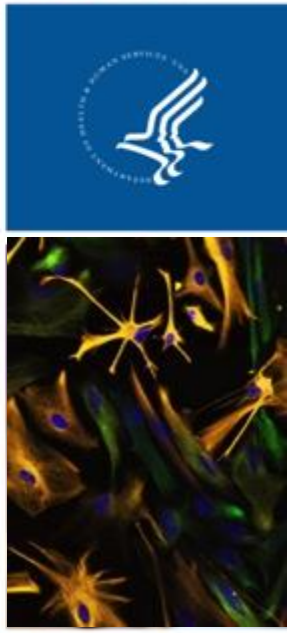
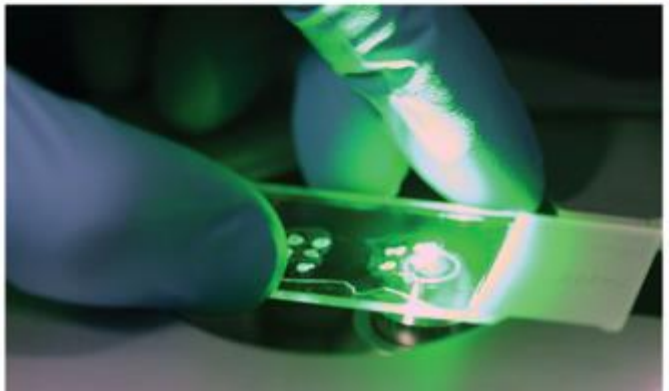
National Institute of Neurological Disorders and Stroke

National Advisory Neurological Disorders and Stroke

Director's Report





2016 AUPN meeting

Walter J. Koroshetz, M.D.

Director, National Institute of Neurological Disorders and Stroke, NIH

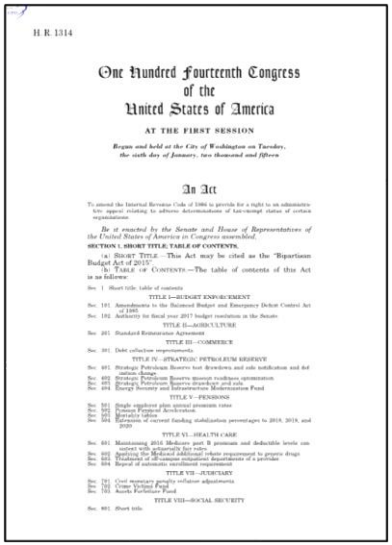
Leadership Changes at NINDS

- Office of Clinical Research:
  - Elizabeth McNeil MD, left for a position at Biogen
  - Claudia Moy, MD, is Acting OCR Director
  - Search is ongoing
- Office of Translational Research:
  - Alan Willard, PhD continues as Acting OTR Director
  - Search is ongoing
- Executive Officer:
  - Caroline Lewis took an Assistant VP position at USUHS
  - Maryann Sofranko is Acting Executive Officer
  - Search is ongoing

Discussion Items

- NINDS Budget (Big thanks to Quynh Ly)
  - ’16 budget and spending plan
  - ’15 spending report (Thanks to Anna Taylor and Christine Torborg)
- BRAIN initiative (Thanks to BRAIN Team members especially Ned Talley and Alan Willard, Amy Adams, Sam White, Khara Ramos)
- Alzheimers Disease Related Dementia program (Thanks to Rod Corriveau and ADRD team)
- Mind Your Risks Public Info Campaign (Thanks to Marian Emr and OCPL and Katie Pahigiannis)
- Programs in Chronic Fatigue (Thanks to Vicky Whittemore)
- Pain research programs (Thanks to Linda Porter, Cherysse Sankar)
- Trans-NIH policy discussions.
  - Select Pay
  - Focus shift from grants to people
  - Others coming soon.

Consolidated Appropriations Act (P.L. 114-113)


H.R. 1314

One Hundred Fourteenth Congress
of the
United States of America

AT THE FIRST SESSION

Begun and held at the City of Washington on Tuesday, the sixth day of January, two thousand and fifteen

An Act

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE; TABLE OF CONTENTS.

(a) SHORT TITLE.—This Act may be cited as the "Bipartisan Budget Act of 2015".

(b) TABLE OF CONTENTS.—The table of contents of this Act is as follows:

Passed December 18, 2015

- $32.1 B for NIH
- $2 B increase (~6.5%) over FY2015 enacted
  - $1.696 B to NINDS
  - $150 M ($85 M boost) for BRAIN Initiative (pooled across ICs)
  - $350 M boost for Alzheimer's disease research (to NIA)
  - $200 M for PMI ($130 to Common Fund and $70 M to NCI)
  - $100 M boost to combat antimicrobial resistance

Other Provisions of Interest:

- National Academies study on policies affecting the next generation of researchers in the U.S. (Partner with National Academy of Sciences)
- Increase stipends for NRSA grantees (consistent with the Federal employee pay raise)
- Strengthen privacy protections for human research participants
- Continued support for high-risk, high-reward research (through Common Fund)

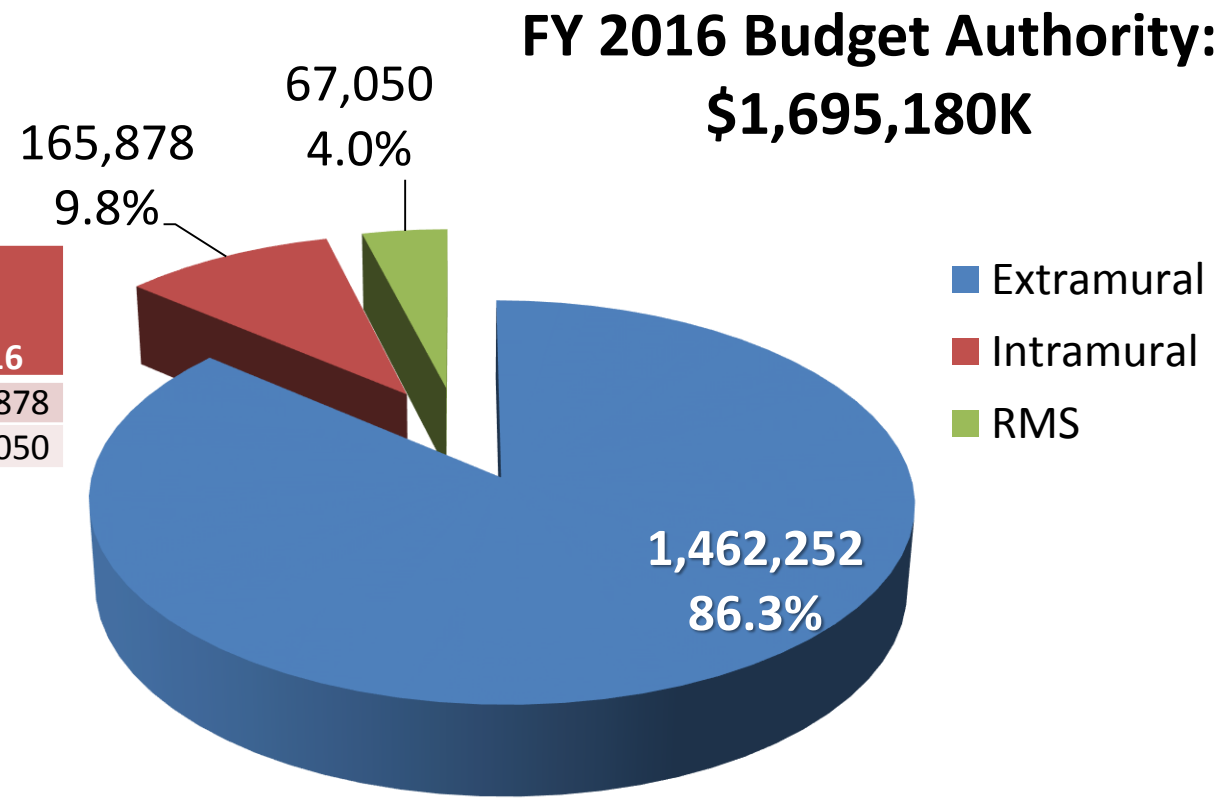
Appropriation History
(Dollars in Thousands)

	FY 2011	FY 2012	FY 2013	FY2014	FY 2015	FY 2016
NINDS	$1,622,003	$1,624,830	$1,533,795	$1,588,904	1,604,607	1,695,180
NINDS % Change	Base	0.2%	-5.6%	3.6%	1.0%	5.6%
NIH	$30,687,290	$30,860,387	$29,151,462	$30,150,853	30,311,349	32,311,349
NIH % Change	Base	0.6%	-5.5%	3.4%	0.5%	6.6%

- NINDS received specific increase of $27.93m for BRAIN Initiative
- Minus the BRAIN initiative increase, the NINDS general increase was 3.925%
- Noncompeting grants to be awarded at full committed levels (amount on most recent NGA)
- Funding up to 15th percentile, our projection prior to the increase in funding was a payline at the 12 percentile.
- Administrative cut 17.5% non-modular & 12.5% modular

FY 2016 Appropriation Budget Distribution

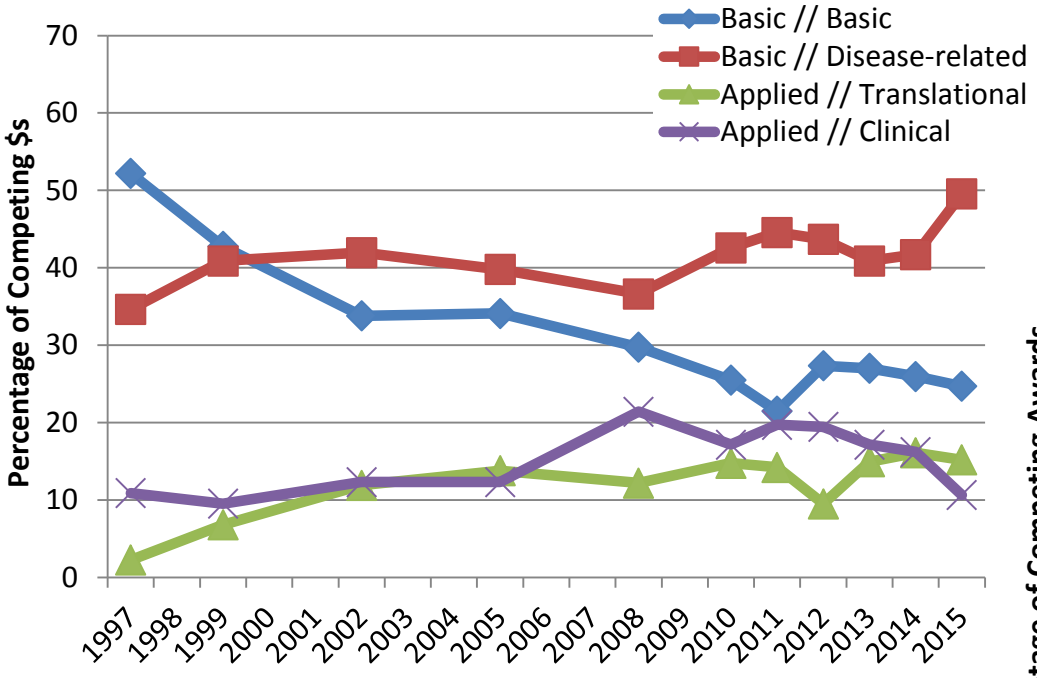
	FY 15 Actuals	FY 16 % increase	FY 16
DIR	159,498	4.0%	165,878
RMS	63,894	4.9%	67,050



