

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



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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.



National Institutes of Health
Office of Extramural Research

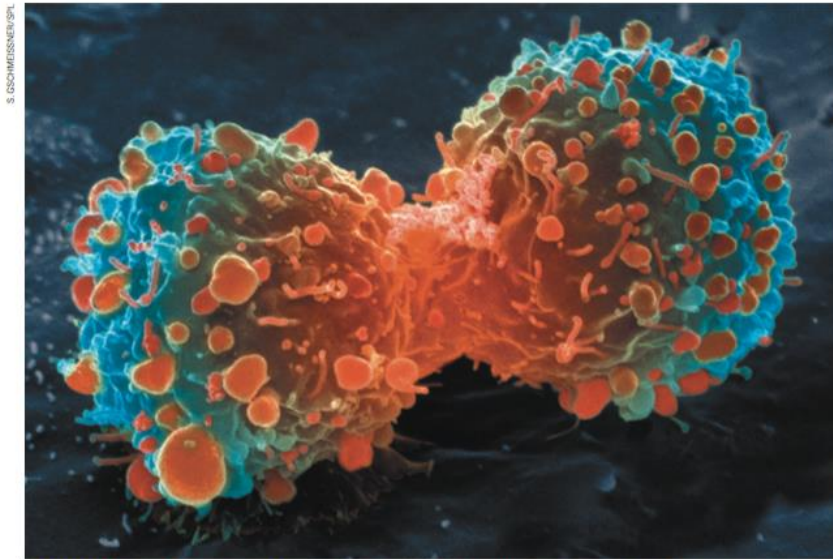
COMMENT

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**



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



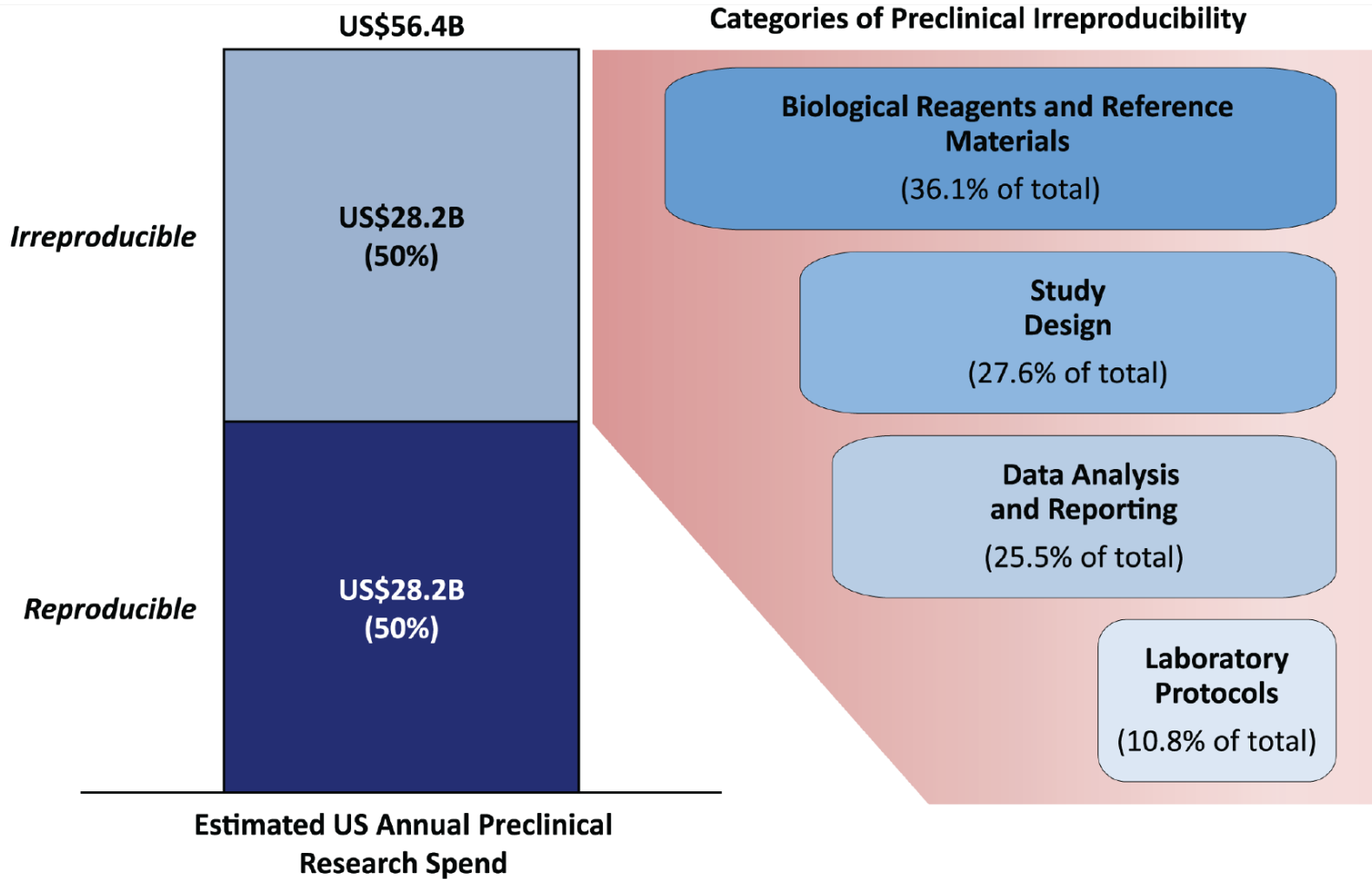


Fig 2. Estimated US preclinical research spend and categories of errors that contribute to irreproducibility. Note that the percentage value of error for each category is the midpoint of the high and low prevalence estimates for that category divided (weighted) by the sum of all midpoint error rates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

PERSPECTIVE

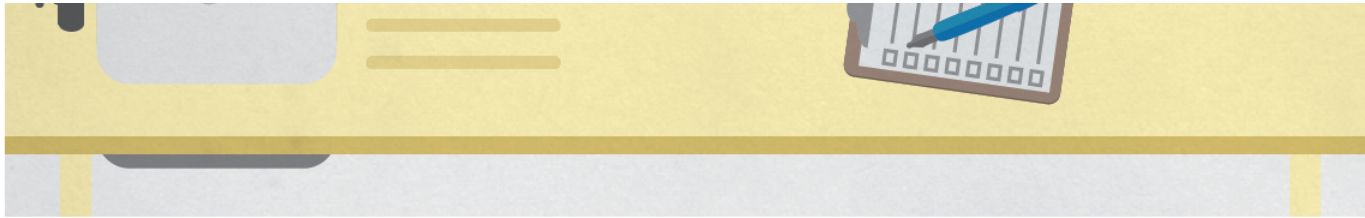
doi:10.1038/nature11556

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

