

# Some Observations from the NIH Director

Francis S. Collins, M.D., Ph.D.

Director, National Institutes of Health

CSR Advisory Council Meeting

March 25, 2019



# NIH and CSR:

## Built on Strong Yet Flexible Foundations

- 1944: National *Institute* of Health and the Public Health Service Act
  - National Cancer Institute a division of NIH
  - Authorized clinical research – and grants program
- 1946: Division of Research Grants established
  - Study sections; dual review

National Cancer  
Institute

Division of  
Research Grants

### The Public Health Service Act

58 STAT.] 78TH CONG., 2D SESS.—CH. 373—JULY 1, 1944

[CHAPTER 373]

AN ACT

July 1, 1944  
[H. R. 4024]  
[Public Law 410]

To consolidate and revise the laws relating to the Public Health Service, and for other purposes.

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

#### TITLE I—SHORT TITLE AND DEFINITIONS

##### SHORT TITLE

Public Health Service Act.

SECTION 1. Titles I to V, inclusive, of this Act may be cited as the "Public Health Service Act".

(d) Make grants in aid to universities, hospitals, laboratories, and other public or private institutions, and to individuals for such research projects as are recommended by the National Advisory Health Council, or, with respect to cancer, recommended by the National Advisory Cancer Council;

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- 1948: National *Institutes* of Health
  - DRG oversees grants process

National Cancer  
Institute

Division of  
Research Grants

National Heart  
Institute

National  
Microbiological  
Institute

National Institute  
of Dental  
Research

Experimental  
Biology &  
Medicine Institute

Fiscal Year	No. of Projects	Total Funds	Percentage Growth in Funds
1946	80	780,158	70.0
1947	354	3,437,280	340.6
1948	1,050	8,874,463	158.0
1949	1,133	10,871,492	22.5
1950	1,533	12,984,000	19.4
1951	1,723	16,374,128	26.1
1952	1,884	18,408,000	12.4
1953	2,000	20,518,000	11.5

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- 1997: DRG becomes CSR



“Establishment of the Center is designed to signal a broadening of the mission to include new emphasis on the development and implementation of innovative and flexible ways to conduct referral and review for all aspects of science.”

~1997

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### In 2018, CSR:

- Received 81,000 NIH grant applications
  - Reviewed ~77 %
- Engaged the expertise of 18,000 extramural reviewers
- Held 1,600 review meetings

*Thank you, CSR!*



# Continuing the Fine CSR Tradition: Welcome, Director Byrnes!



# NIH: Steward of Medical and Behavioral Research for the United States



“Science in pursuit of **fundamental knowledge** about the nature and behavior of living systems ... and the **application of that knowledge** to extend healthy life and reduce illness and disability.”



# NIH's Impact on U.S. Health and Medicine

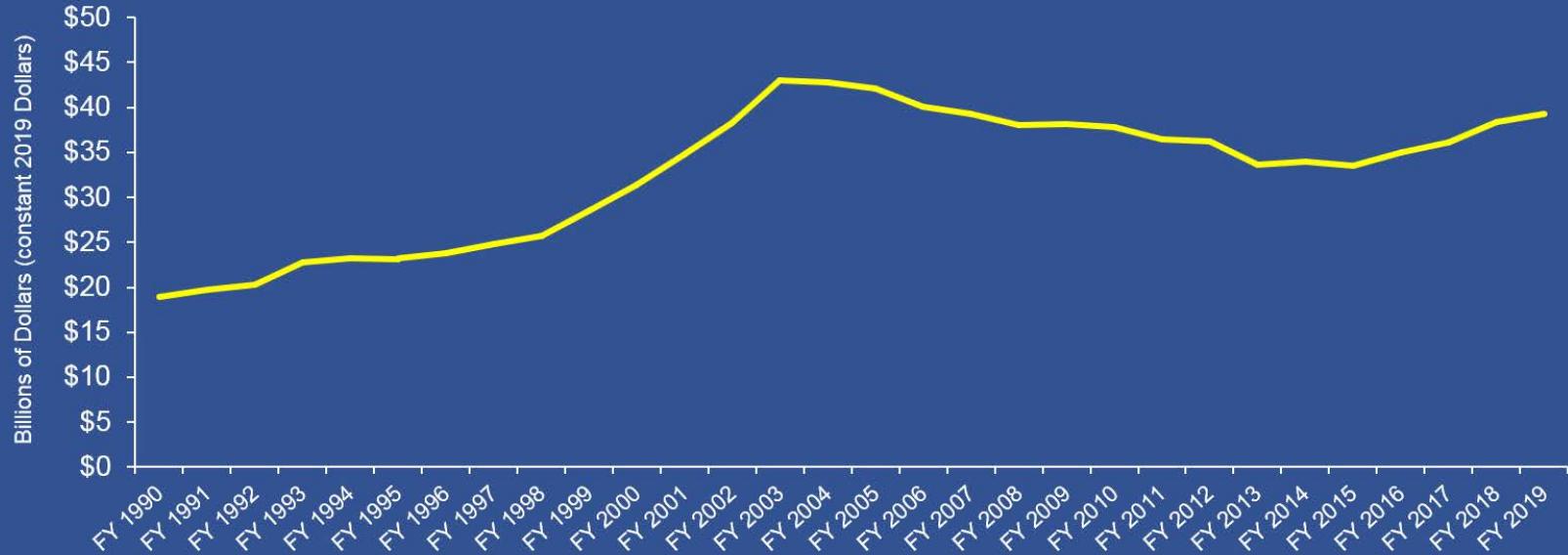
## U.S. Life Expectancy



- Cardiovascular disease death rates have fallen more than 70% in the last 60 years
- Cancer death rates falling more than 1% per year; each 1% drop saves ~\$500 billion
- HIV therapies enable people in their 20s to live to age 70+



