EXHIBIT 28

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

AMERICAN PUBLIC HEALTH ASSOCIATION, *et al.*, *Plaintiffs*, v. NATIONAL INSTITUTES OF HEALTH, *et al.*, *Defendants*.	Case No. 1:25-cv-10787-BEM Leave to File Under Seal Granted April 24, 2025 (ECF No. 36)

DECLARATION OF APHA MEMBER 1

I, [redacted], pursuant to 28 U.S.C. § 1746, depose and say as follows:

1. I am a Professor of Epidemiology at a private university in Massachusetts, where I have been a member of the faculty since 1995.

2. I earned my Ph.D. in Epidemiology from the University of California, Berkeley, in 1989. My academic background also includes training in biochemistry, philosophy of science, and the history of public health. Over the past thirty-five years, I have engaged in scientific research that furthers my longstanding commitment to social justice and public health.

3. My work centers on using etiologic and methodologic research to improve population health, with a strong focus on understanding the societal determinants of health inequities to advance health justice. I have studied the complex intersections between racism, social class, and health in the United States. Grounded in theoretical frameworks such as ecosocial theory, my

research explores how social and environmental conditions shape health outcomes across populations. I also develop innovative methods to better monitor and address health inequities, aiming to inform more equitable and effective public health policies and practices.

4. I am an internationally recognized social epidemiologist and a [redacted]. My honors include the [redacted].

5. I have served as Principal Investigator on multiple National Institutes of Health ("NIH") funded grants focused on structural determinants of health and methodological innovation. These include: a five-year grant investigating how social adversity affects DNA methylation and contributes to health inequities; a five-year grant to develop improved tools to measure multiple forms of discrimination and assess their impact on population health; two three-year grants which examined disparities in breast cancer tumor biology and outcomes; a three-year grant which analyzed the enduring health impacts of Jim Crow laws using age-period-cohort methods. These projects reflect my research into the social and structural causes of health inequities and the development of methods to study them.

6. I am offering this Declaration in my individual capacity and not on behalf of my employer.

7. I am a member of the American Public Health Association, and I pay $225 in annual dues.

8. On June 19, 2019, in support of my research, my institution was awarded a five-year, $4 million R01 grant from the National Institute on Minority Health and Health Disparities ("NIMHD") to develop time-efficient tools for assessing patients' experiences of discrimination based on race, gender, gender identity, sexual orientation, age, and weight. The project, titled [redacted], was motivated by concerns that existing approaches significantly underestimate the impact of discrimination on population health. A true and correct copy of my Notice of Award for this grant is attached as Exhibit A.

9. This project builds on my prior research using both explicit self-report measures and implicit tools, including earlier and updated versions of the Implicit Association Test, a timed reaction test designed to reveal unconscious associations of ideas, including but not limited to

biases. Prior studies—some conducted in collaboration with Boston community health centers—focused on implicit and explicit exposures to discrimination but left key questions unanswered. This new grant-supported project incorporates contemporary methods to compare implicit and explicit approaches across a broader range of discrimination types, aiming to improve the accuracy and efficiency of assessment in clinical settings.

10. The study was conducted at three federally qualified community health centers in Boston, Massachusetts and involved 699 randomly selected adult participants. It used both a refined Implicit Association Test to measure participants' unconscious awareness of being a target of six types of discrimination and a validated self-report survey to assess lifetime exposure to six types of discrimination; these types of discrimination involve: race/ethnicity, gender, gender identity, age, sexual orientation, and weight. Participants also completed standardized assessments of psychological distress and sleep-related health outcomes, including insufficient sleep and sleep-disordered breathing. The goal of the project was to evaluate the effectiveness of combining implicit and explicit tools to more accurately capture exposure to discrimination and its impacts on health. By applying causal mediation analyses, the study aimed to identify which types and combinations of discrimination most strongly mediate health inequities.

11. This project was staffed by over fifteen people, including the Principal Investigator, two co-investigator epidemiologists, the project director, a biostatistician, a social psychologist, a data analyst, a clinic's medical director, a clinic consortium's director and staff member, and numerous research assistants, graduate students, and undergraduate students.

12. Initiated by a federal grant awarded in June 2019, the project was the result of four years of intensive effort. The application itself required significant preparation, including a comprehensive review of the background literature, development of the experimental design, pilot tests, and the assembly and refinement of detailed application materials. The team submitted the proposal to NIH and subsequently revised it based on reviewer feedback to ensure alignment with agency expectations. Once funded, and despite a compressed first year of support, the team fully developed the study infrastructure, including survey design, recruitment protocols, and operational systems. The project was poised to go into the field to recruit participants in March 2020, but the onset of the COVID-19 pandemic at that time and the subsequent lockdowns necessitated an immediate pivot to remote implementation. This required substantial additional effort to redesign

communication systems and study procedures, particularly in collaboration with community health partners serving populations hardest hit by the pandemic.

13. Recruitment during the pandemic proved significantly more challenging than anticipated. While prior studies by the team had achieved response rates near 80% with community center participants, this study's rate dropped to 50%, reflecting the broader public health crisis and its disproportionate impact on participating communities. These challenges were documented in two peer-reviewed publications. Due to pandemic-related delays, the NIH approved a no-cost extension for a fifth project year, permitting the use of unspent funds but not providing additional resources. At the time of termination, the team was actively analyzing data related to one of the study's primary outcomes—psychological distress—with plans to submit a manuscript in the spring. Analyses of the remaining primary outcomes related to sleep disorders were scheduled for the summer, with a goal of submitting a second manuscript by early fall. Final data management and sharing tasks, including the development of a study website, were planned for completion in the fall.

14. The project was fully aligned with the historic mission of NIMHD, which prioritizes research on minority health, health disparities, and the social determinants of health and aims to improve health outcomes for underserved and marginalized communities. Focused on the impact of discrimination on psychological distress, the study directly supported NIMHD's strategic goals and was met with strong enthusiasm from the program officer overseeing the grant. It also advanced NIH-wide priorities around health disparities, particularly aligning with key objectives of the two NIH-Wide Strategic Plans encompassing the study's project period, respectively for Fiscal Year 2016-2020 and Fiscal Year 2021-2025. True and correct copies of both NIH-Wide Strategic place are attached as Exhibit B and C, respectively. Both of these NIH-Wide Strategic Plans discussed the need to understand and reduce health disparities, with the FY 2021-2025 strategic plan in direct support of the purpose of the study that was terminated, stating, "NIH understands that health research needs to routinely incorporate constructs and measurement of structural racism or discrimination across multiple domains and levels of influence if minority health is to be optimized, health equity achieved, and health disparities eliminated." Ex. B, at 33. The project's contributions were recognized through an invitation to present findings at a 2024 NIH-sponsored public workshop on discrimination and health, underscoring its relevance, scientific value, and alignment with national research priorities.

15. On February 28, 2025, my institution received notice from NIH that the final year of the grant—amounting to $650,000—would not be funded because it "no longer effectuates agency priorities." A true and correct copy of this termination notice is attached as Exhibit D.

16. The notice gave no individualized reason why the grant was terminated but merely cited Termination Section 3 (DEI)—"[r]esearch programs based primarily on artificial and non-scientific categories, including amorphous equity objectives, are antithetical to the scientific inquiry. . . and ultimately do not enhance health, lengthen life, or reduce illness," and "[w]orse, so-called diversity, equity and inclusion ("DEI") studies are often used to support unlawful discrimination . . . which harms the health of Americans."

17. Subsequently, on March 3 and March 7, I was sent a first and second revision notice of award. The first stated that no expenses could be charged to the grant going forward. That notice also disclaimed that the termination of the grant was being carried out under any of the president's executive orders. The second included this language and also stated that "with prior approval, a portion of funds may be used to support patient safety and orderly closeout of the project." A true and correct copy of these revised Notices of Award are attached as Exhibit E and F, respectively.

18. I don't understand what the termination notice means by "DEI" in relation to my scientific research study, which is concerned with testing hypotheses about the impact of multiple types of discrimination on health and had no aims regarding who would be employed on the project, nor do I understand how my project is "based on" "DEI." I also do not understand how my project, focused on the harmful effects of discrimination, could in any way be "used to support unlawful discrimination." I received no communication following up with clarification.

19. While the project investigates the broad impacts of discrimination on health outcomes, no individuals have been selected for or excluded from participation based on race, ethnicity, religion, gender, or sexuality. Participants are randomly selected patients from three community health centers who meet the following criteria: U.S.-born, working-age adults (25–64), able to complete an English-language survey, and mentally competent to provide informed consent. The study is not designed to focus on any specific group or protected characteristic; rather, its goal is to examine and quantify the effects of discrimination, which can impact individuals from any background.

20. To the best of my knowledge, it is highly unusual for a grant to be terminated or not renewed midway through a project, particularly after several years of progress. My understanding is that such an action would only occur in cases involving research misconduct or risks to

participant safety. In my decades-long career, I have never personally experienced a grant being discontinued in the middle of a project—until now.

21. The termination has had serious professional and material consequences. Scientifically, it halted progress on completing two of the study's primary aims, preventing us from completing planned analyses and sharing the knowledge generated with the broader scientific community and the community health center members. Logistically, it halted our ability to develop the infrastructure necessary to ethically share our data, via a public website, which is a necessary step to enable the conduct of rigorous reproducible science and also the efficient use of NIH-funded data by other investigators. The inability to complete our work as specified in our study timeline means that the scientific community loses access to valuable data and methods designed to advance understanding of how discrimination affects health outcomes, compromising both rigor and impact.

22. Several members of my research team—dedicated individuals who had committed years to this work—lost job security or experienced significant salary reductions. A full-time research coordinator position we had planned had to be scaled back, limiting our ability to attract and retain qualified candidates. These staffing losses, combined with the abrupt withdrawal of funding, have made it exceedingly difficult to complete the project's central aims or return the results to the community members and study participants who generously contributed their time and trust. Also affected by termination of the federal grant are the institutional staff members whose work is supported by the total grant funds and is vital to the successful conduct of the scientific research, including staff involved in grant administration, IT, data security, and human subjects compliance.

23. Finally, the suppression of critical research into the health impacts of discrimination has broader societal consequences. By halting work that could generate new methodologies and insights into how multiple types of discrimination, singly and combined, harms the health of individuals, the decision effectively curtails scientific inquiry into one of today's most pressing public health issues.

24. Because I no longer have federal funds to complete the study's stated objectives or deliver results to participating community health centers or study participants, I have spent countless hours trying to manage the fallout—supporting displaced team members, reassessing unfinished research, navigating complex administrative issues, and seeking other funding to complete the work. This has taken a considerable toll on my ability to focus on my other responsibilities,

including teaching, mentoring, and institutional service, as well as on my ability to focus on my other funded research projects and publication preparations. Beyond the immediate disruption, the termination has shaken the continuity of my research program and dampened morale among colleagues who fear similar outcomes for their own work. The experience has been both professionally destabilizing and personally demoralizing.

25. I appealed the termination on March 26, 2025.

26. Although I appealed the termination, I remain uncertain about how to respond to NIH's assessment that my project "no longer aligns with agency priorities," especially since I do not fully understand how my research is considered "based on DEI."

27. Additionally, I am unsure whether my appeal stands any chance of success, given the termination notice's statement that "[t]he premise of this award is incompatible with agency priorities, and no modification of the project could align it with agency priorities." Ex. D at 1.

28. I am also concerned that another grant application I have submitted, focusing on the continued impacts of Jim Crow on contemporary health inequities, will not be fairly considered or considered at all under NIH's changed priorities. In November 2024, the Scientific Review Group ranked the proposal in the top 10 percent during peer review. However, the February 2025 NIH NIMHD Advisory Council meeting—where the grant was to be discussed and potentially approved for funding—was canceled and has not been rescheduled. There is concern that the revised and highly rated proposal may remain in limbo due to the disruption in the review process and the nature of its subject matter.

29. I am submitting this declaration under seal due to serious concerns for my personal safety and privacy.

30. Colleagues of mine who have been publicly named in similar contexts have experienced harassment and doxxing. In the current political climate, the fact that my work addresses racism, gender inequality, LGBTQ health issues and societal determinants of health has heightened my concern that defending my work in a lawsuit may make me a target of such harassment.

31. Recently, following a February 2025 national media interview in which I discussed the ways in which key public health data and websites maintained by US health agencies were newly being suppressed due to their focus on health equity, environmental justice, climate change, and LGBTQ health, I received vaguely threatening mailed letter from a stranger, and I called my university's police department to have them open the letter and assess the level of threat involved.

This incident has heightened my fears of being personally targeted. While I welcome academic and public discourse about public health and equity, I do not wish for that engagement to compromise my personal safety.

32. I am also concerned about potential retaliation from the U.S. government. It is unclear why my grant was the first—and for a time, the only—scientific study (R01 grant) terminated under the "DEI" category, especially given the existence of many other federal research grants addressing discrimination and health. The timing of my termination, which occurred immediately after the NIH received authorization on the afternoon of February 28 to begin issuing such terminations, further compounds my concern.

I declare under penalty of perjury that the foregoing is true and correct.
Executed this 23rd day of April, 2025.

EXHIBIT A

Notice of Award

RESEARCH
Department of Health and Human Services
National Institutes of Health

Federal Award Date: 06/19/2019

NATIONAL INSTITUTE ON MINORITY HEALTH AND HEALTH DISPARITIES

Grant Number: [redacted]
FAIN:

Principal Investigator(s):
[redacted]

Project Title: [redacted]

[redacted]

Award e-mailed to: [redacted]

Period Of Performance:
Budget Period: 06/19/2019 – 01/31/2020
Project Period: 06/19/2019 – 01/31/2024

Dear Business Official:

The National Institutes of Health hereby awards a grant in the amount of $726,645 (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to [redacted] in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award including the "Terms and Conditions" is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Institute On Minority Health And Health Disparities of the National Institutes of Health under Award Number [redacted]. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please contact the individual(s) referenced in Section IV.

Sincerely yours,

Priscilla Grant
Grants Management Officer
NATIONAL INSTITUTE ON MINORITY HEALTH AND HEALTH DISPARITIES

Additional information follows

SECTION I – AWARD DATA – [redacted]

Award Calculation (U.S. Dollars)

Salaries and Wages	$189,386
Fringe Benefits	$84,816
Personnel Costs (Subtotal)	$274,202
Materials & Supplies	$5,933
Travel	$7,225
Other	$760
Subawards/Consortium/Contractual Costs	$207,594
Federal Direct Costs	$495,714
Federal F&A Costs	$230,931
Approved Budget	$726,645
Total Amount of Federal Funds Obligated (Federal Share)	$726,645
TOTAL FEDERAL AWARD AMOUNT	$726,645
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$726,645

SUMMARY TOTALS FOR ALL YEARS		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
1	$726,645	$726,645
2	$655,121	$655,121
3	$643,368	$643,368
4	$651,321	$651,321
5	$648,444	$648,444

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

CFDA Name: Minority Health and Health Disparities Research
CFDA Number: [redacted]
EIN: [redacted]
Document Number: [redacted]
PMS Account Type: [redacted]
Fiscal Year: 2019

IC	CAN	2019	2020	2021	2022	2023
[redacted]	[redacted]	$726,645	$655,121	$643,368	$651,321	$648,444

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: [redacted] **/ OC:** [redacted] **/ Released:** [redacted] 06/14/2019
Award Processed: 06/19/2019 12:17:35 AM

SECTION II – PAYMENT/HOTLINE INFORMATION – [redacted]

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – TERMS AND CONDITIONS – [redacted]

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.

c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

An unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.

This grant is subject to Streamlined Noncompeting Award Procedures (SNAP).

This award is subject to the requirements of 2 CFR Part 25 for institutions to receive a Dun & Bradstreet Universal Numbering System (DUNS) number and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a DUNS requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) [redacted] Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.

Treatment of Program Income:
Additional Costs

SECTION IV – [redacted] – [redacted]

Clinical Trial Indicator: No
This award does not support any NIH-defined Clinical Trials. See the NIH Grants Policy Statement Section 1.2 for NIH definition of Clinical Trial.

INFORMATION: In accordance with the National Institute on Minority Health and Health Disparities' (NIMHD's) Fiscal Year (FY) 2019 funding policies, this award has been issued at 85% of the adjusted requested level. Future year committed levels* have been adjusted accordingly.

** committed level: The level of support calculated by applying the NIMHD funding plan to the corrected recommended level for each budget category for all years of the project period.

REQUIREMENT: This award is subject to the conditions set forth in PAR-18-484, NIH Research Project Grant (Parent R01 Clinical Trial Not Allowed), NIH Guide to Grants and Contracts, 12/06/2017, which is hereby incorporated by reference as special terms and conditions of this award.

Copies of this RFA may be accessed at the following internet address: http://www.nih.gov/grants/guide/index.html

Copies may also be obtained from the Grants Management Contact indicated in the terms of award

REQUIREMENT: Use of humans and animals in any new activities must be requested prior to the start of the activity and must be approved in writing in advance by the NIMHD. See NOT-MD-08-002, "Guidance and Clarification on NCMHD Policy on Prior Approval for Subprojects and Pilot Projects Involving Human Subjects or Vertebrate Animals," NIH Guide to Grants and Contracts, April 29, 2008, which is hereby incorporated by reference as special terms and conditions of this award. See also NOT-OD-15-129, "Prior NIH Approval of Human Subjects Research in Active Awards Initially Submitted without Definitive Plans for Human Subjects Involvement (Delayed Onset Awards): Updated Notice," and NIH-OD-15-128, "Guidance on Changes That Involve Human Subjects in Active Awards and That Will Require Prior NIH Approval: Updated Notice."

Copies of these Notices may be accessed at the following internet address: http://www.nih.gov/grants/guide/index.html

Copies may also be obtained from the Grants Management Contact indicated in the terms of award.

RESTRICTION: Stipends and payments made for educational assistance (e.g., scholarships, fellowships, and student aid costs) may not be paid from NIH research grant funds even when they would appear to benefit the research project (NIH GPS Section 7.9.1). Compensation must be in accordance with organizational policies consistently applied to both federally and non-federally supported activities and must be supported by acceptable accounting records that reflect the employer-employee relationship. Under these conditions, the funds provided as compensation for services rendered are not considered stipend supplementation; they are allowable charges to Federal grants, including PHS research grants. (A stipend is a payment made to an individual under a fellowship or training grant in accordance with pre-established levels to provide for the individual's living expenses during the period of training. A stipend is not considered compensation for the services expected of an employee.) See the NIH Grants Policy Statement for allowable forms of student compensation, available at http://grants.nih.gov/grants/policy/nihgps/nihgps.pdf

RESTRICTION: In addition to the PI, the following individuals are named as key personnel:

Written prior approval is required if any of the individual(s) named above withdraws from the project entirely, is absent from the project during any continuous period of 3 months or more, or reduces time devoted to the project by 25 percent or more from the level that was approved at the time of award.

INFORMATION: In order to redistribute awards more evenly throughout the year, budget periods are being adjusted. This award is issued with a 7.4-month budget period and with 12 months of support. Continuation awards will cycle each year on February 1st.

INFORMATION: Although the budget period start date for this award is June 19th, this award includes funds for 12 months of support. Future year budget periods will cycle on February 1st. Allowable preaward costs may be charged to this award, in accordance with the conditions outlined in the NIH Grants Policy Statement, and with institutional requirements for prior approval. The NIH GPS can be found on the internet at http://grants.nih.gov/grants/policy/nihgps/nihgps.pdf.

INFORMATION: See the Certificate of Confidentiality policy at https://humansubjects.nih.gov/coc/major-changes. This policy protects against the involuntary release of personally identified research information of a sensitive nature sought through any federal, state, or local civil, criminal, administrative, legislative, or other proceedings.

INFORMATION: This award reflects the NIMHD's acceptance of the certification that all key personnel have completed education on the protection of human subjects, in accordance with NIH policy, "Required Education in the Protection of Human Research Participants," as announced in the June 5, 2000 NIH Guide (revised August 25, 2000) (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html).

Any individual involved in the design and conduct of the study that is not included in the certification must satisfy this requirement prior to participating in the project. Failure to comply can result in the suspension and/or termination of this award, withholding of support of the continuation award, audit disallowances, and/or other appropriate action.

INFORMATION: See "Federalwide Assurance Requirements" and "Certification of IRB Approval" under the Human Subjects Protections section in the NIH Grants Policy Statement (NIHGPS), for specific requirements and recipient responsibilities related to the protection of human subjects, which are applicable to and are a term and condition of this award. The NIHGPS can found on the internet at http://grants.nih.gov/grants/policy/nihgps/nihgps.pdf.

INFORMATION: Funds awarded for direct cost compensation for Graduate Research Assistants are limited in accordance with the NIH policy.

INFORMATION: None of the funds in this award shall be used to pay the salary of an individual at a rate in excess of the current salary cap. See the new Salary Limitations on Grants: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-19-099.html

INFORMATION: Unobligated balances may be used by the NIMHD to reduce or offset funding for a subsequent budget period.

INFORMATION: Regarding changes in scope, attention is called to the NIH Grants Policy Statement. The Change in Scope section is found in Section 8.1.2 at http://grants.nih.gov/grants/policy/nihgps/nihgps.pdf. The recipient must obtain prior approval from the NIMHD for a change in the direction, aims, objectives, purposes, or type of research or

training or other areas that constitute a significant change in the approved project. Specific examples are provided.

INFORMATION: Regarding allowability of selected items of cost, attention is called to the NIH Grants Policy Statement. The Selected Items of Cost section is found in Section 7.9.1 at http://grants.nih.gov/grants/policy/nihgps/nihgps.pdf.

INFORMATION: Honoraria are unallowable when the primary intent is to confer distinction on, or to symbolize respect, esteem, or admiration for, the recipient of the honorarium. A payment for services rendered, such as a speaker's fee under a conference grant, is allowable. See Section 7.9.1 at http://grants.nih.gov/grants/policy/nihgps/nihgps.pdf.

INFORMATION: This award includes funds awarded for consortium activity. Consortia are to be established and administered as described in the NIH Grants Policy Statement (NIH GPS). The referenced section of the NIH GPS is available at: http://grants.nih.gov/grants/policy/nihgps/nihgps.pdf. See "Consortium Agreements" in Section 15 for specific responsibilities and requirements for recipients and consortium participants, which are applicable to and are a term and condition of this award.

INFORMATION: For administrative and management concerns, contact the Grants Management Specialist, Sy L. Shackleford, at (301) 451-8542. For programmatic and scientific concerns, contact the Program Director, Dr. Nancy Lynne Jones, at (301) 594-8945.

STAFF CONTACTS

The Grants Management Specialist is responsible for the negotiation, award and administration of this project and for interpretation of Grants Administration policies and provisions. The Program Official is responsible for the scientific, programmatic and technical aspects of this project. These individuals work together in overall project administration. Prior approval requests (signed by an Authorized Organizational Representative) should be submitted in writing to the Grants Management Specialist. Requests may be made via e-mail.

