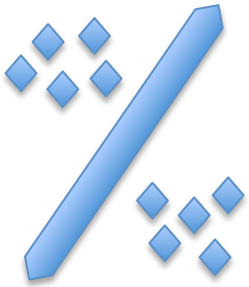
Reference	Source of Medical Record Data	Time Covered by Records	No. records Reviewed	Search Tool or Method	Serious Adverse Events (Class F to I) Found (%)	% Deemed Preventable	Lethal Adverse Events (%)
OIG (2008)	Medicare beneficiaries in 2 counties	1 wk in August 2008	278	Global trigger tool	43 (15%)	n/s	3 (1.1%)
OIG (2010)	Representative Medicare patients	October 2008	838	Global trigger tool	128 (15%)	44%	12 (1.4%)
Classen et al. (2011)	3 tertiary-care hospitals	October 2004	795	Global trigger tool	167 (21%)	~100%	9 (1.1%)
Landrigan, et al. (2010)	10 hospitals in North Carolina	Jan 2002 through Dec 2007	2341	Global trigger tool	332 (14%)	63%	14 (0.6%)

* Ventilator-associated pneumonia.

† Cardiac arrest, pulmonary embolism, hematologic event, neurological event.

"In physical science the first essential step in the direction of learning any subject is to find principles of numerical reckoning and practicable methods for measuring some quality connected with it. I often say that when you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely in your thoughts advanced to the state of Science, whatever the matter may be."

Lord Kelvin



Stratification :

Conditions & Subtypes. Meaningful, computable, measurable, range and variance, of symptomology, biology, pathology, environment, and functional impact of disease

Signal Optimization

Methods, models, & tools that shorten the time to have meaningful confidence about the effectiveness of an intervention in a single patient or model

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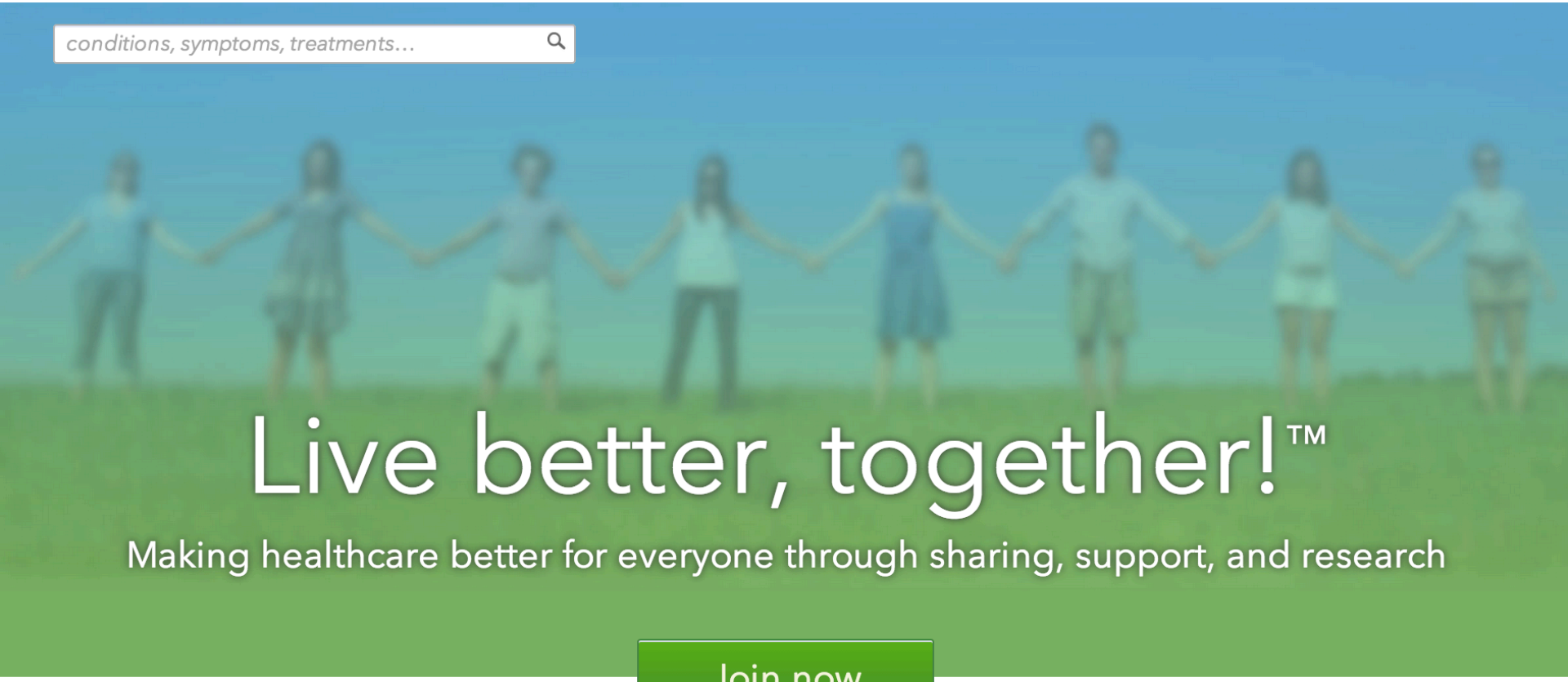
Username or Email | Password | Sign in

Remember me | I forgot

conditions, symptoms, treatments...



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Making healthcare better for everyone through sharing, support, and research

Join now

(it's free!)

Learn from others

Compare treatments, symptoms and experiences with people like you and take control of your health

Connect with people like you

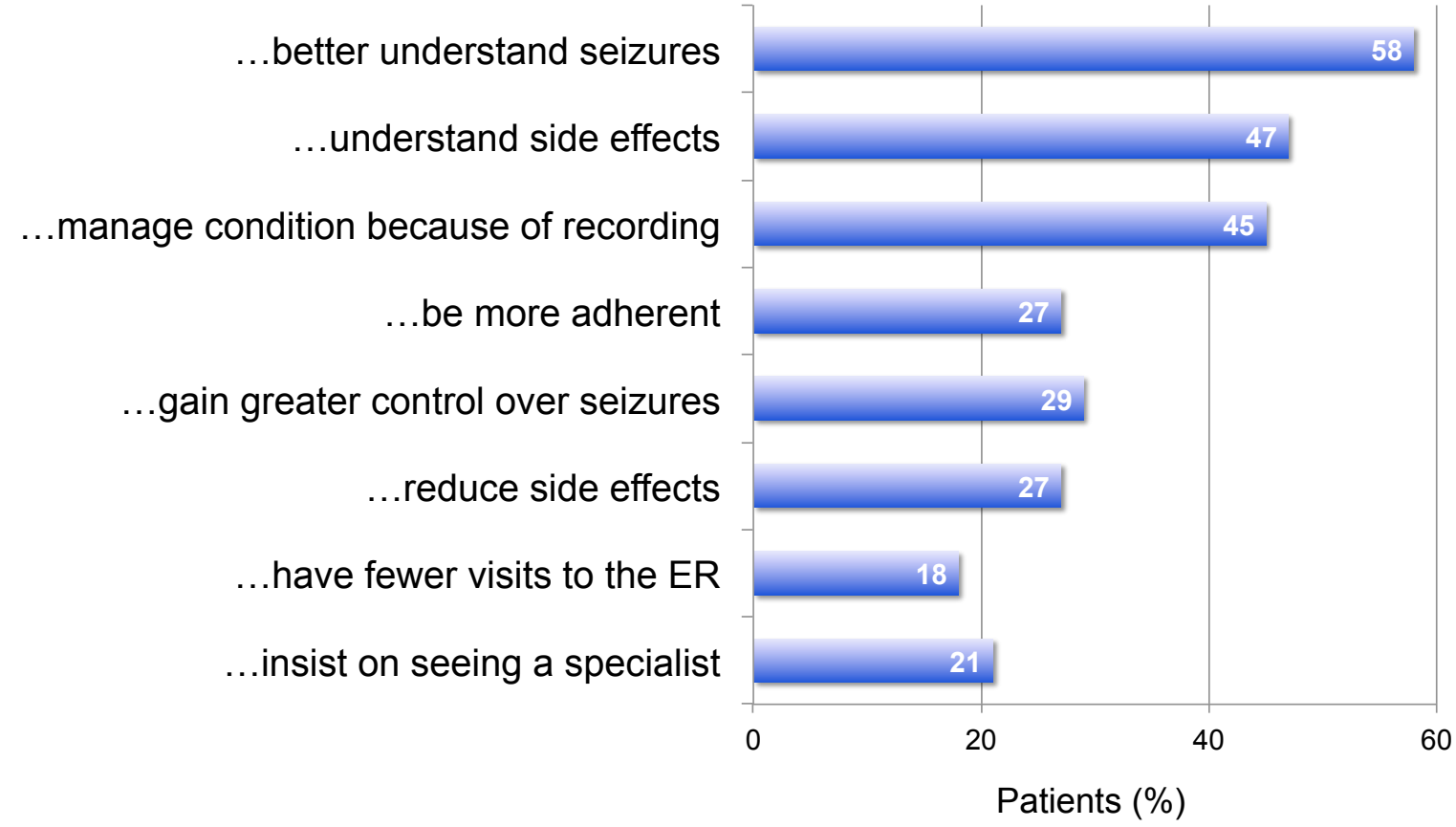
Share your experience, give and get support to improve your life and the lives of others

Track your health

Chart your health over time and contribute to research that can advance medicine for all

Patients Get Better

Users reported that PatientsLikeMe helped them…



ELSEVIER

Epilepsy & Behavior
Volume 23, Issue 1, January 2012,

Perceived benefits of sharing health data between people with epilepsy on an online platform

