Thoughts About Rigor and Reproducibility in Extramural Research

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Disclosures: None

Two Headlines: Pre-Clinical and Clinical

PERSPECTIVE

The Economics of Reproducibility in Preclinical Research

PLOS BIOLOGY

Leonard P. Freedman[1]*, Iain M. Cockburn[2], Timothy S. Simcoe[2,3]

The NEW ENGLAND JOURNAL of MEDICINE

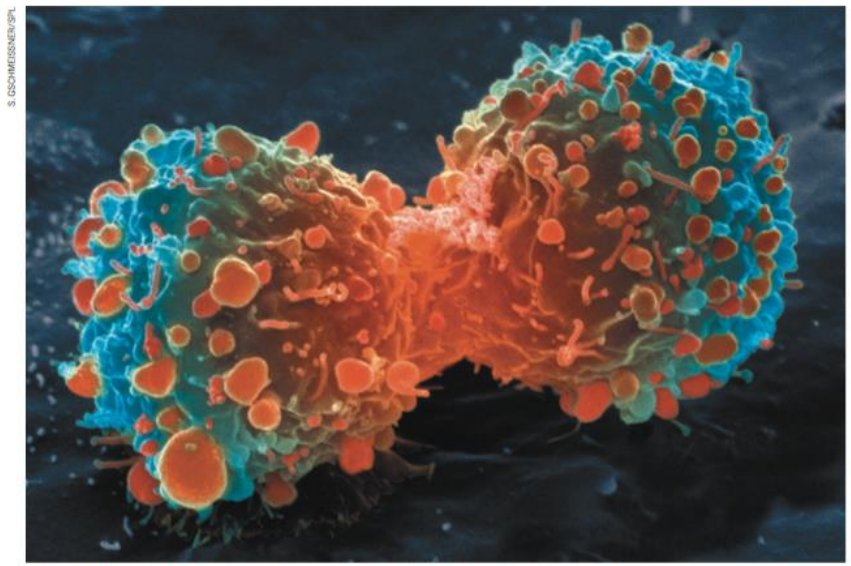
When It Comes to Trials, Do We Get What We Pay For?

P.J. Devereaux, M.D., Ph.D., and Salim Yusuf, M.B., B.S., D.Phil.

Not Just an Academic Problem …

COMMENT

AVIAN INFLUENZA Shift expertise to track mutations where they emerge p.534 | EARTH SYSTEMS Past climates give valuable clues to future warming p.537 | HISTORY OF SCIENCE Descartes' lost letter tracked using Google p.540 | OBITUARY Wylie Vale and an elusive stress hormone p.542



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 incentives must change if patients are to benefit.

"Amgen … tried to confirm published findings ... 53 papers were deemed landmark ... confirmed in only 6 cases ... This was a shocking result."