Grants Management Specialist: Sy Shackleford
Email: shacklefords@mail.nih.gov **Phone**: 301-402-1366

Program Official: Nancy Lynne Jones
Email: jonesna@mail.nih.gov **Phone**: 301-594-8945

SPREADSHEET SUMMARY
GRANT NUMBER: [redacted]

INSTITUTION: [redacted]

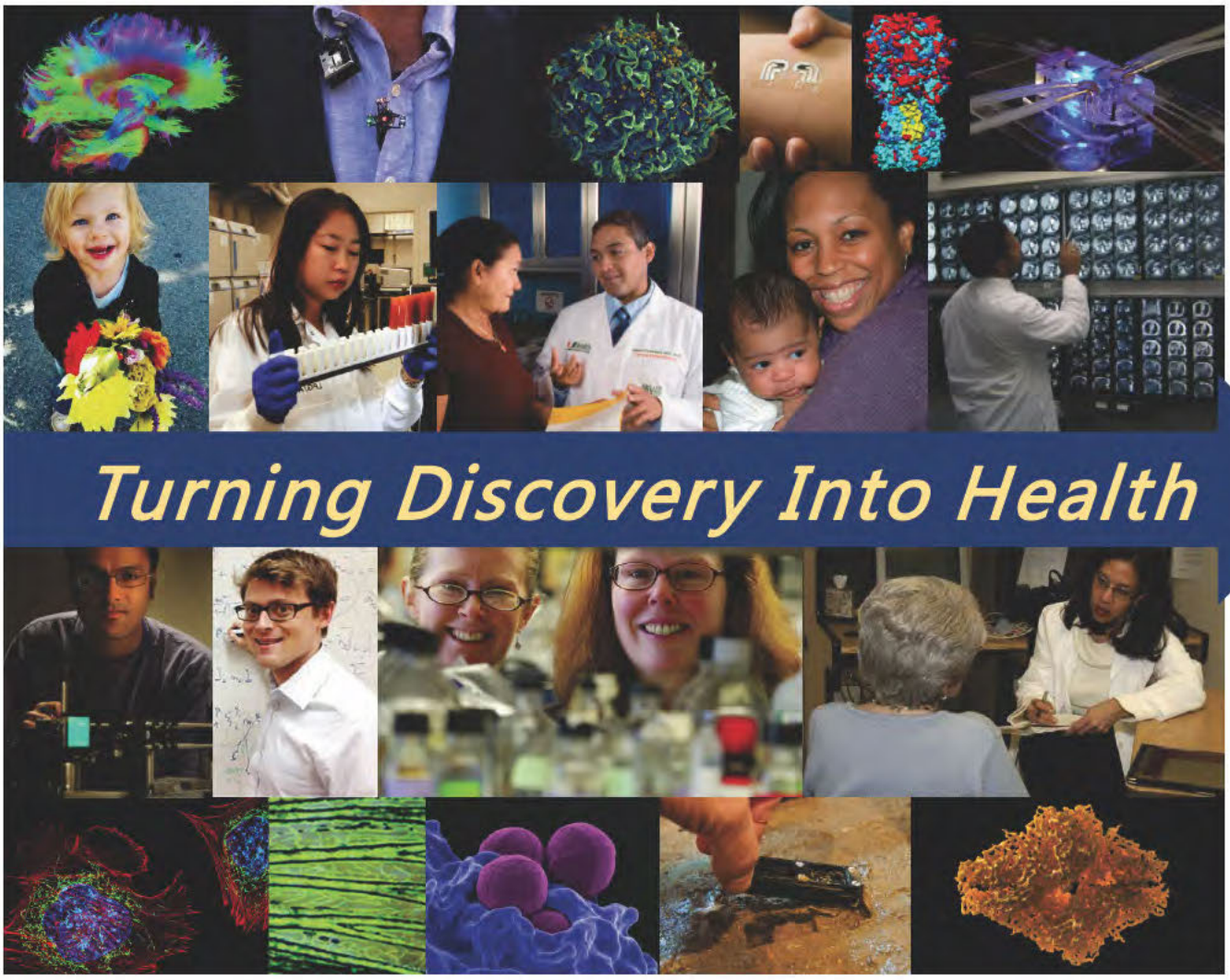
Budget	Year 1	Year 2	Year 3	Year 4	Year 5
Salaries and Wages	$189,386	$181,328	$176,239	$206,169	$215,395
Fringe Benefits	$84,816	$81,208	$78,928	$92,333	$96,465
Personnel Costs (Subtotal)	$274,202	$262,536	$255,167	$298,502	$311,860
Materials & Supplies	$5,933	$816	$816		
Travel	$7,225	$7,225	$7,225	$7,225	$7,225
Other	$760	$14,736	$14,736		
Subawards/Consortium/Contractual Costs	$207,594	$200,047	$200,047	$155,552	$127,302
Publication Costs				$5,100	$7,650
TOTAL FEDERAL DC	$495,714	$485,360	$477,991	$466,379	$454,037
TOTAL FEDERAL F&A	$230,931	$169,761	$165,377	$184,942	$194,407
TOTAL COST	$726,645	$655,121	$643,368	$651,321	$648,444

Facilities and Administrative Costs	Year 1	Year 2	Year 3	Year 4	Year 5
F&A Cost Rate 1	59.5%	59.5%	59.5%	59.5%	59.5%
F&A Cost Base 1	$388,120	$285,313	$277,944	$310,827	$326,735
F&A Costs 1	$230,931	$169,761	$165,377	$184,942	$194,407

EXHIBIT B

NIH-Wide Strategic Plan

Fiscal Years 2016-2020



NIH

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

To the American People,

As the United States' biomedical research agency, the National Institutes of Health (NIH) has been the driving force behind many decades of advances that have improved health of people in every corner of America and the world. The vast majority of NIH's funds go to support scientists at universities, research institutions, and small businesses in all 50 states, with their many discoveries serving to fuel the U.S. biomedical industry and keep our Nation globally competitive.

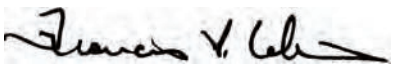
Yet, much remains to be done. The coming years are certain to pose new challenges for human health and offer new opportunities for scientific exploration. NIH will address this rapidly changing landscape by pursuing, with greater vigor than ever, our mission of seeking fundamental knowledge about the nature and behavior of living systems and applying that knowledge to enhance health, lengthen life, and reduce illness and disability.

In this research strategic plan for Fiscal Years 2016-2020, prepared at the request of Congress, we share a framework that places NIH's enduring mission in the context of tomorrow's challenges and opportunities. Working with our many partners in the public and private sectors, NIH will use this framework as we strive to turn scientific discoveries into better health, while upholding our responsibility to be wise stewards of the resources provided to us by the American people.

This research strategic plan is designed to harmonize decision making across the Agency. It will complement, but not replace, the strategic plans of the individual Institutes, Centers, and Program Offices, because these organizations have their own strategic plans that align with their Congressionally mandated missions. Moreover, the plan is not meant to catalogue all of the many things NIH has done or will do in the future. Rather, we have selected examples to provide the reader with clear illustrations of the points being made.

Your support of NIH's mission is vital to our success. Every dollar that our Nation invests in NIH is an investment in options for a healthier, more productive life for you—and for future generations.

With sincere appreciation,



Francis S. Collins, M.D., Ph.D.
Director, National Institutes of Health

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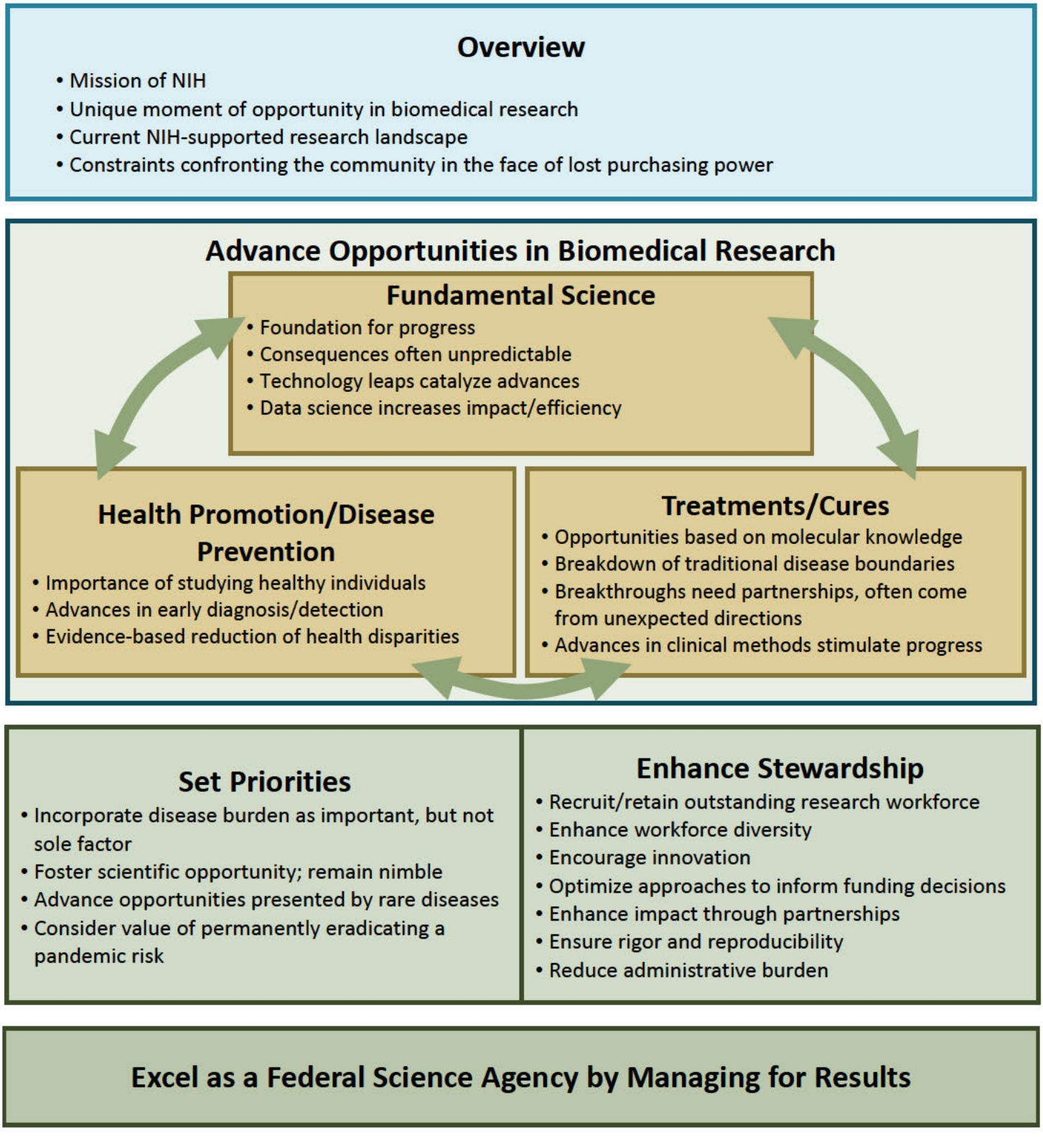
NIH-Wide Strategic Plan Framework

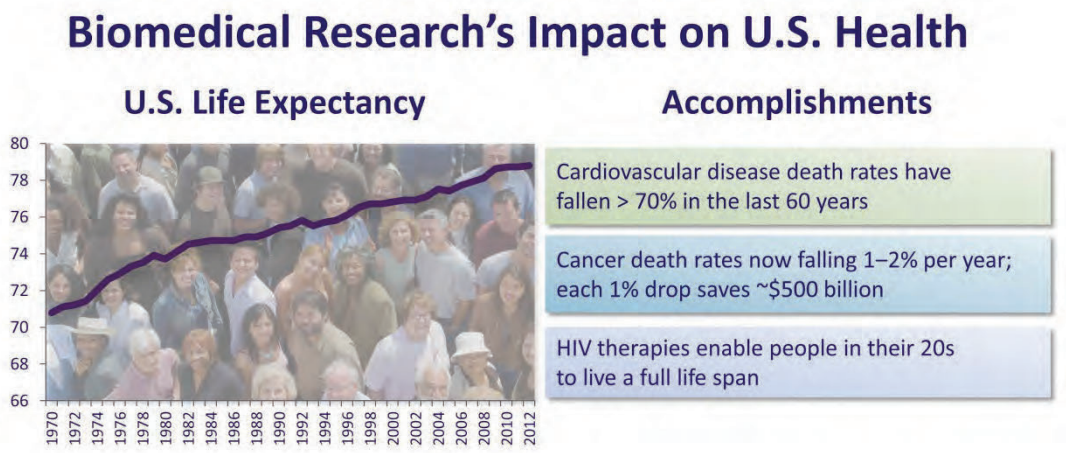


OVERVIEW

The National Institutes of Health (NIH) is the United States' premier agency for biomedical research, which spans the broad spectrum of basic, translational, clinical, behavioral and social sciences research dealing with many aspects of biology and almost every human disease and disability.

Begun in 1887 as a one-room laboratory on Staten Island, NY, the agency was officially designated "NIH" by Congress in 1930. Since then, NIH has grown to be the world's largest source of medical research funding, and the driving force behind decades of advances that have expanded fundamental scientific knowledge and improved health.

To date, 148 NIH-supported researchers have received Nobel Prizes for their groundbreaking achievements. These, along with other NIH-funded research advances, are behind many of the gains that our nation has enjoyed in public health.



A baby born in the United States today can expect to live to nearly age 79—about three decades longer than one born in 1900. Such progress is made possible by NIH's support of many different types of research focused on a wide range of diseases and conditions. Health improvements fueled by NIH-funded research include significant declines in the U.S. death rates from heart disease, stroke, diabetes, and cancer, as well as the transformation of HIV/AIDS from a swiftly fatal disease to a manageable, chronic condition with a near-normal life expectancy.

Mission and Goals

NIH's mission is to seek fundamental knowledge about the nature and behavior of living systems and to apply that knowledge to enhance health, lengthen life, and reduce illness and disability.

To carry out this mission, NIH's goals are: to foster fundamental creative discoveries, innovative research strategies, and their applications as a basis for ultimately protecting and improving health; to develop, maintain, and renew scientific human and physical resources that will ensure the nation's capability to prevent disease; to expand the knowledge base in medical science and associated sciences in order to enhance the nation's economic well-being and ensure a continued high return on the public investment in research; and to exemplify and promote the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science.

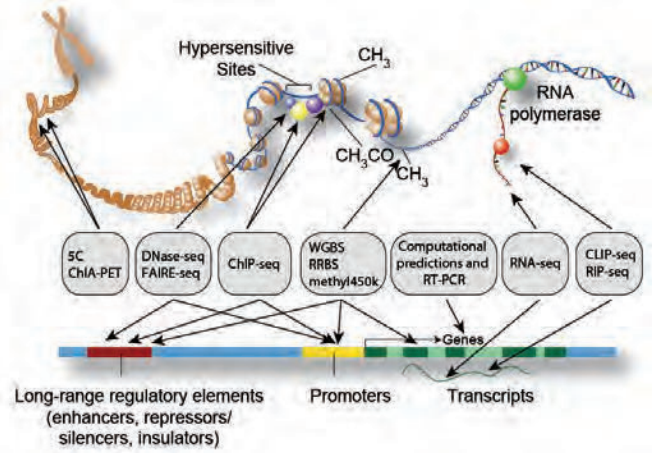
Organization

NIH is an operating division of the Department of Health and Human Services (HHS), responsible for helping the Department realize its strategic goal of advancing scientific knowledge and innovation.

To accomplish this, NIH consists of 27 Institutes and Centers (ICs), along with Program Offices, which collectively are referred to as ICOs. These ICOs have individual strategic plans and specific research agendas, which are aligned with the legislative mandates that are often related to specific diseases or body systems. To support these missions, most of NIH's ICOs receive a specific appropriation from Congress, and support research and research training through extramural funding awarded to universities, academic health centers, and other research institutions. Most also conduct research and research training in their own intramural laboratories, the majority of which are located on the NIH's main campus in Bethesda, MD.

In Fiscal Year (FY) 2014, NIH reviewed more than 51,000 research project grant (RPG) applications and awarded approximately 10,000 new and competing RPGs to institutions/organizations to support specific projects performed by designated investigators in areas representing their research interests and competencies. The average duration of an NIH grant award is about 4 years; funding the out years of a multi-year award is predicated on submission of an acceptable annual progress report. The total number of active grants in FY 2014 was more than 47,000.

Research Landscape



Common Fund: Epigenomics Example. The Epigenomics Program is among 29 innovative areas of research supported by the NIH Common Fund. The epigenome consists of chemical compounds that modify promoters and other regulatory elements within DNA in ways that switch genes off and on, without altering the DNA sequence itself. Such modifications can affect health. The image above lists technologies used to study the epigenome in work that has driven an explosion of new therapies, particularly for cancer.

Extramural. NIH currently devotes approximately 84% of its budget to grants and contracts supporting more than 300,000 members of the research workforce, including 35,000 principal investigators, in the extramural biomedical and behavioral/social sciences research communities. NIH funds researchers at all career stages who are located at many kinds of institutions, organizations, and small businesses in all 50 states.

Decisions about NIH grant awards are informed by a highly competitive, two-stage peer-review process that involves initial evaluation by more than 18,000 reviewers from the scientific community, and second-level review by members of the ICO's national advisory councils, who take into account of the ICO's research program priorities. Ultimately, ICO Directors are responsible for approving funding.

Because a broad research portfolio is critical for carrying out NIH's mission, the agency's portfolio of grants and contracts covers the full range of biomedical, behavioral, and social sciences research, from basic to applied. In addition to research supported by individual ICOs, the NIH Common Fund, within the NIH Office of the Director, funds cross-cutting, trans-NIH scientific programs that are high impact, transformative, and managed against defined milestones. This fund, which currently supports 29 innovative programs, acts as a "venture capital" space, providing the NIH Director with a strategic and nimble approach to address key roadblocks in biomedical research and capitalize on emerging opportunities.

Intramural. Approximately 11% of NIH's budget supports about 7,000 researchers at NIH intramural research facilities. Scientists in the NIH Intramural Research Program include approximately 1,000 principal investigators, 1,500 staff clinicians and staff scientists, and 4,500 trainees.

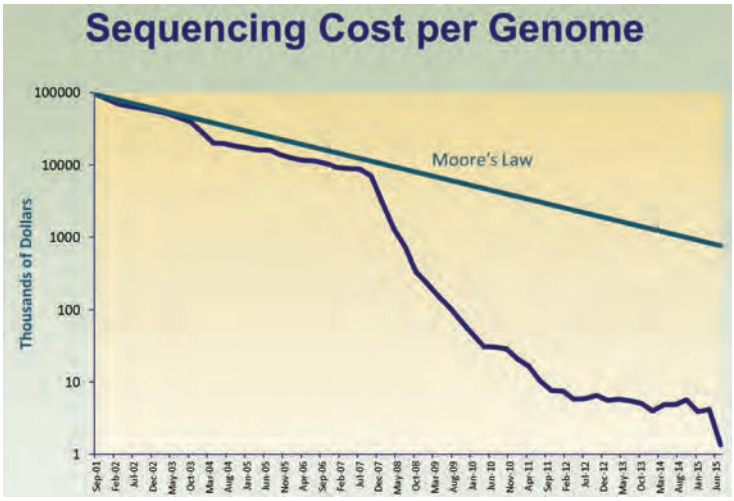
The Intramural Research Program facilitates high-impact science in a variety of important ways. For example, the program serves as a test bed for unique approaches to difficult research challenges, with the resulting solutions often being adopted by the extramural scientific community.

The program is also home to the NIH Clinical Center, the world's largest hospital dedicated to clinical research. Among the many ways in which the Clinical Center promotes translational research is its ability to link patient care directly to basic research discoveries, and its pioneering programs for the study of undiagnosed diseases and rare diseases and conditions.

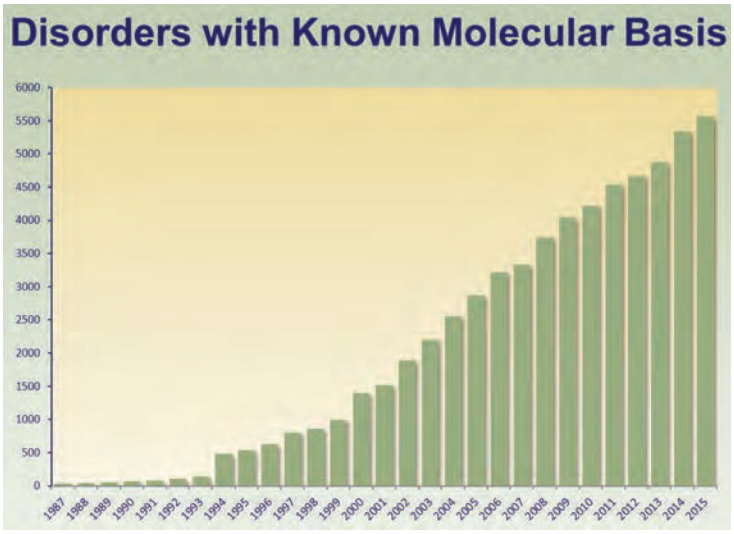
Helping People With Undiagnosed Diseases. An estimated 25 million to 30 million Americans suffer from rare disorders that can be very difficult to diagnose. Building on the success of the NIH Clinical Center's Undiagnosed Diseases Program, NIH has established a nationwide Undiagnosed Diseases Network to promote use of genomic data in disease diagnosis and enlist the help of basic researchers in elucidating disease mechanisms in order that treatments can be developed.

The Vision and The Challenge

Our nation and the world stand at a unique moment of opportunity in biomedical research. Understanding of basic biological mechanisms is growing exponentially, generating vast troves of data and propelling biomedicine into the "Big Data" sphere. Incredible technological advances, including innovations in DNA sequencing, imaging, bioinformatics, and high-throughput screening of potential therapies, are also driving discovery. Fueled by these advances, our approach to biomedical research has changed in revolutionary new ways that span scientific disciplines and take a far more cross-cutting, integrative view of biology and human health.

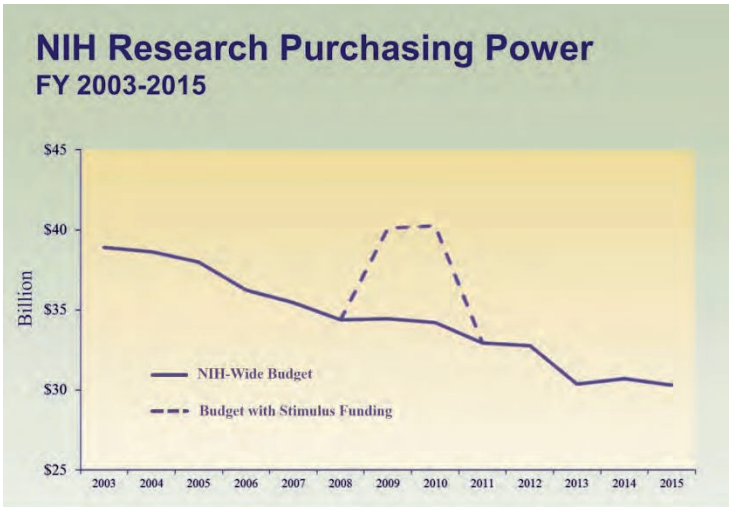


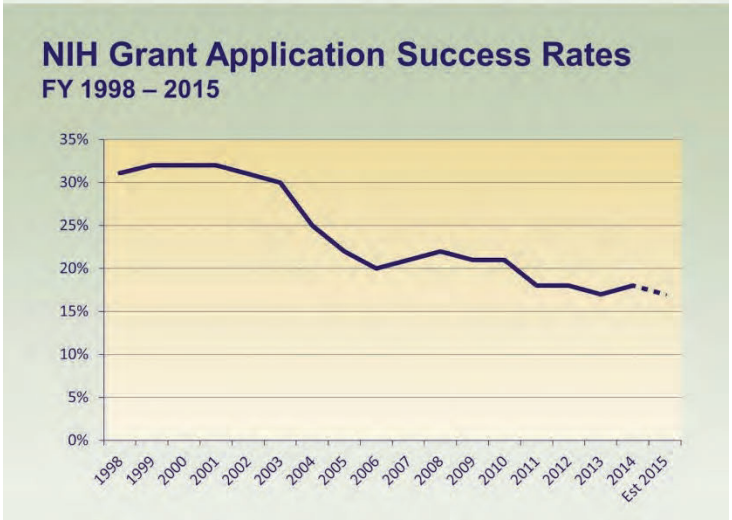
Sequencing Advances. Fueled by technological innovations arising from the NIH-led Human Genome Project, the cost of sequencing a human-sized genome has fallen dramatically since 2001. Also shown are hypothetical data reflecting Moore's Law, which accounts for long-term trends in computer hardware and is considered a benchmark for technological success.