Wicks, P, Keiningerb, D, Massaglia, M, Logeb, C, Brownsteina, C , Isojärvic, J, Heywood, J

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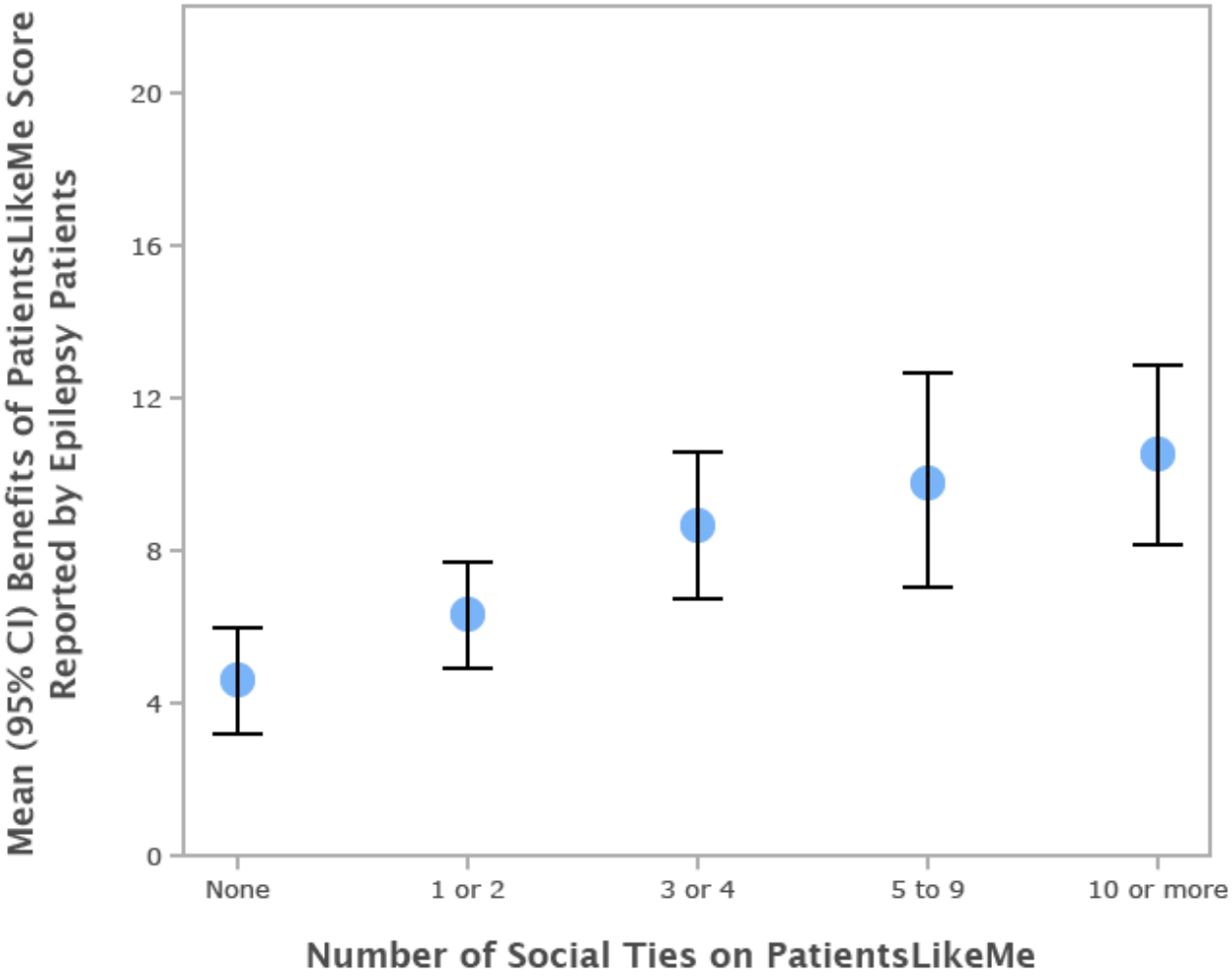
Social 'Dose response' curve



($p<0.001$) for differences between "none" and all other categories

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Patient assessment of physician quality measure performance

Quality measure	Strongly agree (%)	Agree (%)	Disagree (%)	Strongly disagree (%)	N/A (%)
1a. Type of seizures	51	38	8	4	0
b. Frequency of seizures	62	25	5	5	2
2. Know epilepsy syndrome	48	33	13	6	0.5
3. EEG performed	89	10.5	0	0.5	0
4. Neuroimaging performed	86	11	1	2	0.5
5. Side effects assessed	44	24	15	14	2
6. Epilepsy surgery referral*	35	13	14	20	19
7. Discussed safety issues	48	26	9	12	5
8. Birth control**	27	19	10	7	37

n=221 except for *data only shown for patients with intractable epilepsy, **question only asked of females aged 14–44
EEG, electroencephalography

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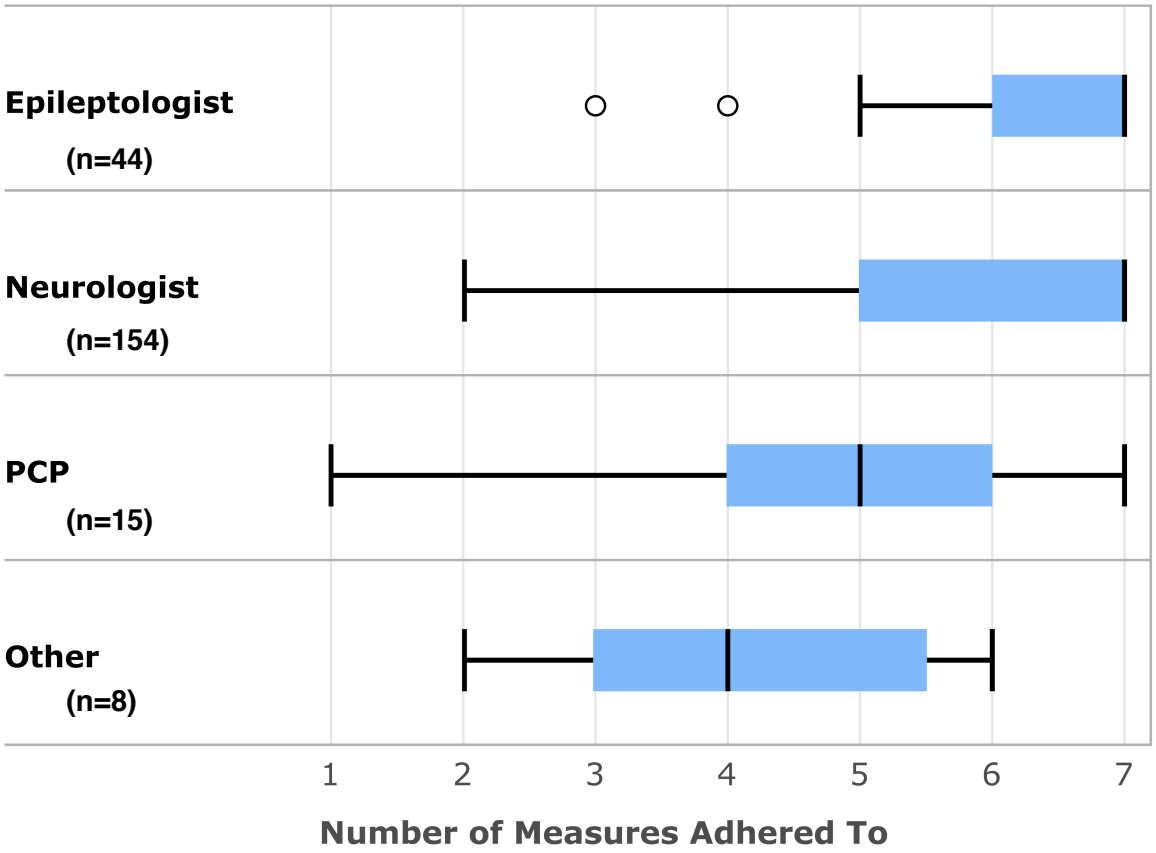
Wicks P, Fountain N. Poster presented at AAN 2011