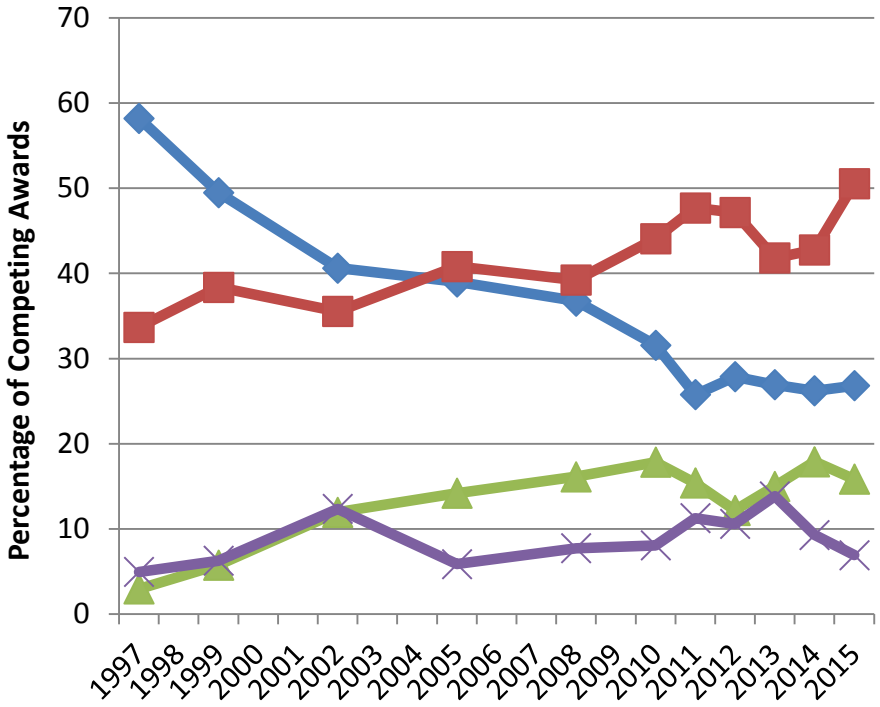
Dollars in Thousands

NINDS Funding Trends

Competing Dollars



Competing Awards

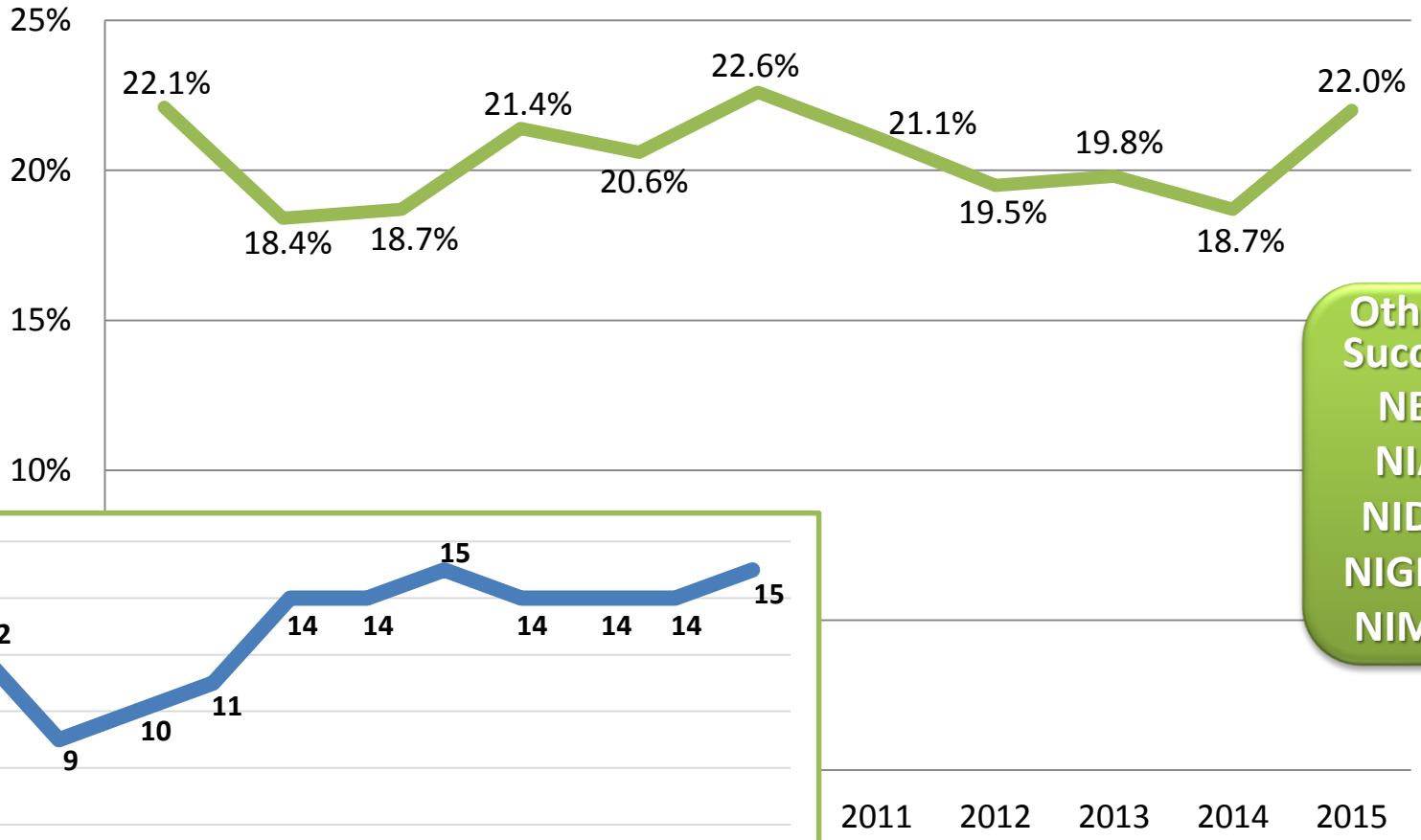


Competing RPG Trends

	2010	2011	2012	2013	2014	2015
Competing Awards	699	749	701	702	750	819
Number of Applications	3,097	3,549	3,588	3,551	4,002	4,007
Success Rate	22.6%	21.1%	19.5%	19.8%	18.7%	20.5%
Average Cost	$405K	$392K	$378K	$378K	$396k	$379k
Payline (Percentile)	14	14	15	14	14	14

Data includes complete RPG portfolio of Unsolicited Announcements, RFAs, PAs, PASs

NINDS Success Rate



Other IC FY15 Success Rates:

NEI: 23.5%

NIA: 20.9%

NIDA: 22.3%

NIGMS: 29.0%

NIMH: 22.2%

Senate L-HHS-Ed Appropriations Subcommittee Hearing:

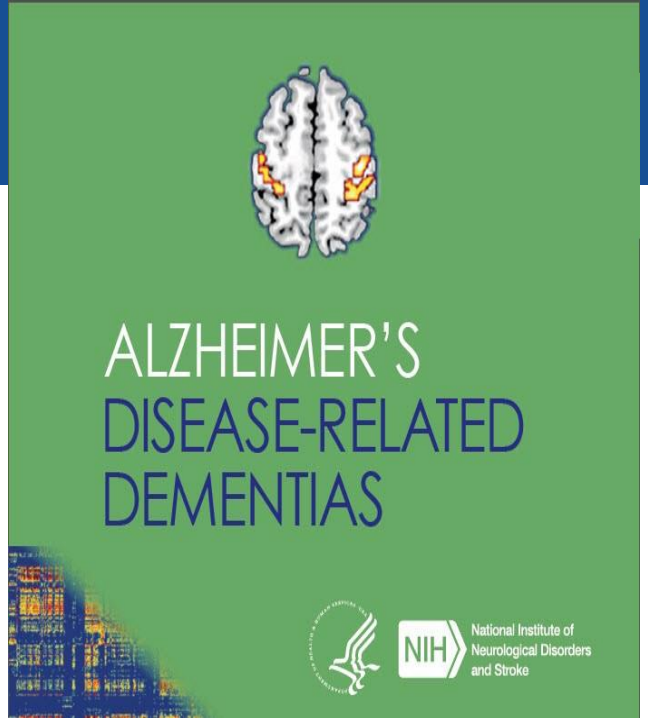
"NIH: Investing in a Healthier Future"

- October 7, 2015
- Witnesses: NIH Director; directors from NINDS, NIGMS, NCI, NIDDK, NIDA
- Chairman Blunt asked witnesses to talk about their research programs and how to increase opportunities and training for young investigators
- Several broad themes emerged
  - What would you do if you had $2-3 billion more money?
  - Ramifications of a Continuing Resolution (e.g. on PMI, BRAIN)
  - Importance of increasing opportunities for young scientists to ensure future discoveries and sustain economic benefits of biomedical research
  - Balance of funding across various diseases at NIH (e.g. HIV)

NINDS Funding Opportunity Announcements on AD-Related Dementias Planned for FY 2016

- NINDS leads Alzheimer's Disease Related Dementia Research
  - Lewy body disease and Parkinson's related Dementia
  - Frontotemporal Dementia
  - Vascular contribution to dementia; AD and Vascular Dementia
- Funding from NIA
- NINDS FOA's in FY16 for ~ $17.8million
  - Biomarkers for small vessel vascular contributions to cognitive impairment and dementia (VCID)
  - Basic research on diffuse white matter disease in VCID
  - Biomarkers for Lewy body dementia
  - Tau biology and contribution to neurodegeneration
  - Health Disparities in Dementia

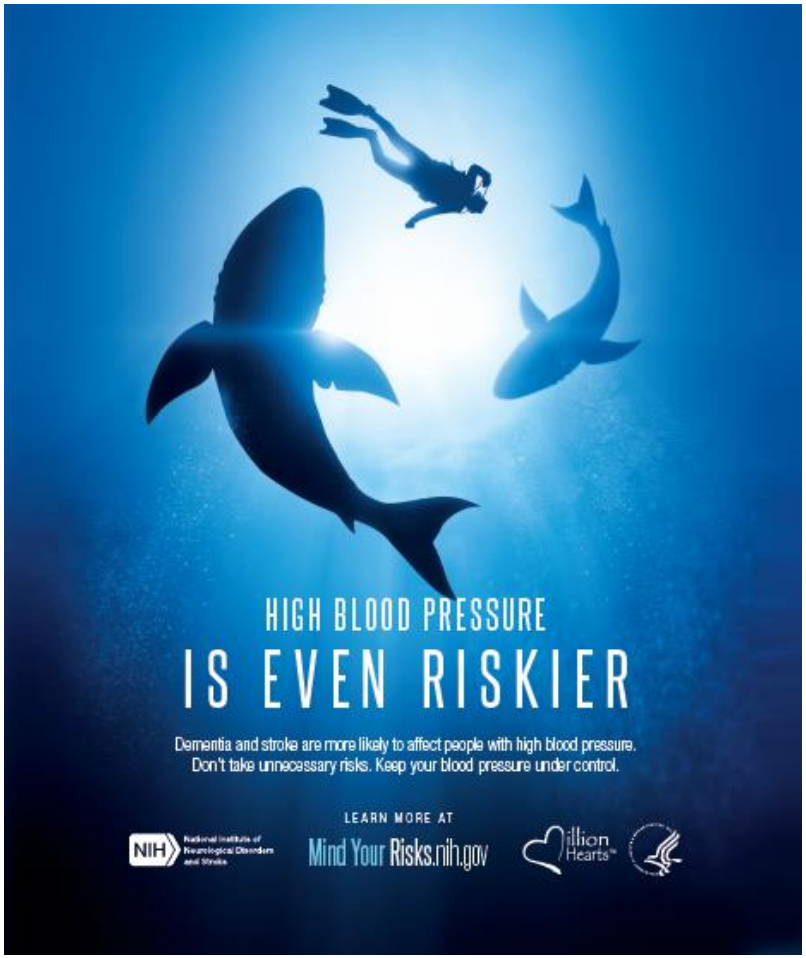
ADRD Summit



- Will take place at NIH March 29-30, 2016
- Update research recommendations:
  - Frontotemporal degeneration
  - Lewy body dementia
  - Multiple etiology dementias
  - Vascular contributions to cognitive impairment and dementia
  - Health disparities
  - New in 2016: NGO Session
- Registration is free and open to the public: https://meetings.ninds.nih.gov/meetings/ADRelatedDementias2016/
- Hosted by NINDS in collaboration with NIA