Credit: Online Mendelian Inheritance in Man

For example, in recent years, more cost-effective DNA sequencing technologies have opened the door to studying the molecular causes of disease, with exciting implications for expanding fundamental understanding, accelerating therapeutic development, and improving disease prevention and health promotion. Much can be learned about the specific biological mechanisms involved in health and disease by using genomic technologies to identify genes that influence the risk of developing a wide range of conditions, both rare and common.





Clearly, NIH needs to capitalize upon this moment of extraordinary opportunity to continue—and to accelerate—its efforts to realize its vision of turning scientific discoveries into improved health. Yet the agency faces a variety of constraints and challenges.

For example, NIH funding has not kept pace with inflation, and the agency has lost approximately 22% of its research purchasing power since 2003. This has resulted in a situation in which many innovative research ideas cannot be funded; NIH currently funds about 1 in 6 grant applications, compared to its historical funding rate of 1 in 3.

A strengthened and sustained commitment to NIH-supported research is critical because delays in scientific progress can have a dire impact on the health of individuals and the communities in which they live, as well as our nation's overall public health and wellbeing. Investments in NIH research also make a strong positive contribution to the U.S. economy, playing an essential role in our nation's ability to retain its world-leading biomedical workforce and to remain competitive in an increasingly global business environment. Without predictable funding, it is becoming increasingly more difficult to attract much-needed new talent to the U.S. biomedical research workforce, particularly physician-scientists who have other stable and satisfying career options.

NIH'S STRATEGY

To establish a framework for carrying out its mission and optimize return on public investment, NIH's strategy will focus on four essential, interdependent objectives. These objectives are: advance opportunities in biomedical research, foster innovation by setting NIH priorities, enhance scientific stewardship, and excel as a federal science agency by managing for results.

Objective 1: Advance Opportunities in Biomedical Research

Over the next 5 years, NIH will capitalize upon a broad range of cross-cutting opportunities to move biomedical research forward in three highly important, interdependent areas: exploration of fundamental science, discovery of treatments and cures, and advancement of health promotion and disease prevention. These activities will be catalyzed by new approaches, strongly supported by NIH, that are aimed at speeding discovery across the biomedical research enterprise. This includes efforts to promote increased data sharing, to enhance the ability of scientists to pursue interdisciplinary studies, and to enable new types of partnerships.

NIH encourages and, in many cases, collaborates with researchers from both the private and public sectors, including other HHS divisions, science agencies, philanthropic foundations, academia, and industry, to advance its mission of improving human health. Among the federal science agencies that NIH often coordinates and works closely with are the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Agency for Healthcare Research and Quality (AHRQ), the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR), the National Science Foundation (NSF), the Department of Energy (DOE), and the Defense Advanced Research Projects Agency (DARPA).

NIH's Frequent Federal Partners		
U.S. Department of Health and Human Services	**Mission**	**Select Collaborations with NIH**
AHRQ Agency for Healthcare Research and Quality	Produces evidence to make health care safer, higher quality, more accessible, equitable, affordable. Partners with others to ensure such evidence is understood and used.	U.S. Preventive Services Task Force (USPSTF)
CDC Centers for Disease Control and Prevention	Works to protect Americans from health, safety, security threats. Conducts science and provides health information to protect against such threats.	SEARCH for Diabetes in Youth
CMS Centers for Medicare and Medicaid Services	Administers Medicare, Medicaid, the Children's Health Insurance Program (CHIP), and parts of the Affordable Care Act (ACA).	Data sharing between CMS and NCI's SEER (Surveillance, Epidemiology, and End Results) Program, NIDDK's U.S. Renal Data System, and NHLBI's Research Cohorts
FDA Food and Drug Administration	Protects public health by ensuring safety, efficacy, and security of drugs, biological products, medical devices, food, cosmetics, and radiation-emitting products. Helps speed innovations to make medical products safer, more affordable, and effective.	Accelerating Medicines Partnership®
HRSA Health Resources and Services Administration	Works to improve health and achieve equity through access to quality services, a skilled health workforce, and innovative programs.	Maternal and Child Health Research Network Programs
Indian Health Service	Raises the physical, mental, social, and spiritual health of American Indians and Alaska Natives to the highest level.	Native American Research Center for Health (NARCH), (also with AHRQ, HRSA)
ASPR Assistant Secretary for Preparedness and Response — Office of the Assistant Secretary for Preparedness and Response	Leads the country in preparing for, responding to, and recovering from the adverse health effects of emergencies and disasters by supporting our communities' ability to withstand adversity, strengthening our health and response systems, and enhancing national health security.	Public Health Emergency Medical Countermeasures Enterprise (PHEMCE), (also with CDC, FDA, VA, DoD, USDA, Homeland Security, USDA)
SAMHSA Substance Abuse and Mental Health Services Administration	Reduces the impact of substance abuse and mental illness on America's communities.	Patient-Reported Outcomes Measurement Information System® (PROMIS®), (also with CDC, CMS, FDA)

NIH's Frequent Federal Partners		
Other Federal Agencies	**Mission**	**Select Collaborations with NIH**
Department of Defense	Provides the military forces needed to deter war and to protect the security of our country.	Federal Interagency Traumatic Brain Injury Research (FITBIR) database, (also with VA)
Defense Advanced Research Project Agency	Makes pivotal investments in breakthrough technologies for national security.	Tissue Chip for Drug Screening, (also with FDA)
Department of Energy	Ensures America's security and prosperity by addressing its energy, environmental, and nuclear challenges through transformative science and technology solutions.	Structural biology with linear accelerator beam lines
Department of Veterans Affairs	Fulfills President Lincoln's promise "to care for him who shall have borne the battle, and for his widow, and his orphan," by serving and honoring the men and women who are America's Veterans.	Interagency Pain Research Coordinating Committee (IPRCC), (also with AHRQ, CDC, DoD, FDA)
Environmental Protection Agency	Protects human health and the environment.	Toxicology Testing in the 21st Century (Tox21), (also with FDA)
National Science Foundation	Promotes the progress of science to advance the national health, prosperity, and welfare; to secure the national defense, and for other purposes.	BRAIN Initiative®, (also with DARPA)
Department of Agriculture	Provides leadership on food, agriculture, natural resources, rural development, nutrition, and related issues based on sound public policy, the best available science, and effective management.	National Collaborative on Childhood Obesity Research

Fundamental Science

To achieve its mission, NIH must support the many types of fundamental scientific inquiry that are so essential to the progress of biomedicine. Fundamental science includes basic biological research that generates the knowledge of how living systems work at the molecular, cellular, and organismal level.

Such knowledge is the foundation for translational and clinical studies that, over time, can lead to major medical advances. Because the private biopharmaceutical sector funds only a limited amount of basic research, NIH-supported research serves as the world's leading source of foundational knowledge of relevance to both the public and private sectors of biomedicine.

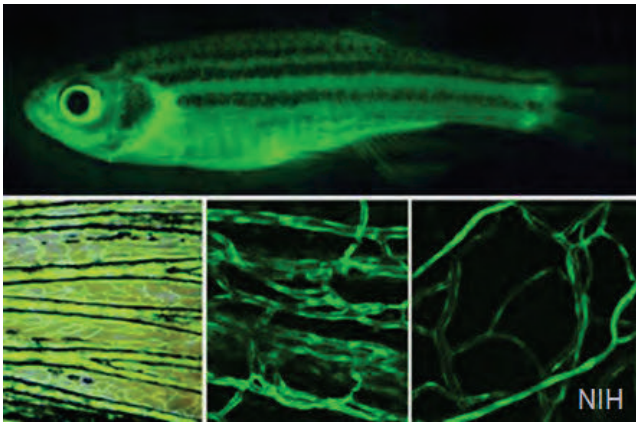
History shows that major biomedical advances frequently spring from unexpected sources. As anyone familiar with the story of penicillin's discovery knows, it is impossible to predict exactly what a basic researcher may uncover and what positive health benefits may eventually arise from such fundamental discoveries.

Furthermore, no one can foresee what threads of foundational knowledge will be woven together to produce a new breakthrough, which could open up entirely new fields or pave the way for new technology that will enable researchers to tackle questions once beyond the reach of biomedical science. Most of the examples cited in this section are those in which a basic science discovery has led to a significant clinical advance—an advance that could not have been foreseen at the time of the original basic research. One dramatic example is the story of how fundamental advances in cell biology led to development of a class of drugs widely used to lower the risk of cardiovascular disease. In the early 1970s, NIH-supported basic researchers Joseph Goldstein and Michael Brown studied families with very high cholesterol levels and discovered that cells have low-density lipoprotein (LDL) receptors that remove cholesterol from the blood. That Nobel Prize-winning work, coupled with the NIH-funded Framingham Heart Study's landmark 1961 finding that high blood cholesterol is a major cardiovascular disease risk factor, set the stage for the first cholesterol-lowering statin drug in 1987.

Credit: University of Texas Southwestern Medical School at Dallas
Cholesterol Pioneers. The basic science discoveries of Michael Brown and Joseph Goldstein paved the way for development of statin drugs for lowering cholesterol.

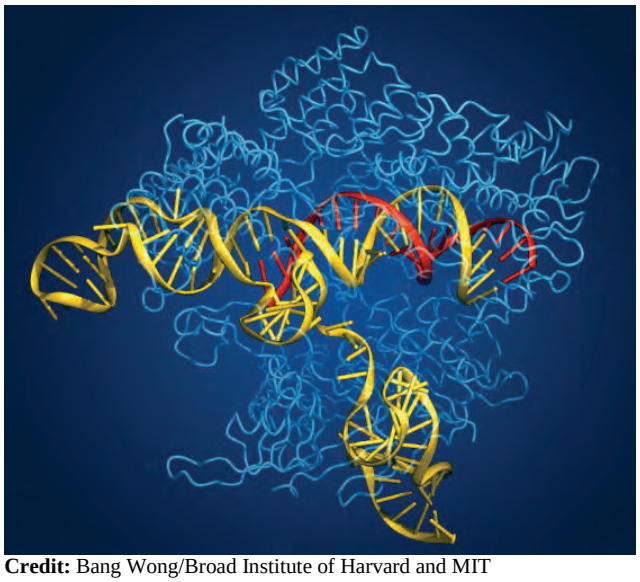
Likewise, NIH-funded basic research was instrumental in the development of

zidovudine (AZT), the first anti-retroviral drug approved for treating the human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS). The drug was developed in the early 1960s to treat cancer, but failed to show efficacy. It faded from view until 1985, when others thought of using AZT as an AIDS drug because of its ability to inhibit reverse transcriptase, an enzyme that HIV uses to replicate. Reverse transcriptase was discovered by basic virology research several years before AIDS was identified. In 1975, NIH grantees David Baltimore and Howard Temin shared a Nobel Prize in Physiology or Medicine for that work.



Green Fluorescent Protein (GFP). Researchers are using transgenic zebrafish engineered to express GFP to study vascular-specific genes. This tool can be used to visualize blood vessels in living fish, improving understanding of vascular growth in cancer and other diseases. Top: adult transgenic fish. Bottom: close-ups of fin (left) and scales (middle, right), showing vascular-specific fluorescence.

Basic innovation is also essential for the advancement of fundamental science because new technologies and methods can open whole new areas of scientific inquiry. In a tale of discovery spanning more than three decades and culminating in the 2008 Nobel Prize in Chemistry, NIH grantees Martin Chalfie, Osamu Shimomura, and Roger Tsien discovered a green fluorescent protein (GFP) in jellyfish and went on to develop GFP into a key tool for observing biological processes that were previously invisible to researchers.

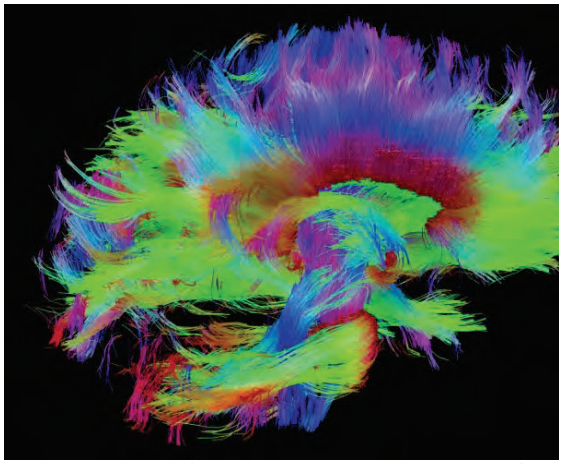


Credit: Bang Wong/Broad Institute of Harvard and MIT

Gene-Editing Technologies. Crystal structure of the new CRISPR/Cas9 system, which enables DNA to be edited with unprecedented precision. Researchers use RNA guides called CRISPRs (red) to steer the Cas9 gene-editing enzyme (light blue) to a specific site on a DNA strand (yellow) that they wish to modify. New mouse models of disease and next-generation antibiotics are among the things this customizable system is being used to create.

More recently, researchers have developed revolutionary customizable, gene-editing tools, such as CRISPR/Cas9. These technologies are enabling efforts to study genes in specific, targeted ways, often in real time.

On the other hand, new scientific challenges can inspire the creation of new technologies. Compelling recent

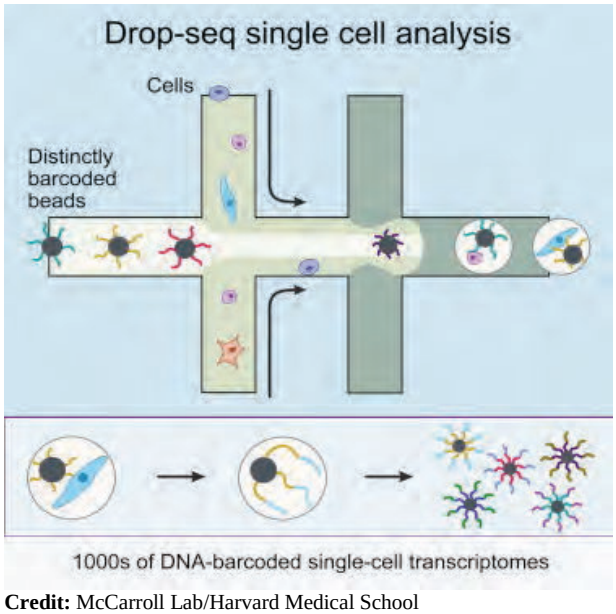


Credit: Laboratory of Neuro Imaging and Martinos Center for Biomedical Imaging/Massachusetts General Hospital

The Human Connectome Project. Wiring diagram of a healthy human brain produced by tracking the movement of water molecules through nerve fibers by diffusion tensor magnetic resonance imaging. This is an example of work being done by the Human Connectome Project.

examples of this innovative force in action include NIH's Human Connectome Project and the multi-agency Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative, in which NIH plays a leadership role. With more than 100 billion cells and 100 trillion connections, the human brain remains one of science's most daunting frontiers and one of medicine's greatest challenges. To revolutionize understanding of how the brain enables the body to record, process, utilize, store, and retrieve vast quantities of information, BRAIN is supporting development of entirely new technologies, including some with the potential to benefit many other areas of biomedical research, such as single-cell analysis methods.

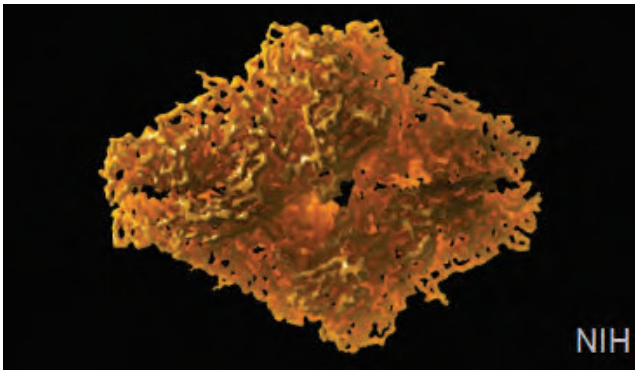
Engineers, computer scientists, nanotechnologists, physicians, and neuroscientists will use these and other leading-edge technologies to work together to achieve BRAIN's goal of measuring real-time cognition, emotion, perception, and behavior at the scale of complex neural networks in living organisms—all at the speed of thought. A bold plan for the BRAIN initiative, extending over a 12-year period, was recently put forward by an expert working group of neuroscientists, and serves as the current blueprint for this project. Ultimately, the foundation of understanding developed by the BRAIN Initiative® will help reveal the underlying pathology in a vast array of brain disorders and provide new therapeutic avenues to treat, cure, and prevent neurological and psychiatric conditions, such as Alzheimer's disease, autism, schizophrenia, depression, epilepsy, and addiction.



Credit: McCarroll Lab/Harvard Medical School

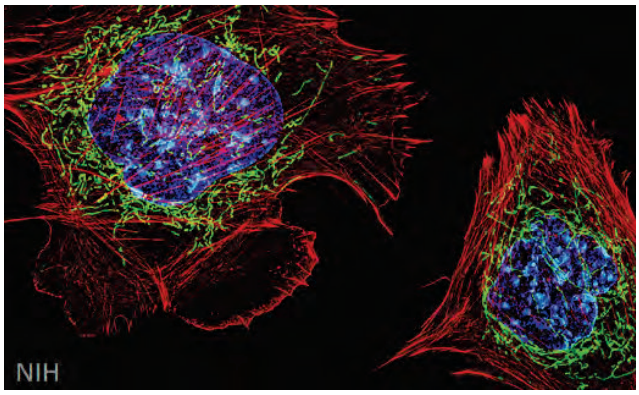
Single-Cell Analysis. New microfluidic technology, including this approach called Drop-seq, now makes it possible to analyze the gene activity of thousands of individual cells separately.

Indeed, the impact of technologies inspired by a specific discovery-driven initiative can extend far beyond the life of the initiative, catalyzing avenues of basic research never imagined at the outset. For example, the goal of sequencing the human genome yielded the technologies now driving many diverse "omic" areas of basic research. That includes microbiomics, in which next-generation DNA sequencing is being used to explore the complex communities of microbes that live on and in the human body and how they interact with human cells to influence health and disease.



New Tools for Structural Biology. Cryo-electron microscopy (cryo-EM) image showing the structure of a metabolic enzyme called beta-galactosidase in near-atomic detail. This imaging technology provides a new path for solving molecular puzzles that may revolutionize many areas of biomedical research and drug development.

Other frontiers in fundamental science include: molecular immunology, which is using RNA seq and other transcriptome analysis tools to characterize in unprecedented detail how immune cell repertoires vary in health and disease; structural biology, which is undergoing a major leap forward in defining three-dimensional submicroscopic structures because of the development of cryo-electron microscopy (cryo-EM); and cell biology, which is benefiting from novel approaches to light microscopy that have pushed resolution below the diffraction limit. In addition, the development of innovative "tissue- and organ-on-a-chip" systems is helping to bridge the gap between fundamental and translational science, providing new models of complex pathology for understanding basic mechanisms of disease.



New Tools for Cell Biology. Super-resolution imaging of fibroblasts, one of the most common cells in mammalian connective tissue. Scientists used these mouse fibroblasts to test the power of a new technique called structured illumination microscopy (SIM). Clearly visible in this image are the cell's nuclear DNA (blue), mitochondria (green), and cellular skeleton (red).

Fundamental science also includes basic behavioral and social science research that generates knowledge of how living systems interact with and are influenced by experiences at the individual, family, social, organizational, and environmental levels. NIH-supported research on the neurobiological and learning mechanisms of goal-directed versus habitual behaviors provide important insights on how unhealthy habitual behaviors can be brought under greater control and how

behavior change can be maintained. The study of stress responses and stress resilience offers potential approaches to help individuals better adapt to negative life events. Understanding decision-making processes, especially under various emotional and cognitive states, also sheds new light on how medical decisions, both by provider and patient, are made and can be improved. NIH-supported basic behavioral and social science research serves as the foundation for the development of innovative approaches to improve health via changes in behavior and the environment.

Data science also holds tremendous potential, not only for enhancing the efficiency of the conduct of science, but also for increasing the impact of fundamental science, along with many other areas of biomedical research. To this end, NIH will serve as a focal point for catalyzing this historic research opportunity, continuing to leverage its roles as an influential convener and major funding agency to encourage rapid, open sharing of data and greater harmonization of scientific efforts. NIH will also maintain and expand its support of research aimed at addressing new computational challenges in accessing, managing, analyzing, integrating, and mining the huge amounts of data, often referred to as "Big Data," being generated by biomedical scientists. One hope is that advances in bioinformatics and computational biology will lead to basic researchers conducting more experiments via computer simulation (*in silico*), with the ensuing results being used to generate and test novel hypotheses that will be rapidly shared with the broad research community.

From FY 2016-2020, NIH will support a broad, balanced portfolio of basic research across a wide range of scientific disciplines, a portfolio that will be complemented by vigorous support of innovations in technology and data science. By maintaining and strengthening its already impressive foundation of fundamental science, biomedical research will be poised to identify and capitalize upon potential opportunities for revolutionary breakthroughs with the potential for preventing, treating, and curing disease.

Treatments and Cures

To achieve its mission, NIH is strongly committed to supporting the process of turning advances in fundamental scientific knowledge into treatments and cures. When integrated with existing knowledge about cells, systems, and organisms, insights generated by this innovative work will provide a new conceptual framework for therapeutic development that is based on a deeper understanding of biological systems and how, depending upon context, these complex mechanisms interact to influence health and disease.

This process begins with basic research discoveries in biology, disease, or behavior that serve to further understanding of the basis of a disease and to identify potential therapeutic targets. Cell or tissue samples, animal models, and/or computer simulations are then used to design and

test candidate approaches for diagnostics, devices, treatments, and/or cures. If the candidate approaches prove to be safe and effective in this pre-clinical testing, the experimental treatments and/or cures are then moved into human clinical trials, where they are tested for safety and efficacy. It must be emphasized that advances in these areas are closely interconnected and often do not progress in a linear manner. In fact, sometimes the process even circles back on itself in a "virtuous cycle," with applied research informing new ideas in basic research.

