# **National Institutes of Health Update**

#### **Council of Councils**

January 25, 2019





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# **Topics for Today**

- Budget Update
- The NIH INCLUDE Project (INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE)
- Artificial Intelligence Working Group Update
- New HEAL Programs



# **Topics for Today**

#### Budget Update

- NIH INCLUDE Project
- Artificial Intelligence Working Group Update
- New HEAL Programs



# National Institutes of Health Funding 1990-2019



Note: Dollar values are adjusted to 2019 dollars using the Biomedical Research and Development Price Index (BRDPI), http://officeofbudget.od.nih.gov/gbiPriceIndexes.html. Source: NIH Office of Extramural Research and Office of Budget source data (February 2, 2018).

### FY 2019 at a Glance

(\$ in thousands)	FY 2018	FY 2019	Change from FY 2018 (\$)	Change from FY 2018 (%)
NIH Program Level	\$37,224,080	\$39,311,349	\$2,087,269	5.6%

- \$2 billion increase over FY 2018 enacted.
- General increase for Institutes and Centers of more than three percent.
- Together with the \$7 billion of increases in FY 2016 through FY 2018, more than half of NIH's loss of purchasing power since FY 2003 has been restored.

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#### **The NIH INCLUDE Project:**

### INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE



Mr. Frank Stephens' testimony to the House Appropriations Committee on October 25, 2017

#### The case for research in Down syndrome

- Each year, ~ 6000 infants with Down syndrome born in U.S.
- Lifespan for people with Down syndrome has doubled in 25 years



### New Opportunity for NIH on Down Syndrome

#### In the FY 2018 budget legislation for NIH:

"Develop a new trans-NIH initiative to study trisomy 21, with the aim of yielding scientific discoveries to improve the health and neurodevelopment of individuals with Down syndrome and typical individuals at risk for:

- Alzheimer's disease
- Leukemia
- Heart defects
- Immune system dysregulation
- Autism
- and other conditions..."

Protected from:

- Many cancers
- Heart disease and heart attacks

 Unique double benefit: understanding both Down syndrome and shared common conditions (risks or resiliencies)

#### Total NIH Funding for Research on Down Syndrome FY 2008 – FY 2018



### The NIH INCLUDE Project: FY18 Kick-Off

- Dual solicitations
  - Expansion of a currently-supported Down syndrome project
  - Amend or augment an existing project to add a Down syndrome component (e.g. biological samples, trial participants)
- Latter strategy may draw fresh perspective into the Down syndrome research community
- Begins to address need to include individuals with Down syndrome into ongoing clinical research

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THE INCLUDE					

#### **INCLUDE Project Research Plan**

#### The INCLUDE Project Research Plan

(INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndrome)

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On this page Budget Introduction Background Research **Future Direction** Engagement Leadership

#### Introduction



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Conclusion

#### URL: <a href="https://www.nih.gov/include-project">https://www.nih.gov/include-project</a>

### The NIH INCLUDE Project: Research Plan

3 components to address key quality-of-life issues for individuals with Down syndrome and their families:

- 1. Targeted, high-risk, high-reward basic science studies on chromosome 21
- 2. Build a large cohort of individuals with Down syndrome for comprehensive analysis and biomarker evaluation
- 3. Include individuals with Down syndrome in existing and future clinical trials

### Fiscal Year 2018 INCLUDE Funding

#### \$22.2 M supported 49 awards

- 14 NIH Institutes participating
- Addressed all 3 INCLUDE plan components
- Data sharing expectation