# 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).

# Exceptional Opportunities in Biomedical Research

- Uncovering the Secrets of Nature
- Unlocking the Clinical Potential of Biomedical Advances
- Translating Discovery Into Health – for *All of Us*
- Supporting Research Essentials

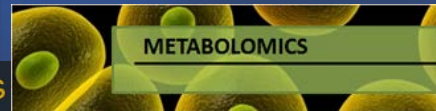
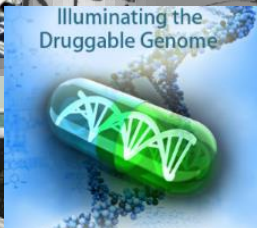
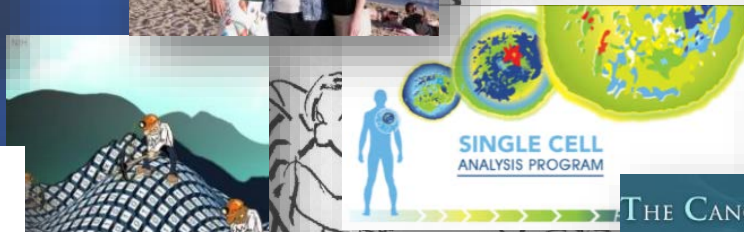




## *The Human Genome Project: 1990–2003*







**Rethinking Clinical Trials™**

*A Living Textbook of Pragmatic Clinical Trials*