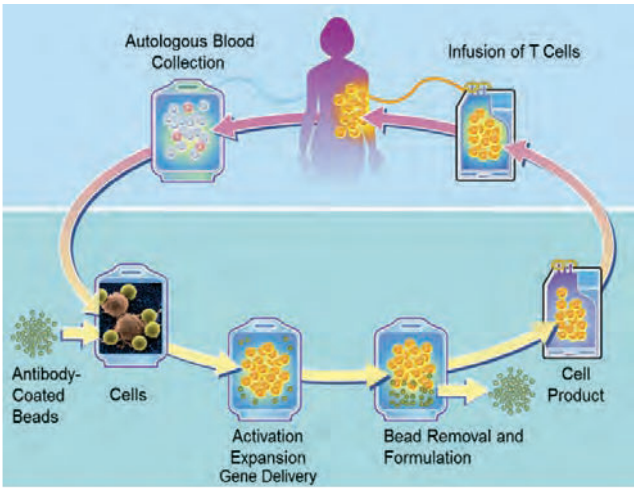
The randomized trial is the gold standard by which clinical researchers determine the safety and/or effectiveness of interventions that are thought to have potential to improve human health. NIH, which currently devotes approximately 10% of its budget to supporting clinical trials, has a distinguished history of funding landmark trials that have led to a wide spectrum of interventions. Such interventions have included coronary bypass surgery, treatments for breast cancer, lifestyle improvements to prevent diabetes, approaches for lowering blood pressure, screening methods for lung cancer, hormone replacement therapy in postmenopausal women, and anti-retroviral drugs in people with, or at high risk for, HIV infection. In recent years, NIH developed an increasing interest in fostering approaches to enhance the speed and efficiency with which trials are conducted, as well as to learn more about the role of "pragmatic trials," which are trials of direct interest to patients and clinicians.

Traditionally, diseases have been researched and treated within an organ-based framework, e.g., diseases of the heart, the eye, the gastrointestinal tract, and so forth. Today, thanks to fundamental research, researchers have learned that many apparently different diseases have commonalities at the molecular level. These molecular similarities have led us to think in new ways about the roots of disease and open the door to identifying therapies that work across different organ systems and disease states. These shifts in thinking have profound implications for the future of scientific research and, ultimately, for the future of medicine. Tools and technologies that offer opportunities to screen rapidly for similarities among seemingly disparate diseases, as well as seemingly disparate drugs, are providing opportunities to repurpose existing drugs for use in conditions other than those for which they were originally developed. For example, thanks to an innovative public-private partnership, an experimental drug originally developed to fight cancer is now being tested for Alzheimer's disease (AD) in human clinical trials. The compound, called saracatinib, is particularly exciting because it acts through a different mechanism than other AD experimental therapies.

As important as this new emphasis on cross-cutting molecular mechanisms may be, there remains much that can be learned by studying the rare or unique. Especially for rare diseases caused by mutations in a single gene, the identification of a specific molecular defect through DNA sequencing can point directly to possible treatment strategies. Still, even in such cases, the

road from discovery to treatment may be long, as evidenced by the two decades between discovery of the gene for cystic fibrosis (CF) and FDA approval of the first drug that directly affects a CF-causing molecular defect. For more common disorders, finding rare individuals carrying a genetic protective factor can provide critical clues to new therapeutic strategies. For example, a search for genes involved in cholesterol metabolism turned up a few healthy individuals with a rare gene variant that leads to very low levels of cholesterol and a very low incidence of cardiovascular disease. Further studies showed this gene variant reduces production of a protein called PCSK9, setting off a race among pharmaceutical firms to develop a new class of drugs that lower cholesterol by blocking this protein. Many experts think there are more such drug targets out there waiting to be discovered through molecular characterization and stratification of common diseases and disease risk factors; NIH is assembling the right research teams and resources to find such targets.

Progress toward treatment and cures is certainly not limited to high-throughput screening and DNA sequencing. Consider the example of cancer immunotherapy. In the early 1970s, basic research, spearheaded in large part by NIH-funded scientists, led to the development of methods to splice fragments of DNA together, giving birth to the field of biotechnology. When merged with fundamental advances in molecular immunology, this set of technologies made it possible to begin pursuing ideas for cancer immunotherapy—a radical new approach that involves enlisting a patient's own immune system in the fight against cancer. In one promising strategy, T cells are collected from patients and engineered to produce special surface proteins, called chimeric antigen receptors. This work has already saved the lives of children with acute lymphoblastic leukemia and adults with chronic lymphocytic leukemia and refractory multiple myeloma.



Credit: Carl June/University of Pennsylvania

Cancer Immunotherapy. The approach illustrated above, called chimeric antigen receptor (CAR) therapy, involves genetically engineering a key part of the immune system (T cells) to recognize specific proteins, or antigens, on tumor cells and attack them.

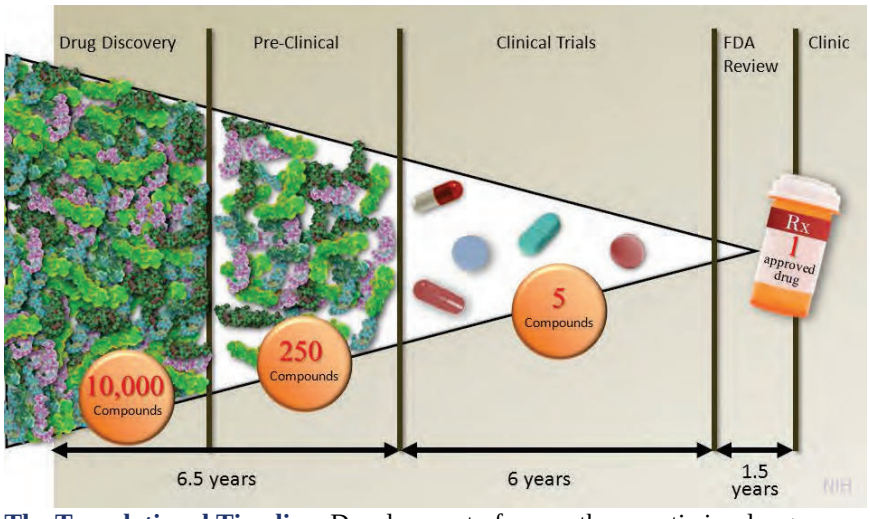
Like the previous examples of statin and HIV drugs, it must be emphasized that cancer immunotherapy owes its success to decades of NIH-funded fundamental science. In fact, a recent analysis of a cancer immunotherapy approach pioneered by NIH grantee James Allison, who is a 2015 Lasker Award winner, documented the contributions of 7,067 scientists over more than a century, with many working on basic research with no clear connection to cancer.

Scientific innovation is also central to the quest to find new ways of combating the growing threat of antibiotic-resistant bacteria, which each year infect more than 2 million Americans and kill at least 23,000. For example, an ingenious microfluidic system that can trap and sort single cells has enhanced efforts to mine one of nature's richest sources of potential antibiotics: dirt. Certain microorganisms that naturally live in soil produce antibiotic-like compounds that are highly toxic to other microbes. Thanks to their improved ability to "dig through dirt," NIH-funded researchers recently uncovered a new class of antibiotic drugs with the power not only to kill a wide range of infection-causing bacteria, but to kill them in a way that may reduce the problem of antibiotic resistance.

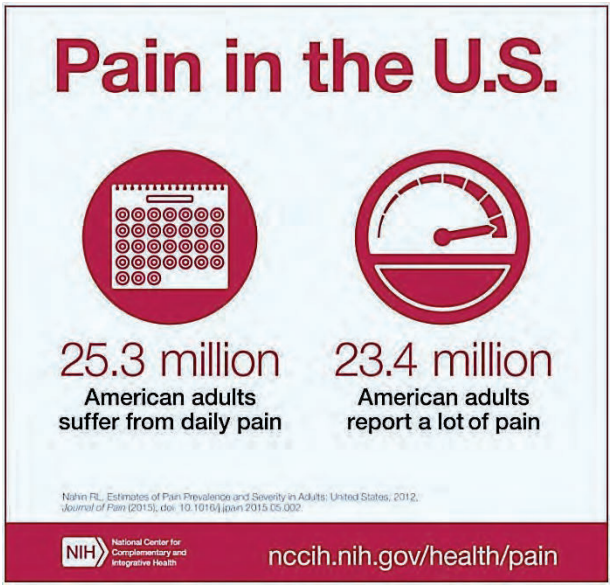
Credit: Slava Epstein/Northeastern University

Digging for New Antibiotics. Innovative microfluidic chip system being used to search dirt for new sources of antibiotics. Besides discovering a powerful new antibiotic called teixobactin, researchers have isolated more than 25 potential new drugs, including an anti-cancer agent and a compound that targets tuberculosis-causing bacteria.

Discovery of potential therapeutic targets and candidate therapies are essential first steps in the development of new treatments and cures, but they are far from the only steps. The transition of scientific discoveries to human clinical trials has become increasingly costly and time consuming, with a great number of candidate therapies failing to cross what has been dubbed the "Valley of Death." NIH-funded research will play an increasingly important role in identifying hurdles in this process, as well as generating approaches for accelerating the development and testing of potential treatments and cures.

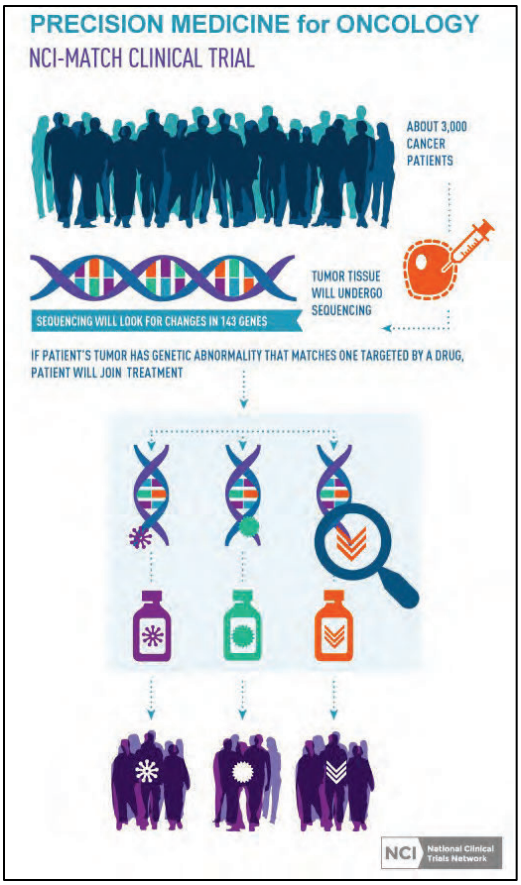


The Translational Timeline. Development of a new therapeutic is a long, costly, and risky endeavor. Currently, a novel drug, device, or other medical intervention takes about 14 years and $2 billion to develop, with a failure rate exceeding 95%.

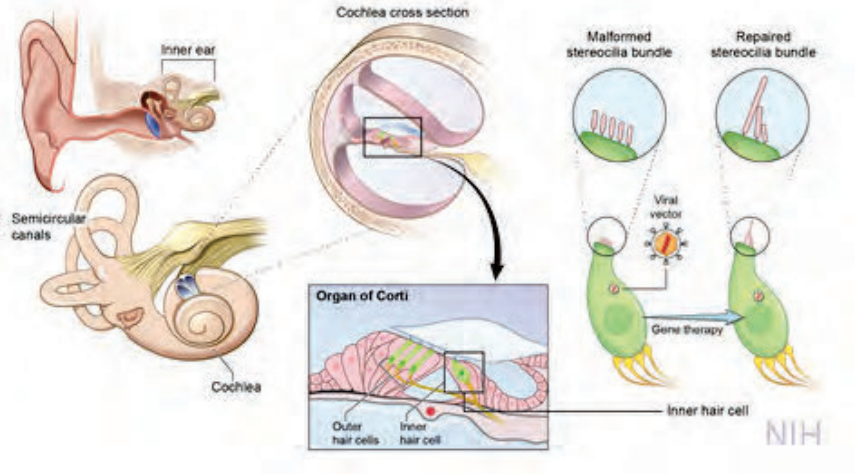


Also, as part of its effort to push research beyond a strictly organ-based view of health and disease, NIH will encourage efforts to study the interactions of various diseases and conditions. The aim is to gain a better understanding of the cumulative and synergistic impacts that multiple chronic conditions and comorbidities can exert upon the human body, thereby informing efforts to develop therapeutic and preventive approaches for these complex challenges. Among the many comorbidities in need of additional research is pain. On behalf of HHS, NIH has established the Interagency Pain Research Coordinating Committee, which has generated a National Pain Strategy and facilitated collaborations aimed at advancing fundamental understanding of pain and improving pain-related treatment.

To speed the movement of discoveries from the lab to the clinic, NIH will also accelerate and expand upon its efforts to encourage development of more precise, individualized ways of managing and preventing disease. Known collectively as precision medicine, these emerging approaches for preventing, diagnosing, and treating disease take into account individual variability in genes, environment, and lifestyle. While individualized, molecularly based strategies are in use for some conditions, including cancer, HIV/AIDS, and hepatitis C, more research is needed to realize precision medicine's promise for all conditions. Among the frontiers in this area is pharmacogenomics, which studies how an individual's genetic makeup (or the genetic makeup of a tumor) affects response to drugs. The goal of such research is to enable health-care providers to prescribe the right drug at the right dose at the right time for each patient. One example of pharmacogenomics is the National Cancer Institute (NCI)-Molecular Analysis for Therapy Choice (NCI-MATCH) clinical trial, which will build a foundation for the oncology component of the multi-agency Precision Medicine Initiative® (PMI), in



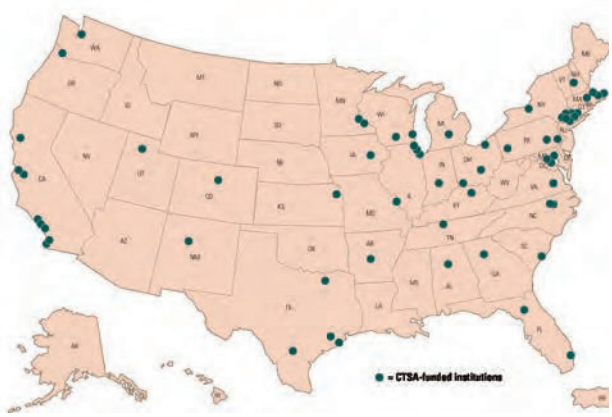
which NIH has a lead role. In this trial, involving up to 3,000 patients with different types of advanced solid tumors and lymphomas, researchers will analyze a patient's tumor for "actionable" genetic abnormalities and use that information to select molecularly targeted drug(s) most likely to work for that particular patient.



Gene Therapy for Hereditary Hearing Loss. Gene therapy delivered to the hearing structure in the inner ear (cochlea) may restore hearing by overcoming structural and functional deficits in sensory hair cells and their stereocilia that arise from inherited genetic mutations. NIH-supported researchers are currently testing this approach in animal models of hereditary hearing loss.

Other innovative approaches with precise therapeutic potential include gene therapies, including approaches aimed at correcting vision and hearing loss; cell-based therapies; and gene editing systems. In a recent proof-of-concept study, NIH-funded researchers paired the latter two technologies to develop a potential cure for sickle cell disease, a painful, life-threatening disorder caused by mutations in the beta globin gene. To accomplish this, the researchers generated induced pluripotent stem cells (iPSCs) derived from the white blood cells of people with sickle cell disease; used CRISPR/Cas9 gene editing to replace the mutant gene; and then converted the iPSCs into normal red blood cells. If the technology proves safe and effective in additional pre-clinical and clinical tests, gene-corrected red blood cells could be generated from individuals with sickle cell disease and used for transfusions, reducing need for donor blood and providing hope for an eventual cure.

Along with advances in basic and translational research, advances in clinical research are essential to NIH's efforts to catalyze the development of treatments and cures. To move clinical science forward, NIH will seek to foster and reward innovations in the design, execution, and management of clinical studies.



NIH's Clinical and Translational Science Awards (CTSA®)

One of the primary ways in which NIH will encourage innovation in the clinical research enterprise is through its support of the Clinical and Translational Science Awards program, which is a national network of institutions engaged in developing and testing new approaches for clinical research and training. To promote the effective research use of clinical data, NIH will engage in efforts to create and implement health data standards in electronic health records and health information exchange systems. The agency will also back the development of alternative clinical trial designs that permit flexibility, while maintaining the utmost priority of patient safety. NIH will also work closely with its sister HHS agencies, including FDA, AHRQ, and CDC, to improve clinical research methodologies in a variety of important areas, such as identifying new approaches for combating antibiotic-resistant bacteria and timely reporting of clinical trial results. These and other steps will increase the rate at which clinical research findings inform current areas of scientific inquiry and stimulate entirely new avenues for biomedical research, which could in turn spark ideas for further treatment and prevention strategies.

Despite the many exciting scientific opportunities for speeding the development of treatments and cures, significant challenges remain. Over the next 5 years, NIH will support research aimed at addressing a wide range of obstacles that lie at various points throughout the therapeutic development process. NIH will strive to forge new connections across research disciplines to advance understanding of molecular mechanisms and discovery of treatments and cures for a wide range of illnesses. Systems-based and interdisciplinary approaches are vital to making progress toward treatments tailored to individual patients. To improve the efficiency, relevance, and accuracy of preclinical research, NIH will catalyze powerful innovations, including molecule cross-coupling methods that will open a vast new frontier of "chemical space" and human 3D organoid technologies that will be better than animal models. Through its National Center for Advancing Translational Sciences, NIH will continue to support efforts to transform and accelerate the translational process, using science to find new ways to bridge the gaps and get more treatments to more patients more quickly. NIH will also work to speed and streamline clinical trials by encouraging the use of molecular knowledge to select the individuals most likely to respond to experimental therapies, and promoting respect for research volunteers though steps such as the updating of the Common Rule protections for human subjects research.

Health Promotion and Disease Prevention

Along with basic research and research aimed at developing treatments and cures, NIH supports research to promote health; to prevent diseases, disorders, conditions, or injuries; and to detect and/or prevent progression of asymptomatic disease. This broad and deep research portfolio encompasses studies of biology, behavior, environment, and health-related policies. Among the many advances in this area are identification and assessment of risk and protective factors; screening and identification of at-risk individuals/groups, (e.g., human papilloma virus testing for cervical cancer screening); development and evaluation of risk-reduction strategies; and translation, implementation, and dissemination of preventive interventions, (e.g., Sudden Infant Death Syndrome campaign).

While NIH supports its own distinct and robust research portfolio, it collaborates with CDC, AHRQ, the Health Resources and Services Administration (HRSA), and other HHS agencies involved in complementary activities related to health promotion and disease prevention, including efforts in dissemination and implementation. Recent collaboration between CDC and NIH on surveillance and initiation of clinical trials of candidate vaccines against Ebola virus disease in West Africa is one noteworthy example. Likewise, NIH, in collaboration with other HHS agencies, is playing a key role in the implementation and dissemination of the HHS Secretary's new multi-pronged, evidence-based initiative to combat the use of opioid drugs.

Ebola Vaccine Research. The U.S. and Liberian governments are partnering with several pharmaceutical firms and other organizations to test effectiveness of several vaccine candidates.

Environmental influences on Child Health Outcomes (ECHO)

Focus Areas

- Upper and lower airway
- Obesity
- Pre-, peri-, and post-natal outcomes
- Neurodevelopment

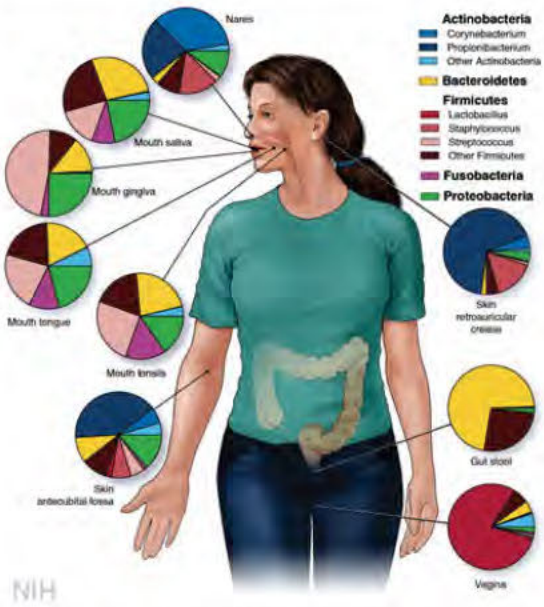
This NIH-funded initiative will bring together multiple existing research cohorts to investigate environmental and genetic influences on pediatric health. Data collection will include demographics, descriptors of early health and development, genetic background, a broad range of environmental factors, and other outcomes reported by patients and caregivers. A significant additional element will be an IDeA States Pediatric Clinical Trials Network.

Over the next 5 years, NIH's health promotion and disease prevention efforts will place particular emphasis on research in several key areas: studying healthy individuals across the lifespan; applying technological advances in early detection, diagnosis, and prevention; and utilizing evidence-based interventions to reduce health disparities.

NIH will promote research on healthy development and aging, as well as on understanding disease susceptibility and prevention across the life span. A lifetime of benefits will result from efforts to establish healthy behaviors early in life and to identify and prevent the mechanistic antecedents to chronic conditions that begin during pre-, peri-, or post-natal periods of development. One example of this is NIH's new Environmental influences on Child Health Outcomes (ECHO) initiative. To understand how things can go wrong in the human body, it is essential to understand how things work when everything goes right. For example, studies of normal embryonic development have informed efforts to understand, prevent, and treat birth defects caused by genetic and a broad range of environmental factors.

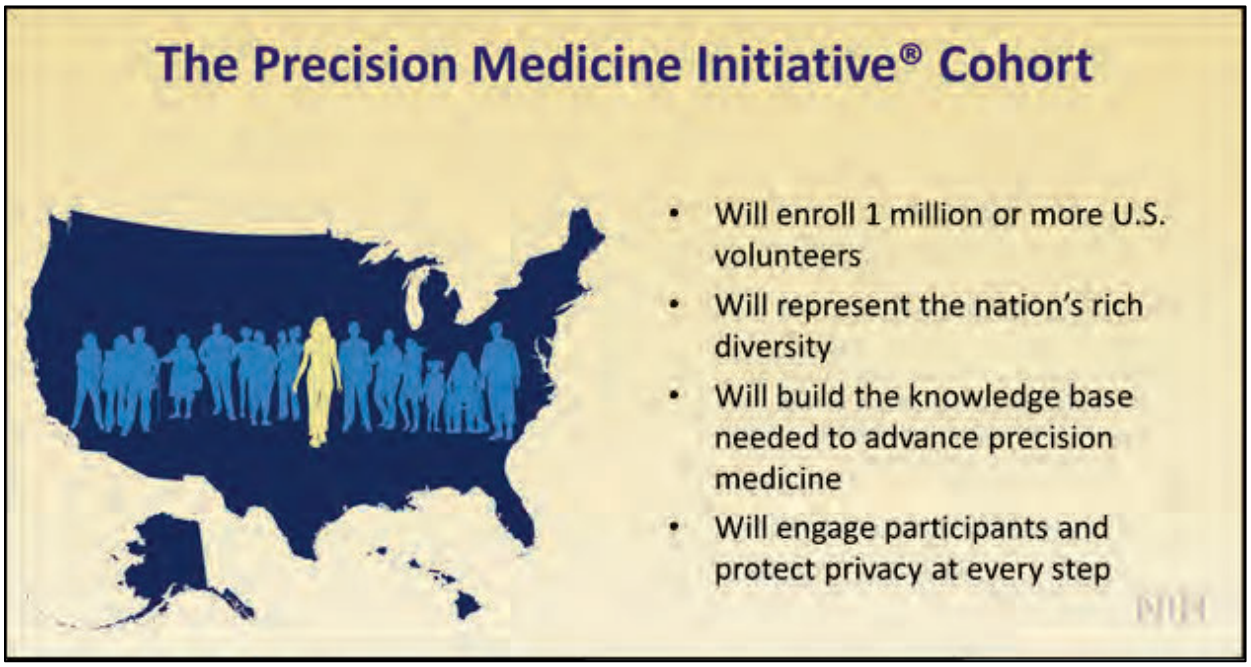
In another example of research aimed at health promotion and disease prevention, NIH will expand efforts to track the composition of microbial communities over the course of an individual's life. Such action is motivated, in part, by the explosion in understanding of the role played by the microflora in the development of the immune system.