Story C. Landis¹, Susan G. Amara², Khusru Asadullah³, Chris P. Austin⁴, Robi Blumenstein⁵, Eileen W. Bradley⁶, Ronald G. Crystal⁷, Robert B. Darnell⁸, Robert J. Ferrante⁹, Howard Fillit¹⁰, Robert Finkelstein¹, Marc Fisher¹¹, Howard E. Gendelman¹², Robert M. Golub¹³, John L. Goudreau¹⁴, Robert A. Gross¹⁵, Amelie K. Gubitzi¹, Sharon E. Hesterlee¹⁶, David W. Howells¹⁷, John Huguenard¹⁸, Katrina Kelner¹⁹, Walter Koroshetz¹, Dimitri Krainc²⁰, Stanley E. Lazic²¹, Michael S. Levine²², Malcolm R. Macleod²³, John M. McCall²⁴, Richard T. Moxley III²⁵, Kalyani Narasimhan²⁶, Linda J. Noble²⁷, Steve Perrin²⁸, John D. Porter¹, Oswald Steward²⁹, Ellis Unger³⁰, Ursula Utz¹ & Shai D. Silberberg¹

- Randomization and blinding
- Sample size and data handling

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



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

Perspective

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

Carol Kilkenny^{1*}, William J. Browne², Innes C. Cuthill³, Michael Emerson⁴, Douglas G. Altman⁵