Begley CG, Ellis LM. Nature 2012;483;531-3

Categories

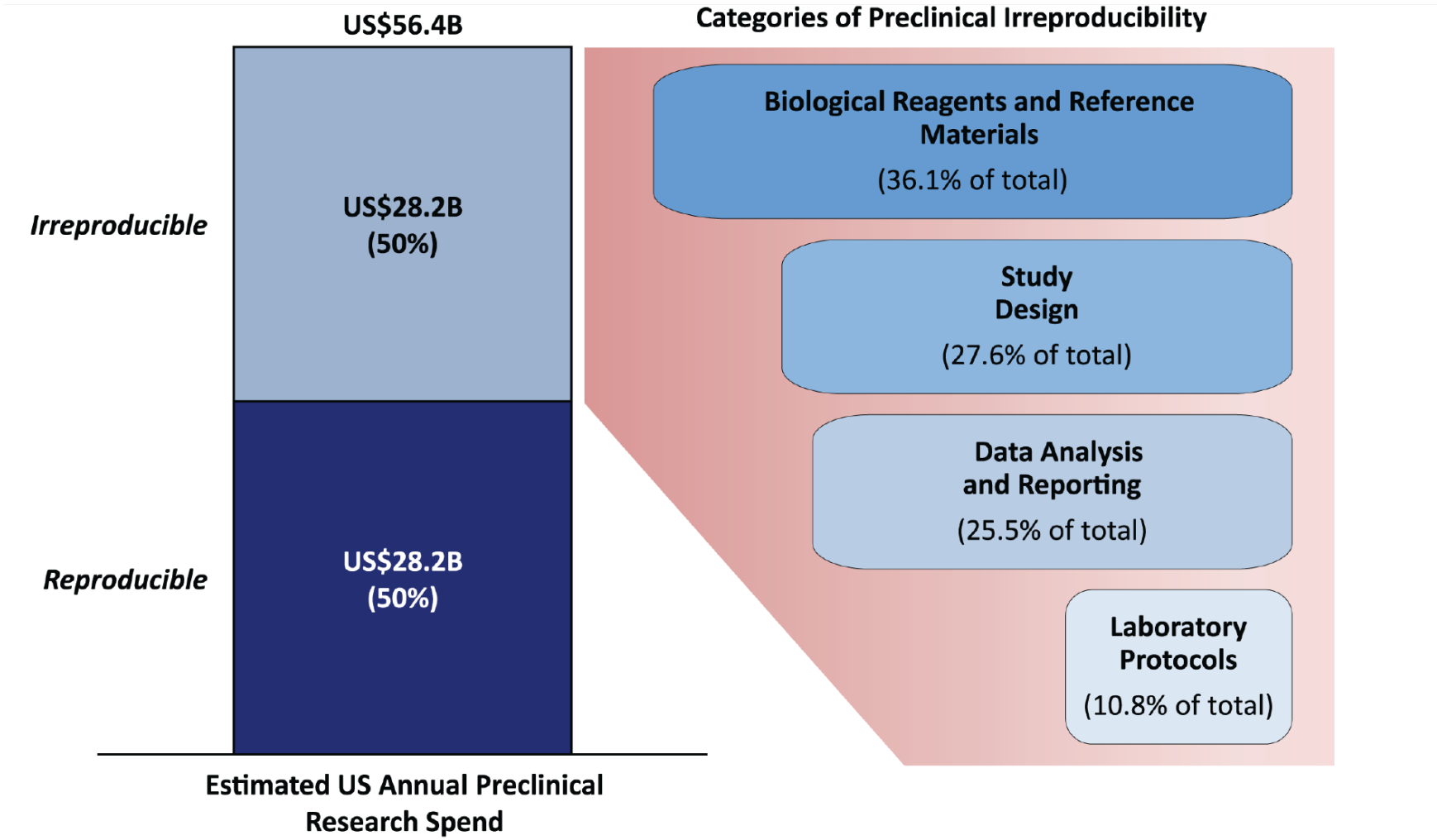


Fig 2. Estimated US preclinical research spend and categories of errors that contribute to irreproducibility. Note that the percentage value of error for each category is the midpoint of the high and low prevalence estimates for that category divided (weighted) by the sum of all midpoint error rates (see S1 Dataset). Source: Chakma et al. [18] and the American Association for the Advancement of Science (AAAS) [19].

PERSPECTIVE

doi:10.1038/nature11556

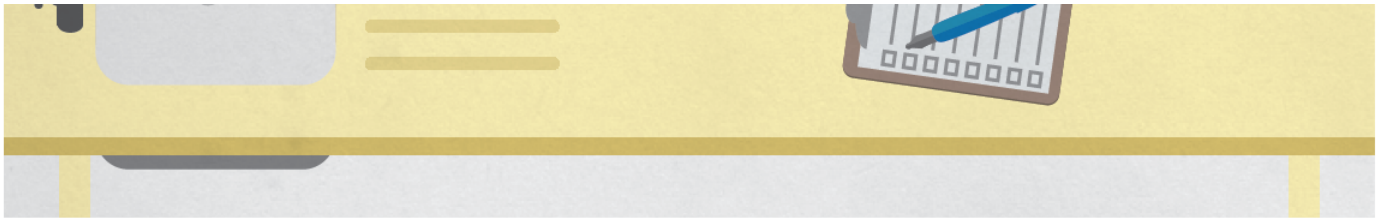
A call for transparent reporting to optimize the predictive value of preclinical research

Story C. Landis[1], Susan G. Amara[2], Khusru Asadullah[3], Chris P. Austin[4], Robi Blumenstein[5], Eileen W. Bradley[6], Ronald G. Crystal[7], Robert B. Darnell[8], Robert J. Ferrante[9], Howard Fillit[10], Robert Finkelstein[1], Marc Fisher[11], Howard E. Gendelman[12], Robert M. Golub[13], John L. Goudreau[14], Robert A. Gross[15], Amelie K. Gubitz[1], Sharon E. Hesterlee[16], David W. Howells[17], John Huguenard[18], Katrina Kelner[19], Walter Koroshetz[1], Dimitri Krainc[20], Stanley E. Lazic[21], Michael S. Levine[22], Malcolm R. Macleod[23], John M. McCall[24], Richard T. Moxley III[25], Kalyani Narasimhan[26], Linda J. Noble[27], Steve Perrin[28], John D. Porter[1], Oswald Steward[29], Ellis Unger[30], Ursula Utz[1] & Shai D. Silberberg[1]