Quality measure performance by specialty



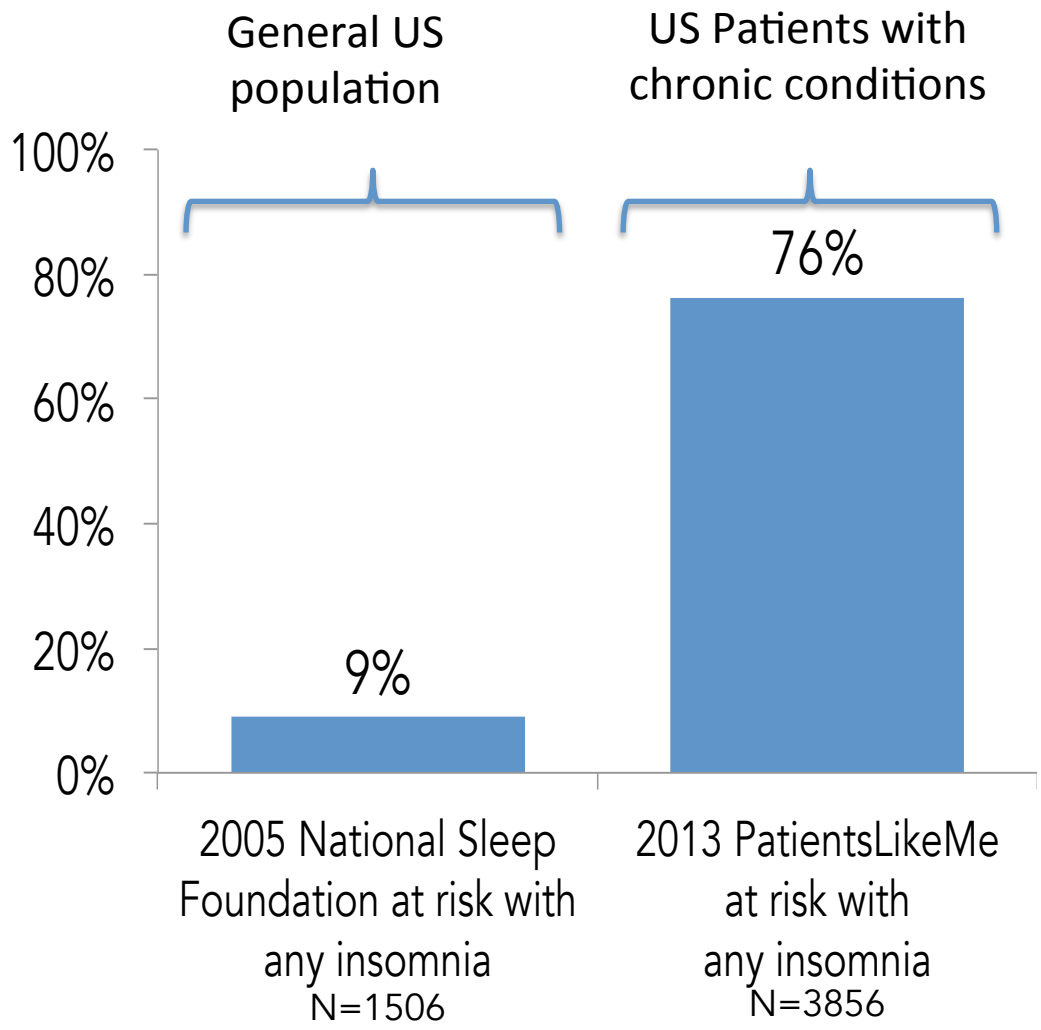
Box plots of total number of measures performed (excluding contraception & surgery referral items) broken down by specialty of treating physician. Black line represents the median, box is the inter-quartile range (IQR), whiskers are 1.5x IQR, and circles are outliers (>1.5x IQR)

PCP, primary care physician

Wicks P, Fountain N. Poster presented at AAN 2011

Sleep & chronic illness

PatientsLikeMe 2013 Sleep Survey



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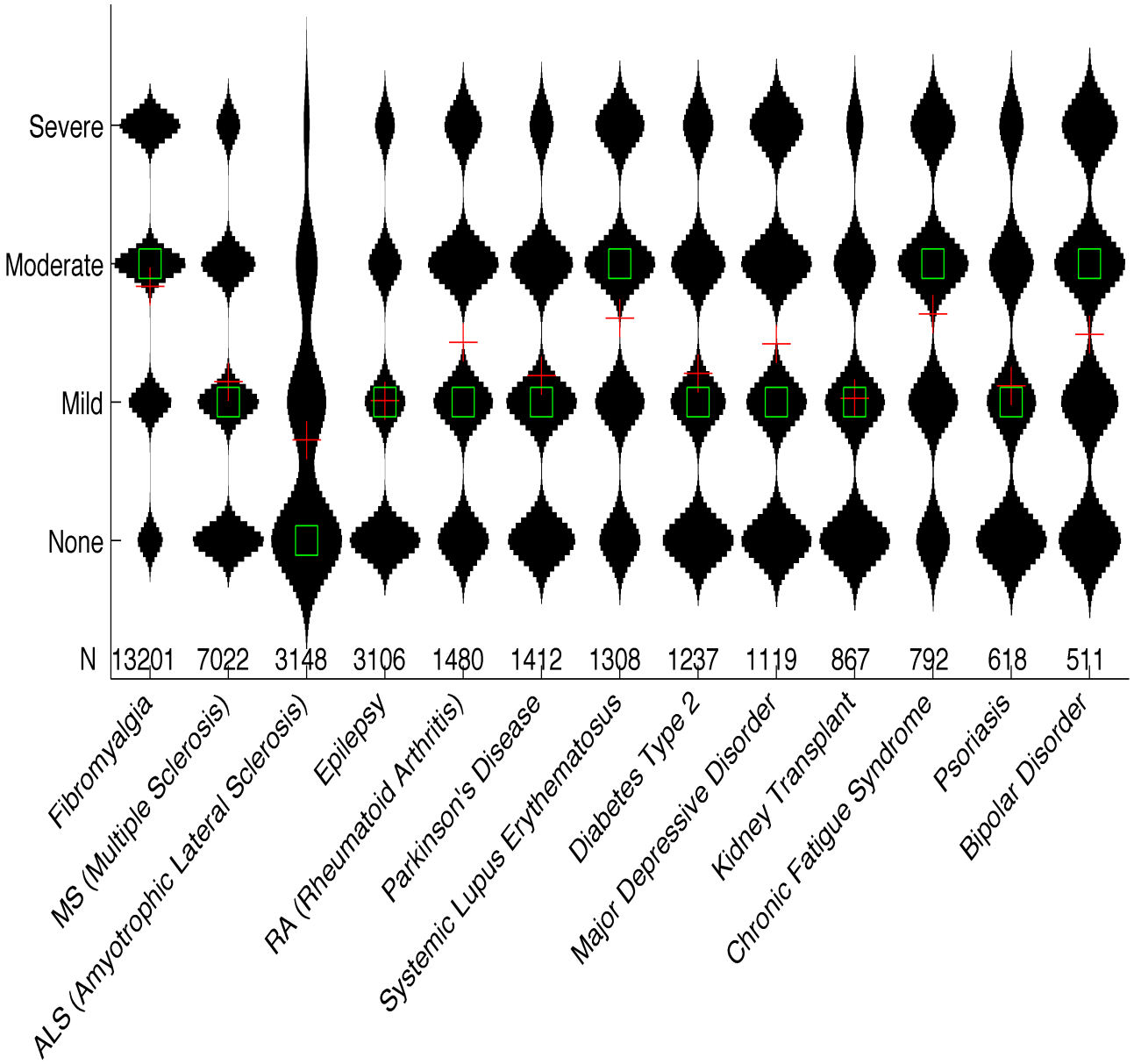
Cross Condition Research

Insomnia severity by condition

N=67,000

PLM Profile Data



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

George Edward Pelham Box

Mozilla Firefox

http://www.forestandthetrees.com/plm/1024/frsPrediction/FRS_prediction.html

http://www.forest..._prediction.html

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Welcome | Inbox | Account | Display options | Logout

Home | My Profile | Patients | Forum | Treatments | Symptoms | Research | Search | Help | Crisis

ALS: <1yr

humberto-from-brazil

Male, 42 years
Brasília, Distrito Federal

Diagnosis
Onset: Arms
First symptom: 09/06
Diagnosis: 03/07
X Genetics: Non-SOD1 ALS