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

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](#) →

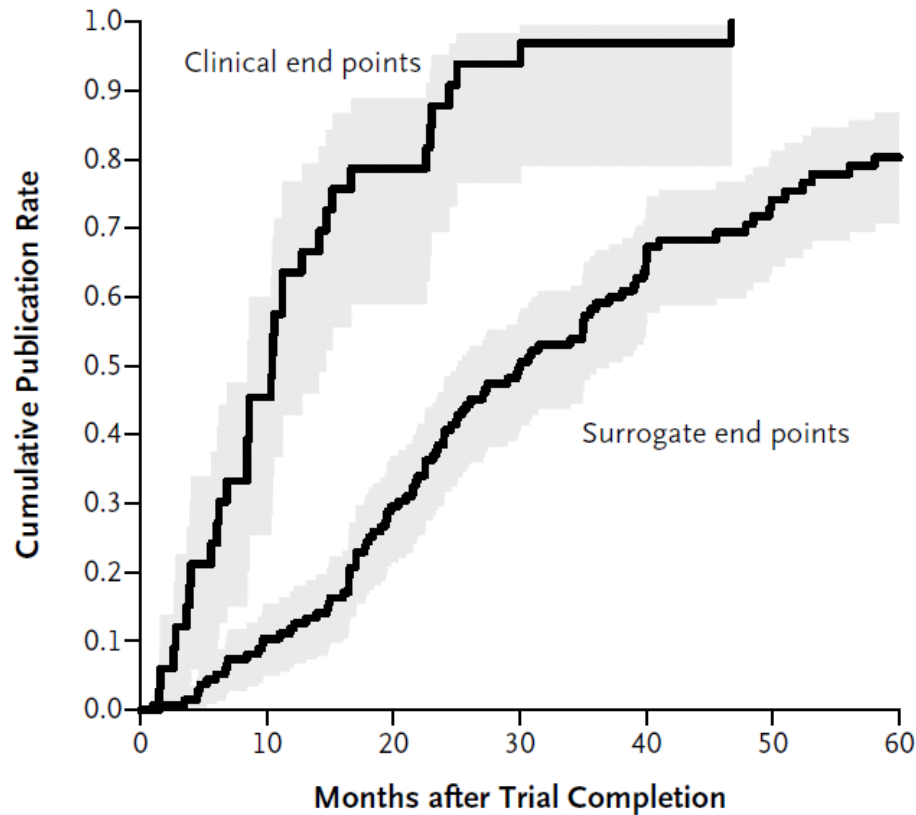


Dr. Michael Lauer is NIH's Deputy Director for Extramural Research, serving as the principal scientific leader and advisor to the NIH Director on the NIH extramural research program.



Clinical Research: Our Experience

Unadjusted rate ratio, 5.47 (95% CI, 3.74–7.98); P=0.001
 Adjusted rate ratio, 2.11 (95% CI, 1.26–3.53); P=0.004

