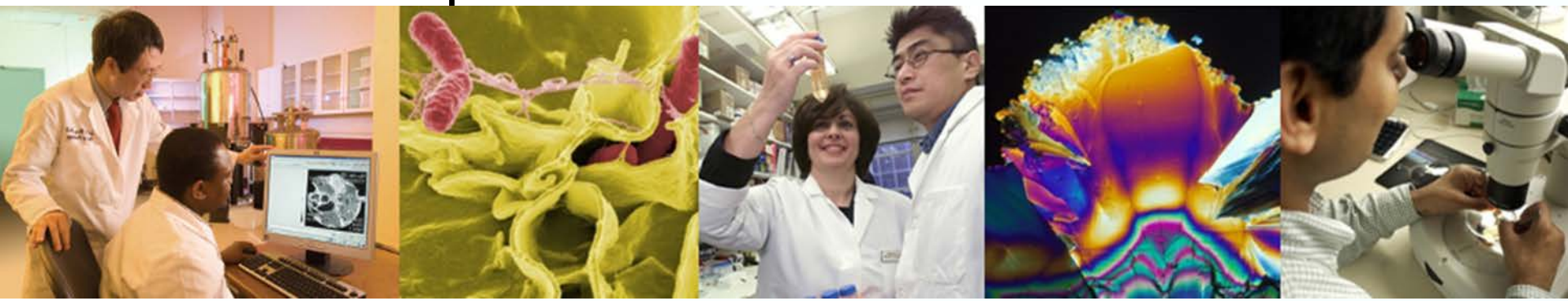
Enhancing Reproducibility and Transparency of Research Findings
Update on Activities and IC Pilots

Council of Councils
September 5, 2014

James M. Anderson, MD, PhD
Director, DPCPSI
Office of the Director, NIH
Department of Health and Human Services



COMMENT

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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.

A growing chorus of concern, from scientists and laypeople, contends that the complex system for ensuring the reproducibility of biomedical research is failing and is in need of restructuring[1,2]. As leaders of the US National Institutes of Health (NIH), we share this concern and here explore some of the significant interventions that we are planning.

Science has long been regarded as 'self-correcting', given that it is founded on the replication of prior work. Over the long term, that principle remains true. In the shorter term, h
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"Efforts by the NIH alone will not be sufficient to effect real change in this unhealthy environment."

Feedback on Commentary

- Range of respondents: Investigators, reagent suppliers, professional associations, industry
- Reaction mostly supportive
- Ideas/materials shared:
  - Dedicated funding for replication studies
  - Additional literature on reproducibility issues (books, publications)

Trans-NIH Actions
Stakeholder Engagement

- June 2 workshop with Journal Editors to identify common opportunity areas
  - Attendees discussed and agreed on a set of principles and guidelines that journals can adopt to improve the transparency and reproducibility of published work.
  - Principles and guidelines are being reviewed by the journal boards for final approval. The involved organizations will share the principles and guidelines when they have been finalized.

Trans-NIH Actions
Stakeholder Engagement

- Recent workshop with Journal Editors to identify common opportunity areas
- Planning a workshop with PhRMA to identify areas of common interest with industry
- Envisioning a workshop with Academia
- Envisioning a workshop with reagent suppliers

Trans-NIH Actions
Stakeholder Engagement

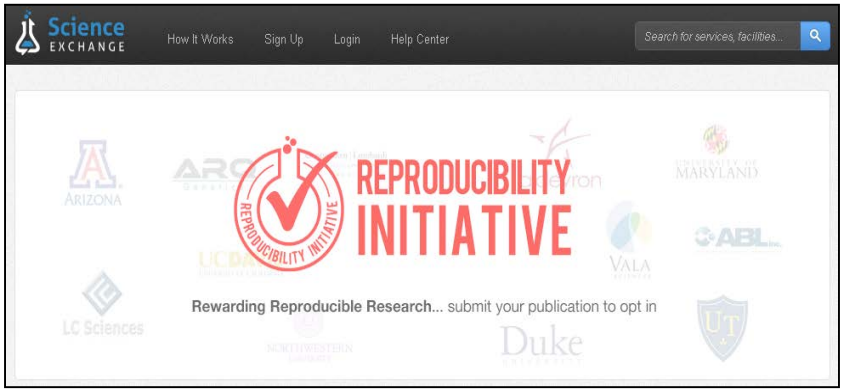
Meetings with/Presentations to:

- Virginia Commonwealth University – September 22nd, 2014
- Society for Neuroscience (SfN) – November 2014, led by NINDS
- Life Sciences Subcommittee of Committee on Science – May 28th, 2014
- Clinical Research Forum and Association for Clinical and Translational Sciences (ACTS) – joint meeting in April 2014
- American Society for Pharmacology & Experimental Therapeutics (ASPET) – April 2014
- Coalition for the Life Sciences (CLS) – March 2014
- Health Research Alliance (HRA) – January 2014
- Consortium of Social Science Associations (COSSA) – November 2013

Stakeholder Engagement: Workshops

- Evaluating options to effectively convene multiple stakeholder groups
- Possible workshop including journal editors, professional societies, and funders (public and private)
  - In discussions with Nature and Science regarding options
- Envisioning separate workshops for industry and for reagent suppliers
  - Engaging with industry to explore options for a workshop
  - Establishing communication with suppliers (e.g., Sigma Aldrich)

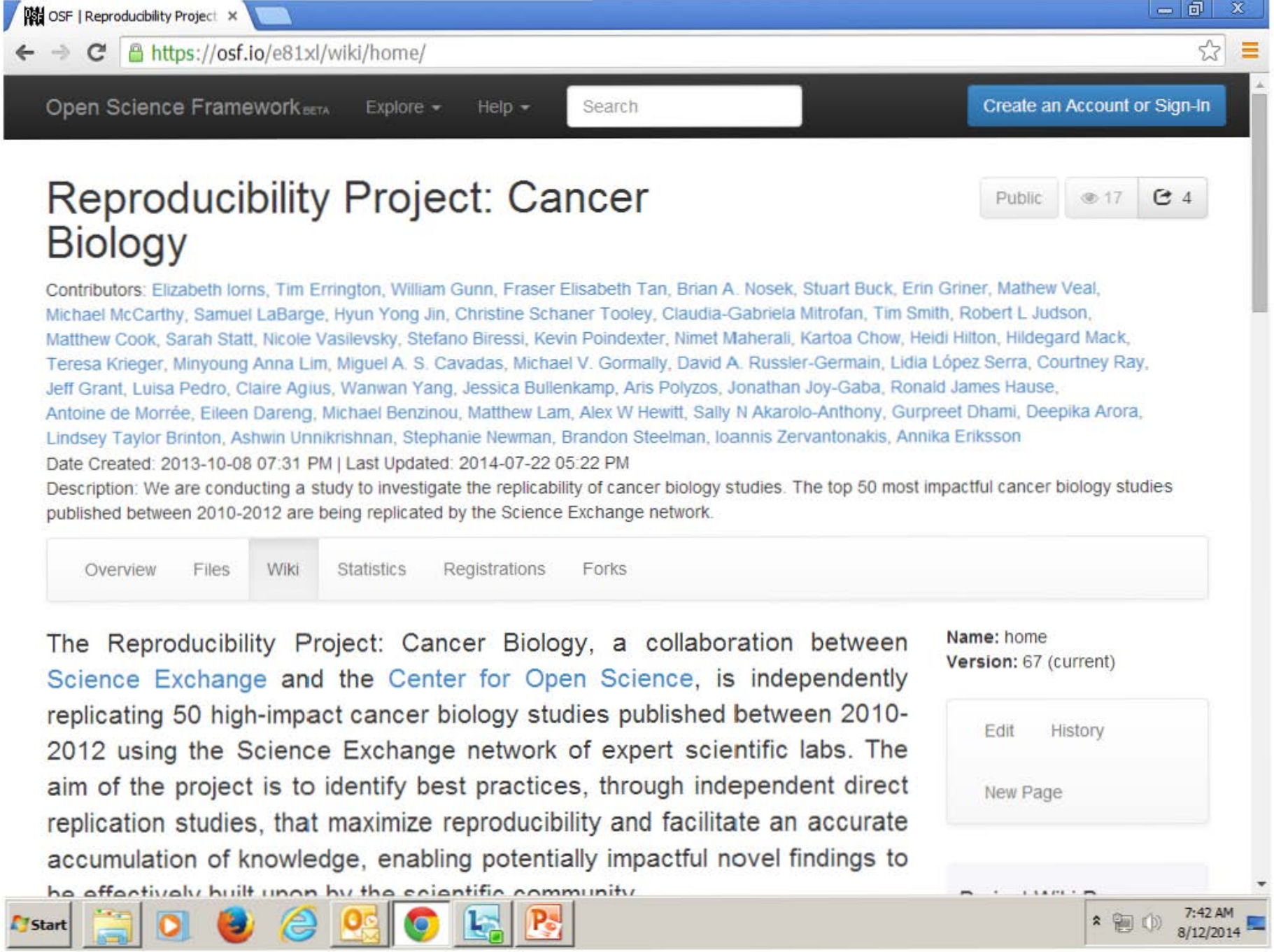
Extramural Research Community



- Collaboration by ScienceExchange, Mendeley, figshare, and PLOS, offers to validate findings through independent replicationhttp://validation.scienceexchange.com/#/

- Center for Open Science (COS), dedicated to improving alignment between scientific values and scientific practices to improve the accumulation and application of knowledge

  - COS also supports the Open Science Framework (OSF), a free web application that supports documentation, archiving, registration, and collaboration, i.e., a “virtual” lab notebook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Contributors: Elizabeth Iorns, Tim Errington, William Gunn, Fraser Elisabeth Tan, Brian A. Nosek, Stuart Buck, Erin Griner, Mathew Veal, Michael McCarthy, Samuel LaBarge, Hyun Yong Jin, Christine Schaner Tooley, Claudia-Gabriela Mitrofan, Tim Smith, Robert L Judson, Matthew Cook, Sarah Statt, Nicole Vasilevsky, Stefano Biressi, Kevin Poindexter, Nimet Maherali, Kartoa Chow, Heidi Hilton, Hildegard Mack, Teresa Krieger, Minyoung Anna Lim, Miguel A. S. Cavadas, Michael V. Gormally, David A. Russler-Germain, Lidia López Serra, Courtney Ray, Jeff Grant, Luisa Pedro, Claire Agius, Wanwan Yang, Jessica Bullenkamp, Aris Polyzos, Jonathan Joy-Gaba, Ronald James Hause, Antoine de Morrée, Eileen Dareng, Michael Benzinou, Matthew Lam, Alex W Hewitt, Sally N Akarolo-Anthony, Gurpreet Dhami, Deepika Arora, Lindsey Taylor Brinton, Ashwin Unnikrishnan, Stephanie Newman, Brandon Steelman, Ioannis Zervantonakis, Annika Eriksson