Member since: 02/08
Last updated: 12/25/07
Last login: 01/02/08

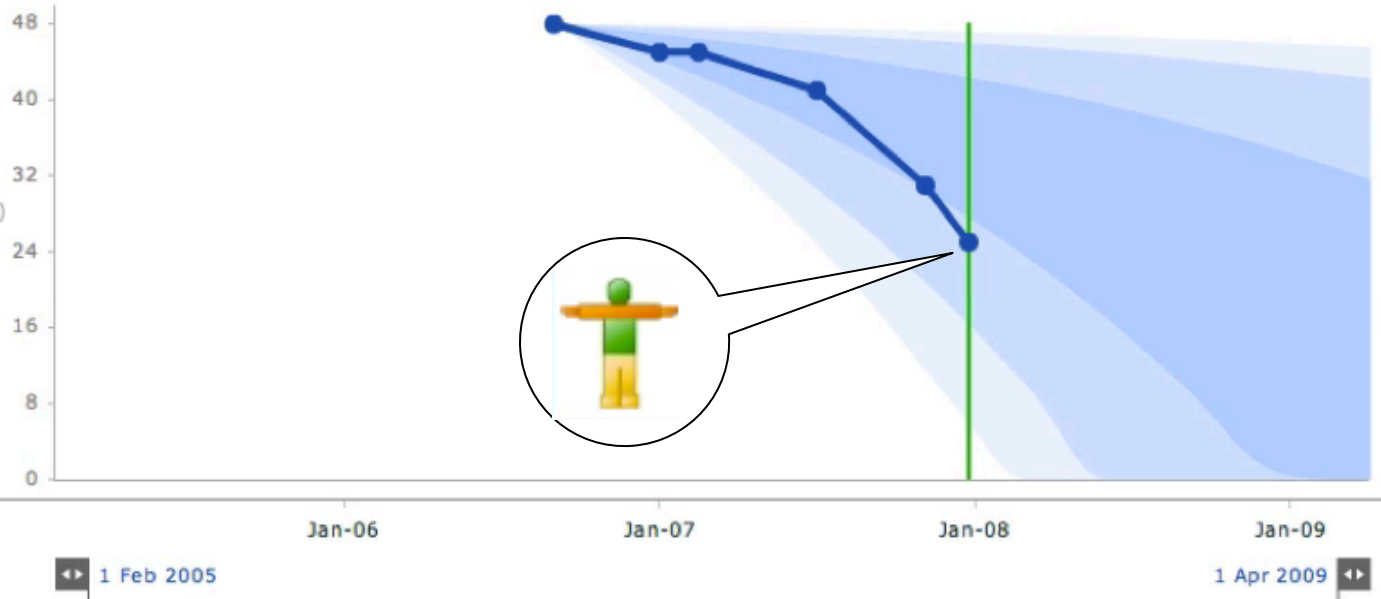
ALS Public Registry

ALS Condition

▼ FRS

Progression rate percentile

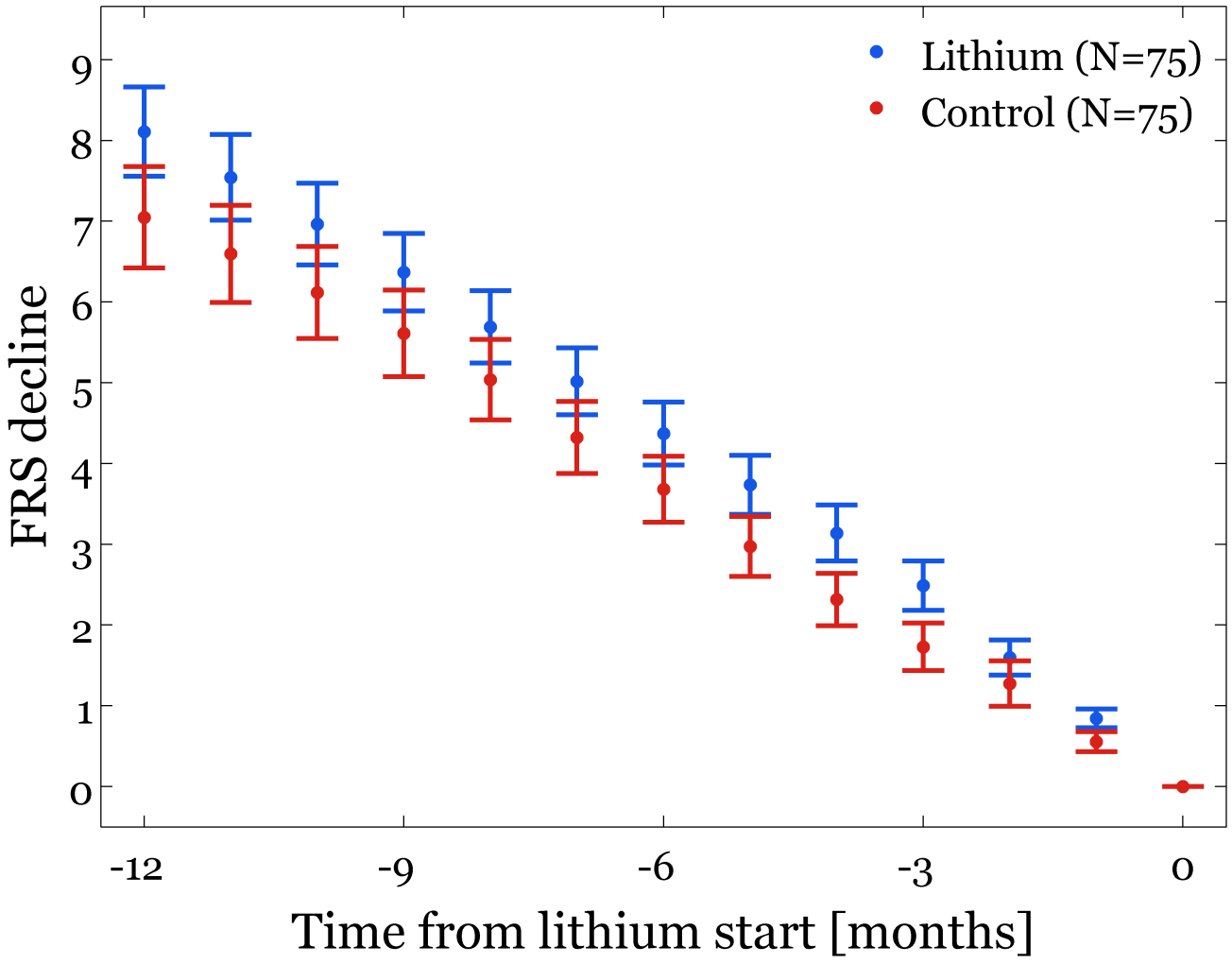
- 5-10th (rapid)
- 10-25th
- 75-90th
- 25-75th (average)
- 90-95th (slow)



FRS: 25
latest update:
25 Dec 2007

Random Control Matching

Mean decline in FRS over time



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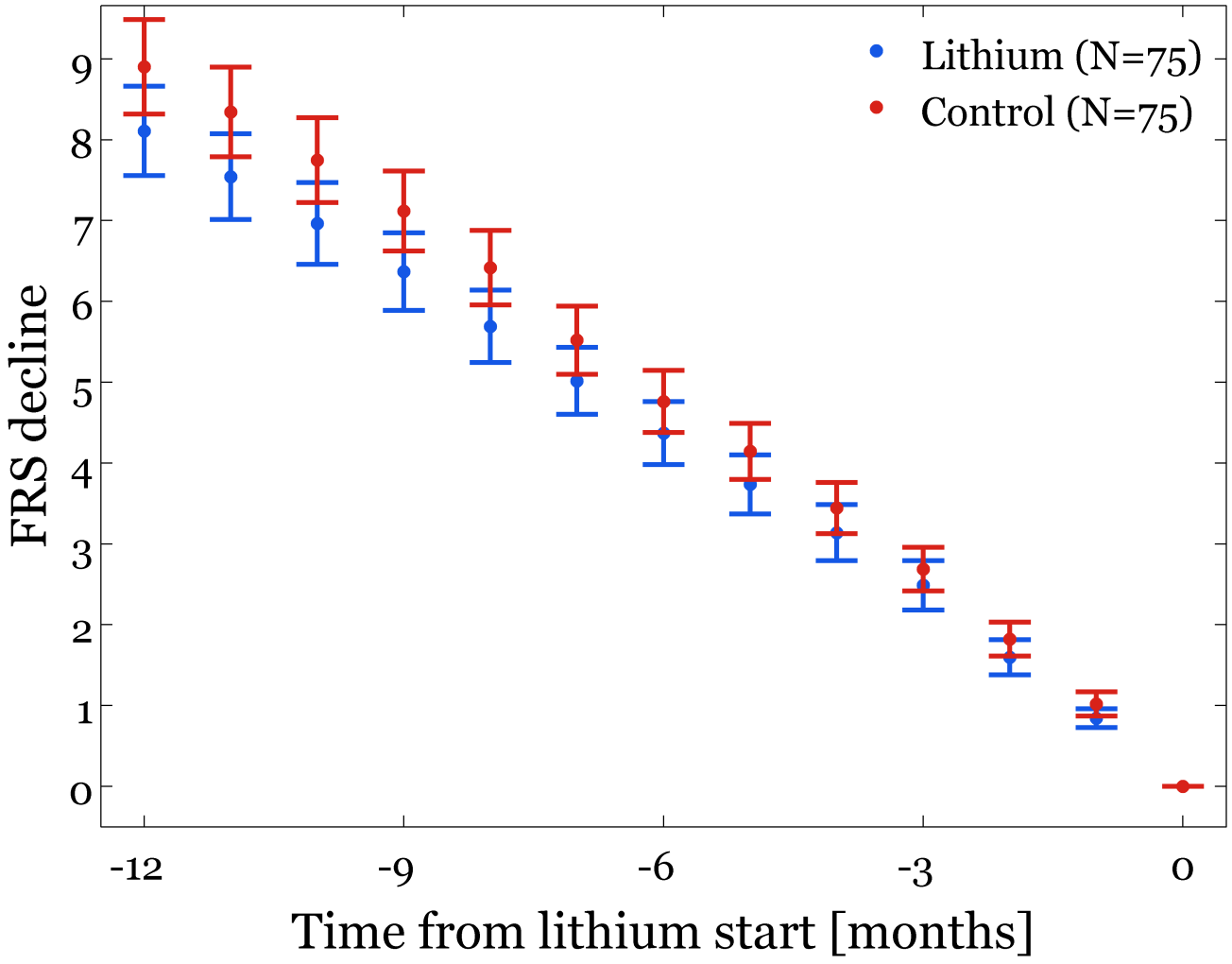
Disease Duration & Disability Matching