**GTR: GENETIC TESTING REGISTRY**

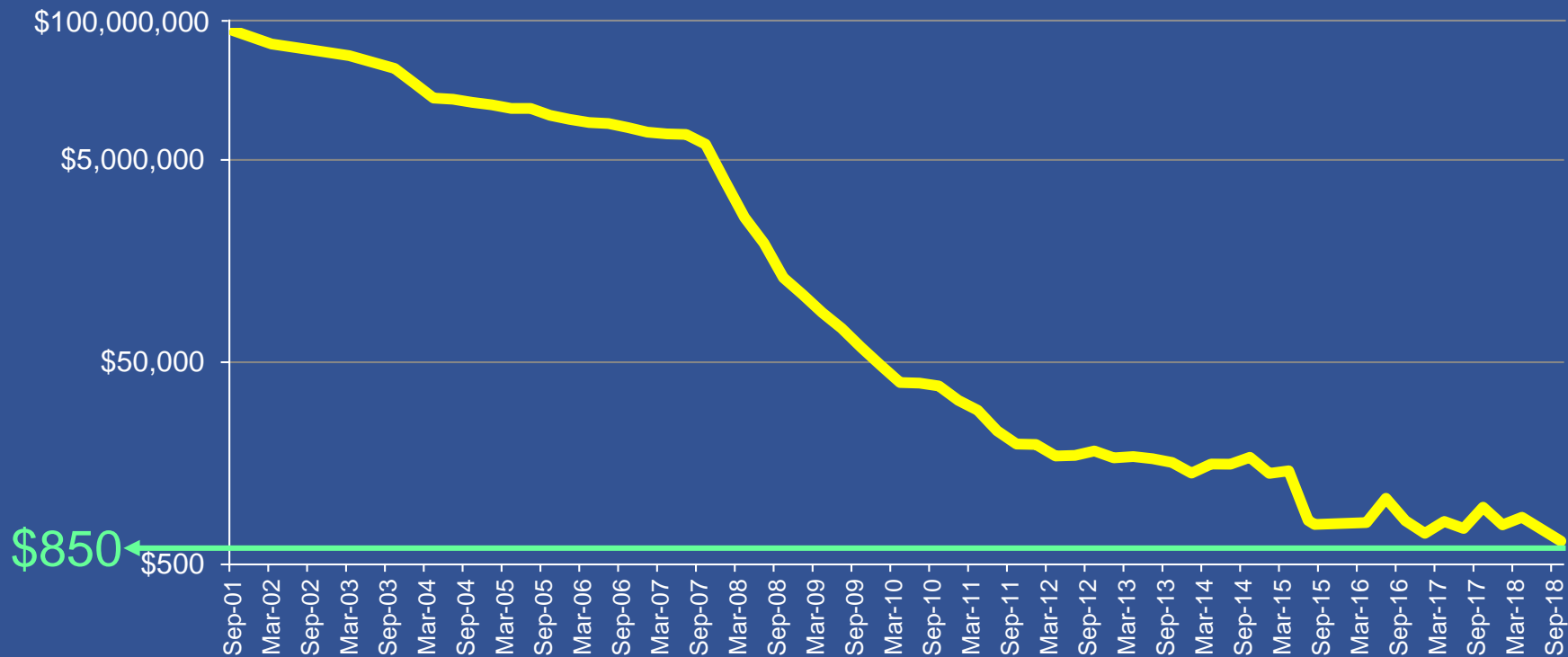


**1000 Genomes**  
A Deep Catalog of Human Genetic Variation



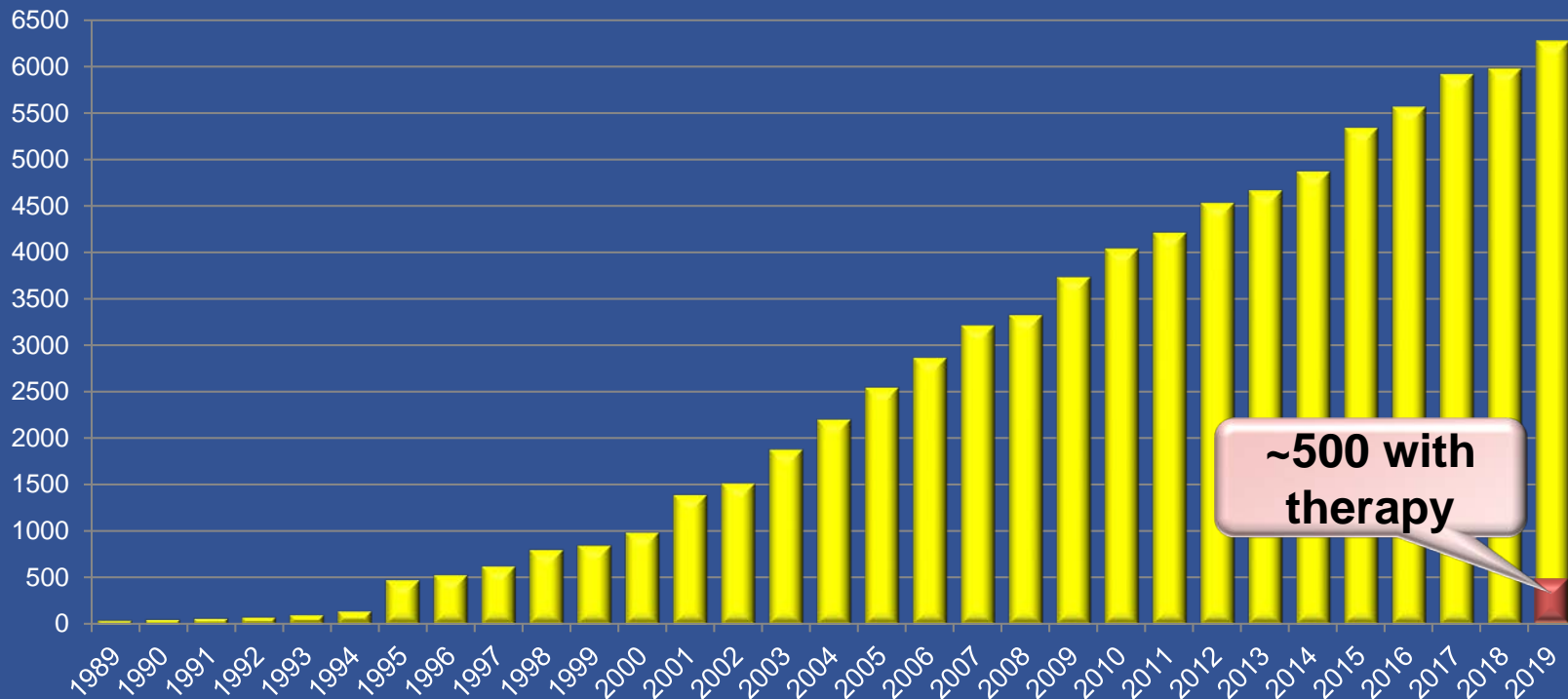
# Cost of Sequencing a Human Genome

September 2001–October 2018





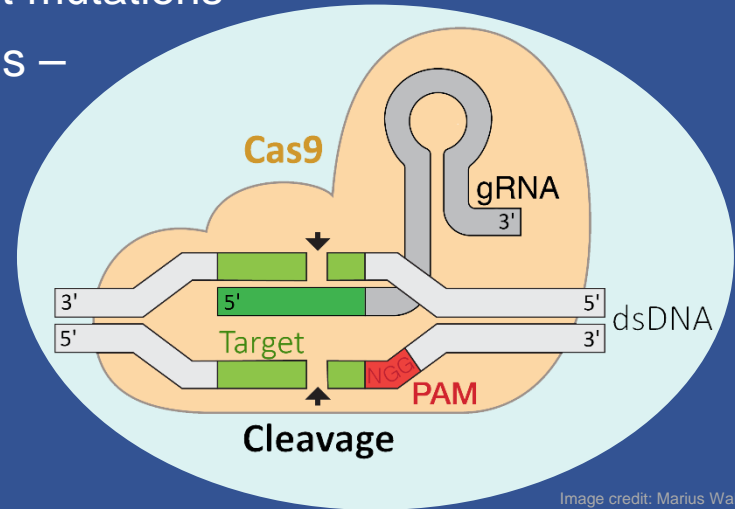
# Disorders with Known Molecular Basis



Source: Online *Mendelian Inheritance in Man*, Morbid Anatomy of the Human Genome

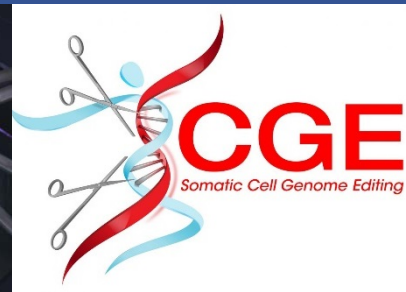
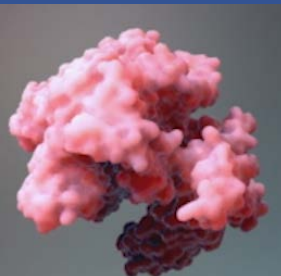
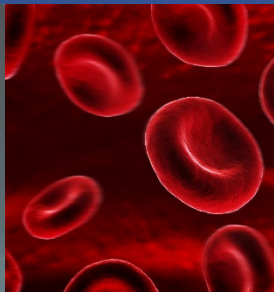
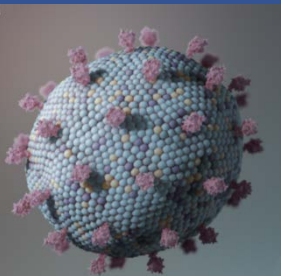
# CRISPR-Cas9 Gene Editing