- Randomization and blinding
- Sample size and data handling

Landis SC et al. Nature 2012;490:187-191

NIH Plans



NIH plans to enhance reproducibility

Francis S. Collins and **Lawrence A. Tabak** discuss initiatives that the US National Institutes of Health is exploring to restore the self-correcting nature of preclinical research.

"Efforts by the NIH alone will not be sufficient to effect real change in this unhealthy environment."

Nature 2014;505:612-13

Not Alone …

OPEN ACCESS Freely available online

PLoS BIOLOGY

Perspective

Improving Bioscience Research Reporting: The ARRIVE Guidelines for Reporting Animal Research

Carol Kilkenny[1]*, William J. Browne[2], Innes C. Cuthill[3], Michael Emerson[4], Douglas G. Altman[5]

1 The National Centre for the Replacement, Refinement and Reduction of Animals in Research, London, United Kingdom, 2 School of Veterinary Science, University of Bristol, Bristol, United Kingdom, 3 School of Biological Sciences, University of Bristol, Bristol, United Kingdom, 4 National Heart and Lung Institute, Imperial College London, United Kingdom, 5 Centre for Statistics in Medicine, University of Oxford, Oxford, United Kingdom

"Study design": Numbers, reduce bias, unit of study
"Sample size": Numbers, calculations, replications
"Statistical methods": Unit of analysis, assumptions

PLoS Biology. 2010;8: e1000412

Some Steps We're Taking

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Open Mike

Helping connect you with the NIH perspective, and helping connect us with yours

Updates on Addressing Rigor in Your NIH Applications

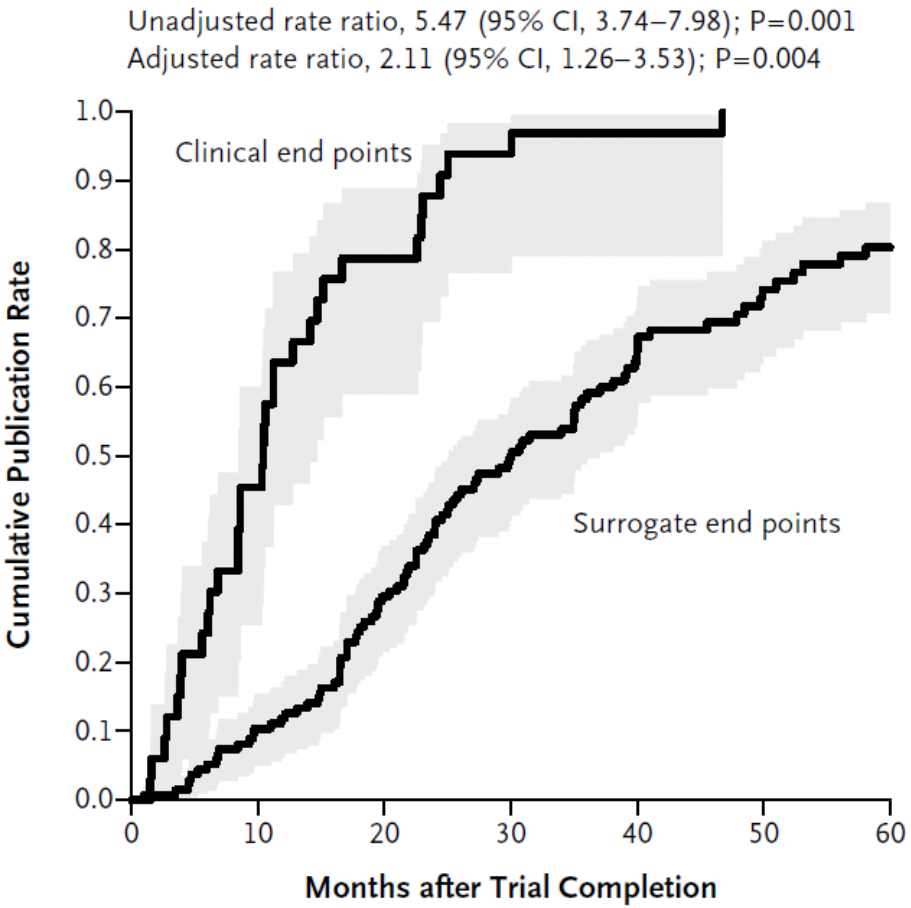
Posted on **January 11, 2016** by **Mike Lauer**