Mean decline in FRS over time



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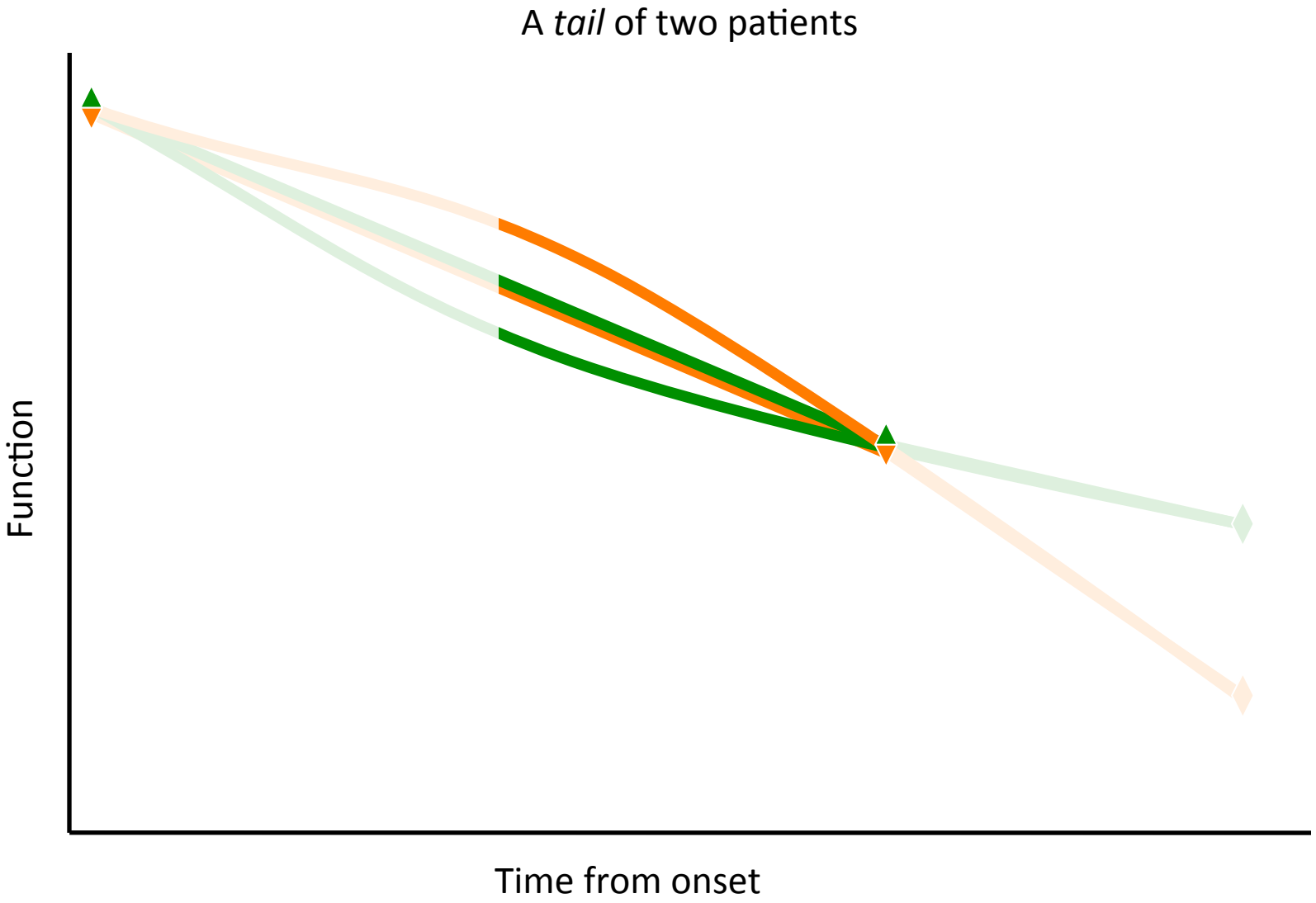
A *tail* of two patients
Function
Time from onset

Mozilla Firefox

http://www.forestandthetrees.com/plm/1024/frsPrediction/FRS_prediction.html

http://www.forest..._prediction.html

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Home | My Profile | Patients | Forum | Treatments | Symptoms | Research | Search | Help | Crisis

ALS: <1yr

humberto-from-brazil

Male, 42 years
Brasília, Distrito Federal

Diagnosis
Onset: Arms
First symptom: 09/06
Diagnosis: 03/07
X Genetics: Non-SOD1 ALS