- Arose from basic science studies of yogurt, bacteria viruses
- Achieves targeted editing of genomes with enzyme + guide RNA
  - Initial approaches created knockouts; expanded to induce repair by homologous recombination
  - Base editing technologies can correct point mutations
- Has accelerated production of mouse models – and revolutionized basic molecular biology
- Paves the way for new therapeutics



# Somatic Cell Genome Editing Program

- New NIH Common Fund program to speed development of safe, effective editing tools for *in vivo* applications in human patients
- Is awarding \$190M over six years to:
  - Develop new technologies for improving *in vivo* delivery of genome editing tools
  - Improve safety and efficacy testing
  - Make tools, data widely available



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# Fulfilling The Promise...

## *Toward 1st Cure for 1st Molecular Disease?*

### Sickle Cell Disease (SCD)

- 1910: Disease described
- 1949: Inheritance shown to be recessive
- 1957: Genetic basis determined
- 1980: Hemoglobin genes cloned
- 1998: Hydroxyurea, first approved SCD drug
- Recently: Bone marrow transplants, but few patients have match
- Today: Genetic therapy

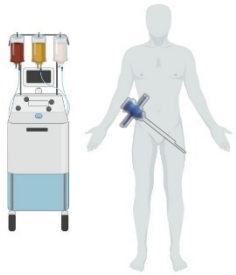




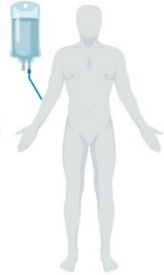
# Gene Therapy for Sickle Cell Disease

*John Tisdale, NIH in Collaboration with Bluebird Bio*

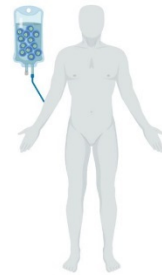
Hematopoietic  
stem cell (HSC)  
collection



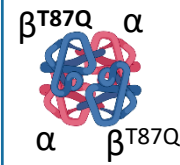
Bone marrow  
conditioning



Gene-modified HSCs  
infusion



Modified HSCs reconstitute  
blood with functional red  
blood cells (RBCs)



Modified RBCs  
express gene  
therapy-derived  
HbA<sup>T87Q</sup>

2-yr follow-up

Long-Term  
Follow-Up Study

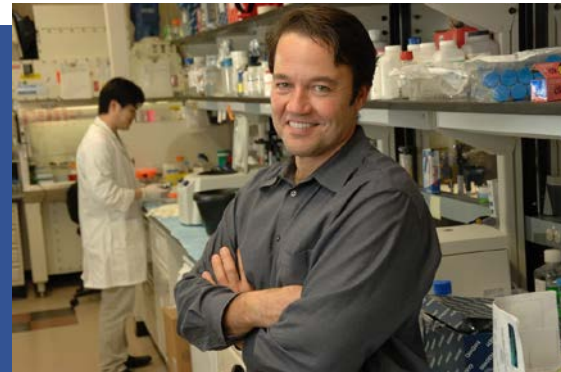
Making the Gene Therapy Product



Select specific  
HSCs (CD34+)

Introduce lentiviral  
vector (HbA<sup>T87Q</sup>)

Cryopreserve  
and test gene-  
modified HSCs



# Dr. Tisdale's Research Featured on *60 Minutes*\*



Jennelle Stephenson

A screenshot of the National Institutes of Health (NIH) website. The header includes the NIH logo, the text 'National Institutes of Health' and 'Turning Discovery Into Health', a search bar, and links for 'NIH Employee Intranet', 'Staff Directory', and 'En Español'. A navigation bar contains links for 'Health Information', 'Grants &amp; Funding', 'News &amp; Events', 'Research &amp; Training', 'Institutes at NIH', and 'About NIH'. The main content area features a blue banner titled 'NIH on 60 Minutes' with the text 'Learn more about Jennelle's journey with NIH to cure her sickle cell disease, as featured on CBS 60 Minutes.' and a 'Learn more »' button. To the right of the text is a photograph of Jennelle Stephenson looking up while a hand places a white cloth on her forehead. At the bottom of the blue banner are five white dots, with the fourth dot from the left being filled.

\*March 10, 2019

# First US Trial of Gene Editing for SCD Has Begun


*Ex vivo* treatment of hematopoietic stem cells – knockout BCL11A enhancer



*Source: CRISPR Therapeutics AG*

*January 04, 2019 07:00 ET*

**CRISPR Therapeutics and Vertex Announce  
FDA Fast Track Designation for CTX001 for the  
Treatment of Sickle Cell Disease**

 U.S. National Library of Medicine

*ClinicalTrials.gov*

**A Safety and Efficacy Study Evaluating CTX001 in Subjects With Severe Sickle Cell Disease**

ClinicalTrials.gov Identifier: NCT03745287

[Recruitment Status](#) ⓘ: Recruiting

[First Posted](#) ⓘ: November 19, 2018

[Last Update Posted](#) ⓘ: January 18, 2019

See [Contacts and Locations](#)