Mind Your Risks

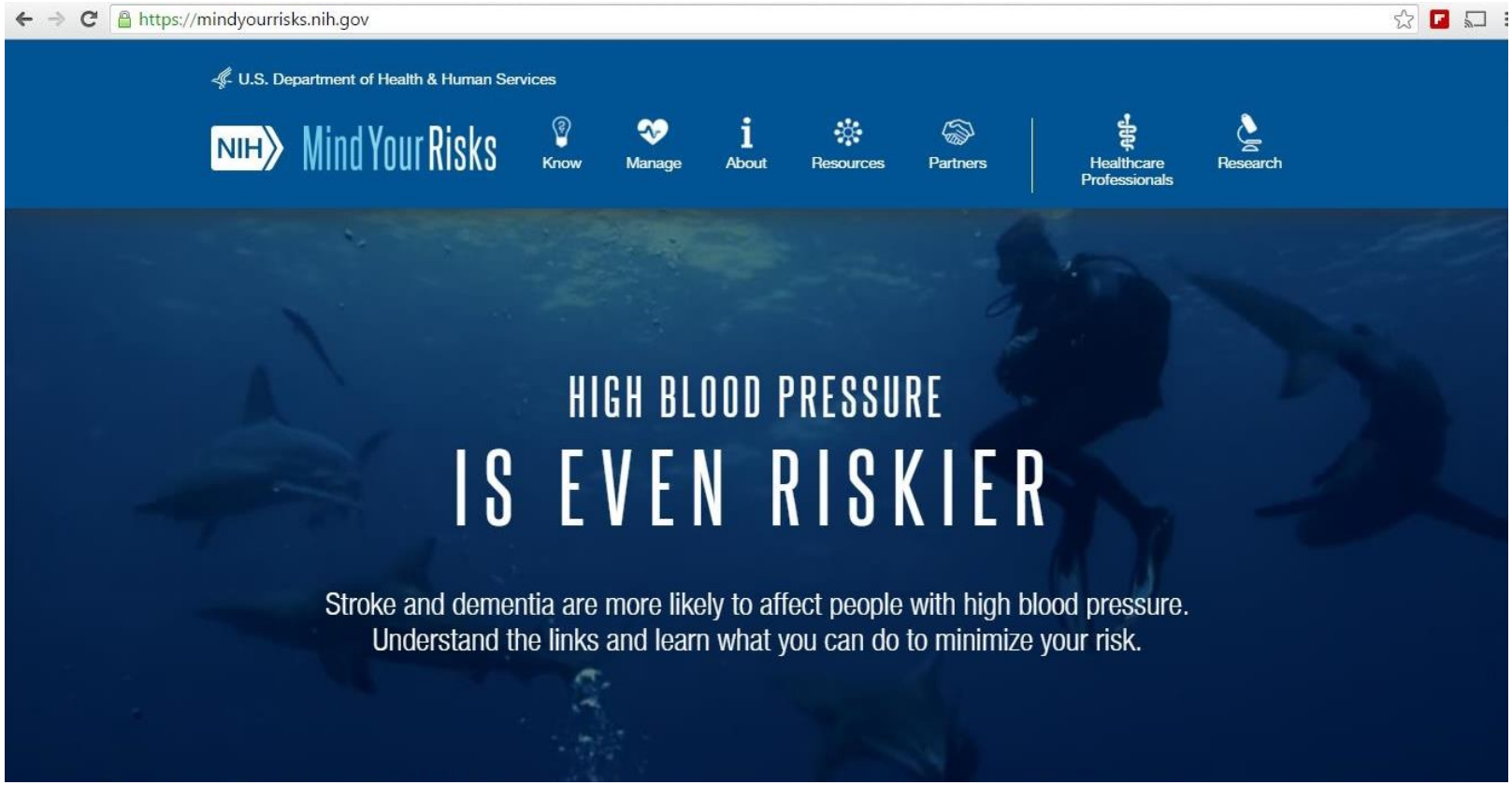
A New NINDS Public Education Campaign



- Raise awareness among middle-aged people with hypertension that controlling blood pressure may decrease risk for dementia, as well as stroke, in later life
- Provide scientific evidence for doctors who wish to discuss this topic with their patients
- Campaign launched with PSA placement in Stroke Belt States
- NINDS-led campaign in partnership with Million Hearts®, NHLBI and NIA

Mind Your Risks Website

Offers information for the public and healthcare



www.MindYourRisks.nih.gov

FY 2016 BRAIN Appropriation (approx.)

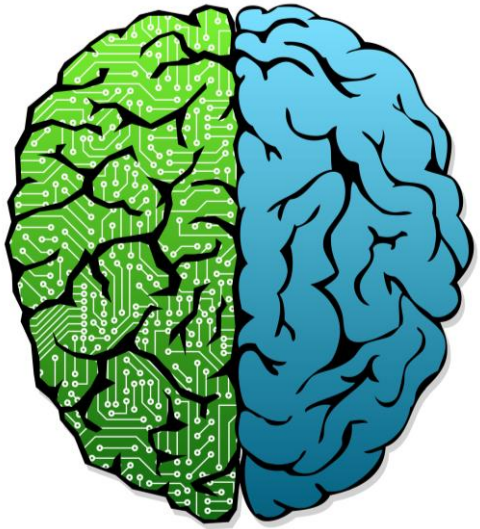
IC	FY 2014	FY 2015	FY 2016 Δ	FY 2016 Total
NINDS	12,850,000	25,150,000	*27,929,000*	$53,079,000
NEI			*4,857,000*	$4,857,000
NIDCD			*1,821,000*	$1,821,000
NIMH	12,850,000	25,231,000	*27,929,000*	$53,160,000
NIA				
NIDA				
NIAAA				
NCCIH			*1,214,000*	$1,214,000
NIBIB	1,000,000	1,000,000	*3,643,000*	$4,643,000
NICHD			*2,732,000*	$2,732,000
Blueprint	10,000,000	19,107,785		To be determined
ICO* Add'l $	5,431,142	10,492,257		To be determined
Total	**$46,131,142**	**$84,981,042**		**~$150,000,000**

FY16 President's Budget request: $70M new
FY16 BRAIN appropriation: $85M new

*ICO – Institutes, Centers, and OD Offices that provided additional $ beyond BRAIN appropriations

BRAIN Neuroethics

BRAIN Neuroethics Workgroup



- A consultative ethics group to work with BRAIN leadership and BRAIN investigators
- Co-chaired by Dr. Christine Grady and Hank Greely
- Services:
  - Advise NIH on neuroethics questions important for BRAIN that could be answered through focused empirica research
  - Draft relevant guidance documents to address critical ethical issues associated with BRAIN research
  - Consider proposed funding areas for BRAIN projects for questions of ethical risk
- Workgroup meeting February 9th with BRAIN PIs conducting invasive human studies
- New joint BRAIN/Blueprint neuroethics project team (Team N)
- http://braininitiative.nih.gov/about/newg.htm

Brain Alliance

Mission Statement: *The aim of the BRAIN Initiative Alliance is to coordinate and facilitate communications from its members related to the White House BRAIN Initiative.*

Short Term Focus: Website that serves as a single point of communication for all BRAIN Initiative-related announcements of funding opportunities and accomplishments

International Partnerships

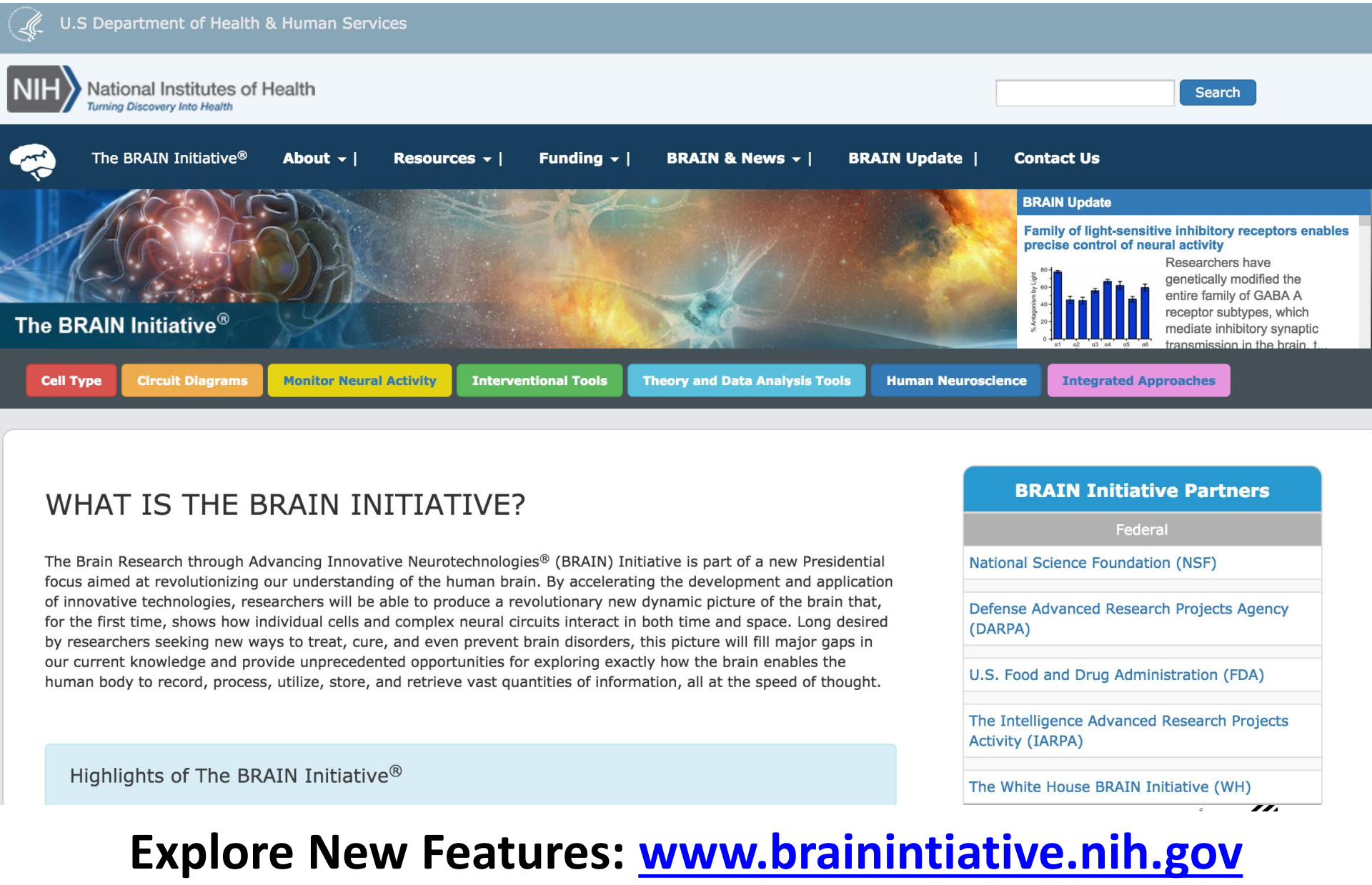
LUNDBECK FOUNDATION

Goals:

- Develop a coordinated program to foster collaborative research in areas of mutual interest within the BRAIN Initiative
  - Jointly support research projects involving Danish and U.S. scientists; exchange of scientific information.
  - Funding for projects in Denmark funded by Foundation.