Member since: 02/08
Last updated: 12/25/07
Last login: 01/02/08

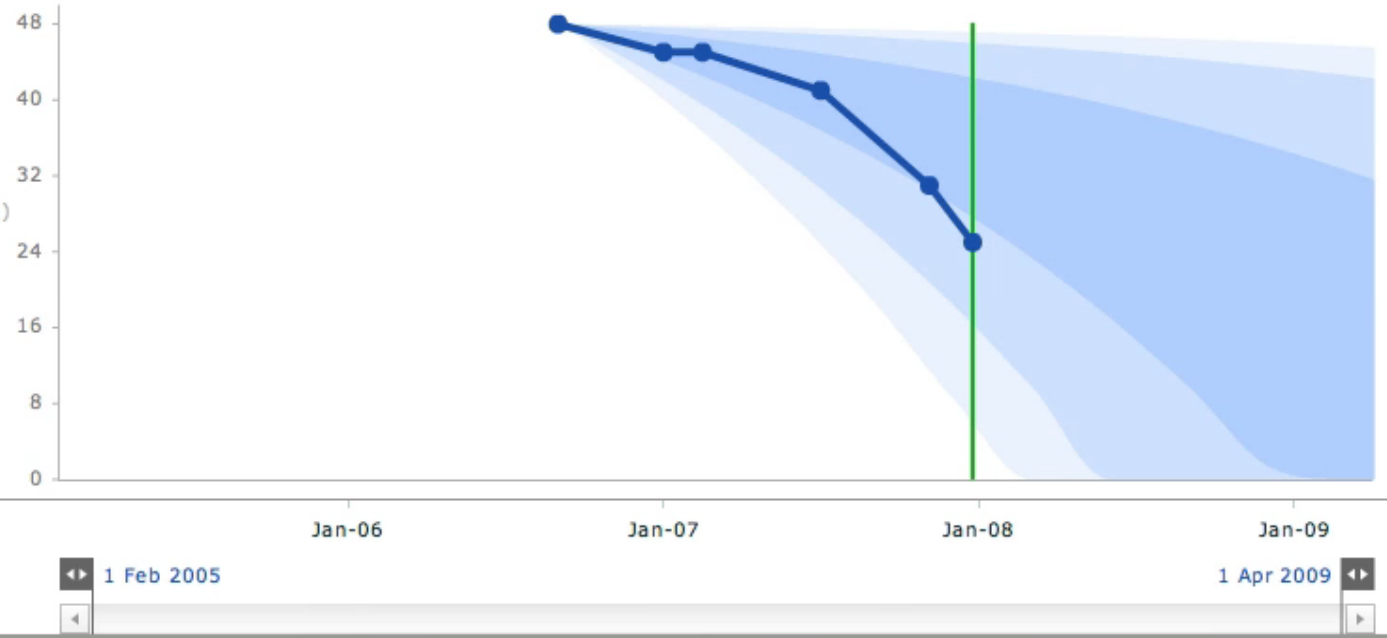
ALS Public Registry

ALS Condition

▼ **FRS**

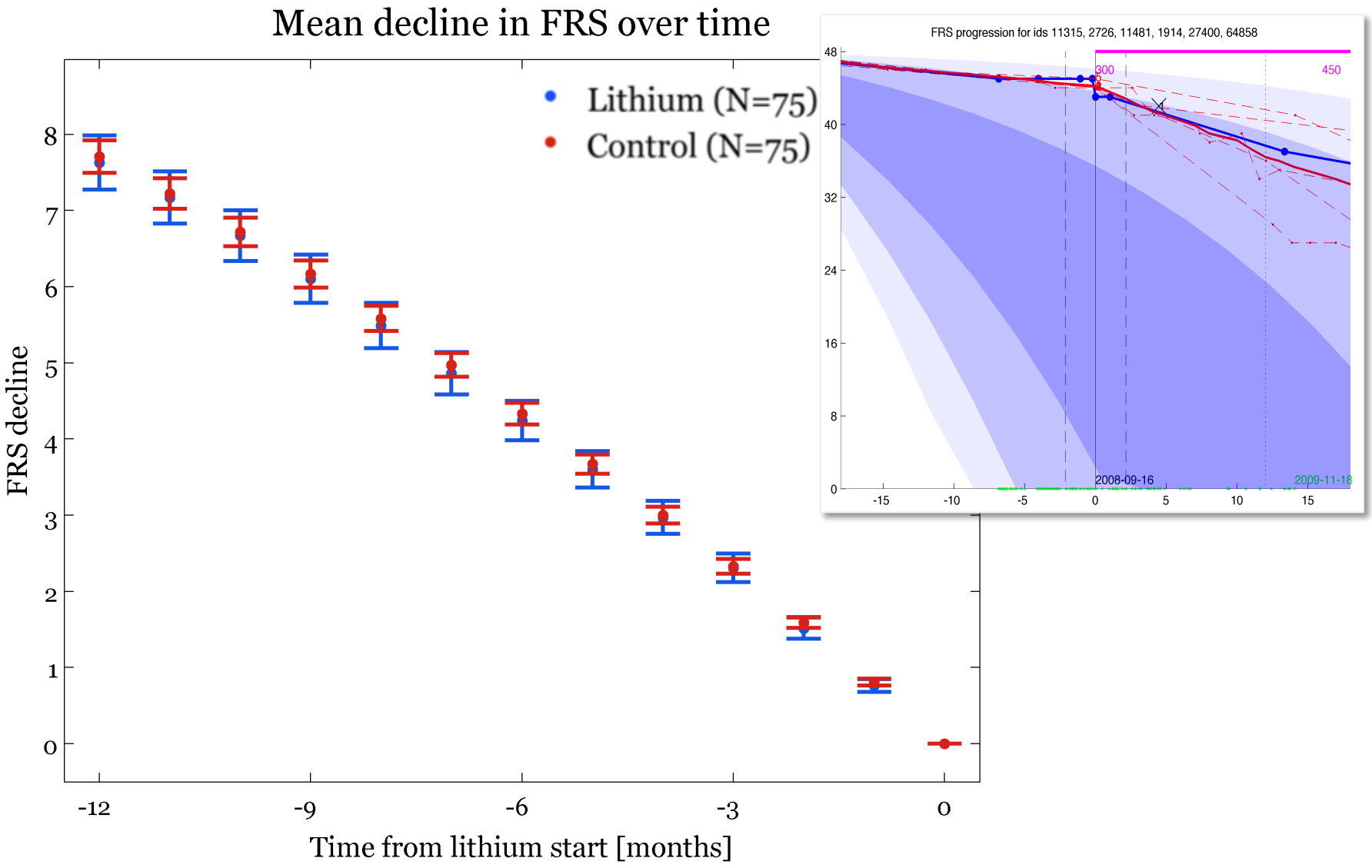
Progression rate percentile

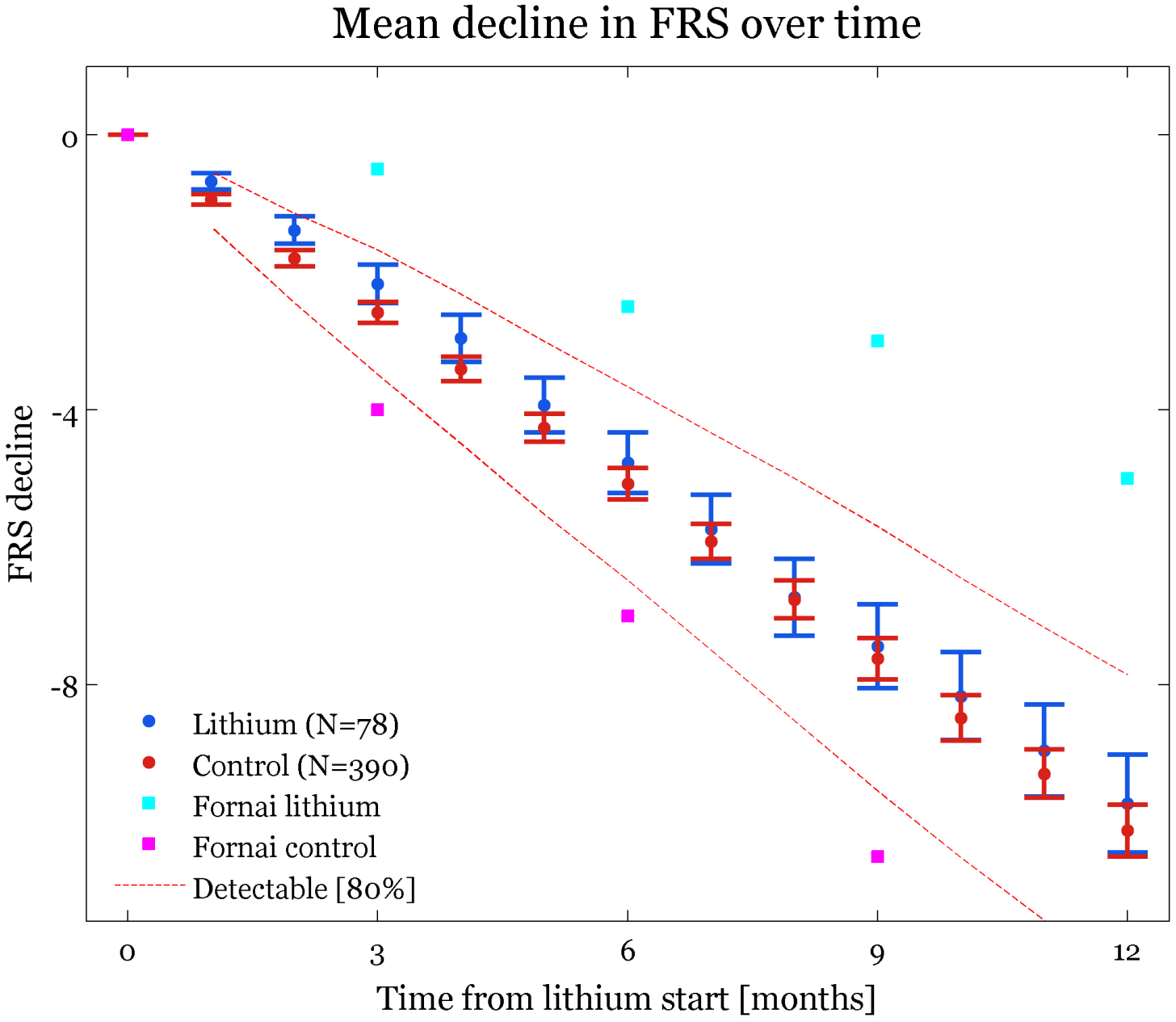
- 5-10th (rapid)
- 10-25th
- 75-90th
- 25-75th (average)
- 90-95th (slow)



FRS: 25
latest update:
25 Dec 2007

Algorithmic matching




Mean decline in FRS over time
FRS decline
0
-4
-8
0
3
6
9
12
Time from lithium start [months]
Lithium (N=78)
Control (N=390)
Fornai lithium
Fornai control
Detectable [80%]

nature biotechnology
VOLUME 29 NUMBER 5 MAY 2011
www.nature.com/naturebiotechnology
THE SCIENCE AND BUSINESS OF BIOTECHNOLOGY

_computational BIOLOGY

ANALYSIS

Accelerated clinical discovery using self-reported patient data collected online and a patient-matching algorithm

Paul Wicks, Timothy E Vaughan, Michael P Massagli & James Heywood

Patients with serious diseases may experiment with drugs that have not received regulatory approval. Online patient communities structured around quantitative outcome data have the potential to provide an observational environment to monitor such drug usage and its consequences. Here we describe an analysis of data reported on the website PatientsLikeMe by patients with amyotrophic lateral sclerosis (ALS) who experimented with lithium carbonate treatment. To reduce potential bias owing to lack of randomization, we developed an algorithm to match 149 treated patients to multiple controls (447 total) based on the progression of their disease course. At 12 months after treatment, we found no effect of lithium on disease progression. Although observational studies using unblinded data are not a substitute for double-blind randomized control trials, this study reached the same conclusion as subsequent randomized trials, suggesting that data reported by patients over the internet may be useful for accelerating clinical discovery and evaluating the effectiveness of drugs already in use.

Online communities such as PatientsLikeMe that provide robust methods for patients to record and share data may have the potential to be used to conduct observational studies to assess the effectiveness of treatments. Although observational studies inherently cannot meet

to investigate the use of self-experimentation, complementary and alternative medicine, and off-label drug usage[5]. There are a number of benefits to systematically studying patients' self-experimentation. First, it is im
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combination
efficacious, l