Funding Opportunities

#### Funded Projects

- The Alzheimer's Clinical Trial Consortium Down Syndrome Network (ACTC- DSN)
- Neurodegeneration in Aging Down Syndrome (NiAD): A Longitudinal Study of Cognition and Biomarkers of Alzheimer's Disease
- Identification of optimum spectacle prescriptions for patients with Down syndrome
- Neurobehavioral Research on Infants at Risk for Language Delay and ASD
- MRI & CT studies of the developing vocal tract
- National Alzheimer's Coordinating Center (NACC)
- Treating with Gamma-Secretase Modulators to Prevent Neurodegeneration in Mouse Models of Down Syndrome and Alzheimer
  Disease
- Biomarkers of Alzheimer's Disease in Adults with Down Syndrome (ADDS)
- Mechanisms of white matter development in Down syndrome
- Data Fusion: A Sustainable, Scalable, Open Source Registry Advancing PVD Research
- Generation of isogenic trisomy 21 iPSC resource
- A Computational Biomechanical Airway Model for Obese Children at Risk for OSAS
- Human ISG15 and USP18 deficiencies underlying type-I interferonopathies
- Mechanisms of IL-6 mediated T cell pathogenesis in autoimmunity
- Genome-wide search for inborn errors of IL-17 immunity underlying chronic mucocutaneous candidiasis
- Dimensional Analysis of Developmental Brain Disorders using an Online, Genome first Approach/Dimensional, Sleep, and
  Genomic Analyses of Down Syndrome to Elucidate Phenotypic Variability

#### URL: https://www.nih.gov/include-project

#### **INCLUDE Component 1** *Targeted, high-risk, high-reward basic science studies*

#### **Emerging scientific areas:**

- Examine the roles of multiple genes on chromosome 21 simultaneously
- Explore chromosome silencing
- Evaluate epigenetic/ metabolomic/ transcriptomic profiling in model organisms/iPSCs/brain organoids in several model systems
- Develop novel model systems, including a molecular atlas for cardiac and other specimens

#### **Emphasis on studies that can inform the other two components for a cohesive approach and have potential for clinical translation**<sub>15</sub>

#### **INCLUDE Component 2: A Few Examples of Funded Studies** *Assemble a large cohort for pan-'omics and biomarker studies*

- Two Gabriella Miller/Kids First Studies (NIH Common Fund with NHLBI, NCI and NICHD)
  - Genomic Analysis of CHD and ALL in Children with Down Syndrome
  - Germline and Somatic Variants in Myeloid Malignancies in Children
- Alzheimer's Biomarkers Consortium-Down syndrome multi-site projects (PIs: Handen, Schupf, NIA)
- Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Center at Vanderbilt University-ASD cohort that would expand to Down Syndrome (PI: Neul, NICHD)
- Clinical Evaluation of Pulmonary Hypertension in Down syndrome-pediatric cohort would expand to Down syndrome (PI: Abman, NHLBI)

#### *Emphasis on building cohort across life stages to address key health and quality-of-life issues*

### **INCLUDE Component 3**

Build a clinical trials network for inclusion in existing and future clinical trials

- Extremely limited medication trials in DS have been underpowered and lacked efficacy
- Need to test how commonly used medications affect people with Down syndrome
- Need to develop clinical measures appropriate for Down syndrome

# Emphasis on building clinical research resources to achieve full inclusion now and in the future

### INCLUDE Workshop: "Alzheimer's Disease Clinical Trials in Down Syndrome" Planning Meeting

- Alzheimer's Disease is major concern among Down syndrome community
- Held November 7 at NIH, coordinated with NICHD and NIA
- Down syndrome and Alzheimer's Disease advocacy communities participated
- Investigators engaged in clinical trials and cohort studies of Alzheimer's Disease and/or Down syndrome

#### Partnership through the Down Syndrome Consortium



NIH convened in July and November to engage on the INCLUDE Project



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THE INCLUDE	PROJECT				

### 2019 Support and beyond:

- FY19 Funding Opportunity Announcements

   Notice of Intent to Publish released Jan. 3
- Workshops in early 2019:
  - "Planning a Virtual Down syndrome Cohort across Lifespan" (April 15-16)
  - "The State of the Science for Meaningful Clinical Trials in Down syndrome" (Date TBD)

#### **INCLUDE Project Research Plan**

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#### URL: <u>https://www.nih.gov/include-project</u>



#### **INCLUDE** Steering Committee

Anna Mazzucco, Office of the Director, NIH Lawrence Tabak, Office of the Director, NIH



#### Malcolm Smith





Melissa Parisi

NICHD



Lisa Kaeser NICHD



Gail Pearson NHLBI



**Robert Riddle** NINDS



**Charlene Schramm** 

NHLBI



Donna Krasnewich NIGMS



Sujata Bardhan NICHD



**NINDS** 



Laurie Ryan 21 NIA

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### **Industrial Revolutions**