To make similar advances in other areas, NIH will continue to support research into the basic mechanisms of development and aging in healthy individuals. This will



Microbiomics. The NIH Human Microbiome Project is analyzing trillions of bacteria, fungi, viruses, and other microbes that live in and on the human body. Microbial communities vary among individuals, making many beneficial contributions to health and influencing susceptibility to a wide range of conditions, including gut disorders, cancer, allergies, and autoimmune diseases.

include intensifying studies of "resilience"—that is, to understand why some individuals' bodies age more slowly and/or are better able to resist disease risks posed by particular genetic, lifestyle, and/or environmental factors. NIH will also strive to develop tools to enhance measurement of physical, social and environmental exposures, as well as to assess the impacts of such exposures on development, health, and longevity. In addition, NIH-funded research will explore why people make unhealthy or risky choices, generating valuable information for devising risk reduction and/or early intervention strategies.



Technological innovations will also be instrumental for research aimed at making advances in the early detection, diagnosis, and prevention of disease. At the forefront of this effort will be the NIH-led PMI cohort. Taking advantage of emerging biomedical tools and technologies, such as availability of electronic health records, DNA sequencing, and exposure monitoring, PMI's longitudinal research cohort of 1 million or more U.S. volunteers will establish a base of scientific knowledge that can be used to develop prevention and screening strategies tailored to individuals at the most opportune times across the course of their lives.

PMI will also take advantage of the latest methods and approaches in data science, including advances in large-scale databases, computational tools, and -omics methodologies to characterize individuals. In addition, PMI will offer researchers the ability to test whether mobile technologies are useful in adapting preventive strategies to individuals' needs and preferences, enhancing delivery of interventions, and improving monitoring of compliance and outcomes. PMI will pioneer efforts to merge, integrate, and analyze data from a wide variety of sources with implications for prevention, including basic biological data, health status

mHealth. Capitalizing upon advances in mobile health (mHealth) technologies, the PMI research cohort will use smart phones, along with other mHealth devices and applications, to correlate activity, physiologic measures, and environmental exposures with health outcomes. mHealth will also give PMI participants ready access to data and information to improve their own health.

information from electronic health records, individual data on environmental exposures, geospatial data on community environmental exposures, and so on.

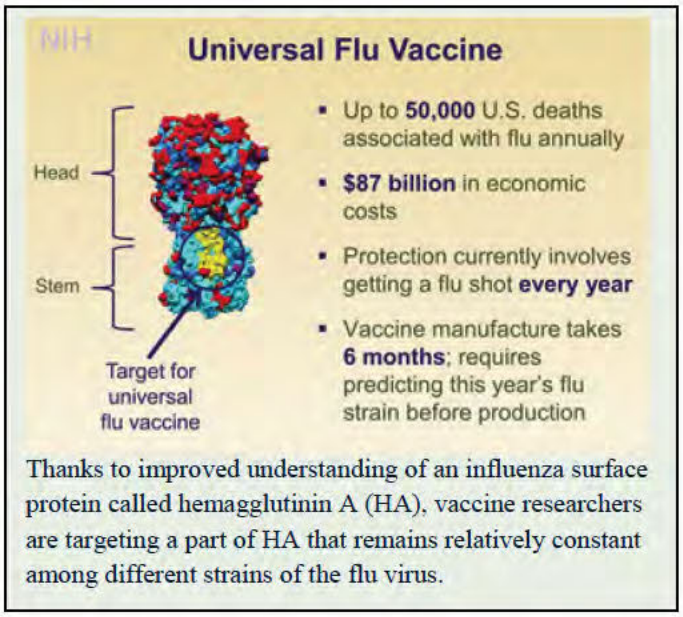
NIH will also build upon ongoing efforts to develop better methods for screening, assessing, and identifying those at risk for onset or progression of asymptomatic diseases/disorders. One notable success in the realm of prevention of a common, chronic disease is the NIH-led Diabetes Prevention Program (DPP) trial, which involved overweight or obese U.S. adults with prediabetes. DPP researchers found that exercise and dietary changes leading to modest weight loss (5%-7% of body weight) could prevent or delay development of type 2 diabetes. Furthermore, the prevention program was shown to be effective in both men and women and all racial/ethnic groups studied, including those disproportionately burdened by obesity.

Also needed are molecular, cellular, and imaging technologies that provide greater power to identify diseases and conditions in early, more readily treatable states before they progress to symptomatic or metastatic disease. To further facilitate early diagnosis and detection, NIH will encourage the development of point-of-care technologies that lead to less costly, more rapid results, and improved patient outcomes.

NIH will also cultivate efforts to provide clinicians and researchers with access to efficient, precise, and valid patient-reported measures of health and well-being. For example, NIH currently supports the Patient-Reported Outcome Measurement Information System® (PROMIS®), which is using measurement science to create a state-of-the-art assessment system for self-reported health.

Vaccines—one of biomedicine's most powerful tools for preventing and eradicating disease—also are heavily reliant upon NIH-funded research and innovation. Over the next 5 years, NIH will take advantage of its intramural Vaccine Research Center, along with its network of Vaccine and Treatment Evaluation Units located across the nation, to support the full spectrum of vaccine development from early discovery to clinical evaluation for a wide variety of infectious diseases.

Particular emphasis will also be placed upon innovative approaches, such as a universal influenza vaccine and other DNA-based vaccines, to improve protection and optimize production.



NIH also will promote health and encourage disease prevention by facilitating collaboration across biomedical, behavioral and social sciences, as well as disciplines not traditionally considered to involve health, such as architecture, transportation, and urban planning. Although many behaviors that increase disease risk have been identified, more effective approaches to promoting behavior change are still needed. Basic, behavioral, and social sciences research can inform new strategies for preventing distinct conditions caused by high-risk behaviors that share an underlying basis. One example is the wide range of cancers and other diseases associated with use of various forms of tobacco.

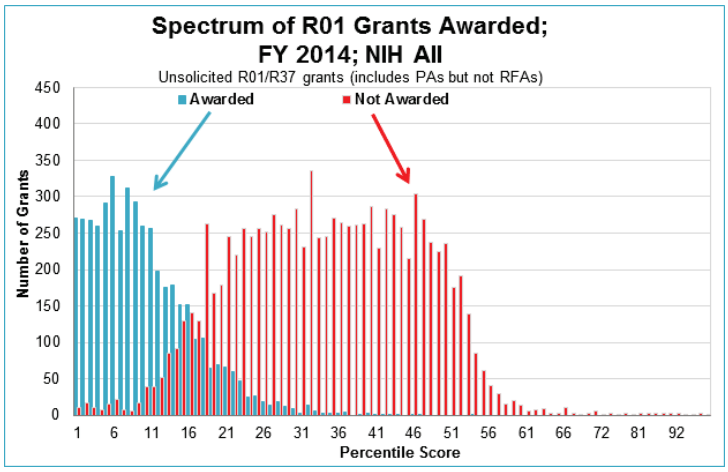
Importantly, NIH will continue to pursue research aimed at developing evidence-based interventions to reduce health disparities. Such efforts will address the importance of understanding social determinants of health, disease, and disability; disproportionate disease risk; and opportunities for progress in prevention. For instance, an NIH-supported study of women who received housing vouchers that enabled them to move from high-poverty to low-poverty neighborhoods found that such women were less likely to be obese or have diabetes than similar controls. NIH-funded research will also evaluate methods to disseminate evidence-based interventions to promote health and prevent disease—with particular emphasis on comorbid conditions—in a variety of community health and clinical settings, as well as identify barriers to adoption of such interventions. Understanding mechanisms that lead to disparities in health outcomes by race/ethnicity and socioeconomic status will require multi-disciplinary collaboration of population, clinical, and basic scientists. An NIH-wide assessment of current minority health and health disparities research using standardized coding will inform the development of a strategic plan to guide this emerging scientific area.

Health promotion and disease prevention clearly represent a critical facet of the NIH mission and its aim of improving the health of whole populations. It is imperative that NIH act upon opportunities to advance this vital area, which is complementary to the discovery of treatments and is integral to the entire biomedical research continuum.

Objective 2: Foster Innovation by Setting NIH Priorities

In order for NIH to achieve its mission, it must serve as an effective and efficient steward of public resources. To advance these efforts over the next 5 years, NIH will focus intensely on prioritization. The process of setting NIH's research priorities must balance the opportunities presented by the best science, public health needs, and the unique ability of NIH to address challenges in human health that would otherwise go unmet. These priorities, which will require NIH's constant review and adjustment, must be flexible and based on the best science of the moment; formulas and fixed percentages are inconsistent with NIH's efforts to carry out its mission in an effective and efficient manner that is driven scientifically.

NIH has long relied upon a multifaceted approach for funding decisions that involves peer review by scientific experts to determine scientific merit of a research proposal, review for program priority by a second set of scientific experts and thought leaders from the lay public serving on ICO national advisory councils, individual ICO strategic plans, and, ultimately, the scientific expertise of ICO Directors, informed by their staff. NIH will continue and strengthen its commitment to a transparent, evidence-based process that encompasses these action-oriented principles: enhance the nimbleness needed to meet public health needs and capitalize upon scientific opportunity, using new portfolio analysis tools; incorporate burden of disease as an important, but not sole, factor; take advantage of opportunities presented by rare diseases to advance research; and consider the value of permanently eradicating a disease.



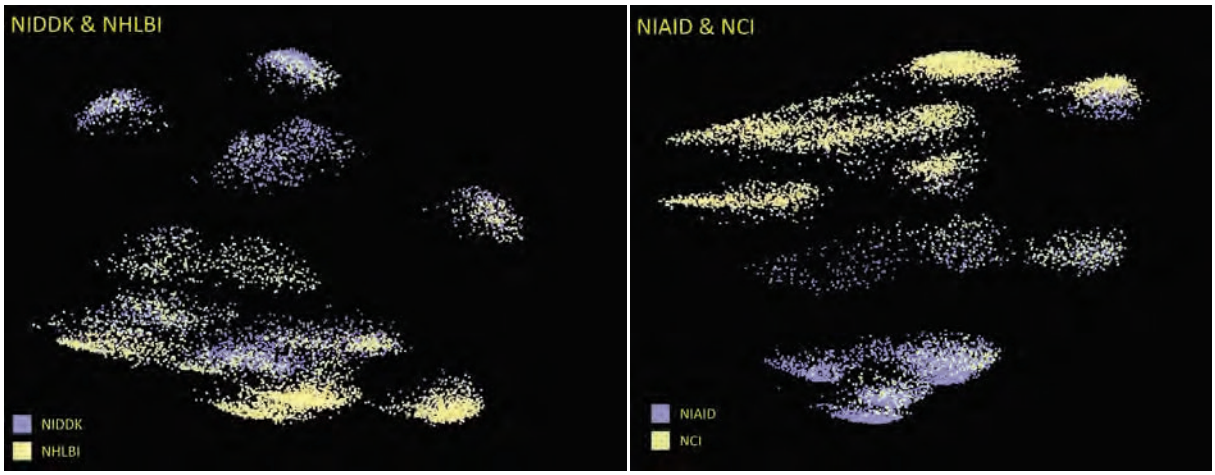
Enhancing Transparency of Decision Making. NIH will encourage each of its ICOs to make public a standard metric each year that includes clear information about its funding threshold for grant applications. Above is an example for FY 2014 showing the NIH-wide funding threshold for Research Project Grants (R01), which is the agency's most common type of grant.

Going forward, NIH will take additional steps to enhance the transparency of its decision process by making public a standard metric for funding each year. NIH will also harmonize approaches to decision making by ensuring ICOs set their individual paylines—the funding cutoff point for grant applications based solely upon peer-review scores—to provide maximum flexibility for use of the select pay option. Select pay refers to funds set aside to support grant applications that, based upon scores from peer review, do not fall within the payline, but that fill an important research gap and/or are of particular programmatic relevance to an ICO's scientific and health priorities. Final decisions on

the use of select pay are made by the NIH ICO Directors following discussions with their Advisory Councils and appropriate ICO staff.

Enhance Nimbleness. NIH and all of its ICOs will nurture the nimbleness necessary to shift resources in response to unexpected scientific breakthroughs, to capitalize on scientific opportunities on the horizon, and to address emerging public health needs. Advancing human health requires taking advantage of scientific opportunities as they arise. It is important to recognize that different scientific fields mature at different rates, and the same amount of funding in two fields can lead to very different scientific returns.

To help inform these decisions, NIH will explore the strengths and weakness of different types of grant programs, along with other funding mechanisms, to identify optimal approaches. Among the nimble approaches currently at NIH's disposal are Other Transaction Authority, which enables support of high-risk, milestone-driven research supported through the NIH Common Fund and various ICOs; fast-track review of Small Business Innovation Research and Small Business Technology Transfer awards, in which Phase I and Phase II grant applications are reviewed together, reducing funding gaps between phases; and various scientific challenge prizes, which include competitions to encourage development of novel methods for analyzing individual cells; point-of-care diagnostics for antibiotic-resistant infections; and new products or services to harness the power of Big Data to improve health. Of course, it requires more than investment to drive biomedical progress—scientific opportunities also need to be present. To enhance surveillance of the scientific landscape, NIH will utilize a network of internal and



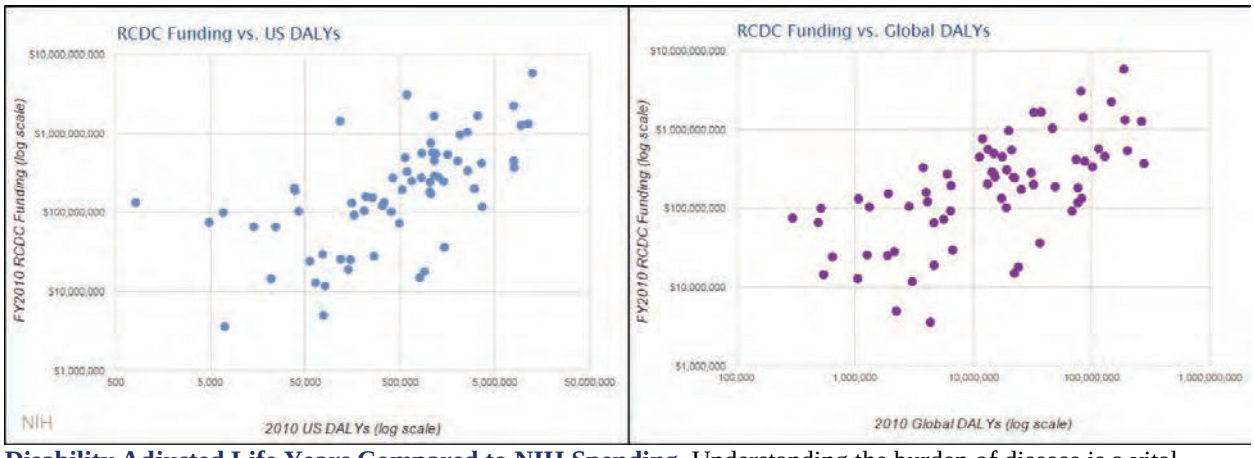
Examples of NIH Portfolio Analysis. Grant application content can be used to monitor overlap in research areas relevant to more than one NIH Institute/Center. Each dot above represents an R01 grant application; dot proximity is proportional to relatedness. Left image shows relatively high degree of overlap between areas considered for funding by the National Heart, Lung, and Blood Institute (NHLBI) and National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK), which focus on diseases with many biological synergies. Right image shows less overlap between areas considered for funding by the National Institute of Allergy and Infectious Diseases (NIAID) and National Cancer Institute (NCI), which focus on diseases with fewer biological synergies. Such analyses help to ensure NIH investments avoid overlaps and maximize synergies.

external expertise, and will continue to develop, improve, and use new tools for portfolio analysis to identify scientific opportunities, high-performing areas of research, and areas of potential overlap among ICOs. To further empower its ability to monitor highly active or emergent areas of public health concern and scientific opportunity, NIH will train staff in the effective analysis of social media trends and other nontraditional sources of information.

A recent example of how NIH's rapidly responsive flexibility has served to address an urgent public health crisis is its pivotal role in the development and accelerated clinical testing of a vaccine against the deadly Ebola virus. Likewise, NIH's nimbleness in the face of unexpected scientific breakthroughs has enabled it to take a leadership role in the BRAIN Initiative®, which has the ambitious goal of producing the first dynamic picture of the human brain, showing how individual cells and complex circuits interact in both time and space.

Consider Burden of Disease. The relative burden that various diseases place upon human health and wellbeing will serve as a crucial, but not the only, consideration in aligning NIH's research priorities with public health needs. To this end, NIH will work with its many partners, including CDC, to strengthen the collection of high quality, comparable data on the burden of disease and will integrate analyses of such data into its priority setting process.

It must be emphasized that there currently are multiple types and sources of disease burden data, and these data vary depending on whether researchers measure death or disability, direct or indirect economic costs, and domestic or global populations. However, none of these measures incorporates the cost of conducting basic research, which is essential for finding interventions. Another important variable is the degree to which subjective judgments factor into the process, making it extremely difficult to compare all diseases and conditions with a



Disability Adjusted Life Years Compared to NIH Spending. Understanding the burden of disease is a vital consideration for setting NIH's research funding priorities. These graphs show how NIH's FY 2010 funding levels for a variety of diseases and conditions (RCDC) related to U.S. and global disability-adjusted life years (DALYs)—a measure that quantifies the number of healthy years of life lost due to morbidity or premature mortality caused by disease. Such data can help NIH monitor the public health landscape for unmet needs and emerging challenges.

single measurement. Additional caveats regarding the use of current disease burden datasets to establish research priorities include the lack of patient-derived assessments and inconsistent accounting of the burden on caregivers. Finally, it is imperative to keep in mind that current burden of disease does not necessarily predict future burden of disease.

Advance Research Opportunities Presented by Rare Diseases. If NIH had used burden of disease as the sole determinant for setting its priorities over the past century, rare disease research, in all likelihood, would have been seriously neglected. While any given rare disease affects a relatively low number of people, such conditions represent a significant health problem when they are considered together, affecting some 25 million Americans collectively.

In recent years, FDA approvals of "orphan drugs" to treat diseases and disorders affecting fewer than 200,000 people in the United States have been increasing. However, effective treatments are lacking for many rare diseases, constituting an important public health need that NIH research still needs to address. Besides helping individuals affected by rare diseases, such research can provide insights that spill over into other, more common diseases and greatly enhance understanding of healthy physiology. For example, studies of the molecular mechanisms involved in a very rare premature aging condition called progeria have revealed valuable insights into the normal aging process.

NIH is uniquely situated to tackle the challenges, as well as capitalize on the opportunities, presented by rare diseases over the next 5 years. In contrast to the typical situation in private industry, public funding enables researchers to pursue scientific questions, such as those posed by rare diseases, on the basis of opportunity, not just perceived market value.

Consider the Value of Permanently Eradicating a Disease. Achieving the complete cure or eradication of any disease is one of the ultimate goals of medical research. While each year brings NIH-funded science closer to improved treatments for any number of diseases and conditions, the ability to completely remove the threat of a single disease from the face of the Earth is a rare opportunity. Just think of the monumental effort it took to eradicate smallpox and how, even after decades of intense vaccination campaigns, the world is just now on the verge of eliminating polio.

Biomedical research stands at another such pivotal moment today: the very real possibility of entirely eliminating HIV/AIDS. Decades of robust investment in HIV/AIDS research has resulted in extraordinary improvement in the health of infected individuals, and NIH now plans to support the best science to eliminate HIV/AIDS as a public health threat domestically and globally. While the traditional, non-statutory 10% set aside for HIV/AIDS research, overseen by the Office of AIDS Research, was an appropriate response to the crisis more than two decades ago, NIH no longer sees the value in this formula-driven approach. That does not mean taking

HIV/AIDS Research Priorities

- Reduce incidence, including vaccines
- Safer, easier-to-use therapies
- Work toward a cure
- HIV-associated comorbidities, co-infections
- Cross-cutting areas: Basic research, health disparities, training

Over the course of the next 3-5 years, NIH-supported HIV/AIDS research will center on the scientific opportunities that are most likely to contribute to: ending the AIDS pandemic, developing a cure for HIV/AIDS, taking care of people who are already infected, and achieving an AIDS-free generation.

the foot off the accelerator, however. To seize this unique moment, NIH will prioritize its research efforts to end the worldwide scourge of HIV/AIDS and usher in the first AIDS-free generation in more than half a century.

Not only does this research strategy hold out the hope of eliminating the death and suffering caused by this worldwide epidemic, it makes good economic sense: every new case of HIV diagnosed in the United States (currently, about 50,000 per year) translates into a lifetime cost of approximately $350,000 for treatment with antiretroviral drugs. Getting to zero new cases of HIV/AIDS would save our nation an estimated $17.5 billion annually.

As NIH takes these and other factors into account in setting biomedical research priorities, it is imperative that the agency be judicious and transparent in decisions about investing the monies entrusted to it by the American public. Going forward, NIH will consider using the previously described HIV/AIDS research prioritization process as a potential model approach for shaping its research focus in other scientific areas. Through concerted efforts to improve and refine key priority-setting activities, the agency is committed to increasing the already high rate of return that NIH-supported research delivers to the nation in the form of scientific advances and improved human health.

Objective 3: Enhance Scientific Stewardship

To achieve its mission and maintain its role as the world's premier biomedical research agency, NIH must support the best scientific ideas and brightest scientific minds while, at the same time, earning and maintaining public trust. NIH's role as a steward of public resources also requires not only supporting innovative research, but also fostering innovation across the entire research enterprise by enhancing individual and collective scientific stewardship. NIH must live up to the commitment that every dollar is being spent in a way that maximizes long term public benefit. Over the next 5 years, NIH will take several significant steps to strengthen and sustain its most valuable resource—the scientific workforce—and to strive for the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science.

Recruit and Retain an Outstanding Biomedical Research Workforce. To ensure that the nation cultivates a thriving and talented next generation of scientists, NIH will seek ways to strengthen the biomedical research work force. Such efforts will include improving the outlook and opportunities for new and early stage investigators through policies and grant mechanisms that are designed to support investigators at the outset of their careers. NIH will continue to take steps to enable exceptional early career scientists to flourish independently by bypassing the traditional postdoctoral training period, to bridge the gap from early- to mid-career investigator, and to normalize grant success rates between early stage investigators and more experienced investigators. For example, within the next 4 years, NIH will be evaluating its Early Independence Awards program to gauge its success in fostering independent and productive research careers.