- Similar to partnerships between NIH and research organizations in Canada and Australia

Launch of New BRAIN Website



Explore New Features: www.brainintiative.nih.gov

BRAIN Initiative: *Exciting Advances Beginning to Emerge*

Technical Note

Human brain diffusion tensor imaging at submillimeter isotropic resolution on a 3 Tesla clinical MRI scanner

Hing-Chiu Chang [a], Mark Sundman [a], Laurent Petit [b], Shayan Guhaniyogi [a], Mei-Lan Chu [a], Christopher Petty [a], Allen W. Song [a], Nan-kuei Chen [a,*]

Neuron

A Comprehensive Optogenetic Pharmacology Toolkit for In Vivo Control of $GABA_A$ Receptors and Synaptic Inhibition

Highlights

- Tools for optogenetic pharmacology are introduced for all $GABA_A$ receptors
- Photo-control is rapid, reversible, and isoform specific in

Authors

Wan-Chen Lin, Ming-Chi Tsai, Christopher M. Davenport, ..., Neil M. Wilson, Hillel Adesnik, Richard H. Kramer

nature COMMUNICATIONS

ARTICLE

Received 24 Jul 2015 | Accepted 22 Oct 2015 | Published 24 Nov 2015

DOI: 10.1038/ncomms9968 OPEN

Optical focusing inside scattering media with time-reversed ultrasound microbubble encoded light

Haowen Ruan[1,*], Mooseok Jang[1,*] & Changhuei Yang[1]

Multiscale photoacoustic tomography using reversibly switchable bacterial phytochrome as a near-infrared photochromic probe

Junjie Yao[1,6], Andrii A Kaberniuk[2,3,6], Lei Li[1,6], Daria M Shcherbakova[2,3], Ruiying Zhang[1], Lidai Wang[1,5], Guo Li[1], Vladislav V Verkhusha[2–4] & Lihong V Wang[1]

BRAIN Initiative: *Exciting Advances Beginning to Emerge*

Sciencexpress

High-speed recording of neural spikes in awake mice and flies with a fluorescent voltage sensor

Yiyang Gong,[1,2,3*] Cheng Huang,[1] Jin Zhong Li,[1,2] Benjamin F. Grewe,[1,2] Yanping Zhang,[1,2,4] Stephan Eismann,[1,2] Mark J. Schnitzer[1,2,4*]

CrossMark

PNAS PLUS

Functional divisions for visual processing in the central brain of flying *Drosophila*

Peter T. Weir[a] and Michael H. Dickinson[a,1]

Cell

Article

Molecular Identity of Human Outer Radial Glia during Cortical Development

Alex A. Pollen,[1,2,5,*] Tomasz J. Nowakowski,[1,2,5] Jiadong Chen,[1,2] Hanna Retallack,[1,2] Carmen Sandoval-Espinosa,[1,2] Cory R. Nicholas,[1,6] Joe Shuga,[3] Siyuan John Liu,[1,2] Michael C. Oldham,[1] Aaron Diaz,[1,4] Daniel A. Lim,[1,4] Anne A. Leyrat,[3] Jay A. West,[3] and Arnold R. Kriegstein[1,2,*]

Scanning color optical tomography (SCOT)

Poorya Hosseini,[1,2] Yongjin Sung,[1,3,*] Youngwoon Choi,[4] Niyom Lue[1] Zahid Yaqoob[1] and Peter So[1,2]

ARTICLES

nature neuroscience

An acetylcholine-activated microcircuit drives temporal dynamics of cortical activity

Naiyan Chen[1–3], Hiroki Sugihara[1,3] & Mriganka Sur[1]

NATURE | LETTER

日本語要約

Distinct relationships of parietal and prefrontal cortices to evidence accumulation

Timothy D. Hanks, Charles D. Kopec, Bingni W. Brunton, Chunyu A. Duan, Jeffrey C. Erlich & Carlos D. Brody

NIH National Institute of Neurological Disorders and Stroke

Update on Concussion Research

Two neuropath studies ongoing

- Published guidelines for pathologic diagnosis of CTE
- Screen of May neuro brain bank for CTE
  - Found in 30% of those with some history of playing contact sports. 0% in matched non-sports cohort and 0% in female cohort.
- Screen of Queen's Square neuro bio bank
  - CTE in 12% and history of TBI in 94%, but TBI not sports related, question raised whether TBI related to falls from neuro conditions.
  - NINDS funded longitudinal study to characterize clinical syndrome of CTE from its appropriated budget.

NINDS-funded longitudinal study to characterize clinical syndrome of CTE from its appropriated budget

NINDS will form a working group of Council to discuss next highest priority opportunities in concussion research

  - In concert with NICHD
  - Jonathan Mink to lead
- Will hold a workshop and create research plan
- Concept clearance for Council
- Discuss research plan with FNIH

Chronic Fatigue Syndrome

- Affects between 800,000 - 2.5 million in the US
- 75% affected are women
- Cause unknown but many have distinct onset with flu-like symptoms
- Plans for CFS/Myalgic Encephalitis Research
  - NIH-wide intramural protocol through IRB to begin phenotyping, neuro and immunologic studies
    - Led by Dr. Avi Nath
  - Trans-NIH working group developing an extramural research program
    - Led by Dr. Vicky Whittemore

NINDS's Role in CFS

- NINDS leads Trans-NIH ME/CFS Working Group
  - **Goals**
    - Advance research on the cause, prevention, diagnosis, pathophysiology and treatment of ME/CFS
    - Communicate ME/CFS research information with ICs, OD
  - **Activities**
    - Organize Federal Partners meeting (follow-up to 2014 Pathways To Prevention (P2P) Workshop)
      - Develop disease parameter
      - Create new knowledge
        - » Diagnostics, Epi studies, Prognostics
        - » Causation- immunologic, neurologic, genomic
      - Develop outcome measures
      - Develop and test treatment
      - Training and education

Fatigue Prominent in Many Disorders

Central Nervous System

Multiple Sclerosis

Post Stroke

Post TBI

Post Polio Syndrome

Post posterior fossa surgery/path

Aging

Neuroendocrine

Hypothyroidism

Hypothalamic Pituitary Adrenal Axis

Metabolic

Renal failure

Heart Failure

Anemia

Drug AEs

Inflammatory/Rheumatic Diseases

Muscle Nerve

Overtraining Syndrome

Myasthenia Gravis

Mitochondrial disorders

Chronic Guillain Barre

Infectious and Post Infectious

Mononucleosis

Lyme

Influenza

Environmental

Heat

Altitude sickness

Psychological

Depression

Post traumatic stress disorder

Anxiety Disorder

Cancer

Cancer and Post cancer

Radiation and Chemotherapy

What's known: Two Major Categories of Fatigue

Physical fatigue is an exercise-induced reduction in maximal voluntary muscle force.

- The central nervous system fails to drive the motoneurons maximally.
- How the brain interprets signals from muscle to produce sense of fatigue is not clear.

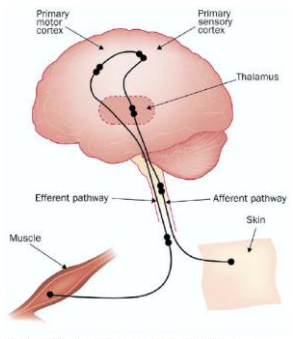
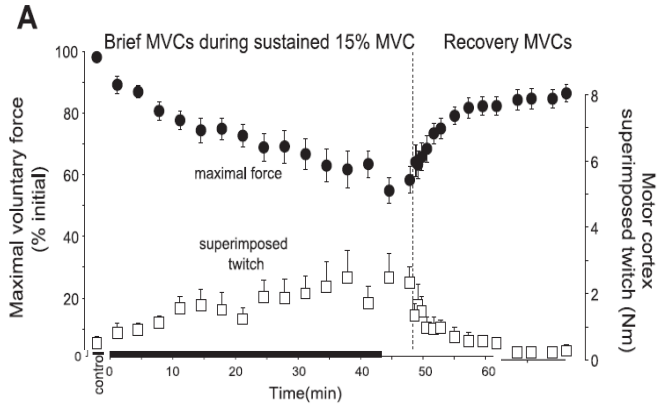


Figure 2: **Integration of sensory and motor pathways for physical activities**



Mental fatigue is associated with affective, behavioral, and cognitive impairments especially in attention, plannin increased distractability.

- N.B. It is not related to ↓ ATP.

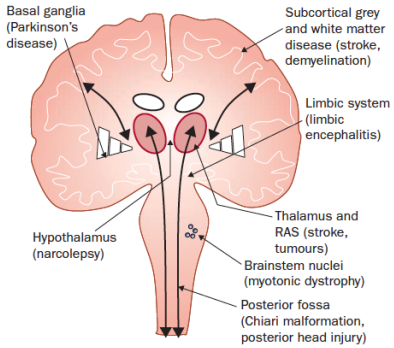


Figure 5: **General sites of pathology in central fatigue**
RAS=reticular activating system.

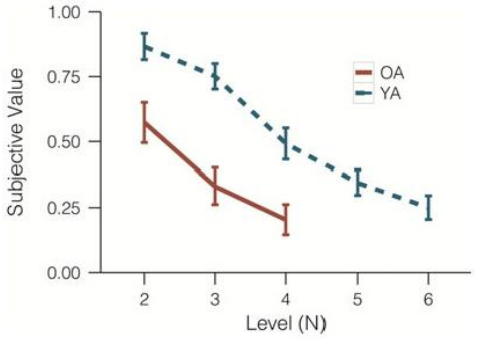


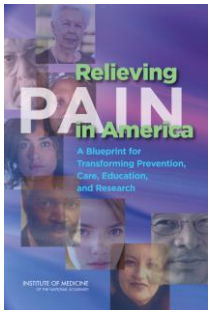
Figure 1 (Westbrook & Braver). Subjective value of a cash offer, or conversely, motivation to engage with a task, decreases with increasing working memory load for both young adults (YA) and older adults (OA).