As NIH moves ahead with implementing measures to enhance rigor, transparency and reproducibility in NIH-supported research, I'd like to give a brief update on these efforts, and highlight some important timeline changes for implementation in applications for institutional training grants (T), institutional career development awards (K12), and individual fellowships (F). …. Continue reading →

Dr. Michael Lauer is NIH's Deputy Director for Extramural Research, serving as the principal scientific leader and advisor to the NIH Director on the NIH extramural research program.

http://nexus.od.nih.gov/all/category/open-mike/

Clinical Research: Our Experience



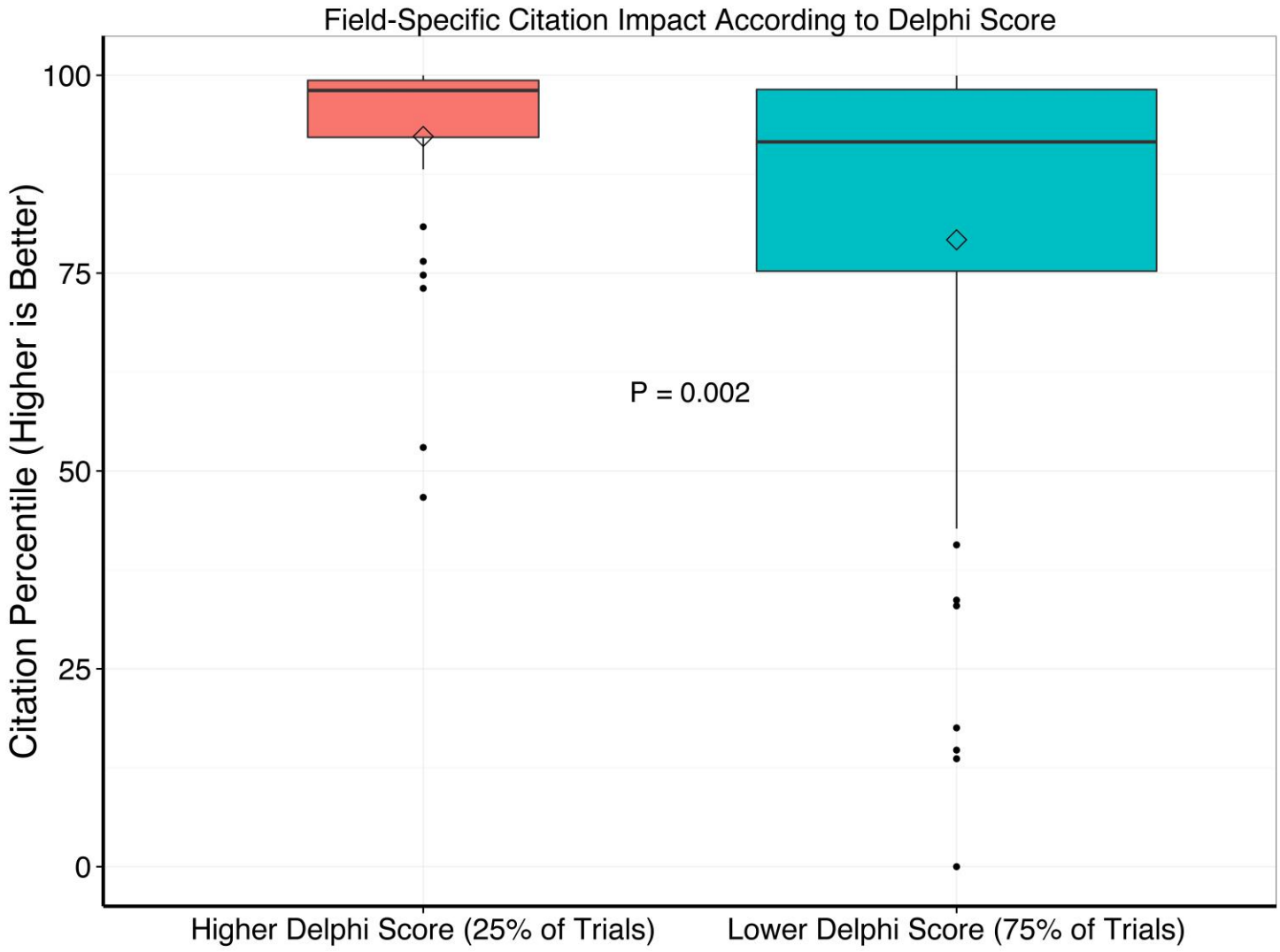
No. at Risk

Surrogate end points	199	158	110	67	40	24	16
Clinical end points	45	22	7	2	1	0	0

National Institutes of Health
Office of Extramural Research

Gordon D, Lauer M et al. N Engl J Med 2013;369:1926-34

Link to Design Flaws



Gordon D, Cooper-Arnold K, Lauer M. JAHA 2015;4:e002292

Flaws are Everywhere

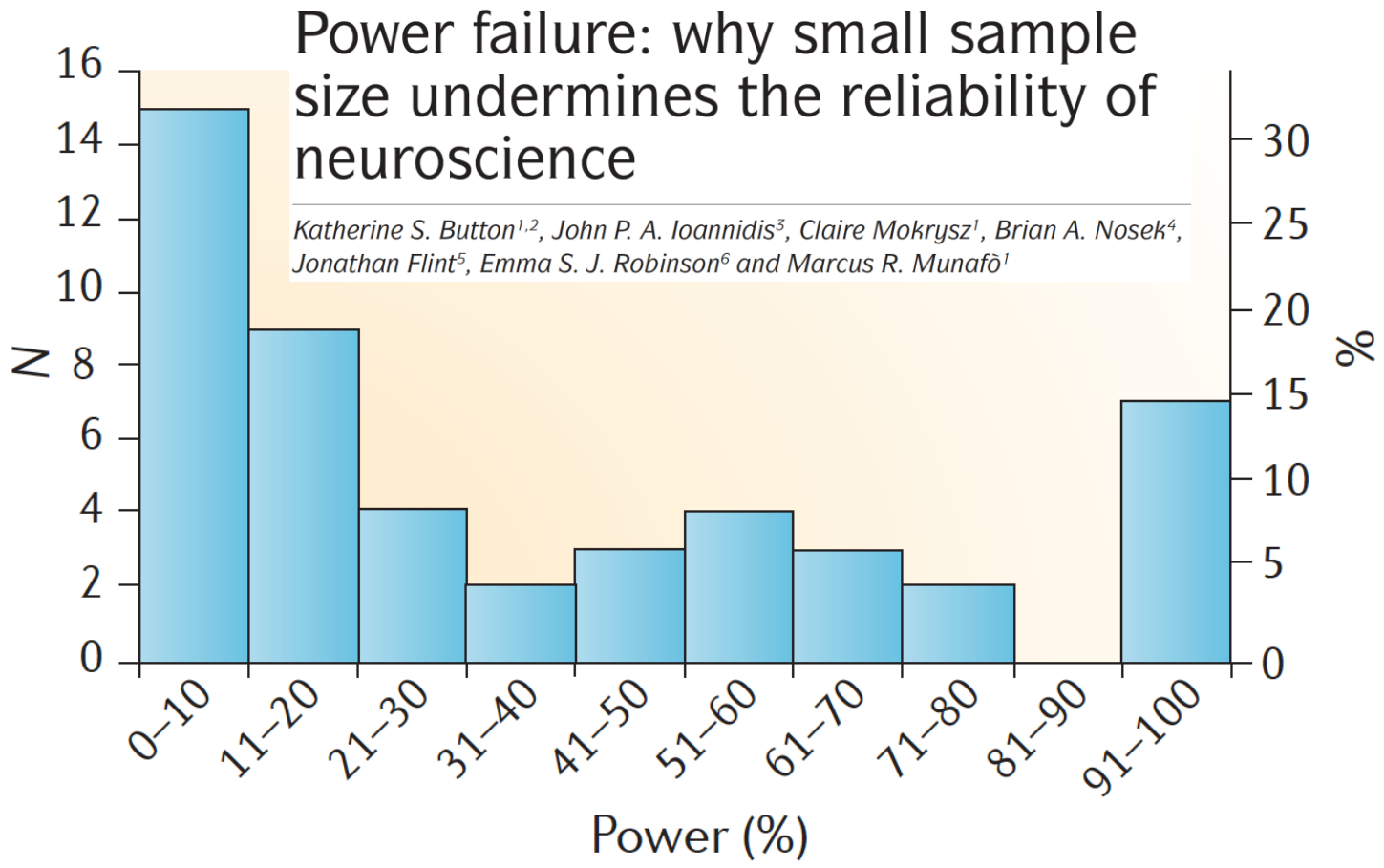