Date Created: 2013-10-08 07:31 PM | Last Updated: 2014-07-22 05:22 PM
Description: We are conducting a study to investigate the replicability of cancer biology studies. The top 50 most impactful cancer biology studies published between 2010-2012 are being replicated by the Science Exchange network.
Overview
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The Reproducibility Project: Cancer Biology, a collaboration between Science Exchange and the Center for Open Science, is independently replicating 50 high-impact cancer biology studies published between 2010-2012 using the Science Exchange network of expert scientific labs. The aim of the project is to identify best practices, through independent direct replication studies, that maximize reproducibility and facilitate an accurate accumulation of knowledge, enabling potentially impactful novel findings to
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Stakeholder Engagement: Examples of Extramural Players

Meetings with:

- Brian Nosek and Center for Open Science (COS)
  - Hosts the Open Science Framework (OSF), which provides options for a virtual lab notebook
- Elizabeth Iorns and the Reproducibility Initiative
  - Currently funded to validate 50 landmark cancer biology studies
  - Collaboration of COS, ScienceExchange, Mendeley
- Len Freedman and the Global Biological Standards Institute
  - Recently released a white paper on the case for biological standards
- ICs also in conversations with extramural players

Development of Training Resources

- NINDS working with IRP on training module in experimental design
  - Basic module expected to be road-tested with IRP staff (trainees, fellows, and faculty) by summer of 2014
  - Film version expected to be completed by end of 2014
- IRP working on TEDMED-like talks on data interpretation considerations for various experimental techniques
  - Talks expected to begin in summer of 2014
- Potential NIH course/resources on experimental design; could be done through FAES and adapted for online use
  - Options being explored for implementation by end of 2014