**Sponsor:**

Vertex Pharmaceuticals Incorporated

**Collaborator:**

CRISPR Therapeutics

**Information provided by (Responsible Party):**

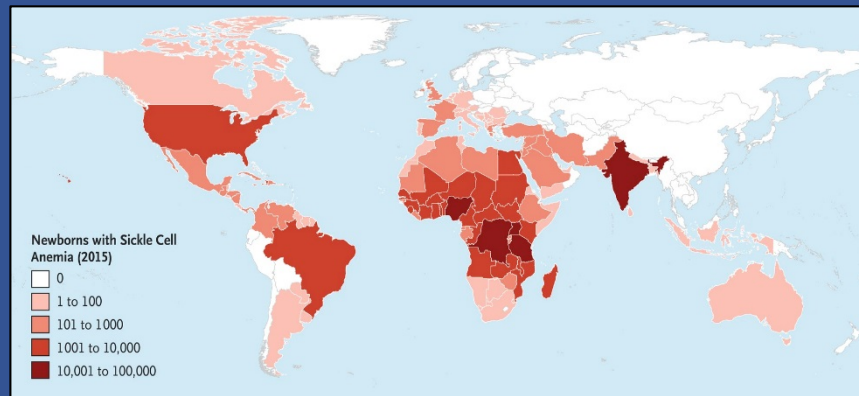
Vertex Pharmaceuticals Incorporated

**Study Description**

This is a single-arm, open-label, multi-site, single-dose Phase 1/2 study in up to 12 subjects 18 to 35 years of age with severe sickle cell disease (SCD). The study will evaluate the safety and efficacy of autologous CRISPR-Cas9 Modified CD34+ Human Hematopoietic Stem and Progenitor Cells (hHSPCs) using CTX001.

# Ultimate Goal: A Cure for SCD Everywhere

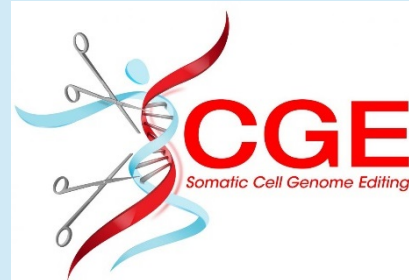
- Most people with SCD do not live in high income countries
- *Ex vivo* approaches may not be practical in sub-Saharan Africa
- What about *in vivo* approaches?
  - Need to develop efficient delivery systems for cas9 and guide RNA



Source: *N Engl J Med* 2017; 376:1561-1573

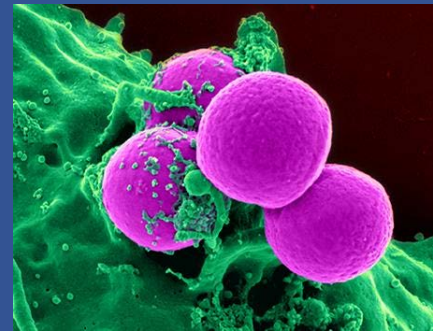


NIH is doing  
everything  
it can to help.



# Antimicrobial Resistance (AMR): Responding to the Challenge

- AMR: a growing public health problem
  - >2M infections; 23,000 deaths/year (US)
- National Action Plan released (2015)
  - Goals include **improved diagnostics**
- Rapid, Point-of-Need Diagnostic Test Challenge launched, 2016
  - \$20M federal prize competition, led by NIH, BARDA
    - Technical, regulatory expertise from CDC, FDA
    - NIH/CSR Technical Review Panel: first level peer review of submissions
  - 2018: 5 finalists received \$100K each to develop prototypes
  - 2020: up to 3 winners will share \$19M to improve prototypes





# Global Alliance for Chronic Diseases (GACD)

- Collaboration of world's major research funding agencies to address growing global burden of chronic disease
  - Supports multi-country, multidisciplinary research focusing on needs of low- and middle-income countries; vulnerable populations

- Priority areas

- Hypertension (2014)
- Diabetes (2014)
- Environmental lung disease
- Mental Health and Neurodegeneration
  - CSR led preclinical research [NIH/NIDA peer review funding]
- Hypertension/Diabetes

	Argentina Ministry of Science and Technology
	Australia National Health and Medical Research Council
	Canadian Institutes of Health Research
	Chinese Academy of Medical Sciences & Chinese Academy of Sciences
	European Commission, Health Directorate at Research & Innovation DG
	Indian Council of Medical Research
	Mexico Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubiran & CONACYT Mexico
	South African Medical Research Council
	Thailand Health Systems Research Institute
	UK Medical Research Council
	US National Institutes of Health

peer review [NIMH/NIDA]

link

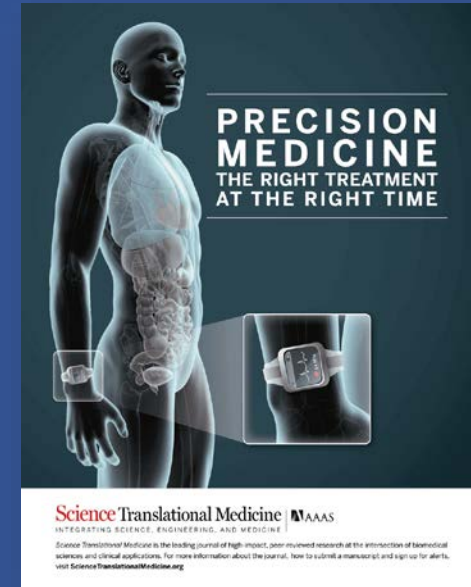
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# Bringing More *Precision* to Medicine

- Emerging approach to disease prevention and treatment that transforms mostly one-size-fits-all approach of Western medicine
- Tailors medical care to fit our unique medical selves
  - Considers individual variability in lifestyle, environment, genes
- Based on an old premise – think prescription glasses
  - But needing new insights, technologies, science to advance