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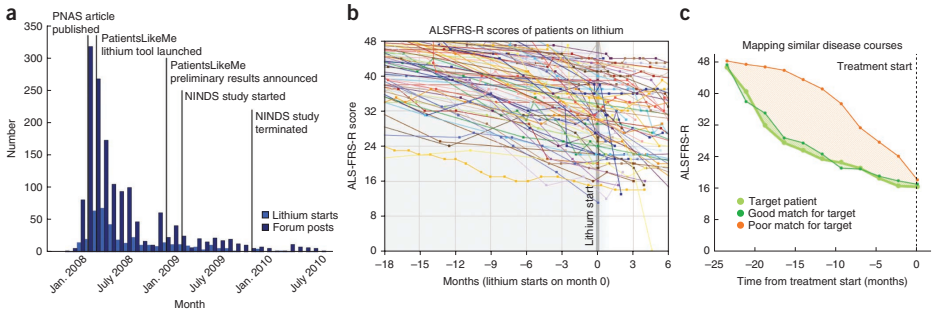
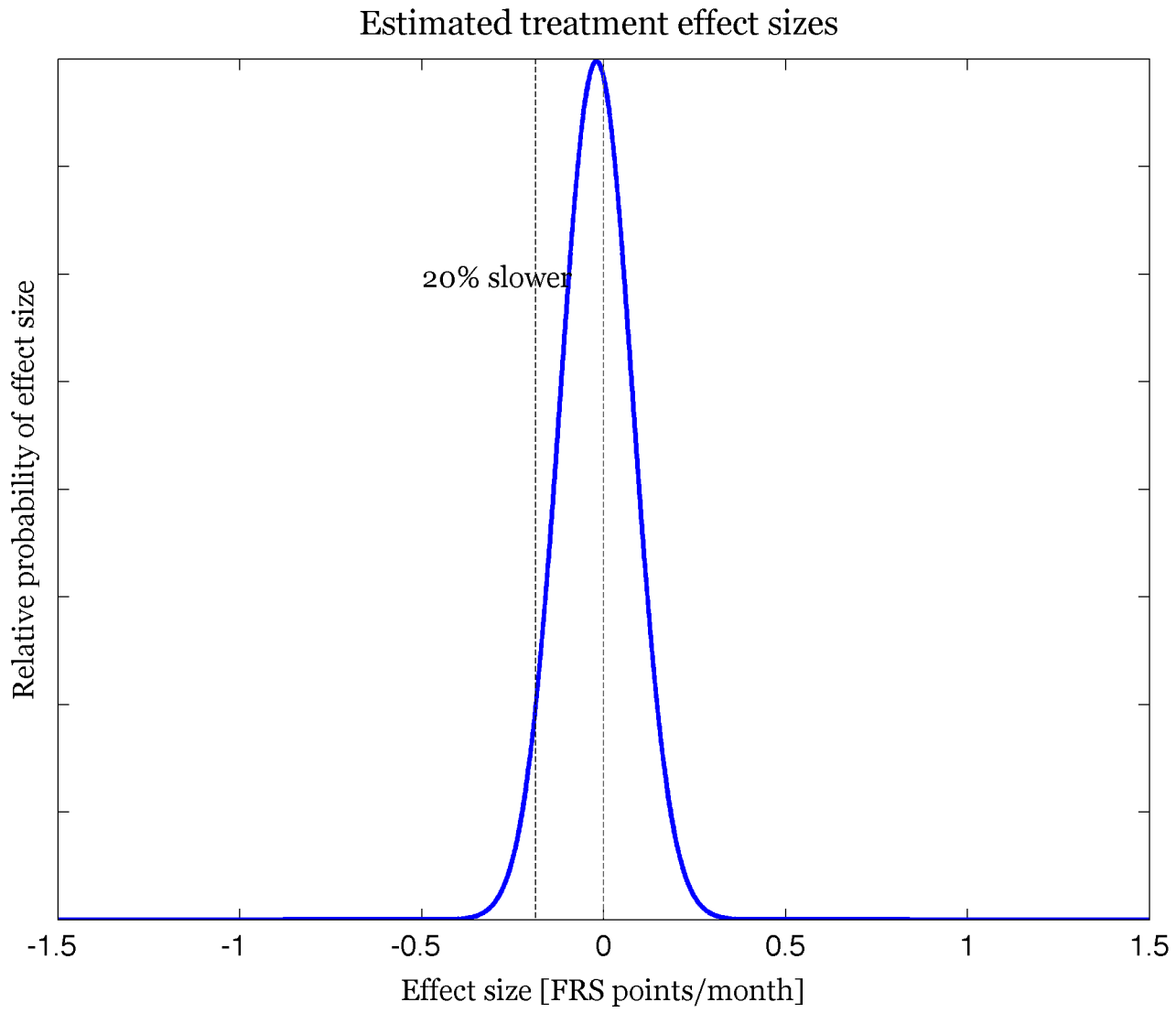
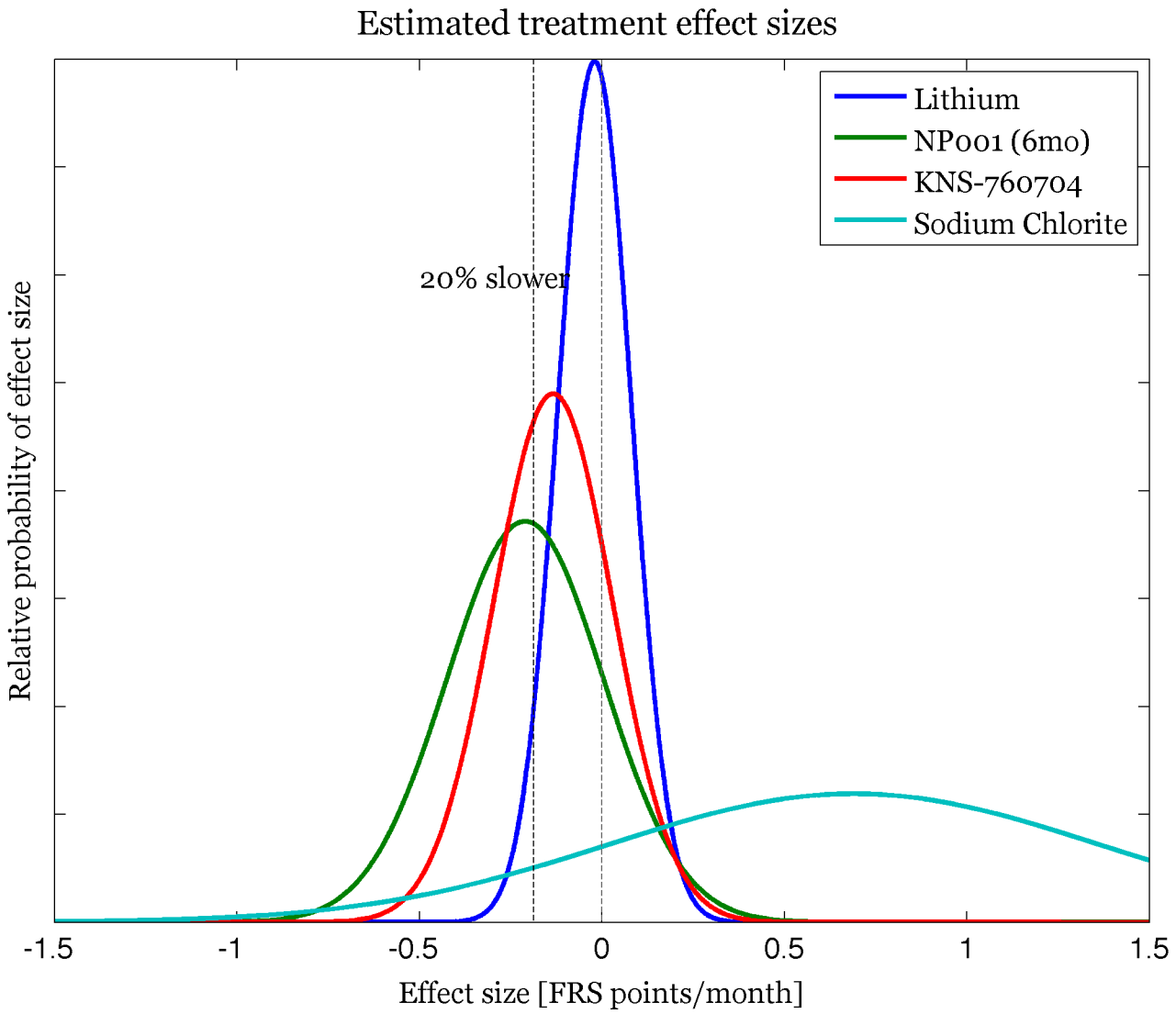


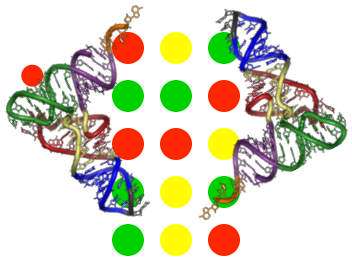
Figure 1 Conceptual overview of the online study environment and matching algorithm. (**a**) The number of patients choosing to experiment with lithium carbonate peaked in the months after publication of a small clinical trial in Italy. Preliminary negative results from this patient-led study were announced before the first randomized control trial had started recruitment. (**b**) Aggregate view of FRS scores for all 348 patients analyzed in this study. These data were publicly available online during the study. (**c**) Illustration of disease progression curves of control individuals that are good and poor matches for a particular patient. Both control individuals would be considered comparable by traditional matching criteria. The PatientsLikeMe matching algorithm minimizes the area between the disease progression curves for a target patient and a control.

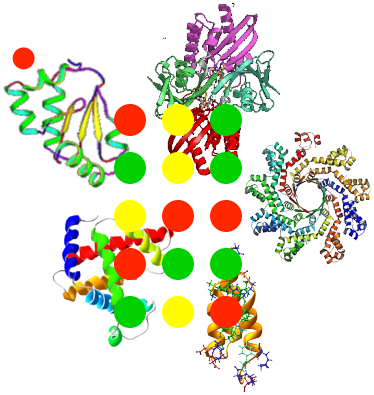

Estimated treatment effect sizes
20% slower
Relative probability of effect size
-1.5
-1
-0.5
0
0.5
1
1.5
Effect size [FRS points/month]


Estimated treatment effect sizes
Lithium
NP001 (6mo)
KNS-760704
Sodium Chlorite
20% slower
Relative probability of effect size
-1.5
-1
-0.5
0
0.5
1
1.5
Effect size [FRS points/month]

"To raise new questions, new possibilities, to regard old problems from a new angle, requires creative imagination and marks real advance in science."

Albert Einstein





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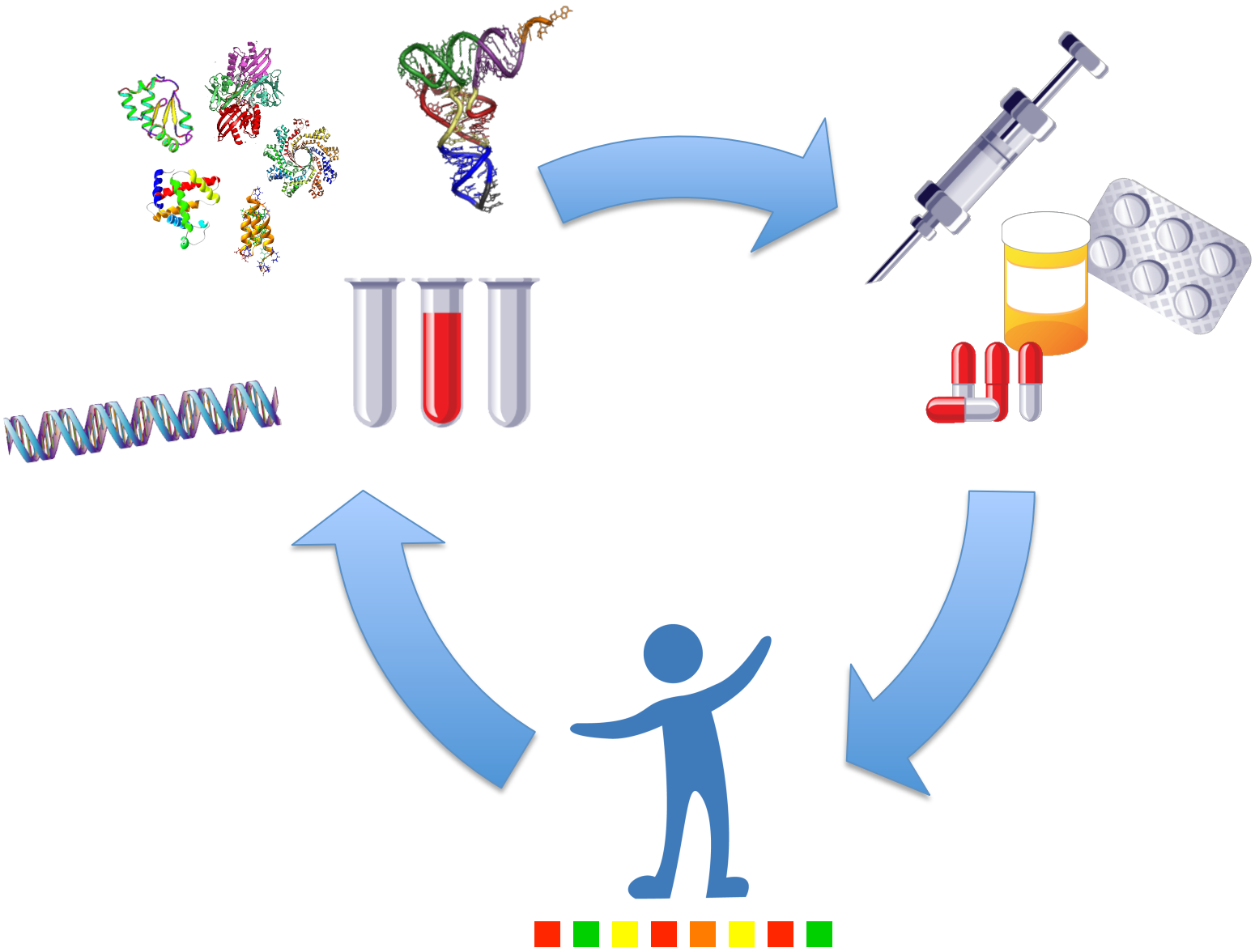