IC Pilot Summary

Pilot Focus	Types of Efforts Being Developed
Evaluation of scientific premise/grant applications	New FOAs with additional review criteria regarding scientific premise
Checklist/Reporting Guidelines	Reviewer checklists regarding reporting standards/scientific rigor
Changes to Biosketch	Biosketch pilot coordinated by the Office of Extramural Research
Approaches to reduce "perverse incentives"	Exploring award options with a longer period of support for investigators
Supporting replication studies	New FOAs or collaborations for replication studies, and exploring options to assess (at the time of application) whether pre-clinical findings should be replicated
Training	Developing materials for the new training module on research integrity
Other efforts	PubMed Commons Pilot system, use of prize challenges to encourage reproducibility of results

Considerations for Implementation/Evaluation of Pilots

- Importance of rigorous metrics and measures to evaluate pilots
- Leveraging existing efforts and expertise:
  - KOMP^2: Knockout Mouse Production and Phenotyping – add IC-specific interventions?
  - NIDDK: Mouse Metabolic Phenotyping Centers - provide scientific community with high quality, standardized phenotyping services
  - NIAID: ImmPort and TrialShare – provide access to clinical trials data
  - NIA Interventions Testing Program Studies – multi-site replication of preclinical studies
  - BD2K initiatives in providing access to data
  - PubMed Commons
- What could work NIH-wide vs. what is best kept IC-specific?

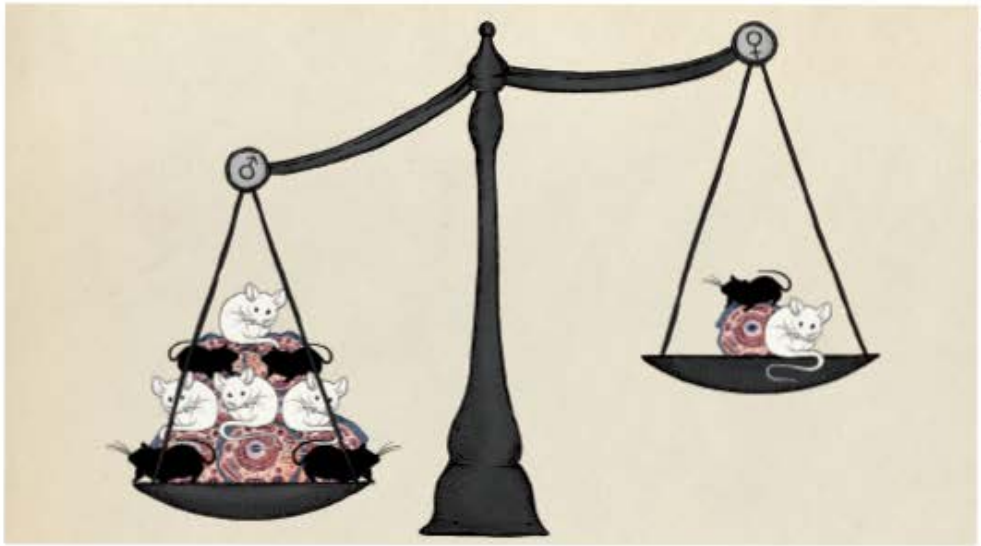

ILLUSTRATION: KATE SCOTT

NIH to balance sex in cell and animal studies

Janine A. Clayton and **Francis S. Collins** unveil policies to ensure that preclinical research funded by the US National Institutes of Health considers females and males.

More than two decades ago, the US National Institutes of Health (NIH) established the Office of Research on Women's Health (ORWH). At that time, the Congressional Caucus for Women's Issues, women's health advocacy groups and NIH scientists and leaders agreed that excluding women from clinical research was bad for women and bad for science. In 1993, the NIH Revitalization Act required the inclusion of women in NIH-funded clinical research.

Today, just over half of NIH-funded clinical-research participants are women. We know much more about the role of sex and gender in medicine, such as that low-dose aspirin has different preventive effects in women and men, and that drugs such as zolpidem, used to treat insomnia, require different dosing in women and men.

There has not been a corresponding revolution in experimental design and analyses in cell and animal research — despite multiple calls to action[1]. Publications often continue to neglect sex-based considerations and analyses in preclinical studies[2,3]. Reviewers, for the most part, are not attuned to this failure. The over-reliance on male animals and cells in preclinical research obscures key sex differences that could guide clinical studies. And it might be harmful: women experience higher rates of adverse drug reactions than men do[4]. Furthermore, inadequate inclusion of female cells and animals in experiments and inadequate analysis of data by sex may well contribute to the troubling rise of irreproducibility in preclinical biomedical research, which the NIH is now actively working to address[5,6].