Another way in which NIH will aim to ensure that all of America develops and maintains an outstanding biomedical research workforce is through its Institutional Development Award (IDeA) program. By broadening the geographic distribution of NIH funding for biomedical research, the IDeA program fosters health-related research and enhances the competitiveness of researchers at institutions located in states in which the aggregate success rate for grant applications to NIH has historically been low. Such activities also benefit unique populations—such as rural and medically underserved communities—in Puerto Rico and the 23 states that are currently part of the IDeA program.

NIH will also continually evaluate the effectiveness of its scientific training programs and efforts. For example, it will identify and target specific areas of biomedical research in which workforce training should be tailored to meet growing needs, including revitalizing physician-scientist training, fostering recruitment to expand the data science workforce, and promoting the cross-training of basic scientists, clinical scientists, and physician-scientists to facilitate the development of inter- and cross-disciplinary research teams and to stimulate translational research. Furthermore, NIH will promote innovative training programs to prepare trainees for

the wide spectrum of career options that will be available in tomorrow's biomedical research workforce. For example, the recently established Broadening Experiences in Scientific Training (BEST) program will enhance training for graduate students and postdoctoral scholars to prepare them for careers outside of conventional academic research. Ultimately, a stable, predictable funding stream is needed to attract and retain new talent for the research workforce.

Enhancing the Diversity of the NIH-Funded Workforce Program. Through this national collaborative, the Diversity Program Consortium, in partnership with NIH, will develop, implement, and evaluate innovative approaches to research training and mentoring. The goal is to engage individuals from diverse backgrounds and help them prepare for and succeed in biomedical research careers.

Enhance Workforce Diversity. NIH strongly believes that diversity in the biomedical research workforce is critical to producing new scientific discoveries. From NIH's vantage point, racial and ethnic diversity is paramount. It is also important to pursue diversity in other areas, including sex and gender, socioeconomic status, geographic location, and disability status.

In an effort to understand why the biomedical workforce does not reflect the diversity of the Nation, NIH sponsored a landmark study that demonstrated a disparity in R01 funding to African-American/Black applicants. Importantly, NIH has launched a broad range of efforts to redress this untenable situation, including a thorough analysis of potential biases in peer review and experiments in anonymized review. Under the leadership of its first Chief Officer for Scientific Workforce Diversity, NIH will work to implement the recommendations of the Advisory Committee to the Director's Working Group on Diversity in the Biomedical Research Workforce. This comprehensive strategy aims to enhance scientific workforce diversity, engaging partners from academia and industry to achieve diversity at all stages of biomedical research career trajectory.

Examples of new NIH programs that are part of this strategy are the BUilding Infrastructure Leading to Diversity (BUILD) initiative, which has the long-term goal of catalyzing cultural changes at academic institutions so that talented students from groups historically

underrepresented in biomedical research are well-prepared to enter research careers, and the NIH National Research Mentoring Network (NRMN), which will facilitate the development of robust mentoring relationships by pairing scientific leaders with early career scientists from underrepresented groups across the nation. A unique attribute of these programs is that they are being run as a "trial" with a data-coordinating center, collecting common measures across all programs. In this manner, NIH will be able to identify subsets of "best practices" and then swiftly apply them across the network. These best practices will also be used to inform enhancement of other programs that are designed to enhance diversity of the biomedical research workforce.

Ensure Rigor and Reproducibility. As a global leader of biomedical research, NIH has a responsibility for maintaining and bolstering the public's confidence in research results. To uphold this responsibility, NIH will take the lead in promoting new approaches toward enhancing the rigor of experimental design, analysis, and reporting. These efforts are not aimed at rare instances of research misconduct or willful deception, which require separate oversight mechanisms, but are intended to improve the biomedical research community's overall culture and training to encourage best practices for rigorous scientific methods.

NIH recently initiated several activities aimed to encourage transparency and reproducibility of research results. Over the next 5 years, NIH will build upon these activities, which include: discussing ways to improve rigor and reproducibility with science journal editors; establishing principles and guidelines for reporting preclinical research; emphasizing the importance of studying sex differences and incorporating sex as a variable in preclinical research; developing training modules and curriculum for the next generation of scientists on approaches to enhance reproducibility of their research; ensuring compliance with policies for open access to the published literature and data sharing; and continuing to expand the studies included in the NIH-supported ClinicalTrials.gov results database to improve dissemination of clinical trial results. Moving forward, NIH will continue to develop and promote other innovative initiatives to promote scientific rigor across the entire biomedical research enterprise.

Clinical Trials Data Sharing

- Provide a way for patients and the public to find trials of interest to them
- Inform future research, improve study design, enhance the evidence base, and prevent duplication of unsafe or unsuccessful trials
- Fulfill an ethical responsibility to people who volunteer to participate in research
- Affirm public trust in clinical research

NIH has a responsibility to share clinical trials data while safeguarding the interests of researchers and research participants. HHS has proposed regulations to implement reporting requirements for clinical trials subject to Title VIII of the Food and Drug Administration Amendments Act of 2007. NIH also has proposed a policy to promote transparency for all NIH-funded clinical trials.

Reduce Administrative Burden. NIH is committed to streamlining its reporting

processes to reduce the administrative burden on its grantees as much as possible, while maintaining the agency's necessary oversight role. These actions have been informed by recommendations from a 2015 report from an ad hoc committee of The National Academies of Sciences, Engineering, and Medicine, "Optimizing the Nation's Investment in Academic Research: A New Regulatory Framework for the 21st Century, Part 1"; and a 2012 report from the National Research Council's Committee on Research Universities, "Research Universities and the Future of America: Ten Breakthrough Actions Vital to Our Nation's Prosperity and Security." NIH has already made changes to many steps throughout the grant award process to optimize the system as much as possible, but there is no easy, one-size-fits-all solution. Over the next 5 years, NIH will continue to evaluate opportunities to streamline and automate this process to allow scientists to focus their attention first and foremost on their research.

Optimize Approaches to Inform Funding Decisions. At NIH, the crucial, initial assessment of a grant application's scientific merit is conducted through the agency's highly respected peer review system. Still, there is always room for further optimization. During FY 2016-2020, NIH will step up efforts to make its peer review and post-grant award system even stronger by: enhancing diversity and fairness; optimizing the process for promoting interdisciplinary and team science; and voicing an expectation that all NIH grantees serve on NIH peer-review study sections when asked, thus ensuring that every researcher "gives back" to the scientific enterprise as a whole.

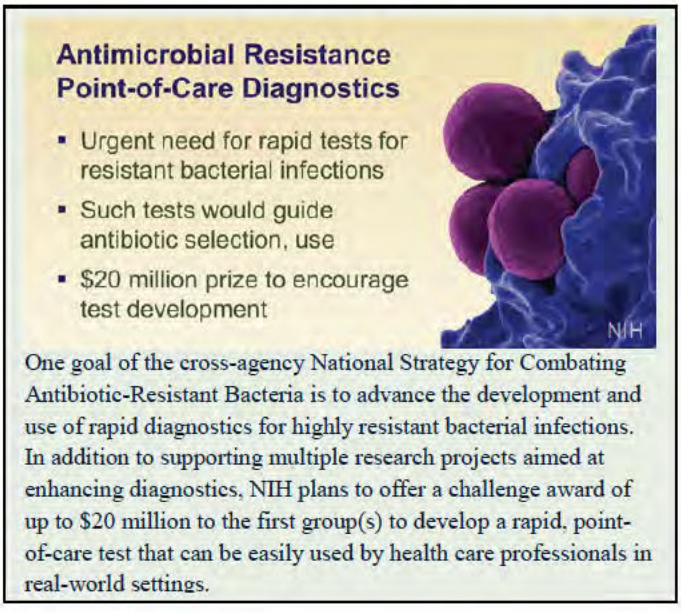
NIH leadership will also encourage sharing of best practices in portfolio analysis and strategic planning among ICOs. Individual ICOs play a key role in funding decisions through their Program Officers, who field grant applicants' inquiries and manage specialized portfolios of grants; their National Advisory Councils, which provide a second level of review for scientific merit; and their Directors, who have the ultimate authority over funding decisions. To help inform these decisions, NIH will continue to explore the efficacy of different funding approaches—comparing mechanisms to ascertain if their strengths and weaknesses and analyzing whether there is an optimal threshold of funding for research groups via RPG mechanisms.

Since it is virtually impossible to predict where the next great breakthrough will emerge, NIH places a heavy emphasis on maintaining a diverse and broad portfolio. However, NIH currently uses the number of projects that it supports as the key metric in assessing program breadth. Emergent data suggest that on average, there are optimal levels of funding for research groups, beyond which, there is only minimal increase in return. NIH must therefore decide if portfolio breadth would be best achieved through an increase in the number of investigators that it supports as opposed to the number of projects it supports. Over the next 5-year period, pilot programs will be put in place to test this important question.

Encourage Innovation. As part of its responsibility to be a wise steward of the resources provided by the American public, NIH will catalyze innovative research through novel funding mechanisms, groundbreaking initiatives, and creative policy approaches. One major way in which NIH will accomplish this is by promoting high-risk, high-reward research through intensely competitive programs that fund individual investigators with the most promising cross-cutting research or ideas. Such programs include the NIH Common Fund's New Innovator, Pioneer, and Transformative Research Awards, the National Institute of General Medical Sciences' Maximizing Investigators' Research Award, the National Cancer Institute's Outstanding Investigator Award, the National Institute on Drug Abuse's Avenir Awards, and the National Institute of Environmental Health Sciences' Method to Extend Research in Time Awards. There is growing evidence that such approaches are working, with a 2012 independent review of Pioneer awards concluding that these awards resulted in higher impact and more innovative research relative to the traditional R01 award.

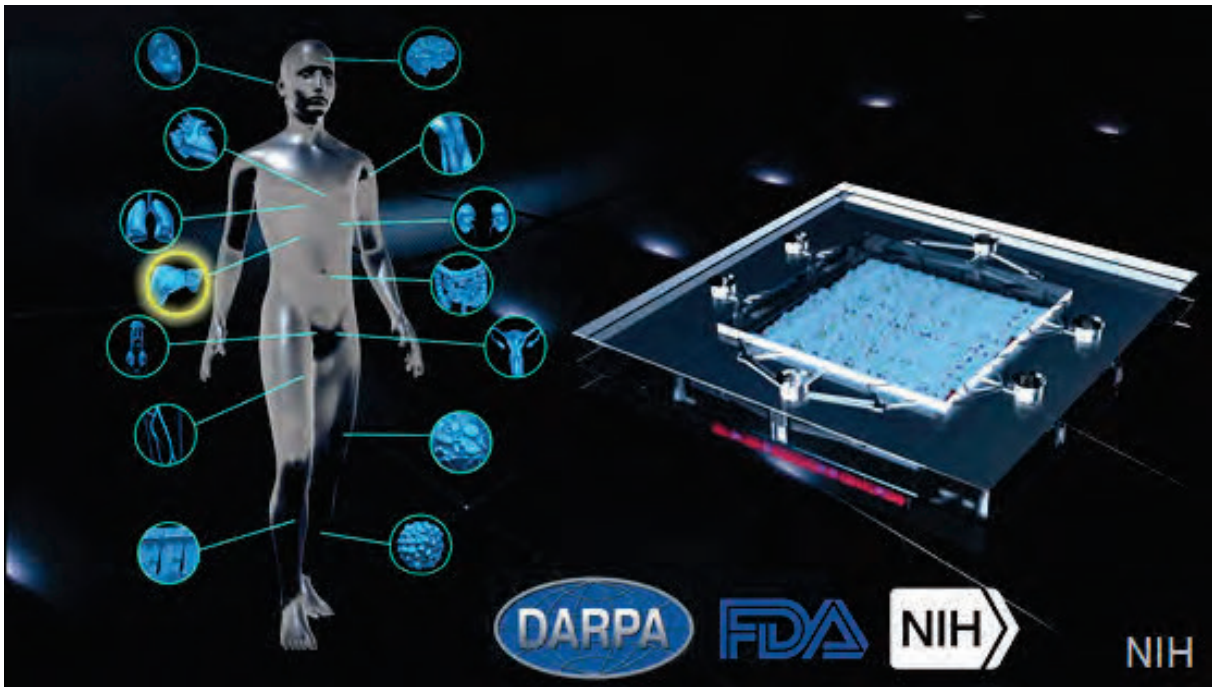
NIH will also support innovative short-term initiatives that take advantage of emerging technologies to focus resources on specific high-impact, trans-NIH basic research questions, such as those posed by the BRAIN Initiative® and various Common Fund initiatives. On the translational and clinical front, NIH will encourage innovative clinical trial design and data-sharing activities through collaborative efforts with the FDA and other stakeholders. In addition, NIH will continue to facilitate communication and coordination among clinical researchers about new trial designs and best practices, whether at the level of policies for funded researchers, interdisciplinary working groups, or clinical trial networks.

Enhance Impact through Partnerships. To increase the reach of NIH-funded research, NIH will leverage its resources by partnering with other organizations in the public and private sectors. Not only do such partnerships enable NIH to make maximum use of finite resources, they can lead to sector-spanning synergies that result in creative new ways of fulfilling NIH's mission. This will include building on current efforts within NIH to capitalize upon trans-disciplinary knowledge, as well as fostering mechanisms to establish new collaborations. As part of this activity, NIH will work closely with FDA, CDC, AHRQ, HRSA, SAMHSA, and other HHS and federal agencies that will provide the necessary knowledge and expertise to



One goal of the cross-agency National Strategy for Combating Antibiotic-Resistant Bacteria is to advance the development and use of rapid diagnostics for highly resistant bacterial infections. In addition to supporting multiple research projects aimed at enhancing diagnostics, NIH plans to offer a challenge award of up to $20 million to the first group(s) to develop a rapid, point-of-care test that can be easily used by health care professionals in real-world settings.

help translate NIH research findings into new drugs, technologies, and evidence-based practices for improving health. For example, NIH recently partnered with other federal agencies to develop the National Strategy for Combating Antibiotic-Resistant Bacteria. Also, NIH's National Institute of Allergy and Infectious Diseases leads an interagency workgroup on developing therapeutics and vaccines against the emerging global public health threat posed by the Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Other federal agencies represented include CDC, FDA, Department of Defense, and Biomedical Advanced Research and Development Authority.



Tissue Chips. Petri dish and animal models often fail to provide good ways to mimic disease or predict how drugs will work in humans, resulting in much wasted time and money while patients wait for therapies. To address that challenge, NIH, DARPA, and FDA are collaborating to develop 3D platforms engineered to support living human tissues and cells, called tissue chips or organs-on-chips. An integrated body-on-a-chip is the ultimate goal.

Other outstanding examples of cross-agency collaboration are the Tissue Chip for Drug Screening program, in which NIH, FDA, and DARPA are collaborating to develop 3D human tissue chips that mimic human physiology. On another highly innovative front, the Interagency Artificial Pancreas Working Group, in which the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Biomedical Imaging and Bioengineering, and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development are working with FDA, patient advocates, and industry toward development of an artificial pancreas, which could be the most revolutionary advance in diabetes care since the discovery of insulin.

Patients, disease advocacy organizations, and community members at the local, state, and federal levels also are playing an increasingly significant role in spurring advances in biomedical

research. Consequently, NIH will embrace these and other members of the public as active partners in the research enterprise, with the aim of generating more effective—and more relevant—research outcomes. This will include seeking input from diverse volunteers at all stages of the research process, from study design to data collection and analysis. The PMI cohort will be among the NIH-led efforts pioneering this highly interactive, proactive participation model. Besides forging partnerships with individuals, NIH's new model for research will underscore the importance of reaching out to previously underrepresented groups, consulting with communities, providing equal access to research studies and results, protecting patient privacy, and conducting research in an ethical and responsible manner.

Another important area of partnership that NIH will seek to encourage over the next 5 years is cultivating public-private partnerships with health-related industries, including small businesses, venture capital companies, biotech companies, and large pharmaceutical companies. Such efforts, exemplified by the Accelerating Medicines Partnership, will bring

Accelerating Medicines Partnership®. This bold public-private partnership seeks to transform discovery and validation of therapeutic targets and biomarkers for complex diseases by integrating cutting-edge molecular profiling and big data analytical approaches. AMP currently has pilot programs for Alzheimer's disease, type 2 diabetes, and the autoimmune diseases rheumatoid arthritis and lupus.

together the expertise and resources necessary to address the gap in the development pipeline between scientific discovery and the commercial marketplace, with the goal of turning breakthrough basic science discoveries into useful drugs and other biomedical products more quickly. Helping to facilitate NIH's public-private partnerships is the Foundation for the National Institutes of Health (FNIH), which Congress established in 1990 as an independent non-profit charged with supporting NIH's mission. For example, FNIH manages The Biomarkers Consortium, which brings together industry, patient advocacy organizations, academia, and government agencies and institutes to develop and support research aimed at qualifying promising biological markers for use in diagnosing disease, predicting therapeutic response, or improving clinical practice. Current members include NIH, FDA, the Pharmaceutical Research and Manufacturers of America (PhRMA), the Centers for Medicare & Medicaid Services (CMS), and the Biotechnology Industry Organization (BIO), along with more than 30 companies and not-for-profit organizations.

NIH, in collaboration with AHRQ and other HHS agencies, will also seek to strengthen its existing ties to and forge new partnerships with clinicians and professional societies. Physicians, nurses, and other healthcare professionals, both individually and collectively, are essential for the design and implementation of NIH-supported research studies, the timely dissemination and implementation of evidence-based practices into healthcare, and the education of fellow clinicians, patients, and the general public about evidence-based interventions and treatments.

In addition to partnerships within the United States, NIH has a responsibility to reach out to partners that are integral to its efforts to address global health challenges and improve the health of all humankind. Such actions are not only consistent with our nation's scientific and humanitarian values, but are frequently in our own best interest because infectious diseases do not respect national boundaries. Forging such partnerships involves negotiating international collaborations with non-governmental organizations, private industry, and governments of other nations. These partnerships may serve to promote biomedical science, for example, by sharing samples and data, or by building research capacity, such as is being done in the Human Heredity and Health in Africa (H3Africa) initiative and

H3Africa. Zambian Deputy Minister of Health Chitalu Chilufya (middle, blue suit) welcomed members of the H3Africa Consortium to Livingstone, Zambia, for their sixth meeting on May 9, 2015. Also present were representatives of NIH and the Wellcome Trust.

the Medical Education Partnership Initiative in sub-Saharan Africa. Other globally oriented partnerships promote the implementation of research results, such as NIH's milestone-driven projects with the Bill & Melinda Gates Foundation to reduce premature births, improve maternal and infant nutrition, develop models to accelerate drug discovery for tuberculosis, design vaccines against HIV and other infectious diseases, and devise affordable point-of-care diagnostic technologies.

Engage in Proactive Risk Management Practices. To meet the evolving needs of an ever-changing and increasingly challenging biomedical research environment, NIH's risk management abilities will continue to grow and mature over the next 5 years. Using standardized approaches, NIH must systematically assess its administrative processes, operational procedures, and scientific programs, for potential risks that could lead to failure. The identified risks must be prioritized and then proactively addressed by applying appropriate human and monetary resources to minimize, monitor, and control the potential impact of these risks to the NIH mission.

Over the next 5 years, NIH will pursue these and many forward-looking measures to reinvigorate our role as a visionary, yet careful, steward of the resources entrusted to us by the American people. Such actions will ensure that the U.S. biomedical research enterprise remains firmly on the pathway to a bright and sustainable future.

Objective 4: Excel as a Federal Science Agency by Managing for Results

As a public science agency, NIH is obligated to use transparent, scientific approaches in its decision making. Ultimately, NIH is accountable to the American people, who have every right to expect all of their government agencies not only to perform, but also to excel. To fulfill this responsibility in a thoughtful manner that goes beyond one-size-fits-all solutions, NIH will build upon its strong tradition of excellence by managing for results in the following ways:

Develop the "Science of Science." NIH will take greater leadership in developing and validating the methodologies that are needed to evaluate scientific investments. For example, new approaches to portfolio analyses have been devised that allow for a rapid assessment of potential overlap and gaps.

Over the next 5 years the portfolio of each ICO will be compared to one another as well as those agencies and foundations for which grant portfolio data is available. NIH has also promoted more robust bibliometric measures through development of disambiguation tools and a normalized citation metric termed the Relative Citation Ratio (RCR). In addition, the agency is considering outside bibliometric approaches, such as those developed by the Eigenfactor® Project. However, more tools are clearly required to help NIH better assess what value each grant in its portfolio provides and to test whether the mechanisms that it is employing for supporting investigators is optimal. For example, several recent studies have suggested that there is a limit to the value added in providing more and more funding to a single laboratory.

Balance Outputs with Outcomes. By their nature, outputs are easier to measure and have a shorter lag time between the onset of the activity and the "result." In contrast, outcomes, which should have some effect on the external environment, are much harder to measure, in part, because the lag time between the activity and the "result" is longer and often unpredictable. Further, because outputs are easier to measure, organizations often use them without full consideration of the perverse incentives they may be creating.

Much of NIH's investment is made through its grant portfolio. In an attempt to evaluate the "success" of a grant, a wide range of scientific outputs can now be assembled, each with its own inherent flaws. Nevertheless, the use of bibliometrics that account for variations in publication and citation practices among different scientific disciplines can provide a preliminary indication of a program's "value." The number of patents and/or investigational new drug (IND) applications filed can also be a surrogate for program worth, but again, these take time, and by themselves are not necessarily predictors of outcomes that may take much longer to realize. For example, who would have assigned a very high value to early research on thermophilic microorganisms in the late 1960s that ultimately led to the discovery of Taq

polymerase and the development of the polymerase chain reaction (PCR) technique that fueled the biotech revolution?

For evaluation of NIH-supported training, a standard approach is to count the number of trainees in tenure-track or tenured positions at universities around the world. This is a relatively facile measure in the era of social media. But this has led to a systematic undervaluation of trainees who have gone on to important careers in industry, policy development, intellectual property adjudication, or teaching, to list a few. NIH has recently made providing postdocs and graduate students with a broad exposure to career options as a critical part of a successful training program, and will now align its stated goals with the measures used to assess the programs that undergird the efforts.

Improving the health of the nation and the world is the ultimate outcome that NIH aims to achieve. And over the last several decades, it is clear that NIH-supported research has had a major positive impact on human health. Major prizes, such as the Laskers and Nobels, are also an indication of how the world views major advances in science, and NIH has been responsible for supporting the work of a very large number of those honored with such prizes over the last few decades. But within the 5-year horizon contemplated for this Strategic Plan, it would be difficult to chart a course toward widespread population benefit from NIH investments in research—the timelines are just too long.

Conduct Workforce Analyses. In general, workforce analysis has proven to be challenging for many fields, but NIH has created a static representation of the Ph.D. workforce and is currently working on a dynamic model that can be used in concert with all relevant stakeholders (universities, research institutes, industry, the federal government, policy think tanks, and the K-community college educational system) to better predict the number of Ph.Ds. and postdoctoral fellows that would be optimal for NIH to support. Particularly vexing is the continued decline of physician-scientists. A recent snapshot has been generated of the M.D., M.D.-Ph.D. census, but more work must be done to design interventions that will increase the number of these invaluable members of the workforce. While NIH has engaged in many research partnerships, it will also formulate and evaluate new approaches to engaging physician-scientists through inclusion of professional organizations, academic health center leadership, and, of course, the trainees themselves.