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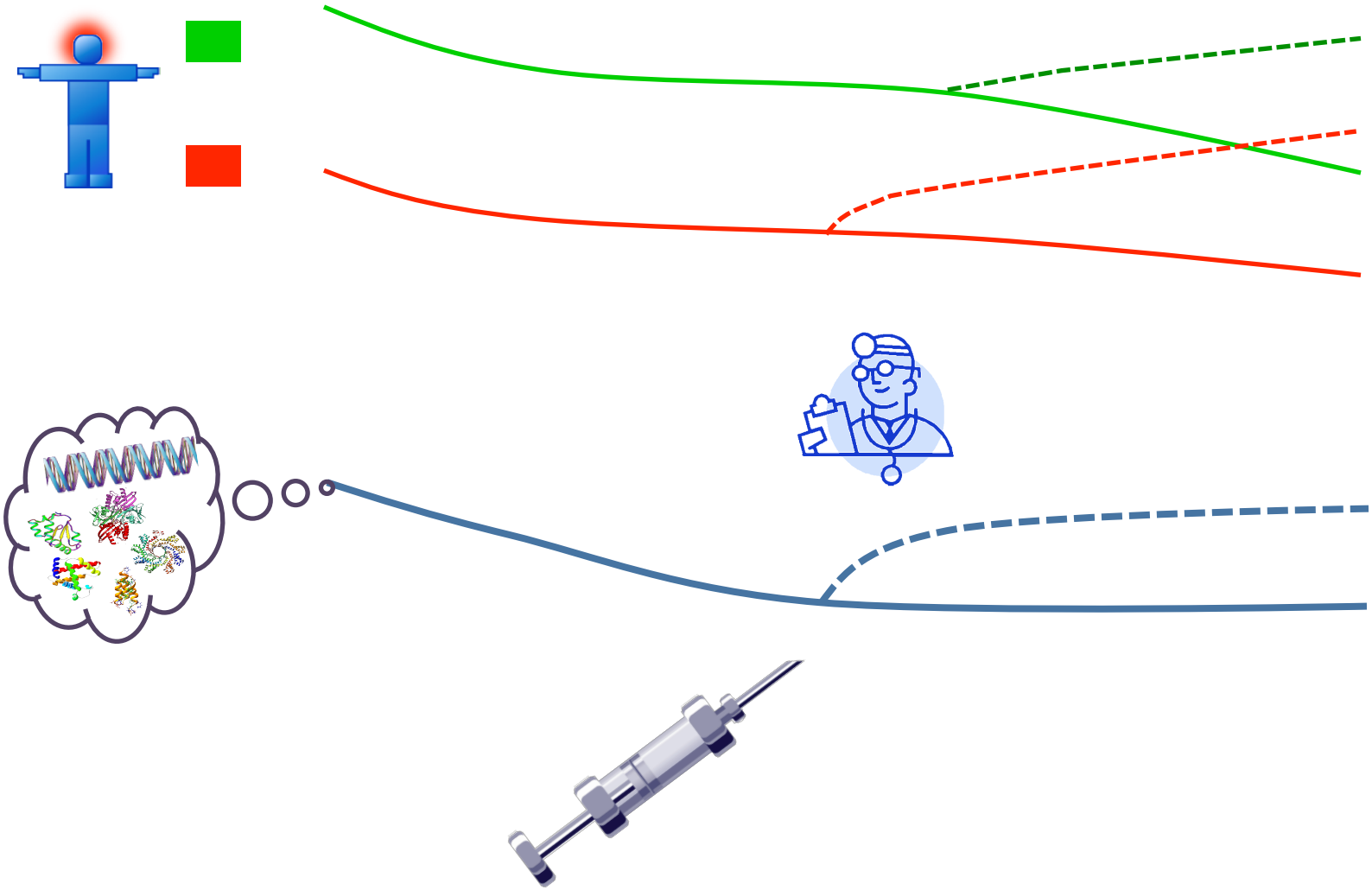

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"The future is already here —
it's just not very evenly distributed"

William Gibson

Personal Omics Profiling Reveals Dynamic Molecular and Medical Phenotypes

Cell

Rui Chen,[1,11] George I. Mias,[1,11] Jennifer Li-Pook-Than,[1,11] Lihua Jiang,[1,11] Hugo Y.K. Lam,[1,12] Rong Chen,[2,12] Elana Miriami,[1] Konrad J. Karczewski,[1] Manoj Hariharan,[1] Frederick E. Dewey,[3] Yong Cheng,[1] Michael J. Clark,[1] Hogune Im,[1] Lukas Habegger,[6,7] Suganthi Balasubramanian,[6,7] Maeve O'Huallachain,[1] Joel T. Dudley,[2] Sara Hillenmeyer,[1] Rajini Haraksingh,[1] Donald Sharon,[1] Ghia Euskirchen,[1] Phil Lacroute,[1] Keith Bettinger,[1] Alan P. Boyle,[1] Maya Kasowski,[1] Fabian Grubert,[1] Scott Seki,[2] Marco Garcia,[2] Michelle Whirl-Carrillo,[1] Mercedes Gallardo,[9,10] Maria A. Blasco,[9] Peter L. Greenberg,[4] Phyllis Snyder,[1] Teri E. Klein,[1] Russ B. Altman,[1,5] Atul J. Butte,[2] Euan A. Ashley,[3] Mark Gerstein,[6,7,8] Kari C. Nadeau,[2] Hua Tang,[1] and Michael Snyder[1,*]

[1]Department of Genetics, Stanford University School of Medicine
[2]Division of Systems Medicine and Division of Immunology and Allergy, Department of Pediatrics
[3]Center for Inherited Cardiovascular Disease, Division of Cardiovascular Medicine
[4]Division of Hematology, Department of Medicine

Measurement Based Medicine

- We should measure of the severity of each condition and its impact on the patient.

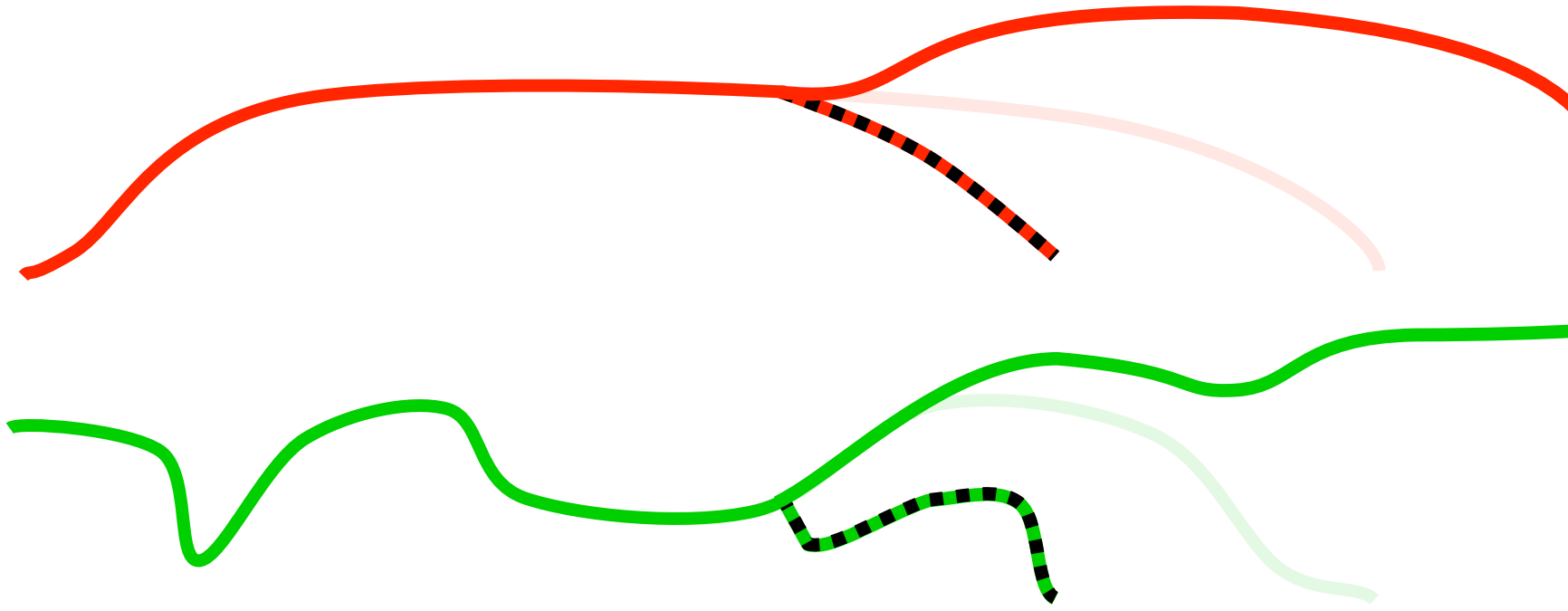
  Measures should effectively support the patient in their life choices, the clinician in their care choices, and the researcher in learning what is effective

  Measures should evolve to increasingly support the patient, clinician and researcher.

  Measures should be evaluated based on their ability to predict the patients future state with highest accuracy

  Every patient is measured as part of care to the degree that is appropriate for their condition(s) such that their experience will guide next patient.

Health



Disease