# **Data Science at NIH: A Snapshot**

- CIT supports a 100GB Network moving 4PB of data per day
- Datasets and resources
  - List of extramural programs generating datasets (only a subset)
  - Datasets supported across IC and topic area
  - Range in size from several hundred terabytes to several petabytes
    - SRA and dbGaP, ~15 PB of genomic sequence data
      - Controlled access ~8 PB
      - Open access ~6 PB
    - GTEx, ~200 TB

DATASET	Primary IC
ABCD (Adolescent Brain Cognitive	
Development)	МН
Accelerating Medicine Partnership - Parkinson's	
Disease (AMP PD)	NS
Age-Related Eye Disease Study (AREDS2)	EY
All of Us Research Program	OD
BRAIN Initiative	many
Biomedical Translational Research Information	
System (BTRIS)	СС
dbGAP	NL
Framingham Studies	HL
Gabriella Miller Kids First Pediatric Research	
Program	CF/HL
Genotype-Tissue Expression (GTEx)	CF/HG
Cancer Genome Characterization Initiative	
(CGCI)	NCI
Analysis, Visualization, and Informatics Lab-	
space (AnVIL)	HG
Chest and Cardiac Image Archive	HL
Genetics of Alzheimer's Disease Project	
(NIAGADS)	NIA
RSNA Radiology Image Share	EB
The Cancer Genome Atlas Project (TCGA)	NCI
TOPMed	HL
Alliance for Genome Resources Model Organism	า
Databases (MODs)	HG
ClinVar	NL
dbSNP	NL
ENCODE	HG
Gene Expression Omnibus (GEO)	NL
MACS/WIHS Longitudinal AIDS Data	AI
Neuroimaging Tools & Resources (NITRC)	EB
SRA	NL
UniProt	HG/GM
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### **Every Day Artificial Intelligence Applications**



### AI/ML/DL in Biomedicine

#### Clinical applications

- Pathology diagnostics
- Dermatology, ophthalmology diagnostics
- Radiology mammograms, CXRs,...
- Inferring treatment options for cancer
- Robotic surgery
- Natural language processing of EHR data

#### Basic science applications

- Interpretation of images: cryo-EM, confocal, etc.
- Neuroscience and the BRAIN initiative
- Genomics: variants and risk of disease, gene structure
- Microbiome/metagenomics
- Epigenomics: histone marks, TF binding, enhancers, DNA methylation



**H** National Institutes of Health Turning Discovery Into Health

#2018biomedAl

**NIH WORKSHOP** 

Harnessing **Artificial** Intelligence and Machine Learning to **Advance Biomedical** Research

**JULY 23, 2018** 

### **Newly Formed AI Working Group Members**



Rediet Abebe Cornell



Greg Corrado, PhD Google



David Glazer Verily (Co-Chair)

Insitro



Eric Lander, PhD **Broad Institute** 



Lawrence Tabak, DDS, PhD NIH (Co-Chair)



Michael McManus, PhD Intel



Barbara Engelhardt, PhD Princeton



Dina Katabi, PhD MIT Computer Science & AI Lab



Anshul Kundaje, PhD Stanford University



Jennifer Listgarten, PhD Berkeley



Serena Yeung, PhD Harvard

# **Charge to the AI Working Group**

- Are there opportunities for cross-NIH effort in AI? How could these efforts reach broadly across biomedical topics and have positive effects across many diverse fields?
- How can NIH help build a bridge between the computer science community and the biomedical community?
- What can NIH do to facilitate training that marries biomedical research with computer science?
  - Computational and biomedical expertise are both necessary, but careers may not look like traditional tenure track positions that follow the path from PhD to post-doc to faculty
- Identify the major ethical considerations as they relate to biomedical research and using AI/ML/DL for health-related research and care, and suggest ways that NIH can build these considerations into its AI-related programs and activities

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## **The Crisis: National Overdose Death Rates**

#### In 2017, there were 70,237 overdose deaths (9.6% higher than 2016)



Source: https://www.cdc.gov/nchs/data-visualization/drug-poisoning-mortality/index.htm