# Precision Medicine Cohorts: Timing Is Everything!

				
		<b>insight commentary</b>		[VOL 429   27 MAY 2004]
Cost of sequencing genome		<h2>The case for a US prospective cohort study of genes and environment</h2>		
Amount of Time to Sequence a genome		Francis S. Collins		
Americans Want Health Insurance Phones		<p><i>National Human Genome Research Institute, National Institutes of Health, Building 31, Room 4B09, MSC 2152, 31 Center Drive, Bethesda, Maryland 20892-2152, USA (e-mail: fc23a@nih.gov)</i></p> <p>Information from the Human Genome Project will be vital for defining the genetic and environmental factors that contribute to health and disease. Well-designed case-control studies of people with and without a particular disease are essential for this, but rigorous and unbiased conclusions about the causes of diseases and their population-wide impact will require a representative population to be monitored over time (a prospective cohort study). The time is right for the United States to consider such a project.</p>		
EHR Adoption (% providers) Computing Power				





## Patient Partnerships



## EHRs



## Technologies



## Genomics



## Data Science



# The *All of Us* Research Program

**All of Us**  
RESEARCH PROGRAM | The  
Future of  
Health Begins  
With You

**Description:** a historic, longitudinal effort to gather data from **one million or more** people living in the US ... that takes into account individual differences in lifestyle, socioeconomics, environment, and biology

**Mission:** accelerate health research and medical breakthroughs, enabling individualized prevention, treatment, and care – for all of us



# All of Us: Objectives

- Nurture enduring relationships with participant partners
  - Who reflect the nation's diversity – across ages, races/ethnicities, genders, geographies, backgrounds...
- Build richest, largest-ever biomedical resource
  - Dataset that's as easy, safe, and free to access as possible
- Catalyze a robust biomedical research ecosystem
  - Engaging a wide array of researchers, funders



# Participant Engagement

DIRECT VOLUNTEERS



HEALTH CARE PROVIDER  
ORGANIZATIONS



Enroll &  
Consent



Surveys



Baseline  
Measurements



Electronic  
Health Records

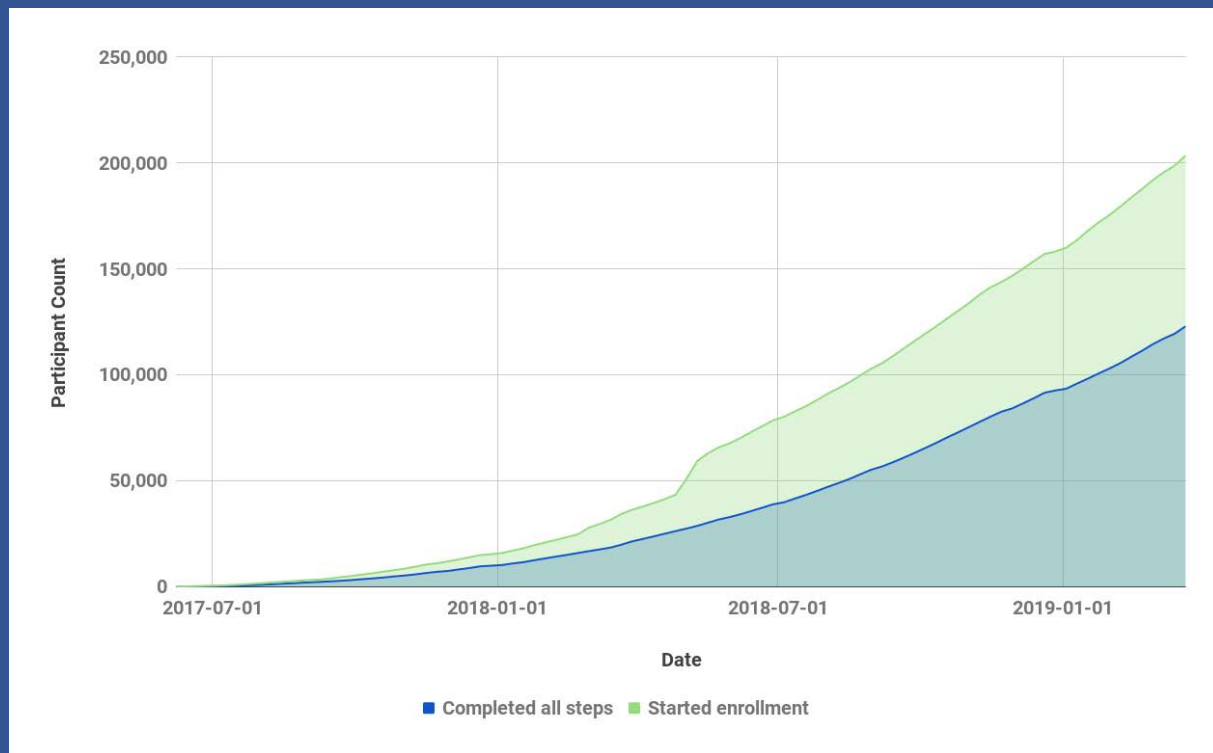


Apps, Phones  
& Wearables



Bio-Samples  
(Blood/Urine)