FY 2018 Common Fund Proposals

- **Mechanisms of Fatigue**
  - The concept for this program is to determine whether universal molecular, chemical, or imaging signatures of fatigue can be established; if so, a program in this area would explore mechanisms through which fatigue occurs and how it is resolved by rest/sleep in healthy individuals.
- **Transformative Cryo-Electron Microscopy**
  - The concept for this program is to increase capacity for high resolution Cryo-EM analyses in the US through infrastructure support, training, and further enhancements to the technology.
- **Human Cell Atlas**
  - The concept for this program is to define human tissues at a single cell level over time and in different conditions, such as different phases of life or in health versus disease

National Pain Strategy:
A Comprehensive Population Health Level Strategy for Pain

2010 Patient Protection & Affordable Care Act

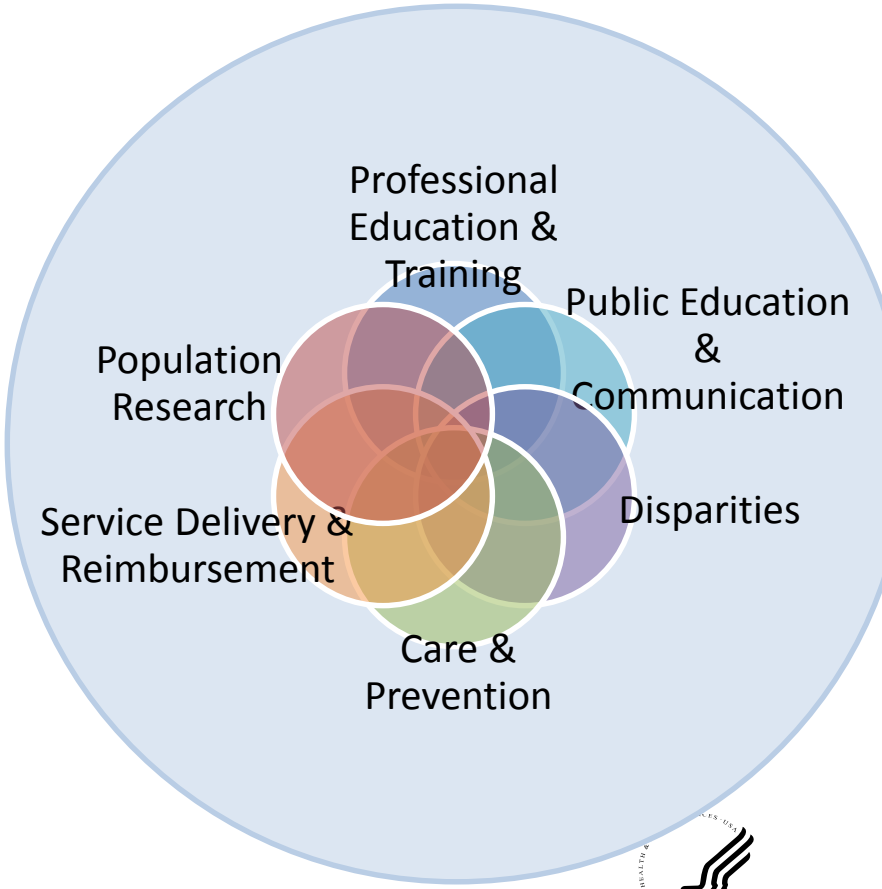


INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

2011: *Relieving Pain in America*

NIH The Interagency Pain Research Coordinating Committee

2012 Assistant Secretary for Health, HHS tasked IPRCC and NIH to address IOM Recommendation: "*develop a comprehensive, population health-level strategy for pain prevention, treatment, management, education, reimbursement, and research that includes specific goals, actions, time frames, and resources*."



NIH National Institute of Neurological Disorders and Stroke

Agency clearance February 2016

National Pain Research Strategy

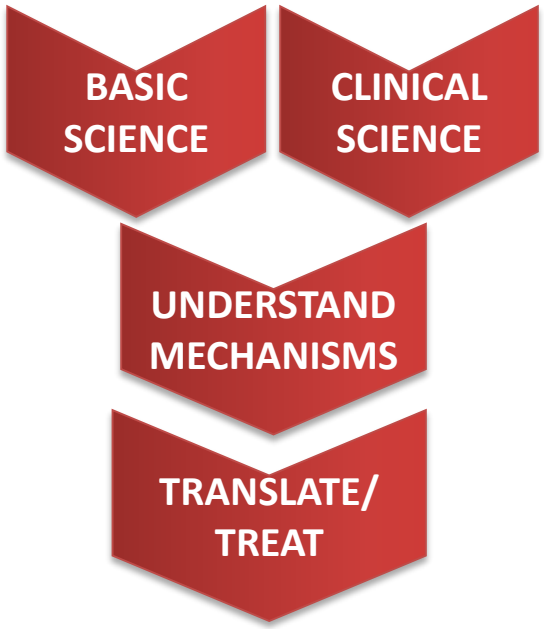
Focus on the Continuum of Pain: pain as a temporal process, beginning with an acute phase that may progress to a chronic maladaptive state

- PREVENTION OF ACUTE & CHRONIC PAIN
- ACUTE PAIN & ACUTE PAIN MANAGEMENT
- TRANSITION FROM ACUTE TO CHRONIC PAIN
- CHRONIC PAIN & CHRONIC PAIN MANAGEMENT
- DISPARITIES

WHAT HAPPENS AND TO WHOM?

WHY AND HOW DOES IT HAPPEN?

HOW TO MANAGE?



NIH National Institute of Neurological Disorders and Stroke

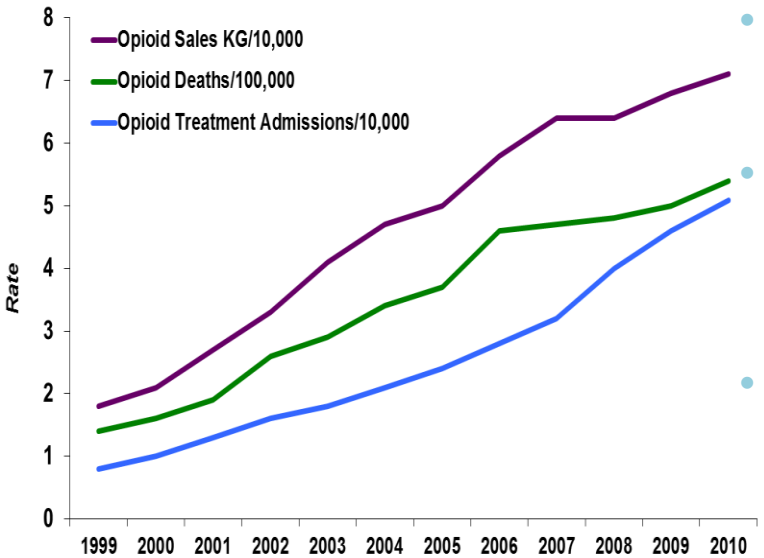
Completion January 2017

CDC Guideline for Prescribing Opioids for Chronic Pain: *Primary Care*

Clinical Questions

- Determining when to initiate or continue opioids for chronic pain
- Opioid selection, dosage, duration, follow-up, and discontinuation
- Assessing risk and addressing harms of opioid use

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION



12 Recommendations

- Non-opioid therapy is preferred for chronic pain outside of active cancer, palliative, and end-of-life care.
- When opioids are used, the lowest possible effective dosage should be prescribed to reduce risks of opioid use disorder and overdose.
- Providers should always exercise caution when prescribing opioids and monitor all patients closely.

NIH National Institute of Neurological Disorders and Stroke

FY16 NIH PMI Appropriation - Enacted

NIH PMI Research Program	*Appropriation*
• *PMI Cohort Program* • *PMI for Oncology*	$130 million $70 million
TOTAL	$200 million

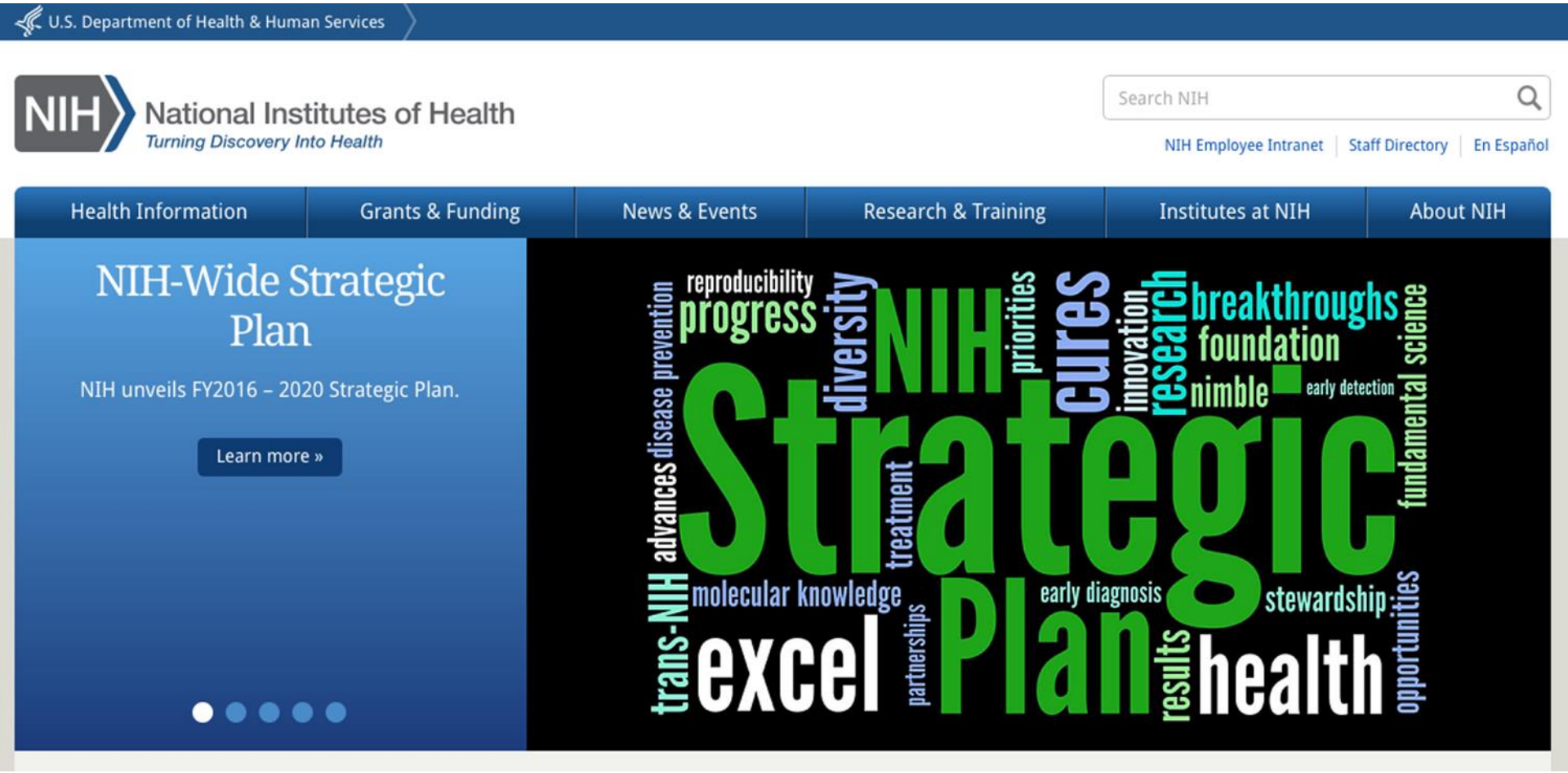
The President's PMI has many components:

- FDA
- ONC
- OCR
- etc.