Continuous Review of Peer Review. There are many other elements of peer review that demand continuous evaluation. As science becomes more interdisciplinary in nature, new approaches to review need to be tested and validated, including asynchronous, electronic reviews and two- or three-stage “editorial board” models. In addition, the cost/benefit ratio of each must be evaluated. NIH will also continue to seek measures to compare the “performance” of each study section.

Evaluate Steps to Enhance Rigor and Reproducibility. NIH, in partnership with fellow science agencies, journal publishers, professional societies, universities, foundations, and a number of other stakeholder groups, has launched a series of initiatives to enhance the rigor and reproducibility of the conduct of science and reporting of scientific results. Each of these initiatives will be evaluated over the next 5 years for beneficial effects, as well as for any unanticipated, negative consequences.

Reduce Administrative Burden. There are a wide range of administrative burdens placed upon NIH's stakeholders, and several recent studies have enumerated many of these. In approaching this issue, NIH first must classify each burden with regard to origin—some are mandated in law; others are rooted in policy; and still others can be traced to historic custom. NIH's goal over the next 5 years will be to reduce or, wherever possible, eliminate those burdens that arise from custom and/or policy. NIH will also work with Congress to ascertain which of the burdens arising from laws can be modified to provide some relief.

Track Effectiveness of Risk Management in Decision Making. Winston Churchill once said: "Never let a good crisis go to waste." When unexpected issues arise, it is important to do a formal analysis of not only what events occurred, but also why they occurred. In this manner, NIH's risk management system can be continuously adapted to include new elements that had not previously been considered or even anticipated.

A Few Bold Predictions for America's Future

Despite the risks associated with making short-term predictions, it behooves NIH to lay out ambitious outcome objectives for the next 5 years. Below are just a few of the outcomes that NIH will strive to deliver for the benefit of the American people and all humankind. This list of potential advances should be taken as "stretch goals" that can only be achieved by stable funding support and intense scientific effort. These are definitely aspirational goals, rather than guaranteed outcomes. This list also is not exhaustive; it is entirely possible that the greatest research achievements by 2020 will come from directions no one can currently anticipate. Finally, it is likely not all of these goals will be attained by 2020, but they are offered in hope that this kind of bold visioning can inspire the rapidly moving field of biomedical research to aim even higher.

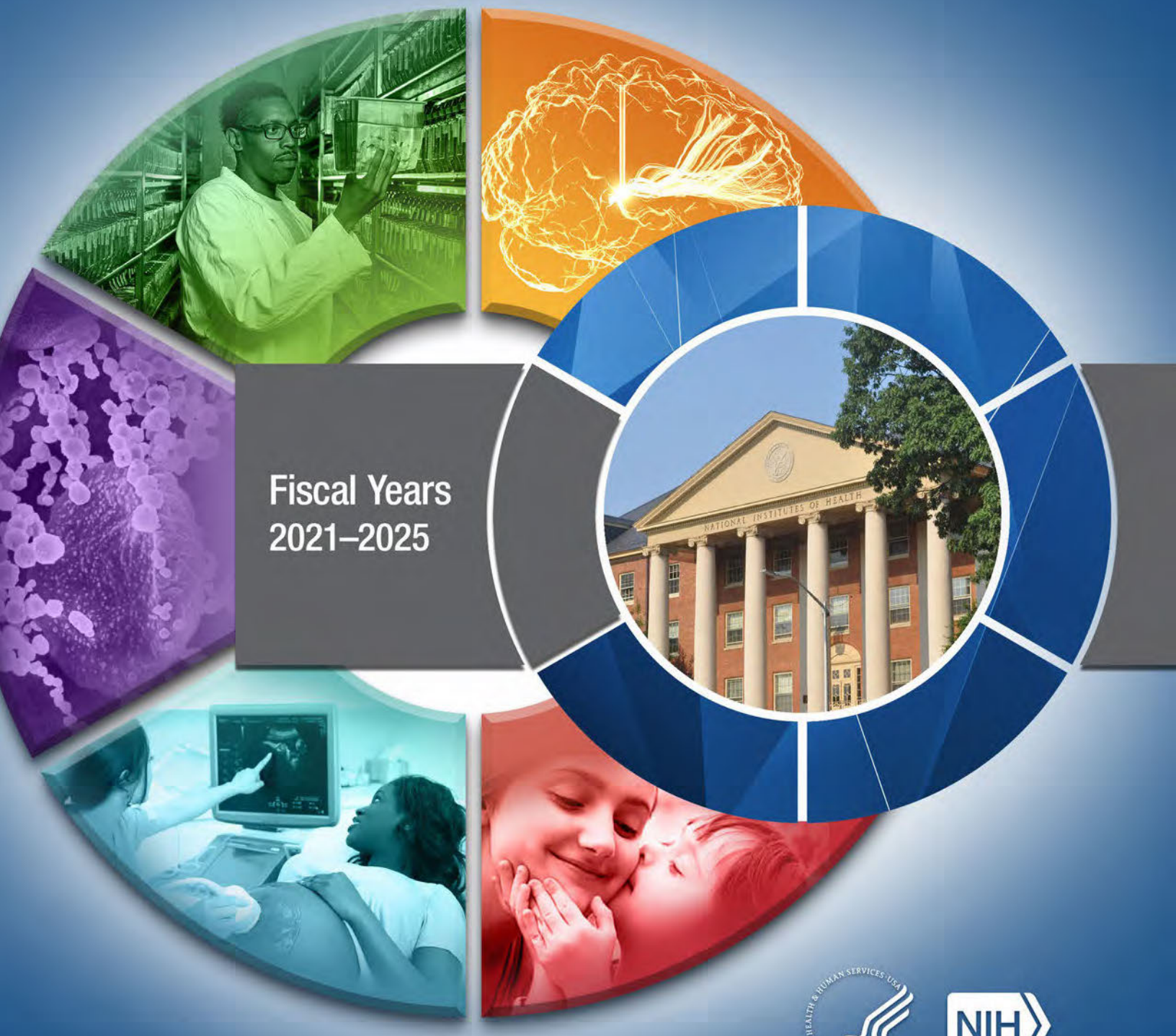
- Many thousands of cancer patients will experience enhanced survival from application of precision medicine.
- A candidate vaccine that induces a broad antibody-binding response to multiple strains of the influenza virus will be in clinical trials—a critical step towards a universal flu vaccine.
- NIH-supported research will develop effective, tailored behavioral and social interventions to promote health and prevent illness in populations that experience health disparities.
- Application of pharmacogenomics in real-world clinical settings will lead to improved outcomes in the use of several drugs.
- A pivotal efficacy trial of a novel HIV vaccine, expected to begin in the Republic of South African in 2016, will confer at least 50% protection against the acquisition of HIV.
- NIH-supported clinical trials will show that at least a half-dozen interventions thought to be clinically beneficial actually have no value.
- Radical new methods for structural biology will revolutionize drug screening and optimization.
- NIH-supported research will directly contribute to FDA-approved therapies for at least a dozen rare diseases.
- Application of certain mobile health (mHealth) technologies will provide rigorous evidence for their use in enhancing health promotion and disease prevention.
- A wearable biosensor for monitoring blood-alcohol levels in real time will be developed and show efficacy for preventing alcohol-related injury and disease.
- Technologies to reverse paralysis and restore some normal functions will be available to spinal cord injury patients.
- Vaccines against respiratory syncytial virus will be field test for efficacy, promising a solution for this leading cause of childhood pneumonias.
- Research on the artificial pancreas will lead to advanced trials showing significantly better management of diabetes, without dangers of hypoglycemia.
- NIH will be known as the model agency for applying the scientific method to itself—for learning and implementing in a rigorous way, how best to support biomedical research.

Acknowledgments

The NIH Office of the Director would like to thank the following stakeholders, committees, and staff for their time and effort in helping to develop this strategic plan: **Stakeholder Communities of NIH; NIH Advisory Committee to the Director; Institute, Center, and Office Directors**; **NIH Director's Executive Committee**; **NIH OD staff** (Carla Garnett, Jill George, Nirupa Goel, Rebecca Kolberg, Tara Schwetz); and **NIH Strategic Plan Working Group** (Ronit Abramson, Hugh Auchincloss, Elizabeth Baden, Michelle Bennett, Laura Berkson, Juliana Blome, David Bochner, Maureen Boyle, Rosalina Bray, Penny Burgoon, John Burklow, Andrew Burton, Anna Calcagno, Cindy Caughman, Laura Cole, Christine Cooper, Ned Culhane, Christine Cutillo, Jessica Escobedo, Meredith Fox, Bekah Geiger, Taylor Gilliland, Sarah Glavin, John Grason, Pamela Harris, Rebecca Hawes, Gene Hayunga, Jill Heemskerk, Jennifer Hobin, Jonathan Horsford, Lisa Kaeser, Mary Beth Kester, Wendy Knosp; Ellen Liberman, Jaron Lockett, Jane Lockmuller, Karin Lohman, Dwayne Lunsford, Sheila Newton, Morgan O'Hayre, Marie Parker, Amy Patterson, Wilma Peterman Cross, Stephane Philogene, Patricia Powell, Michele Rankin, Barbara Rapp, Sarah Rhodes, Samir Sauma, Peggy Schnoor, Elka Scordalakes, Paul Scott, Allan Shipp, Keisha Shropshire, Ellen Silva, Megan Singh, Rachel Sturke, Kimberly Thigpen-Tart, Santa Tumminia, Dave Vannier, Susan Vasquez, Samantha White, Betsy Wilder, Bridget Williams-Simmons, Carrie Wolinetz, Buck Wong).

EXHIBIT C

NIH-WIDE STRATEGIC PLAN



Fiscal Years
2021–2025

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

NIH

Photo page ii: Cell-to-Cell Communication.
Credit: NCATS, NIH.

Photo page vi: Enzyme Repairing DNA.
Credit: Tom Ellenberger, Washington University School of Medicine in St. Louis, and Dave Gohara, Saint Louis University School of Medicine.

Photo page 41: Neurons.
Credit: Leterrier, NeuroCyto Lab, INP, Marseille, France.

Director's Message

To the American People,

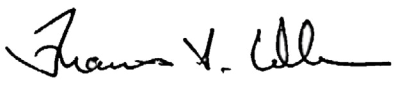
As our nation's biomedical research agency, the National Institutes of Health (NIH) has been the driving force behind many of the recent innovations in science and technology that are improving the health of all humankind. The coming years are certain to offer many exciting new opportunities for scientific exploration—and to pose some serious new challenges for human health. To rise to those opportunities and challenges, it is imperative that NIH, along with all sectors of society, work together in unprecedented ways with unprecedented speed.

Indeed, science is moving faster than ever before. To fuel this engine of discovery, NIH must continue to support the highest caliber research throughout the country and the world, while at the same time take vigorous steps to uphold the ethical conduct of science. NIH will further enhance the science of tomorrow by continuing its efforts to build a next generation of researchers that better reflects the rich, creative diversity of our great nation. The increasingly complex scientific questions that our society will face in the future will require not only diversity of scientific disciplines, but also diversity of thought, experience, and demographics.

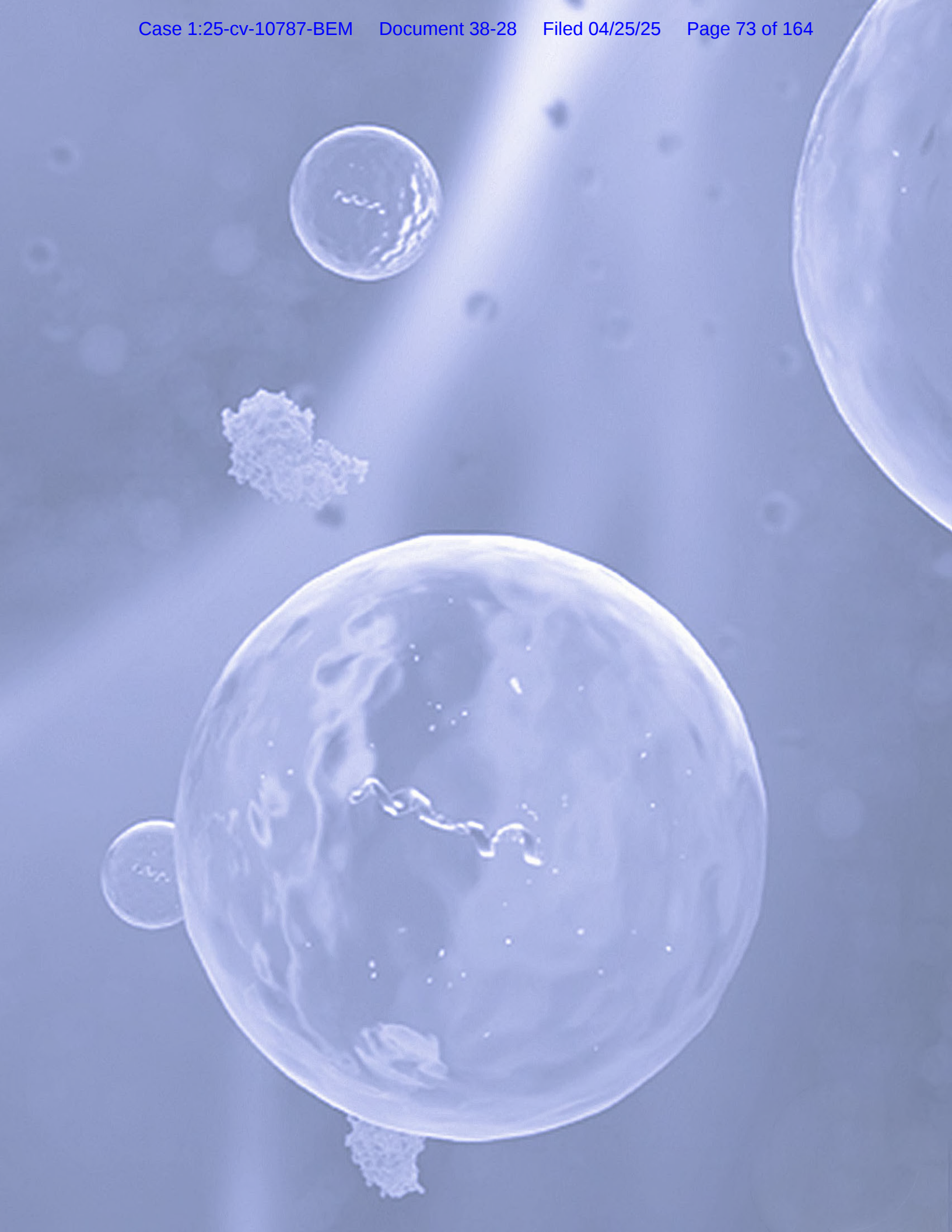
As a publicly funded agency, NIH has a responsibility to be a good steward of the funds entrusted to us by the U.S. taxpayers. NIH will do this by investing efficiently and effectively in a wide range of basic, translational, clinical, and applied research, while at the same time supporting the workforce and infrastructure required for a sustainable research enterprise. As outlined in this Strategic Plan, this approach will enable NIH to build a solid foundation of fundamental knowledge about living systems that will serve to accelerate research aimed at addressing our most pressing health needs.

NIH's mission is to turn discovery into health. We thank you for your strong and steadfast support of this crucial mission, and we look forward to your continued support as we strive to use the power of science to create a healthier and more productive life for all.

With sincere appreciation,



Francis S. Collins
Director, National Institutes of Health



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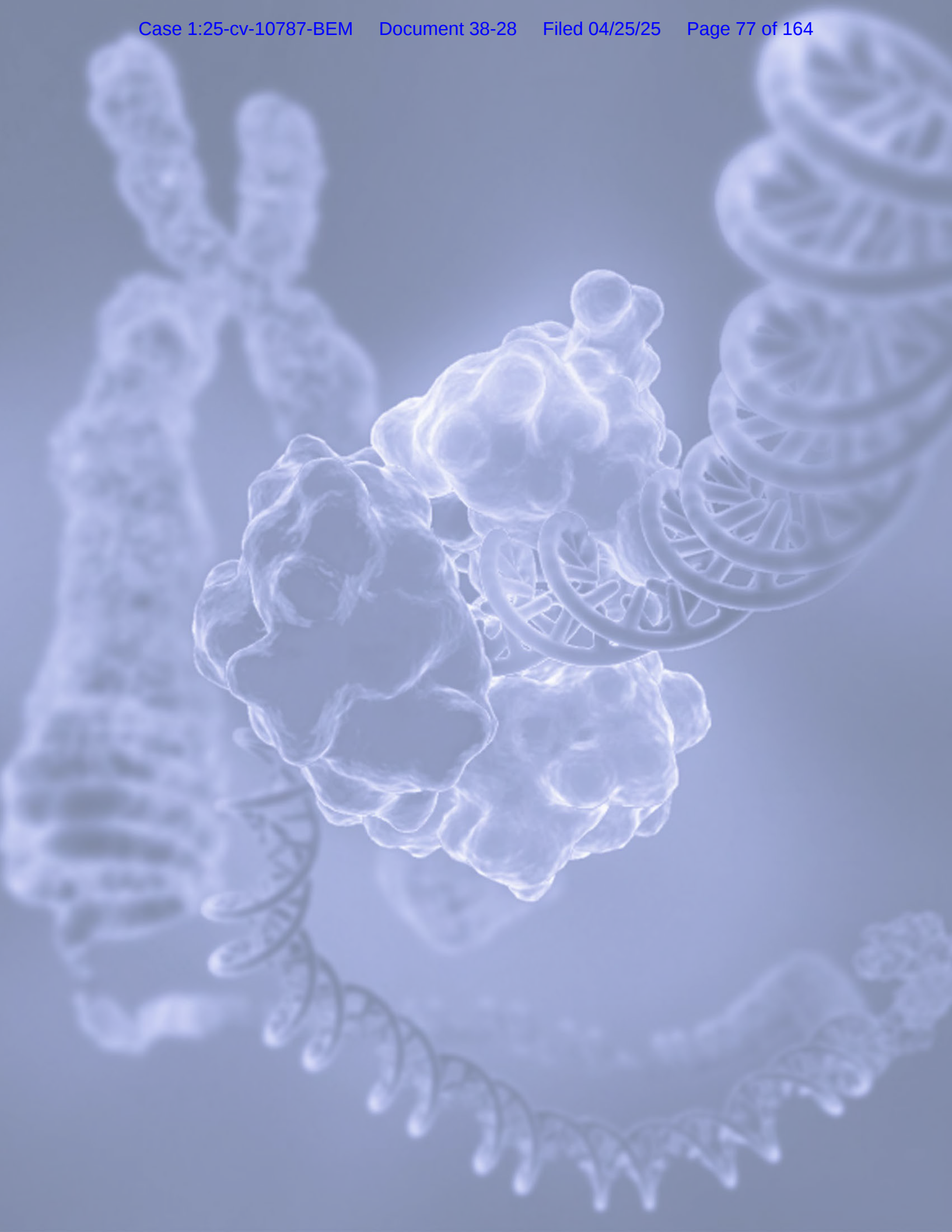


NIH-Wide Strategic Plan Framework

OVERVIEW OF NIH

MISSION:
To seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to **enhance health**, **lengthen life**, and **reduce illness and disability**

ORGANIZATION: 27 Institutes and Centers and the Office of the Director
- Extramural program: supporting research across the U.S. and beyond
- Intramural program: supporting research on NIH campuses

NIH'S STRATEGY

OBJECTIVES

Research Areas
- Foundational Science
- Disease Prevention and Health Promotion
- Treatments, Interventions, and Cures

Research Capacity
- Workforce
- Infrastructure and Resources

Research Conduct
- Stewardship
- Partnerships
- Accountability and Confidence
- Management and Operations

CROSSCUTTING THEMES

- Minority Health and Health Disparities
- Women's Health
- Public Health Challenges Across the Lifespan
- Collaborative Science
- Data Science

NIH National Institutes of Health

Figure 1. NIH Main Campus

Credit: NIH.

The James H. Shannon Building (Building One) at the NIH main campus in Bethesda, MD.

Overview of NIH

Mission and Goals

At the National Institutes of Health (NIH), "Turning Discovery into Health" is what its tens of thousands of employees—and the hundreds of thousands of scientists it supports—strive to accomplish every day. As the foremost agency for funding biomedical research[a] in the U.S., NIH's mission is to seek fundamental knowledge about the nature and behavior of living systems and to use that knowledge to enhance health, lengthen life, and reduce illness and disability (Figure 1).[1] To achieve this mission, NIH works to support innovative research ultimately aimed at protecting and improving human health; train the biomedical research workforce and develop scientific infrastructure; contribute to the nation's economic growth by expanding the biomedical knowledge base; and promote integrity, public accountability, and societal responsibility in scientific research. As an operating division of the U.S. Department of Health and Human Services (HHS), NIH is responsible for carrying out the Department's goal of advancing scientific knowledge and innovation. NIH catalyzes life-saving research breakthroughs by providing critical funding to eligible research institutions throughout the nation and the world, and through the research conducted in NIH laboratories.

While NIH's primary mission is the conduct of research, the agency is also a trusted resource for accurate and timely biomedical information. NIH's biomedical information platforms are among the most visited websites in the federal government, giving researchers, health care professionals, and the public highquality information and data necessary to make informed decisions.

Organization

NIH is made up of 27 Institutes and Centers (ICs), and the NIH Office of the Director (OD).[2] Each IC has its own mission and research priorities focused on specific diseases, body systems, life stages, or fields of science. The NIH OD sets policy and provides guidance, in addition to serving as a resource for planning, managing, and coordinating the programs and activities of all of NIH.

NIH receives its annual funding, or appropriation, from the U.S. Congress. More than 80 percent of this funding is passed on to researchers and research institutions around the country—the extramural research community—through a rigorous, competitive process, while about 11 percent of NIH's budget supports intramural projects conducted by scientists in its own laboratories, which are subject to an equally rigorous review.[3]

Supporting Researchers and Universities Through the Extramural Research Program

Every year, NIH receives more than 54,000 research project grant applications[4] and funds almost 50,000 new and continuing grants. These grants support more than 300,000 researchers at all career stages, including more than 43,000 principal investigators at approximately 2,500 universities, medical schools, and other research institutions in every state of the U.S. and around the world. This enterprise is managed by NIH staff who facilitate and administer scientific programs, consult with scientific experts to inform priority setting, and act as agency experts for specific scientific areas.

NIH's funding decisions are made through a highly competitive, rigorous dual-level peer review process that emphasizes fairness and accountability and prioritizes support of the best scientific ideas.[5] NIH relies on the expertise of more than 25,000 external reviewers annually to assess the scientific merit of incoming grant applications in the first stage of peer review, which is followed by a second-level review for mission relevance by members of national advisory councils for ICs and the OD.[6] Final funding decisions are made by IC Directors, taking into consideration their IC's research program priorities in the context of the existing funding portfolio.

A variety of funding mechanisms—including grants, cooperative agreements, research contracts, prize competitions, and other less frequently used

[a] For the purposes of this Strategic Plan, the term biomedical is used broadly to include biological, behavioral, and social scientific perspectives.

mechanisms—are used to support NIH's broad scientific portfolio,[7] allowing maximum flexibility to fund the rapidly advancing needs of the biomedical research community. These mechanisms are used to support a wide range of efforts—from individual research projects, to international consortia and networks, to training opportunities—each of which may be tailored to meet specific goals. For example, to create innovative technologies that advance its mission and move them toward uptake in the market, NIH supports the Small Business Innovation Research and Small Business Technology Transfer programs.