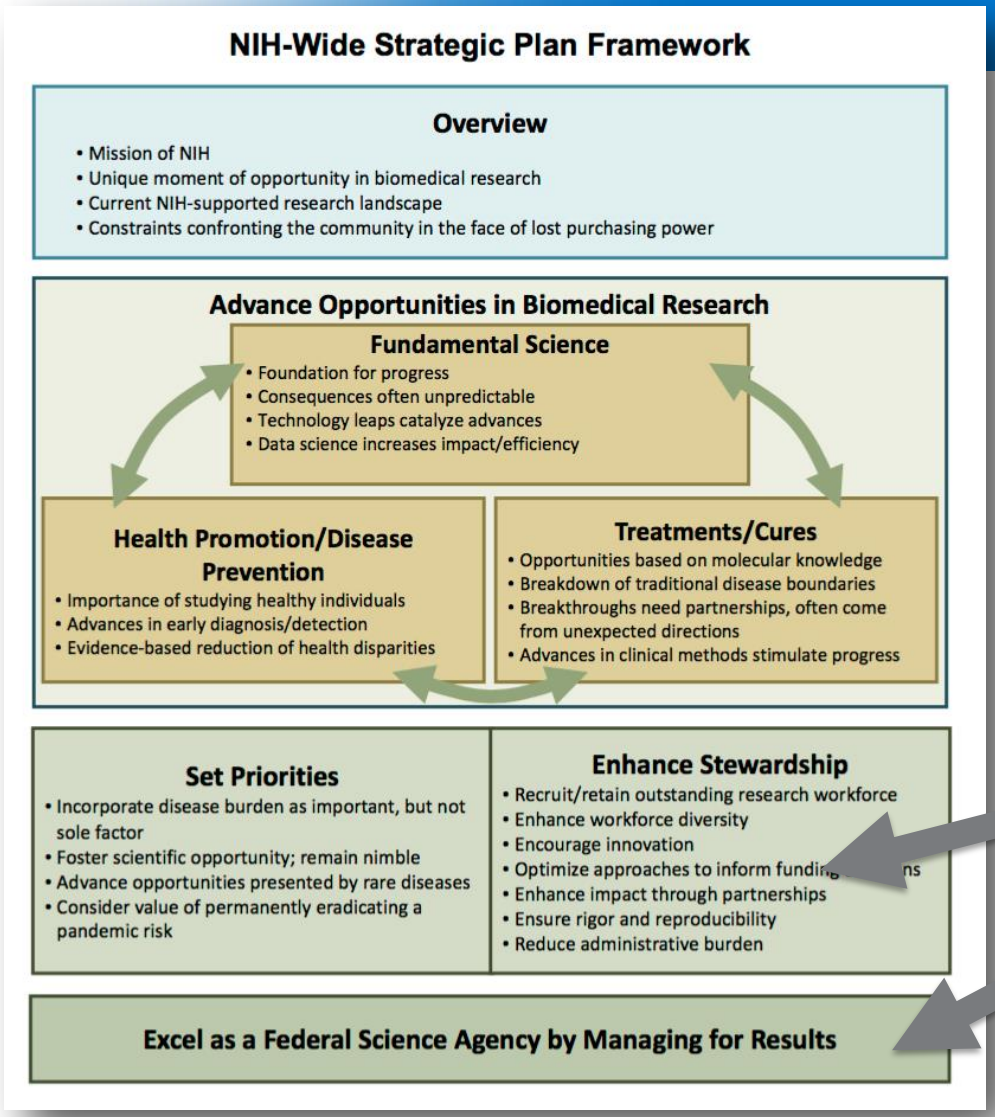
Figure 3 | **Median power of studies included in neuroscience meta-analyses.** The figure shows a

Nature Reviews Neuroscience. 2013;14:365-376

Steps in the Clinical Sphere …

Mullard A. Nature Reviews Drug Discovery. 2016;15:297-8

NIH Strategies



- Science of science
- Outputs, outcomes
- Workforce analyses
- Review peer review
- **Rigor, reproducibility**
- Administrative burden
- Risk management

http://www.nih.gov/sites/default/files/about-nih/strategic-plan-fy2016-2020-508.pdf