Approach to Assembling the PMI Cohort

- **One million or more** U.S. volunteers
  - Broadly reflect the diversity of America (including family members of all ages, health statuses, geographic areas, etc.)
  - Strong focus on underrepresented groups
- **Longitudinal cohort**, with continuing interactions, recontact for secondary studies
  - Collect EHR data, provide biospecimen(s) and survey, and complete a baseline exam
- Two methods of **enrollment**
  - Direct volunteers: anyone can sign up
  - Healthcare provider organizations (incl. FQHCs): diverse participants, robust EHRs, participant follow-up
- Substantial **participant engagement** in development, implementation, governance

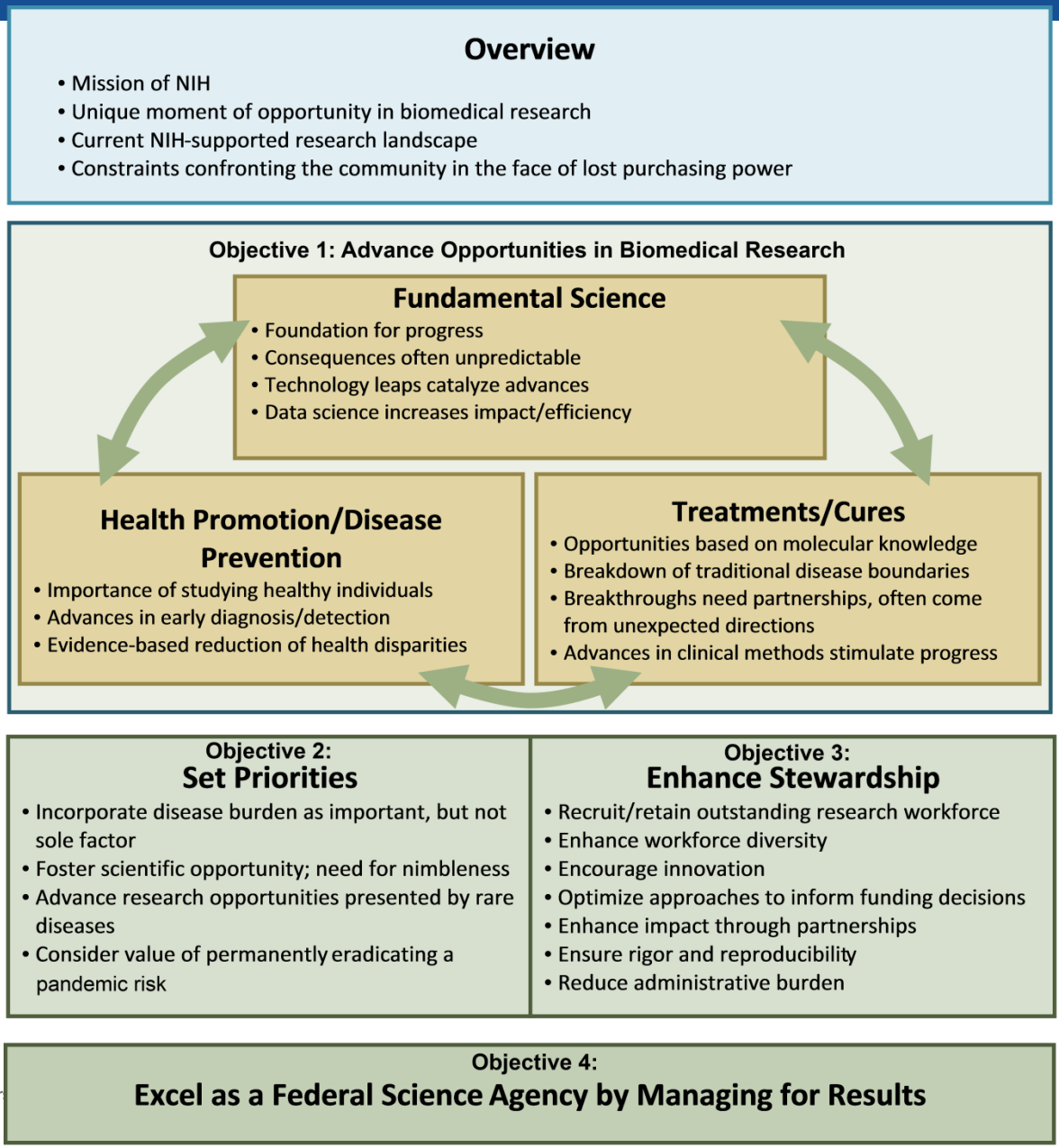
Plan Published on December 16, 2015



National Institute of Neurological Disorders and Stroke

http://www.nih.gov/about/strategic-plan

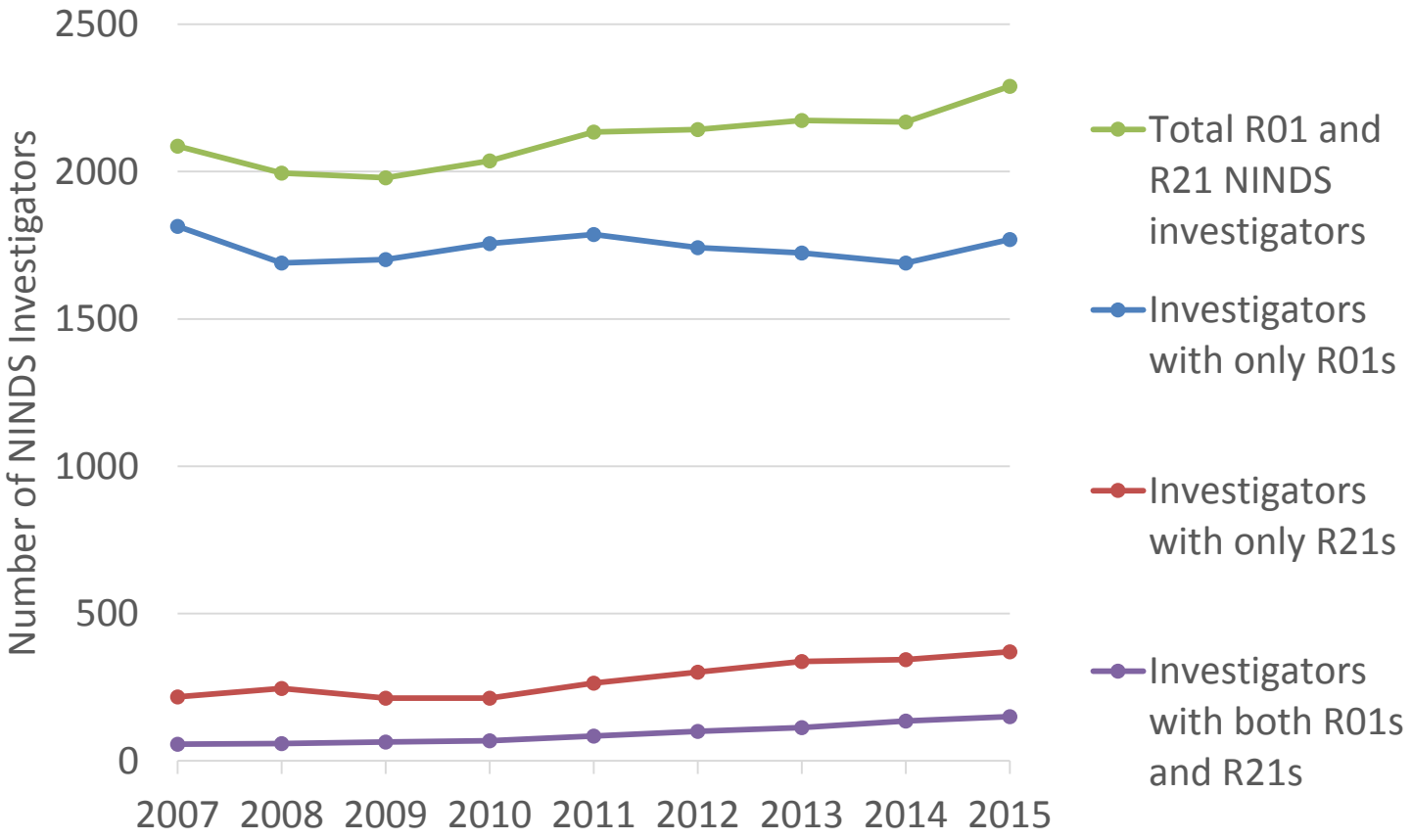
NIH-Wide Strategic Plan Framework



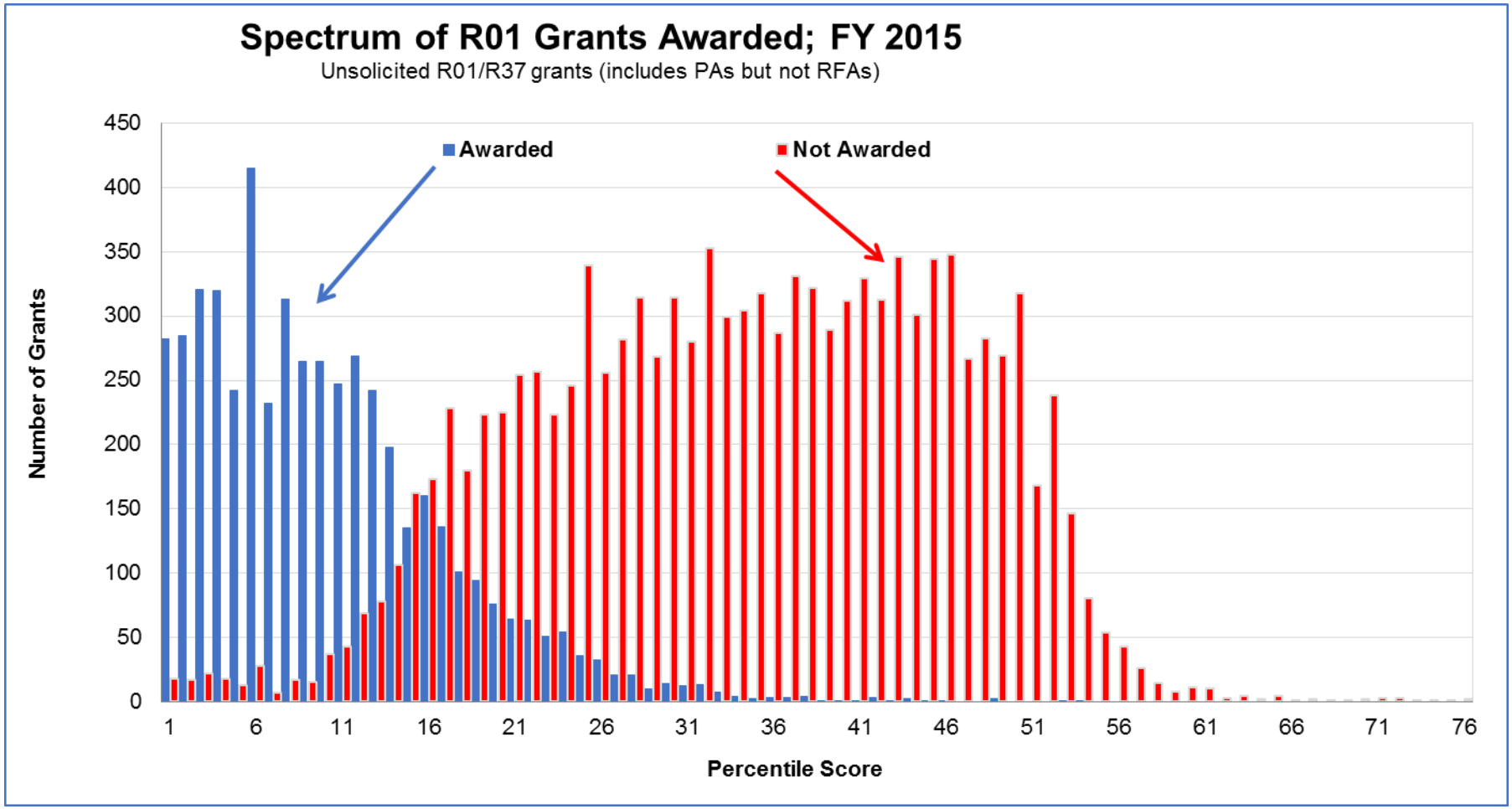
NIH is Always Trying to Improve its Stewardship Currently Circulating Ideas