### The Response: Helping to End Addiction Long-term (HEAL) Initiative

- Trans-NIH research initiative to:
  - Improve prevention and treatment strategies for opioid misuse and addiction
  - Enhance pain management
- Goals are scientific solutions to the opioid crisis
- Coordinating with the HHS Secretary, Surgeon General, federal partners, local government officials and communities



### www.nih.gov/heal-initiative

### Helping to End Addiction Long-term (HEAL) Initiative: At a glance

- \$500M/year Trans NIH effort
  - Over \$850M to be obligated in FY2019
- 12 NIH Institute and Centers leading 26 HEAL research projects
  - Over 20 collaborating Institutes, Centers and Offices
  - From prevention research, basic and translational research, clinical trials, to implementation science
  - Multiple projects integrating research into new settings
    - e.g. health care, criminal justice, Medicare populations etc.
- Released 36 funding announcements for FY2019

### Improving Prevention and Treatment for Opioid Misuse and Addiction

#### **Priority Research Areas:**

Expand Therapeutic Options

#### *Optimize Effective Treatment Strategies*

Develop New/Improved Prevention & Treatment Strategies

Enhance Treatments for Infants with NAS/NOWS

#### **Research Opportunities:**

- New formulations
- Longer duration
- Respiratory depression
- Immunotherapy
- New targets and approaches

- Clinical trials expansion
- Criminal justice innovation
- Behavioral interventions
- Multi-site implementation (HEALing Communities Study)
- Transition to adulthood
- Sleep dysfunction
- Early/moderate OUD
- Optimal length of Tx
- Collaborative care

- Advancing ACT NOW
- Cognitive development of opioid-exposed infants

# **Recent Advances in Medications Development**

- Narcan Nasal Spray
  - First FDA-approved nasal spray version of naloxone, November 2015
- Sublocade<sup>™</sup> (Buprenorphine ER)
  - Once-a-month injectable
  - FDA Approval, November 2017
- XR-Naltrexone and Buprenorphine-Naloxone
  - Shown to be equally safe, effective in preventing relapse, January 2018
- Lofexidine
  - Treat opioid withdrawal symptoms
  - FDA approved, May 2018



THE LANCET

Vol 391 January 27, 2018

Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial

Joshua D Lee, Edward V Nunes Jr, Patricia Novo, Ken Bachrach, Genie L Bailey, Snehal Bhatt, Sarah Farkas, Marc Fishman, Phoebe Gauthier, Candace C Hodgkins, Jacquie King, Robert Lindblad, David Liu, Abigail G Matthews, Jeanine May, K Michelle Peavy, Stephen Ross, Dagmar Salaza Paul Schkolnik, Dikla Shmueli-Blumberg, Don Stablein, Geetha Subramaniam, John Rotrosen

#### Medscape

### FDA Panel Backs Approval of Lofexidine for Opioid Withdrawal

March 28, 2018

## **Research Priority: Expand Therapeutic Options**

- New Formulations of Existing Medications
  - promote adherence to treatment and prevent medication misuse
- Longer Duration Formulations
  - Opioid antagonists to reverse overdose
- Interventions Against Respiratory Depression
  - New classes of compounds and devices
- Novel Medications, Immunotherapies and Devices
  - Treatment of withdrawal, craving, and relapse
- New Medication Targets
  - New addiction treatments via focused medications development



## Research Priority: Optimize Effective Treatment Strategies

- NIDA Clinical Trials Network (CTN) Expansion
  - New research sites and studies (e.g., duration of treatment) in general medical/other settings
- Opioid Innovation in the Criminal Justice System
  - Justice Community Opioid Innovation Network (JCOIN)
  - Generate real-world evidence to address needs of individuals with OUD in justice-settings
- Behavioral Interventions
  - Behavioral Research to Improve Medication Assisted Treatment (BRIM)
  - Collaboration with SAMHSA to enhance behavioral or social interventions to improve adherence to medication assisted treatment for OUD
- HEALing Communities Study
  - Test integrated strategies in communities highly-affected by opioid crisis