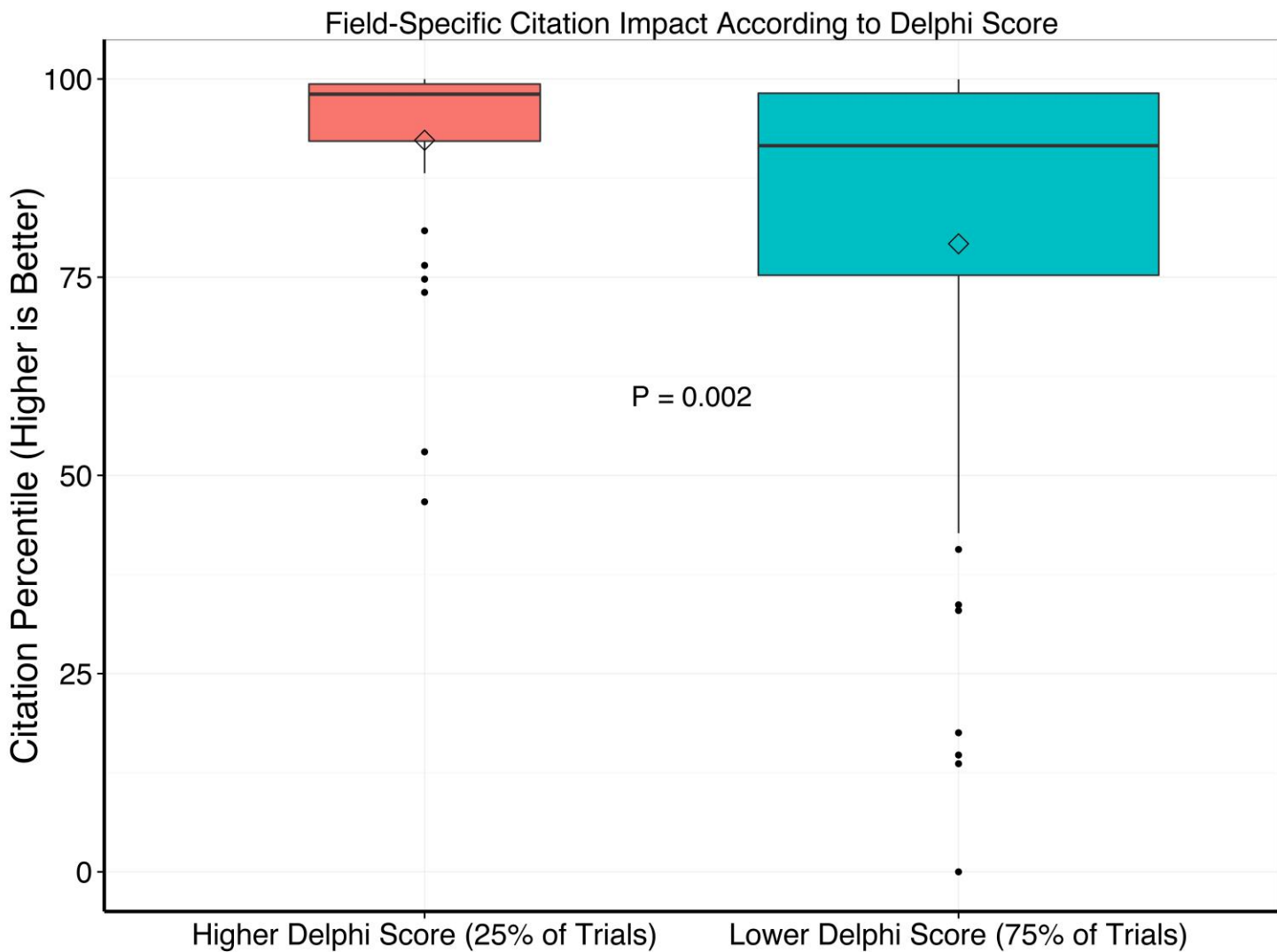


No. at Risk

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



Link to Design Flaws



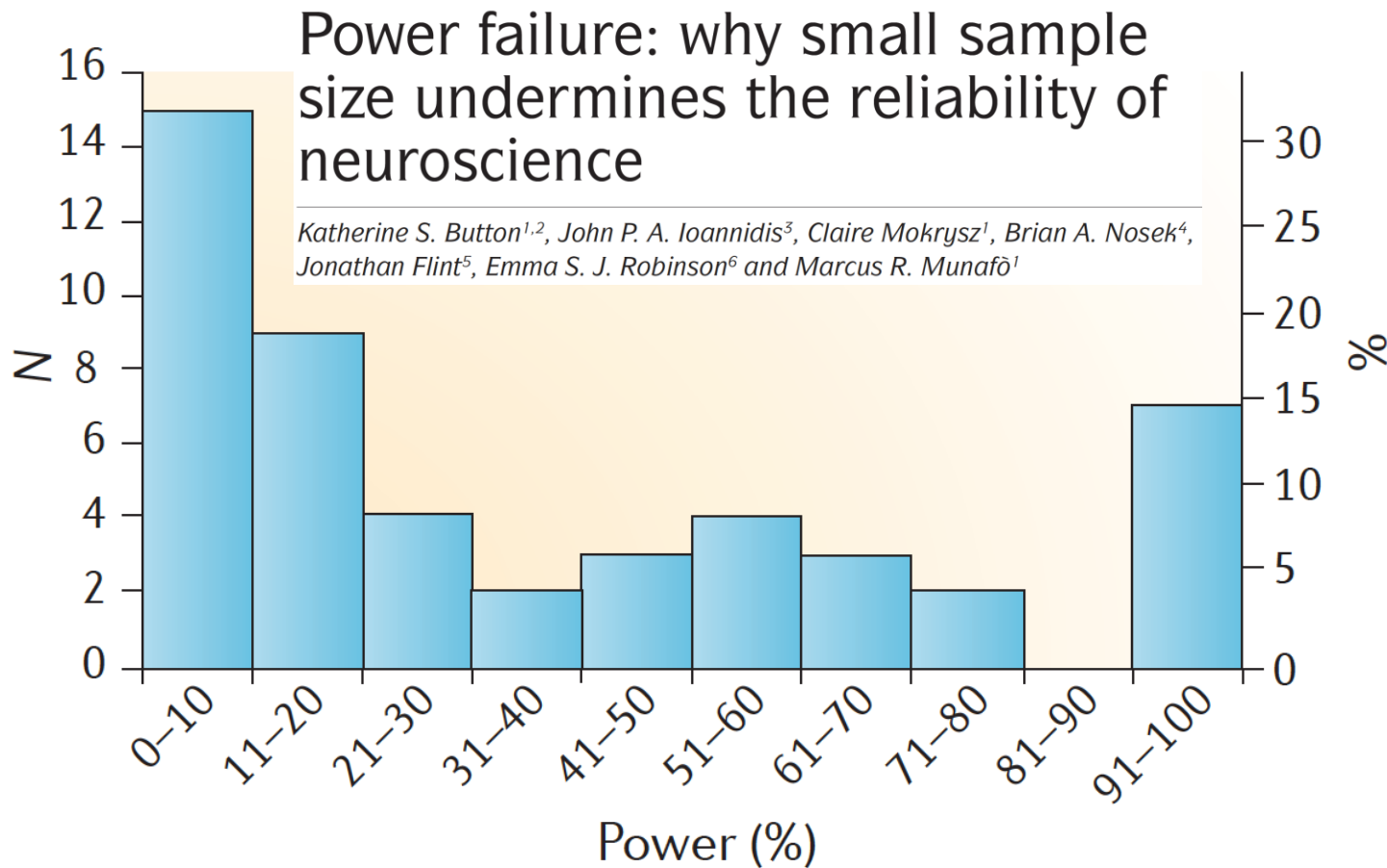


Figure 3 | **Median power of studies included in neuroscience meta-analyses.** The figure shows a

Steps in the Clinical Sphere ...



NEWS & ANALYSIS

NIH tackles clinical trial shortcomings

The NIH is developing new tools, and overhauling its clinical trial funding system, to improve the stewardship of NIH-funded clinical trials



NIH-Wide Strategic Plan Framework

Overview

- Mission of NIH
- Unique moment of opportunity in biomedical research
- Current NIH-supported research landscape
- Constraints confronting the community in the face of lost purchasing power

Advance Opportunities in Biomedical Research

Fundamental Science

- Foundation for progress
- Consequences often unpredictable
- Technology leaps catalyze advances
- Data science increases impact/efficiency

Health Promotion/Disease Prevention

- Importance of studying healthy individuals
- Advances in early diagnosis/detection
- Evidence-based reduction of health disparities

Treatments/Cures

- Opportunities based on molecular knowledge
- Breakdown of traditional disease boundaries
- Breakthroughs need partnerships, often come from unexpected directions
- Advances in clinical methods stimulate progress

Set Priorities

- Incorporate disease burden as important, but not sole factor
- Foster scientific opportunity; remain nimble
- Advance opportunities presented by rare diseases
- Consider value of permanently eradicating a pandemic risk

Enhance Stewardship

- Recruit/retain outstanding research workforce
- Enhance workforce diversity
- Encourage innovation
- Optimize approaches to inform funding decisions
- Enhance impact through partnerships
- Ensure rigor and reproducibility
- Reduce administrative burden

Excel as a Federal Science Agency by Managing for Results

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