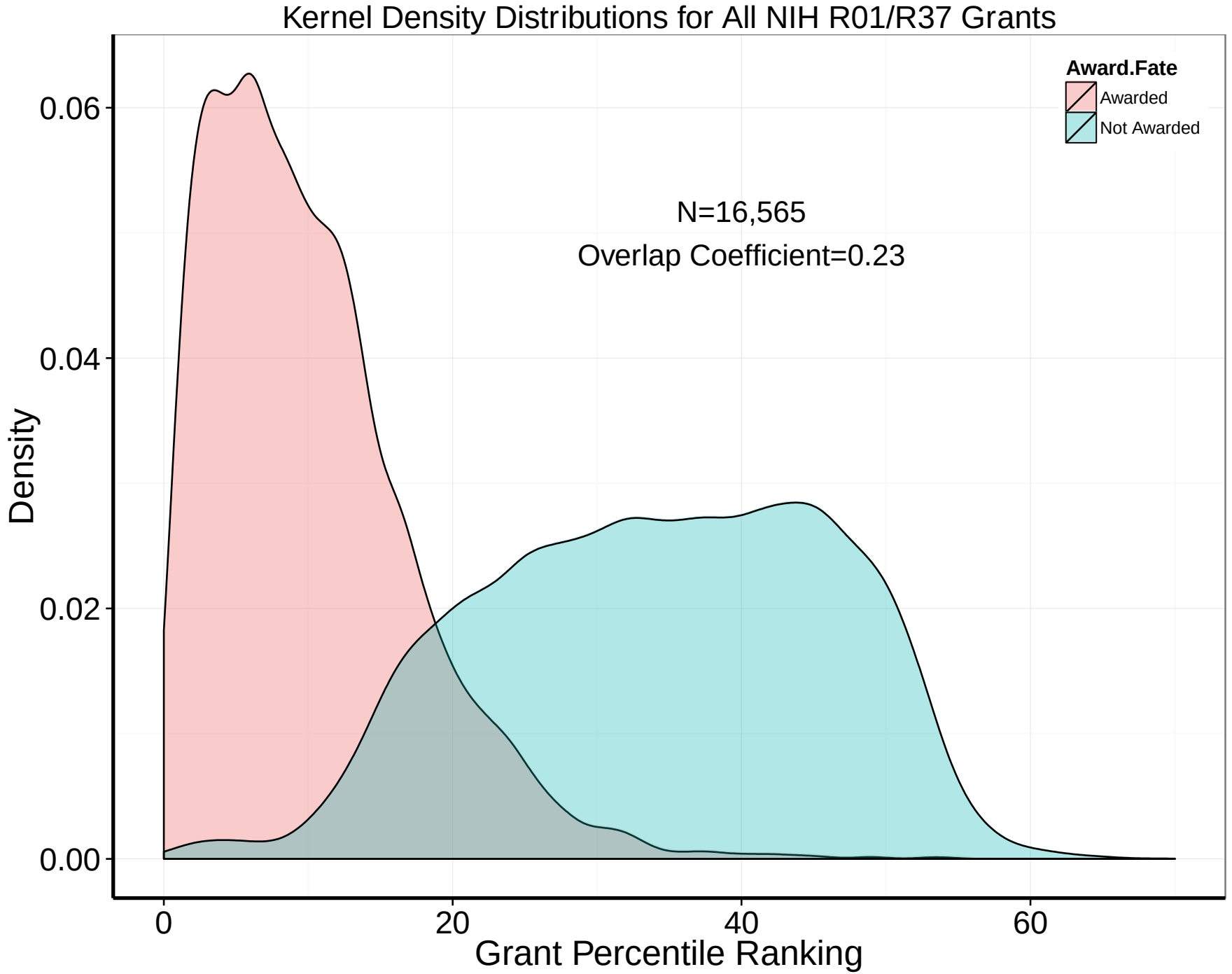
1) Should NIH focus more on supporting a broad and diverse portfolio of investigators?
2) Should NIH require a minimum percent effort by principal investigators?
3) Should NIH establish shared regional research resources and facilities to improve access to cutting-edge technologies and reduce costs by economies of scale?

Number of NINDS-funded Investigators

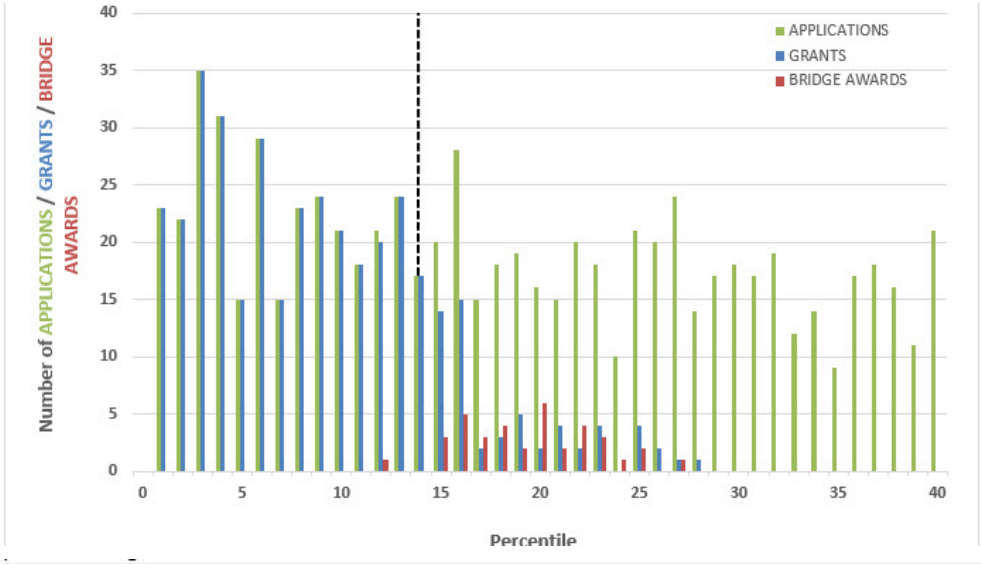


NIH All

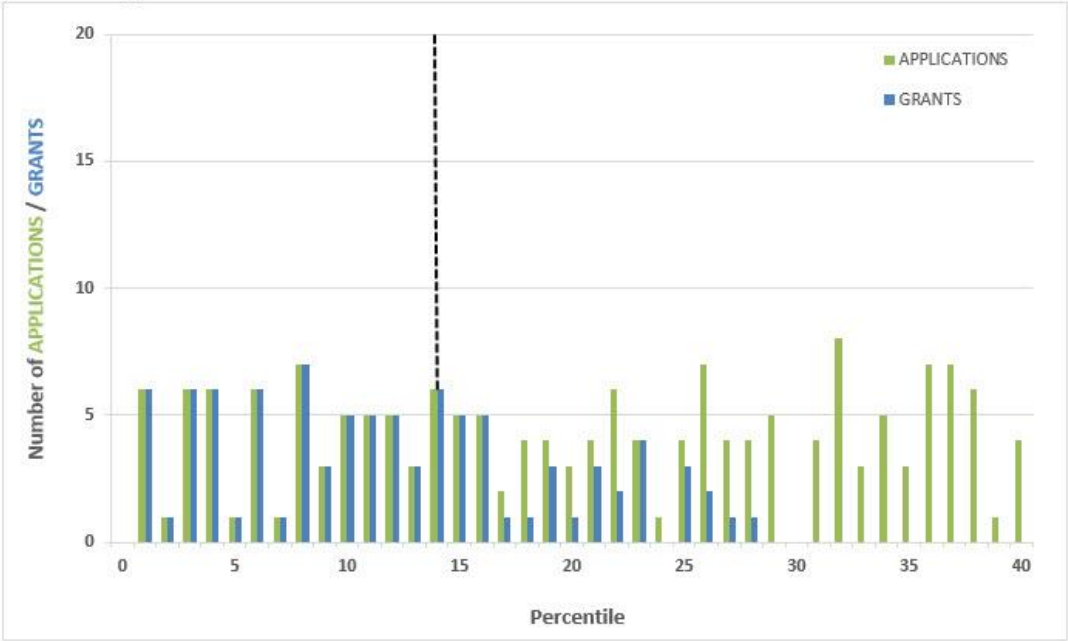

Spectrum of R01 Grants Awarded; FY 2015
Unsolicited R01/R37 grants (includes PAs but not RFAs)
Awarded
Not Awarded
Number of Grants
0
50
100
150
200
250
300
350
400
450
1
6
11
16
21
26
31
36
41
46
51
56
61
66
71
76
Percentile Score


Kernel Density Distributions for All NIH R01/R37 Grants
Award.Fate
Awarded
Not Awarded
N=16,565
Overlap Coefficient=0.23
Density
0.06
0.04
0.02
0.00
0
20
40
60
Grant Percentile Ranking