### **Research Priority:**

#### **Develop New/Improved Prevention and Treatment Strategies**

#### Transition to Adulthood

- Studies to prevent OUD in older adolescents and young adults
- Sleep Dysfunction
  - Sleep and circadian factors relevant to addiction
- Management of Subsyndromal and Low-severity OUD
  - Identify and treat patients in general medical settings with co-occurring pain/mental health disorders
- Optimal Length of Medication Treatment
  - Randomized clinical trial of buprenorphine and methadone
- Collaborative Care Model
  - Adapted to patients with OUD and mental health conditions



# Research Priority: Enhance Treatments for Infants with NAS/NOWS

- Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome (ACT NOW)
  - Innovative ways to identify and treat newborns exposed to opioids
- Cognitive Development of Opioid-exposed Infants
  - Understand changes in brain and behavior resulting from early exposure to opioids
- HEALthy Brain and Child Development Study



### Heal Programs for Pain Cover the Research Spectrum



## Translating Discoveries into Effective Devices for Pain Treatment

#### Reduce reliance on opioids through the enhanced targeting and reduced invasiveness of diagnostic and therapeutic pain management devices

<u>B</u>rain <u>R</u>esearch through <u>A</u>dvancing <u>I</u>nnovative <u>N</u>eurotechnologies



<u>Stimulating Peripheral</u> <u>Activity to</u> <u>R</u>elieve Conditions



- Leverage ongoing mapping / target discovery activities
- Late stage device development
- Verification and validation to accelerate regulatory approval
- Early clinical studies to de-risk new treatments

## Early Phase Pain Investigation Clinical Network + Data and Asset Sharing Partnership

#### Improve quality, consistency, efficiency of early phase pain clinical trials

- EPPIC-net will test peer-reviewed compounds and devices from industry and academia
- Clinical Coordination Center, Data Coordination Center, 10 specialized clinical sites (hub and spoke design)
- Incentivize, accelerate Phase II trials
- Focus on well-defined pain conditions with high-unmet need
- Reduce the time to start, enroll, run, and complete trials
- Incorporate biomarker studies
- Accommodate platform trial designs

#### Data and Asset Sharing Partnership

 EPPIC-net Data Coordination Center will host data and biosample repositories from HEAL programs and industry partners



#### Back Pain Research Consortium: BACPAC

# Probe biopsychosocial mechanisms of back pain, test new precision treatments, and develop predictive algorithms for integrated, multimodal back pain care

- Explore linkages between structural, dynamic, cellular, or molecular abnormalities to specific patient-reported symptoms and function
  - Characterize mechanisms and improve phenotyping in clinical cohorts
  - Develop and deploy technology for discovery, diagnostics, and treatment
  - Data integration and modeling
- Conduct clinical trials for new non-addictive drugs, biologics, devices and complementary approaches to relieve pain and improve physical function
  - safety and efficacy trials
  - integrated care trials
  - mechanistic trials
- Develop patient-centered algorithms to predict optimal treatment
  - Collect and analyze data from across the consortium's studies



### Pain Management Effectiveness Research Network and Trials

#### **Evaluate effectiveness of pharmacologic and nonpharmacologic therapies for a broad array of pain conditions**

- Comparative Effectiveness Research leveraging NCATS' Trial Innovation Network
- Pain expertise in coordinating centers
- NIH will solicit proposals for Phase 3 clinical trials to inform best practices in pain management and minimize risk of addiction
- Coordinate data elements and storage with EPPIC-net and PRISM

### Integrated Approach to Pain and Opioid Use in Hemodialysis Patients

#### Develop tailored interventions for pain control for hemodialysis patients

- Evaluate non-addictive analgesics to reduce pain
- Evaluate behavioral approaches for pain management
- Identify risk factors for opioid dependence
- Assess and treatment co-morbid conditions
- Enhance electronic health records to capture study outcome data

#### Pragmatic and Implementation Studies for Management of Pain to Reduce Opioid Prescribing: PRISM

# Integrate evidence-based pain management interventions with demonstrated efficacy into health care systems

- Embed the intervention under study into real world settings
- Collect data through the electronic records
- Leverage the NIH Health Care Systems Collaboratory
- Focus on non-pharmacological approaches
- Collaborate with CMS for Medicare coverage consideration











# Lawrence.Tabak@nih.gov Turning Discovery Into Health