# Enrollment Status (as of 22 March 2019)



**JoinAllofUs.org**

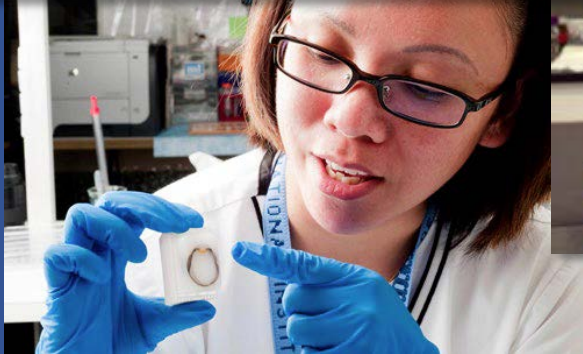
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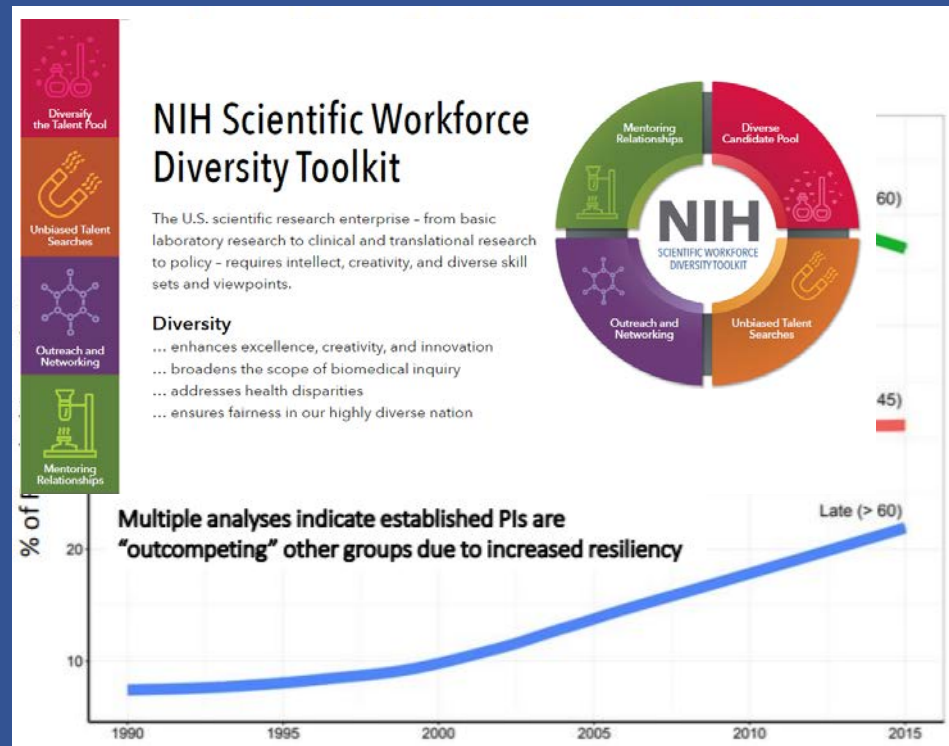
# Building a Vibrant Scientific Workforce



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NIH will:

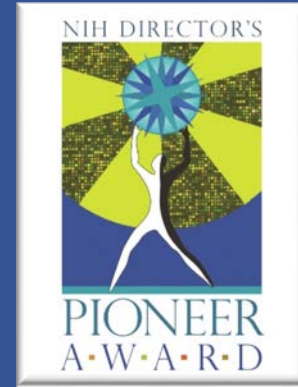
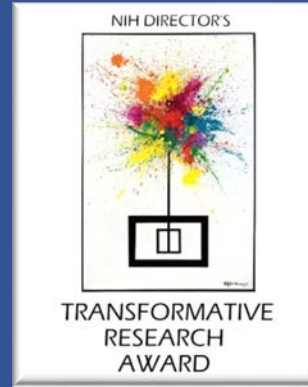
- Enhance diversity by expanding recruitment and retention
- Strive to change the culture of science to end sexual harassment
- Promote opportunities for new researchers, earlier independence



# Encouraging Innovative Researchers

## *NIH Director's Awards*

- Early Independence
- New Innovator
- Transformative Research
- Pioneer



# Expanding Funding Options: NIGMS' **M**aximizing Investigators' **R**esearch **A**ward (**MIRA**)

- Goals
  - Increase stability, distribution – and efficiency, efficacy – of funding
  - Reduce time spent writing, reviewing multiple applications
  - Reduce administrative burden of managing multiple grants
  - Enhance ability to take on ambitious scientific projects, approach problems creatively, follow new directions
- Expanding the program
  - >350 established investigators, >300 early-stage investigators funded so far
    - ~20% of NIGMS' "R01-equivalent" portfolio and growing
  - ESIs will continue to be reviewed on their own with ESI-specific considerations
  - First round of MIRA renewals will be reviewed in 2020 (NOT-GM-19-006)
    - Renewals for those who were ESIs ("first renewals") will be clustered and discussed together during peer review



# Welcome, Noni, to the “Directors Who Blog” Club



## Review Matters

### Welcome to the Center for Scientific Review (CSR)



Dr. Noni Byrnes

Director  
February 14, 2019

I am honored to have the opportunity to work with an incredibly dedicated staff in fulfilling CSR's vital mission of ensuring that *NIH grant applications receive fair, independent, expert, and timely reviews—free from inappropriate influences—so NIH can fund the most promising research.*

CSR's singular focus on the first level of review based on scientific merit, its independence from any specific NIH funding institute or center, and its efficient operation make it a critically important link in advancing new and exciting discoveries across a broad spectrum of biomedical research.