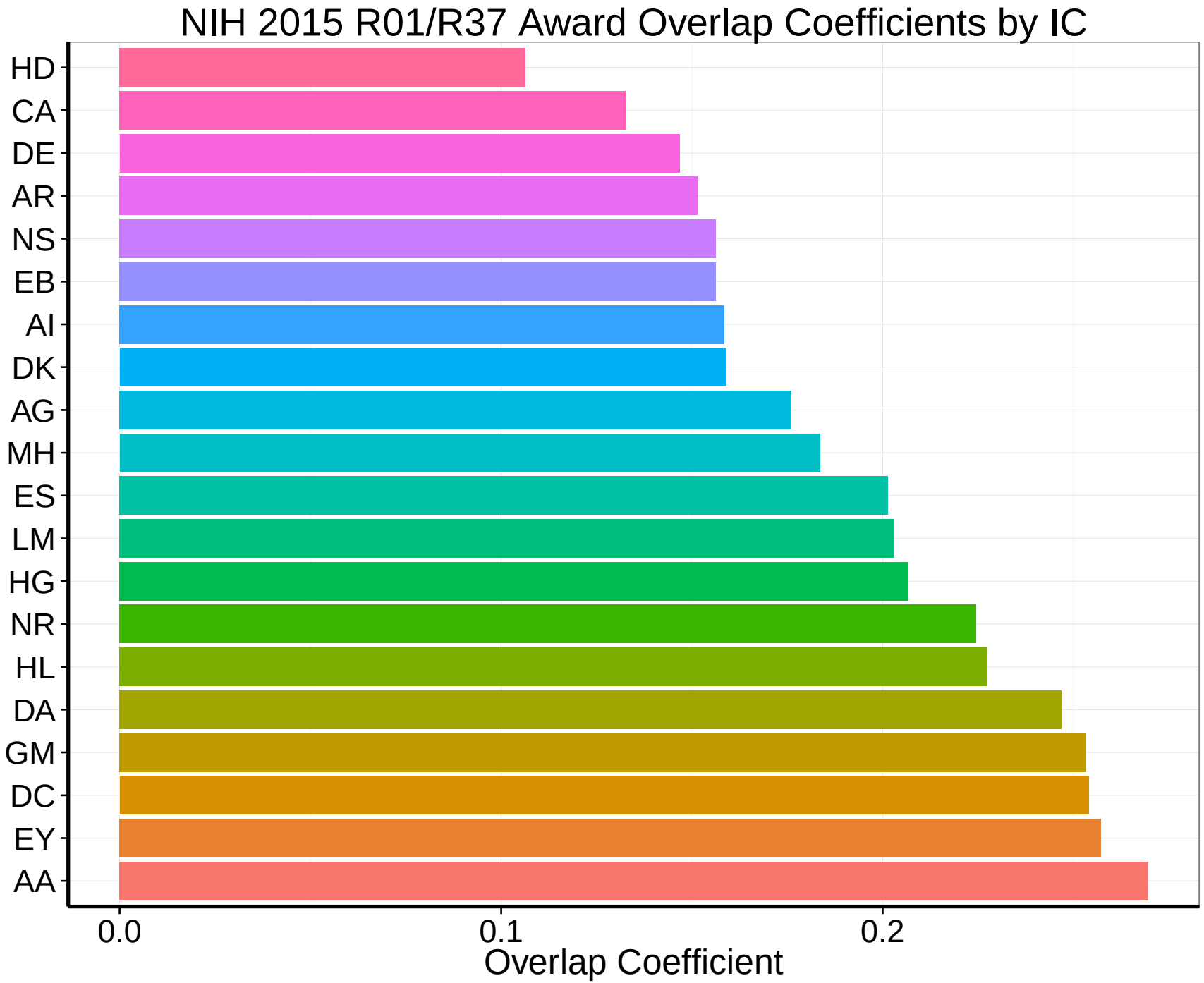
NINDS Funding Outcomes

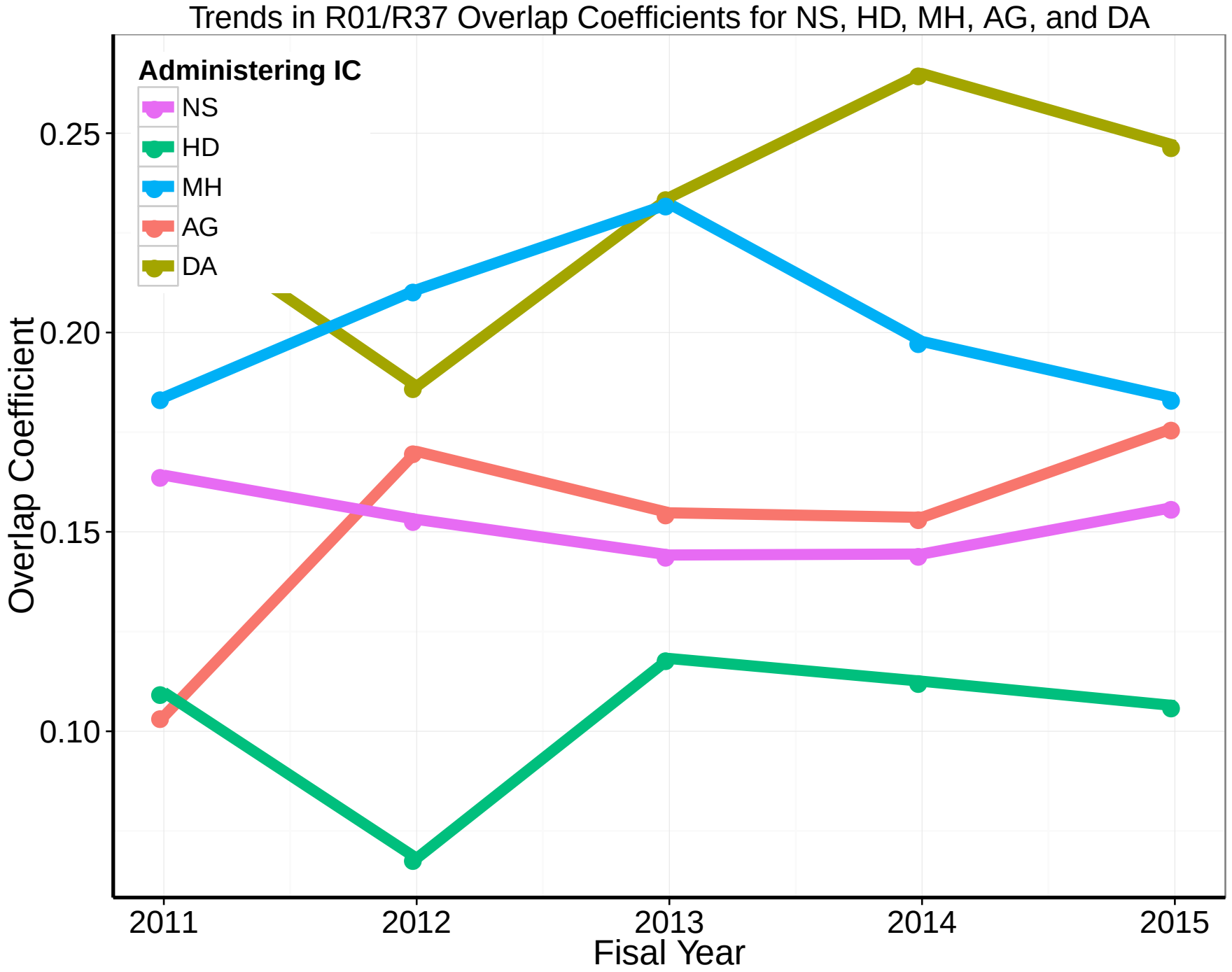


All Investigators



New Investigators


NIH 2015 R01/R37 Award Overlap Coefficients by IC
HD
CA
DE
AR
NS
EB
AI
DK
AG
MH
ES
LM
HG
NR
HL
DA
GM
DC
EY
AA
0.0
0.1
0.2
Overlap Coefficient


Trends in R01/R37 Overlap Coefficients for NS, HD, MH, AG, and DA
Administering IC
NS
HD
MH
AG
DA
0.25
0.20
0.15
0.10
Overlap Coefficient
2011
2012
2013
2014
2015
Fisal Year

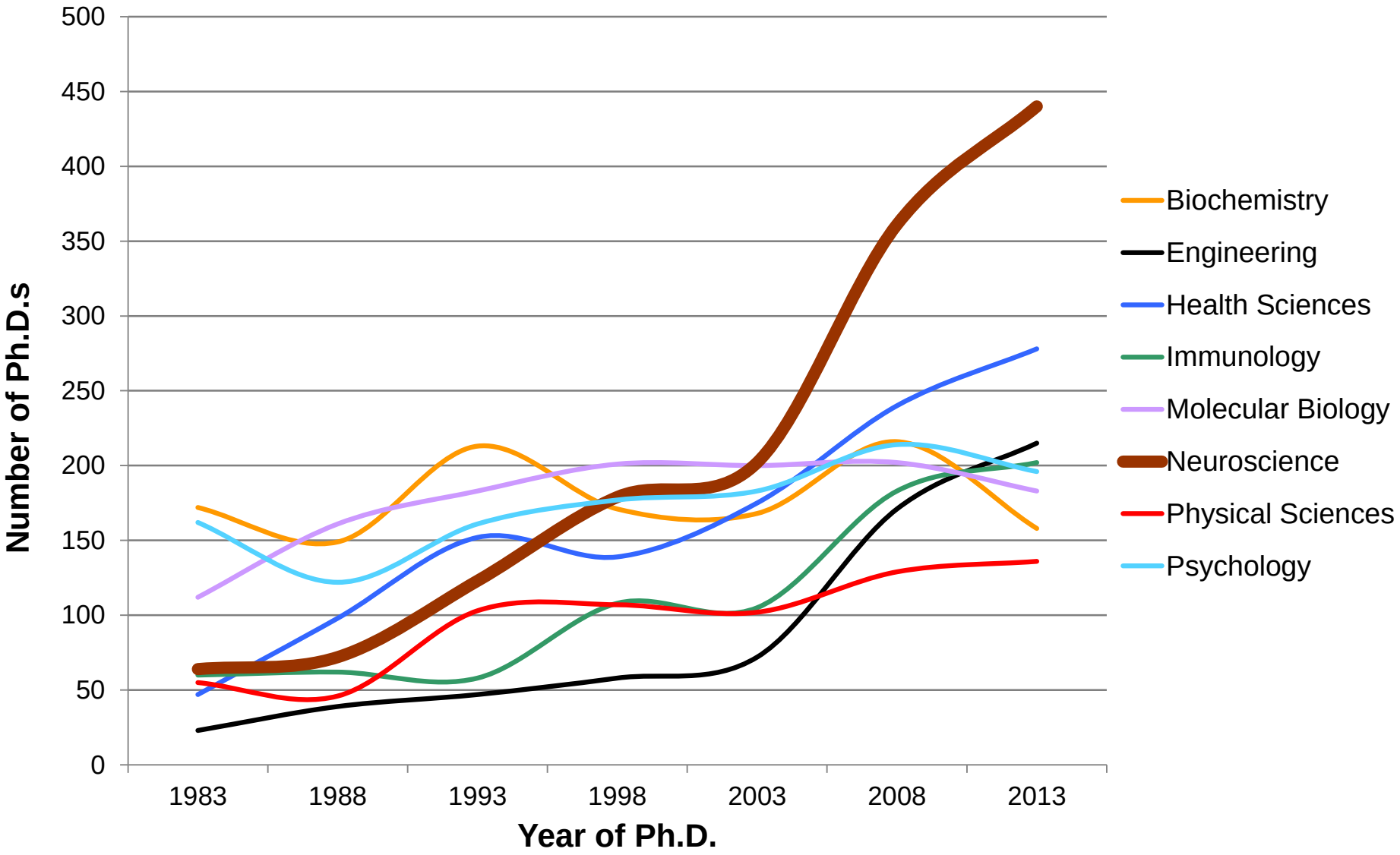
Thoughts

- IC's more similar than different
- Not going strictly by payline
  - NIH overlap coefficient: 0.23; IC range: 0.11 to 0.26
  - Important to understand NINDS data more completely
    - Trend indicates our consistent approach to funding almost all applications below the payline
- How to communicate?
  - Funding strategies
  - Actual funding outcomes
  - Select pay is better seen in funding of initiatives, P's,

Neuroscience Training: *What's Changed?*

- Neuroscience is expanding in multiple directions
- Numbers of graduate students increased dramatically
- Time to independence increased dramatically
- Tools have become more sophisticated, and an increased degree of sophistication is needed for data analysis
- New emphasis on attracting scientists from outside biology
- New emphasis on rigor in experimental design and statistical analysis
- Funding climate became much more competitive during the 12 flat budget years and concern that associated pressures led to decline in career mentoring
- Early movement within BRAIN initiative to adapt a more "physics-like" model to engage team science to attack problems
  - Data platforms and data sharing
- Concern that attempts to increase diversity in trainees not translating as well as hoped into diversity in the academic science workforce

Trends in Fields of Study of Trainees and Fellows Receiving Ph.D.s



IOM Neuroscience Forum:

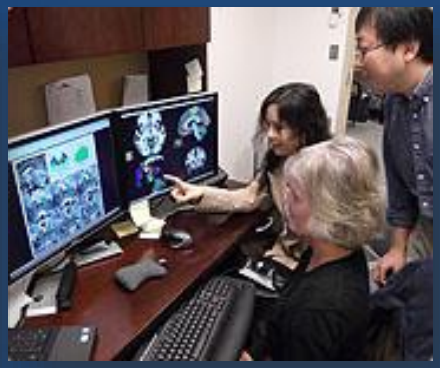
Defining the Expertise Needed for a 21st Century Neuroscience Workforce

- Transdisciplinary training.
  - Training for neuroscientists needs more:
    - mentoring
    - experimental and analytical skills
    - communication and writing skills
    - lab and office management
    - ethics in science
    - fundamental neuroscience knowledge and its history,
    - teaching and mentoring
  - Training "in neuroscience" needs:
    - tracks for those coming from physical and computational backgrounds
    - team science
    - tracks for translational science

IOM Neuroscience Forum:

Defining the Expertise Needed for a 21st Century Neuroscience Workforce

- Experimental and analytical skill development
  - Statistical reasoning and facility in statistical methods
  - Reducing bias by training for rigorous experimental design
  - Demystify neurotechnologies
  - Data analytic skills
    - programing, data management platforms, multidimensional cloud computing, data visualization and feature extraction, algorithm development, machine learning and computer modeling

NINDS

Seeking Knowledge about the Brain . . .

Reducing the Burden of Disease