The NIH plans to address the issue of sex and gender inclusion across biomedical research multi-dimensionally — through programme oversight, review and policy, as well as through collaboration with stakeholders including publishers. This move is essential, potentially very powerful and need not be difficult or costly.

NATURE.COM
Read about NIH reproducibility policy at:
go.nature.com/tsrlaf

BETTER WITH BOTH

Certain rigorous studies evaluating the effects of sex differences have been effective in bridging the divide between animal and human work. One example concerns multiple sclerosis (MS). Women are more susceptible to MS than men are, but develop less-severe forms of the disease. The most widely accepted MS animal model — rodent experimental autoimmune encephalomyelitis (EAE) — has revealed[7] that sex differences in MS are related to both reproductive and non-reproductive factors. Findings[8] that oestrogen therapy provided benefits in rodent EAE supported use of an oestrogenic ligand as a candidate neuroprotective agent for MS that is now being studied.

Moreover, differences between the sexes in both the animal model and human MS have

Example from NIGMS: Reproducibility in Cell Culture Studies

- >400 misidentified cell lines have been cataloged, dating back to the 1960s.
- ~70% of researchers surveyed in 2004 had never checked the identity of their cell lines.
- Major repositories report that 14-30% of cell lines submitted are contaminated.
- In a 2013 survey <50% of cell lines had an unambiguous identifier and source in publications.
- Standards for cell line authentication and affordable methods for cell authentication now available.

Example from NIGMS: (cont.) Reproducibility in Cell Culture Studies

- **Variables**:
  - Cell line contamination & misidentification
  - Genomic instability
  - Infections
  - Growth conditions
- **NIGMS Plans**:
  - Facilitate the development and dissemination of consensus standards for authentication, handling, controls, and reporting
  - Promote development of more efficient and cost-effective tools for characterizing cell lines and reagents

Complementary NIH efforts

Ongoing projects separate from and/or complementary to the proposed pilots

- NIEHS: Developing a check list for publications in Environmental Health Perspectives; conducting a replication study of the effects of BPA, in collaboration with the FDA using good laboratory practice procedures
- NHGRI: Validation studies are an inherent part of the review of functional genomics studies and bioinformatics tool development
- NIA: Supports the Interventions Testing Program, where preclinical studies are conducted with multi-site duplication, rigorous methodology and statistical analysis
- NIDDK: Supports Mouse Metabolic Phenotyping Centers, which provide standardized, high-quality phenotyping services (since 2001)

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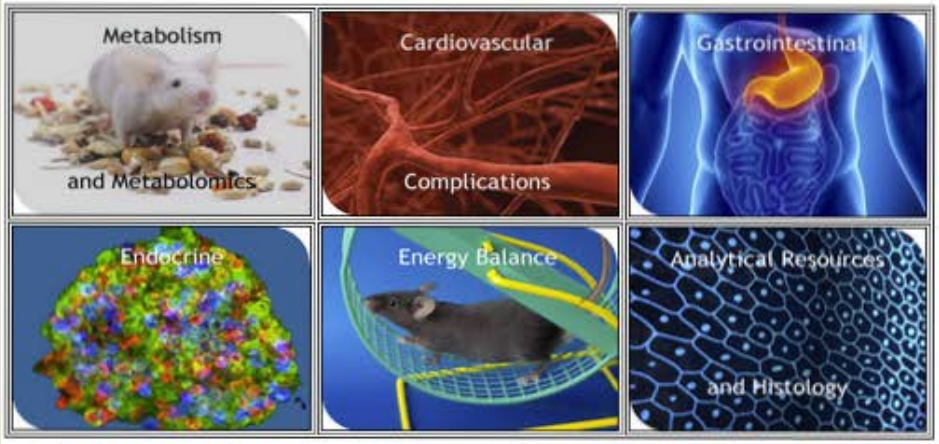

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What have we missed?

- NIH has initiated or is working with others on a variety of activities related to this topic.
- What are your thoughts?
- Is a sufficient effort underway or if not, what else should NIH address?
- Should we wait for information to come in from the activities we have