Below, I have outlined a few initial priorities for the Center. What binds these together is my personal commitment to strengthening the peer review process in a transparent manner, combining objective, data-driven approaches with significant engagement of the scientific community:

1. Evaluating the quality of review and reviewers – making study sections nimble enough to adapt to rapidly evolving, increasingly multidisciplinary scientific fields, broadening input, and reducing risk-aversion in review.
2. Addressing bias in peer review
3. Strengthening the confidentiality and integrity of the peer review process
4. Incentivizing peer review service

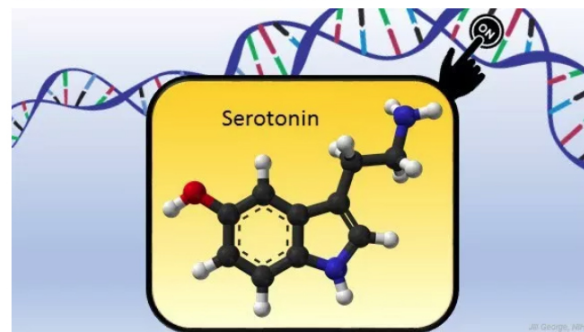
This inaugural **Review Matters** blog is just a small first step in a broader communications and targeted-outreach strategy. Future blog posts will expand upon the topics above, describing some efforts already underway, with more to come as we tackle these issues together.

We want to hear from you. I invite you to explore our newly designed website [csr.nih.gov](http://csr.nih.gov), add to the conversation below, and send us your input at [Feedback@csr.nih.gov](mailto:Feedback@csr.nih.gov). Thank you for your interest in peer review. All of us at CSR look forward to partnering with the broader NIH and extramural scientific communities to carry out our important mission.

## NIH Director's Blog

### Mood-Altering Messenger Goes Nuclear

Posted on March 19th, 2019 by Dr. Francis Collins



Serotonin is best known for its role as a chemical messenger in the brain, helping to regulate mood, appetite, sleep, and many other functions. It exerts these influences by binding to its receptor on the surface of neural cells. But startling new work suggests the impact of serotonin does not end there: the molecule also can enter a cell's nucleus and directly switch on genes.

While much more study is needed, this is a potentially groundbreaking discovery. Not only could it have implications for managing depression and other mood disorders, it may also open new avenues for treating substance abuse and neurodegenerative diseases.

To understand how serotonin contributes to switching genes on and off, a lesson on epigenetics is helpful. Keep in mind that the DNA instruction book of all cells is essentially the same, yet the chapters of the book are read in very different ways by cells in different parts of the body. Epigenetics refers to chemical marks on DNA itself or on the protein “spools” called histones that package DNA. These marks influence the activity of genes in a particular cell.



## Nora's Blog

### Featured Post



### Prenatal and Early Childhood Brain Development: The HEALTHy Brain and Child Development Study

March 11, 2019  
The NIH HEAL (Helping to End Addiction Long-term) Initiative is helping to fund an ambitious research project called the HEALTHy Brain and Child Development (HBCD) study. This study, which will use many of the same neuroimaging and other methods as the ABCD study, will follow a large cohort of children from the prenatal period to age 10. [Read More.](#)

## NIAAA Director's Blog



February 11, 2019

### Be mindful of your drinking throughout the year

As we move from January to February, some people's motivation to keep their New Year's resolutions starts to wane. But it's a good idea to be mindful of how alcohol can adversely affect our health all year long.

Throughout the year, be mindful of how much alcohol constitutes a standard alcoholic drink and how much you are consuming. If you are hosting a gathering, be sure to have plenty of nonalcoholic drinks available for your guests. Other fluids can help them stay hydrated and also may slow the absorption of alcohol in the body, thereby reducing the peak alcohol concentration in their blood. Importantly, please take the necessary steps to help ensure your well-being and the safety of your guests.



that binge drinking is dangerous, and it has many safety risks, and no redeeming value. It can lead to unintentional injuries from car crashes, falls,

## NIH National Institute on Aging

Home / Research & Funding / Blog / What's ahead in 2019

### What's ahead in 2019

January 09, 2019



Richard HODES,  
Director,  
Office of the Director (OD).

In this video post to kick off the New Year, NIA Director Dr. Richard Hodes discusses opportunities ahead for researchers in aging and Alzheimer's and related dementias science, including budget, pay lines, and growing the field, as well as upcoming events and funding opportunities.

## Director's Corner

### March 11, 2019: Applying "Translational Rigor" to Address the Opioid Crisis



we are innovative and helping our collaborators do the same.

The issues surrounding pain and addiction have created a tremendous urgency in this country for new and better treatments. This sense of urgency permeates all we do at NCATS, since patients with many types of diseases are waiting for the promise of science to reach them. In fact, we often paraphrase our Center's mission as "getting more treatments to more patients more quickly." But we are also aware that translational failure can be caused by information generated at one stage of translation not being accurate or reliable enough to support further development. So in our work to address the opioid crisis, we are taking care to be as rigorous as




## NIGMS Feedback Loop Blog

A catalyst for interaction with the scientific community

### Pathways: Inspiring Future Scientists Through a New Collaboration with Scholastic, Inc.



Posted by Dr. Jon Lorsch on March 18, 2019  
[Post a Comment](#) | [No Comments](#) ↓

I'm pleased to announce the debut of [Pathways](#) , a collaboration between NIGMS and Scholastic, Inc., that provides a collection of free educational resources about basic biomedical science and research careers.

## NLM Musings FROM THE Mezzanine

Innovations in Health Information from the Director of the U.S. National Library of Medicine




### NLM and Public Policy



Paul Brennan  
March 19, 2019  
[Leave a comment](#)

Policy—and its cousin, legislation—make the world go 'round. They lay out a course of action, guide decisions, and set the parameters for future choices. While policies and legislation are being crafted, it's a tug of war between details and context, minutiae and meaning, big picture and nuance, with that push and pull yielding documents that govern actions for years, often for decades if not longer.



Hope in every sphere  
of life is a privilege that  
attaches to action.  
No action, no hope.

~ Peter Levi





**NIH...** *Turning Discovery Into Health*

[www.nih.gov/hope](http://www.nih.gov/hope)

[directorsblog.nih.gov](http://directorsblog.nih.gov)

@NIHDirector 