Research in Action in the NIH Intramural Research Program

The NIH Intramural Research Program conducts NIH's in-house research and is the largest institution committed to biomedical and behavioral research, research training, and career development in the world.[8] The mission of the Intramural Research Program is to conduct distinctive, high-impact laboratory, clinical, and population-based research; facilitate new approaches to improve health through prevention, diagnosis, and treatment; respond to public health emergencies; and train the next generation of biomedical researchers. The program supports approximately 8,000 basic, translational, and clinical researchers at NIH research facilities located across the U.S., including the main NIH campus in Bethesda, Maryland; Research Triangle Park in North Carolina; Johns Hopkins Bayview Medical Center in Baltimore, Maryland; Frederick National Laboratory for Cancer Research in Frederick, Maryland; Rocky Mountain Laboratories in Hamilton, Montana; the Perinatology Research Branch in Detroit, Michigan; and the Phoenix Epidemiology and Clinical Research Branch in Phoenix, Arizona. Scientists in the Intramural Research Program include an estimated 1,200 principal investigators, 1,800 staff clinicians and staff scientists, and 5,000 trainees. Many important medical breakthroughs take place in the intramural research laboratories.

Pioneering Clinical Research at the NIH Clinical Center

The NIH Intramural Research Program includes the NIH Clinical Center,[9] the world's largest hospital devoted exclusively to clinical research. The NIH Clinical Center is designed to rapidly transition scientific observations and laboratory discoveries into clinical studies and bedside cures by bringing together talented investigators and specialized infrastructure, including unique patient cohorts, state-of-the-art equipment, and specialized services. Since its opening in 1953, more than half a million patients have been active partners with NIH in medical discovery. This partnership has resulted in a long list of medical milestones, including the development of chemotherapy for cancer; the development of some of the earliest artificial heart valves; the demonstration that lithium treats depression; and the first treatment of HIV/AIDS with azidothymidine.[10]

About 1,600 clinical research studies are in progress at the NIH Clinical Center. Approximately half are studies of the natural history of disease, while most of the other studies are clinical trials, often the first tests of new drugs and therapies in people. Participants come from all 50 U.S. states and around the world. With its unique ability to assemble cohorts of participants with rare diseases, the NIH Clinical Center plays an important role in fostering new multidisciplinary collaborations that study and find treatments for rare diseases, often revealing insights into common diseases, as well.

NIH's Strategy

To carry out its mission and optimize return on public investment, NIH has designed a strategic *Framework* that includes three key *Objectives* that align with the agency's goals. These three Objectives outline NIH's priorities in (1) biomedical and behavioral research areas, (2) research capacity, and (3) research conduct. Across all of these priorities, NIH emphasizes several *Crosscutting Themes*—approaches that are common to all Objectives of the Strategic Plan—including improving minority health and reducing health disparities; enhancing women's health; addressing public health challenges across the lifespan; promoting collaborative science; and leveraging data science for biomedical discovery. Examples of these important crosscutting topics are located throughout the three Objectives.

OBJECTIVE 1 Advancing Biomedical and Behavioral Sciences

The NIH portfolio is designed with the breadth and flexibility to address current public health needs, emerging areas of scientific opportunity, and public health emergencies, such as the coronavirus disease 2019 (COVID-19) pandemic (Figure 2). Over the next 5 years, NIH will drive cutting-edge biomedical and behavioral sciences forward on three interrelated fronts—foundational science, disease prevention and health promotion, and treatments, interventions, and cures.

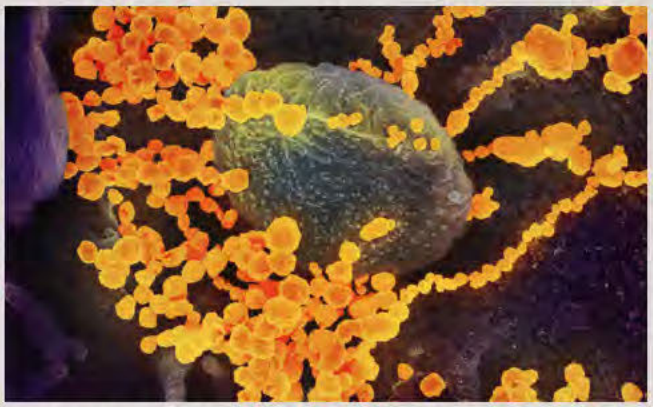
Driving Foundational Science

NIH supports a broad range of foundational scientific research to provide the building blocks for future diagnostics, treatments, and cures across the entire spectrum of health, diseases, and conditions, including those that are emerging, rare, or have yet to be discovered.

Foundational science includes basic biological, behavioral, and social research that generates the knowledge of how living systems work at the molecular, cellular, organismal, behavioral, and social levels.[11] Basic research can be experimental or observational and may involve manipulating molecules in test tubes and cells in culture dishes, studying animal models of disease (Figure 3), or conducting studies to understand human health and disease processes. Basic research also includes epidemiological studies

Figure 2. COVID-19 Research

Coronavirus disease 2019 (COVID-19) is an emergent human disease caused by a naturally arising novel coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This scanning electron microscope image shows SARS-CoV-2 (round gold objects) emerging from the surface of cells cultured in the laboratory. NIH supports research to understand SARS-CoV-2 and mitigate the threat of COVID-19 for the health of all people by building on existing and accelerating the development of new research initiatives focused on five research priorities detailed in the *NIH-Wide Strategic Plan for COVID-19 Research*. NIH is improving basic understanding of SARS-CoV-2 and COVID-19 and developing the necessary tools and approaches to better diagnose, prevent, and treat this devastating disease. Pandemics recur, and NIH is also considering how to enhance preparedness for the next one.



Credit: Rocky Mountain Laboratory, NIAID, NIH.

to examine disease burden, distribution, and potential risk and protective factors in specific populations, as well as natural history studies that follow individuals over time to observe early stages and progression of a disease. NIH-supported research serves as the world's leading source of foundational knowledge of relevance to both the public and private sectors of biomedicine.[12]

Figure 3. Animal Research Models

Both people and animals have unique and important roles as research subjects. Many medical advances that enhance the lives of both humans and animals originate from animal studies. NIH supports research using a wide variety of animal models, from the familiar fruit flies, rodents, and nonhuman primates to more unexpected animal models, such as fish, frogs, and yeast. The types of animals used in research are chosen for their similarity to humans in anatomy, physiology, or genetics. For example, zebrafish (pictured) are frequently used in research because of their small size, rapid breeding, and transparent bodies. Approximately 70 percent of human genes are also found in the zebrafish, and zebrafish and humans share many critical developmental pathways. Not only can we learn how to prevent, treat, and cure human diseases by studying animals, but often the treatments developed can also be used to improve the health of animals. In addition, NIH is acting to reduce the number of animals needed for research by using other approaches, such as tissue chips.

Credit: Grimes DT, Boswell CW, Morante NF, Henkelman RM. Used with the permission of Rebecca D. Burdine, Ph.D.

Much of the research process is carefully planned and conducted, but serendipitous discoveries can also drive progress. Because science explores the unknown, it is not always possible to predict where research will lead. This concept is especially true for basic research, which integrates biology, behavior, environment, medicine, physics, chemistry, engineering, and data science to pioneer novel technologies capable of exploring the individual components of life. Investments in basic science result in unexpected breakthroughs and new fields of inquiry that could not have been envisioned when the original experiments were designed. For example, scientists leveraged the discovery of the CRISPR system, a component of the bacterial immune system that responds to viral infection, to develop a molecular tool for editing genes with exquisite precision. This technology has revolutionized the ability to study genes and holds great promise for treating numerous genetic disorders. By investing in foundational science, NIH is laying the groundwork for important future advances that will improve the nation's health.

Building Data Resources to Enable Research Progress

NIH supports the creation of foundational data resources that enable basic research and improve understanding of the biological and environmental factors that contribute to human health and disease. NIH achieves this effort by funding investigators who are studying and cataloging molecules that are the basic building blocks of life—such as DNA, RNA, and proteins—as well as researchers who are establishing and collecting data from large cohorts of research participants. The resulting datasets have the potential to catalyze whole fields of research, as well as lead to the development of new diagnostic tools and therapies.

The 21st century opened with a crowning achievement of basic science, sequencing the human genome—the complete collection of genetic information within an individual. This achievement became the foundation for the branch of science that studies genomes across individuals to find patterns in health and disease and to uncover mechanisms to understand how genes interact with one another and with a person's environment. The immense amount of data produced by genomic studies is helping researchers understand how the complex interactions among different regions of the genome influence human development, aging, and health. One major genomic data resource is the ENCyclopedia of DNA Elements (ENCODE), which is aimed at identifying the function of all parts of the human and mouse genomes and has already been cited by thousands of research publications.[13] The Clinical Genome (ClinGen) Resource catalogues the physical, clinical, and genetic characteristics of individuals to better understand how small changes, or variants, in a person's genome are related to their health.[14] NIH will continue to support the expansion of these databases and improvement of the tools researchers use to generate and analyze genomic data through the development of new DNA-sequencing technologies and computational methods. NIH will also support new efforts to ensure the inclusion of genomes of individuals from

groups that have been historically underrepresented in genomics research.[15]

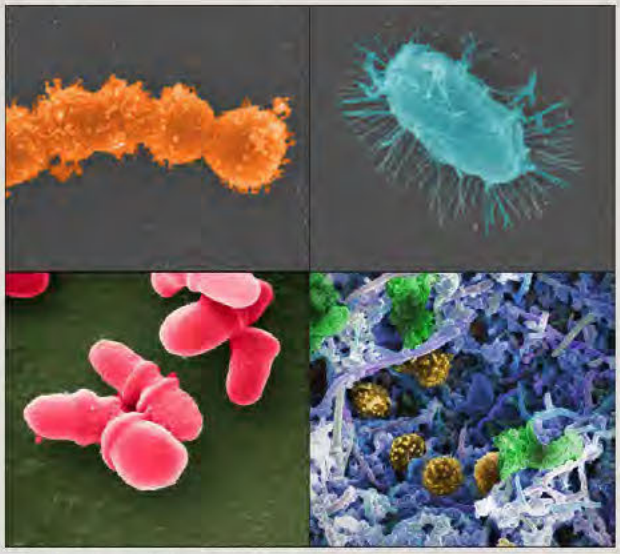
Harnessing the power of DNA-sequencing technologies, NIH-funded scientists have also created fundamental datasets important to microbiome research, or the study of the microbes—including bacteria, viruses, and fungi—that live on and in the human body. The average healthy adult is host to trillions of microbes that live in the gut, in the mouth, or on the skin, for example. The composition of the microbiome influences human health and response to treatment, contributes to early development, affects the immune system, and plays a role in metabolism. The NIH Common Fund's[b] Human Microbiome Project (HMP), conducted from 2007 to 2016, was the first large-scale effort to map and identify the thousands of species of microbes in the human microbiome (Figure 4).[16] HMP generated a comprehensive profile of the microbiome from multiple body sites from more than 300 healthy people and created computational tools and resources to enable more research. HMP also collected microbiome and human data from three longterm cohort studies centered on pregnancy and preterm birth, inflammatory bowel disease, and type 2 diabetes.

Ongoing studies supported by NIH are investigating how the microbiome of pregnant women may affect the risk of preterm birth;[17] exploring the possibility of using complementary foods—foods given in addition to those regularly consumed in the diet—to boost the gut microbiome and treat childhood malnutrition;[18] understanding how beneficial microbes in the mouth protect against periodontal disease or other oral infections;[19] and uncovering how the microbiome influences cancer development and response to therapy.[20] One particularly promising area of research is exploring the role of the microbiome in the onset of chronic conditions involving immune system dysfunction, such as cardiovascular disease and inflammatory diseases of the gut.[21]

Studies that generate large datasets from diverse participants provide vital fundamental research resources. The Adolescent Brain Cognitive Development (ABCD)[22] study is the largest long-term study of brain development and child health in the U.S. This study has recruited more than 11,000 children 9 to 10 years of age, who will be followed into adulthood to explore how childhood experiences affect brain development and a variety of health-related outcomes. Data collection is ongoing, and researchers from within and outside the ABCD study are using the data generated to conduct research on such topics as the link between screen time and brain structure,[23] effects of prenatal exposure to cannabis use,[24] and the relationship between sleep and brain structure and function.[25]

Figure 4. Human Microbiome Project

The Human Microbiome Project, which was launched by NIH in 2007, provided the first glimpse of the microbial diversity of healthy humans and is exploring the possible relationships between particular human diseases and the microbiome.



Credits: Composite image, Jonathan Bailey, NHGRI, NIH. Individual images (Clockwise from top left), Streptococcus, *Tom Schmidt; microbial biofilm of mixed species, from human body, A. Earl, Broad Institute/ Massachusetts Institute of Technology;* Bacillus, *Tom Schmidt;* Malassezia lopophilis, *J.H. Carr, CDC.*

Many NIH-funded projects span multiple areas of research and include both basic and applied science. The ambitious Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative aims to answer fundamental questions about how brain circuits work; how they become impaired in neurological, psychiatric, and substance use disorders; and how to improve the function of these circuits to treat brain disorders (Figure 5).[26] Components of the BRAIN Initiative® include studies to record, image, and manipulate brain circuits with the aim of developing treatments for brain disorders; development and dissemination of informatics tools to allow

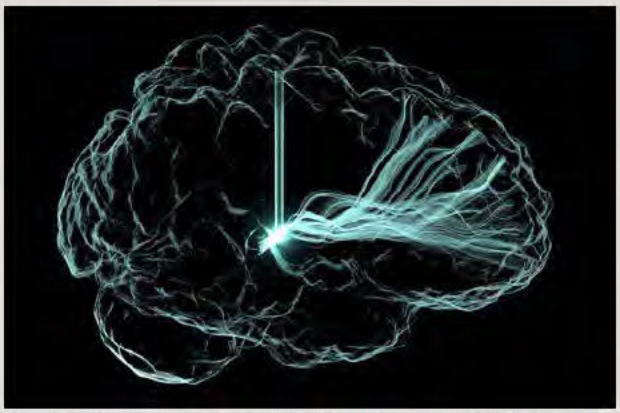
[b] For more information on the NIH Common Fund, see Appendix IV.

widespread sharing and interpretation of research data; and efforts to discover and catalogue the multitude of types of brain cells.

The complexity of the nearly 170 billion cells in a human brain presents a formidable challenge to understanding how different cell types work in brain circuits, their role in disease, and how they might be targeted directly by new therapies. Advances in engineering and highthroughput methods to classify individual cell types have enabled new opportunities to tackle this challenge. The BRAIN Initiative® Cell Census Network is developing a comprehensive mouse brain cell atlas and applying cell type identification methods to studies of human brain tissue.[27]

Figure 5. BRAIN® Initiative

First-place photo winner from the Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative's 2019 "Show Us Your Brains" photo and video contest for BRAIN investigators. "Light Me Up!" is a light-based rendering of deep brain stimulation's electrical excitation of neuronal fiber pathways to treat patients who have traumatic brain injury.



Credit: Andrew Janson, Graduate Student Research Assistant, Scientific Computing and Imaging Institute, The University of Utah.

Scientists have begun to use these methods to determine precisely which human brain cells are affected in a range of conditions, including Alzheimer's disease and related dementias, autism spectrum disorder, and Zika virus infection.

Inventing Tools and Technologies to Catalyze Discovery

Fundamental research includes the creation of advanced biomedical research tools and technologies for scientists to answer questions about biology and human health. For example, imaging technology has transformed science, allowing researchers to "see" individual molecules interacting, measure brain function, study internal tissues, visualize cell functioning in 3-D in real time, and locate specific molecules in the body using chemical tags.

Certain NIH programs are initiated specifically to spur the development of new tools and technologies for research use. The NIH Common Fund's Single Cell Analysis Program (SCAP) focused on developing tools to explore the behavior of single cells, including new ways to track cells in living multicellular organisms, new imaging techniques and technologies, and sequencing of the genome and transcriptome—the collection of all gene readouts present in a cell.[28] Resources developed through SCAP have paved the way for research that may lead to breakthroughs in understanding the human body at the level of individual cells, rather than groups or populations of cells. Such resources include the NIH Common Fund's Human BioMolecular Atlas Program (HuBMAP), a collaborative effort to develop a global open platform to map the approximately 37 trillion cells in the human body to understand how the relationships between cells can affect a person's health.[29]

New technologies are yielding data in quantities and at a level of complexity that requires increased capacity for storage, management, and analysis. Artificial Intelligence (AI) is being used on big datasets to augment human ability to detect patterns and predict outcomes, thus offering significant promise to advance research. NIH will build a large and diverse set of programs to foster machine learning (a subset of AI), support the generation and management of large-scale datasets, convene multidisciplinary teams of researchers, and develop a set of ethical principles for NIH-funded researchers to follow when using AI (Figure 6).[30] Advances in data science facilitate data processing and sharing, but concomitantly raise concerns regarding privacy, security, ethics, and bias. NIH is proactively engaging data and computer scientists, engineers, clinicians, research participants, ethicists, and the public in its plans to address future challenges and opportunities.

Studies are beginning to demonstrate the potential AI has for revolutionizing medical practice. For example, NIH researchers developed a novel data-driven approach for automated diagnosis and prognosis of Age-related Macular Degeneration (AMD), highlighting the potential of these systems to assist early disease detection and enhance clinical decision-making

Figure 6. ELSI Research at NIH

The term *ELSI* refers to the consideration of Ethical, Legal, and Social Implications of research, particularly in emerging biomedical fields; ELSI has its roots in the genomics community, but has expanded to include other areas of NIH research. ELSI complements scientific research by identifying, analyzing, and addressing the ethical, legal, and social implications of research as it is being conducted. NIH supports ELSI research to facilitate the responsible integration of science into society. Today ELSI initiatives are underway across NIH in several areas of biomedical and behavioral research, such as neuroscience, epidemiology, environmental health, new and emerging technology development and use, precision and personalized medicine, clinical research and care, and special and vulnerable population research. Key to NIH's approach to ELSI is collaboration with its multiple stakeholders.

processes.[31,32] The U.S. Food and Drug Administration (FDA) also approved the first automated medical device to use AI to detect diabetic retinopathy.[33] NIH will continue to explore and expand further uses of AI.

Understanding Biological, Behavioral, and Social Determinants of Population Health

Building the foundation for science includes constructing an overall picture of how physiological, behavioral, and social factors alone and in combination may determine human health. Conditions in which an individual is born, lives, learns, works, and ages combined with the behaviors that they engage in can affect a wide range of health outcomes.[34] Understanding how these factors interact with an individual's biological make-up is a vital area of research. The epigenome consists of chemical compounds and proteins that can attach to DNA and turn genes on and off. These changes in gene expression can occur in response to social experiences (both positive and negative) and environmental exposures and may be passed from one generation to the next. NIH supports research on social epigenomics, the study of how social experiences throughout a person's lifetime can affect biology and health status through changes to the epigenome. Similarly, NIH supports research on environmental epigenomics, which looks at how an individual's exposure to factors in the physical environment—such as air, water, and soil—may also impact gene expression. Studies designed to elucidate how social experiences and environmental exposures—such as those experienced through structural racism and lower economic status—affect the individual epigenome among racial and ethnic groups can provide a unique opportunity to identify the changes that occur within and between populations. This knowledge can be used to increase understanding of minority health and decrease health disparities.

Social and behavioral research is crucial to understanding the health and developmental effects of using digital technology and electronic media that have become integral parts of daily life. Findings from the ABCD study and the NIH Intramural Research Program have demonstrated that a significant proportion of children across a wide age range exceed the daily limits on screen time recommended by the American Academy of Pediatrics.[35,36] In light of the COVID-19 pandemic, screen time has dramatically increased for children of all ages, the effects of which will need to be investigated. To assess how technology and media use affect early childhood health and development—as well as the nature of social interactions among families, peers, and society—NIH will support an initiative to study the impact of technology and media exposure on early childhood development and health outcomes. This effort will support coordinated research projects using existing and newly collected data, as well as determining measures for exposure, usage, development, and health outcomes, including neuroimaging, language development, physical activity, and hormone levels.

Integrating different types of research to address health needs for specific populations can improve the health of these populations and also provide insights into common conditions. For example, Down syndrome is the most common genetic disease of mild to moderate intellectual disability, occurring in 1 out of every 700 babies born in the U.S. In 2018, NIH launched the INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE (INCLUDE) project, which studies conditions that affect the general population and often co-occur (i.e., are comorbid) with Down syndrome, such as Alzheimer's disease and related dementias, autism, cataracts, celiac disease, cardiovascular disease, and diabetes (Figure 7). The program focuses on targeted, high-risk/high-reward basic science studies on the causes of Down syndrome comorbidities, cohort studies of individuals with Down syndrome, and inclusion of individuals with Down syndrome in new and existing clinical trials.

Understanding the fundamental processes underlying human health is a key step in determining how to promote and restore health and identify, prevent,

and treat disease. Over the next 5 years, NIH will continue to invest in fundamental research projects that provide new insights into basic biological, behavioral, and social processes across the spectrum—from molecules to cells to humans to communities. These investments will undoubtedly lay the groundwork for unimaginable breakthroughs that will lead NIH one step closer to improving human health.

Figure 7. INCLUDE Project

The INCLUDE (INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE) project is an NIH-wide research initiative involving 18 Institutes and Centers that aims to understand critical health and quality-of-life needs for individuals with Down syndrome. Down syndrome is the most common genetic cause of mild to moderate intellectual disability and occurs in one out of every 700 babies born in the U.S.

Credit: The INCLUDE Project, NIH.

Preventing Disease and Promoting Health

Disease prevention and health promotion are core components of NIH's research mission to improve the health of all Americans. NIH research strengthens the evidence base on which national public health objectives and related disease prevention and health promotion strategies are built. Prevention research targets biological, social, and environmental factors, individual behaviors, and health services and informs health-related guidelines, policies, and regulations. NIH supports a broad portfolio of research that examines the best way to bring effective disease prevention and health promotion strategies into communities.

Developing New and Improved Vaccines

Vaccines provide a safe, cost-effective, and efficient means of preventing illness, disability, and death from infectious diseases. NIH supports a comprehensive spectrum of immunology and infectious disease research focused on developing improved or novel vaccines. This includes study of pathogen–host interactions and technological advancements in vaccine development that have led to innovative and exciting vaccine research strategies. For example, NIH-supported researchers are working to identify new platforms to deliver vaccine components and explore how adjuvants (i.e., vaccine components that enhance the immune response) affect the potency, durability, and other aspects of vaccine-induced immunity.[37]

An important remaining need is the rapid development of new vaccines to mitigate emerging infectious disease outbreaks, such as COVID-19, Ebola virus disease (EVD), and influenza (flu). NIH, in collaboration with its industry partner, developed an experimental vaccine for COVID-19 in just weeks using the genetic sequence of SARS-CoV-2 (i.e., the virus that causes COVID-19).[38] As of late 2020, the vaccine co-developed by scientists at NIH and Moderna was granted an Emergency Use Authorization by the FDA, after rigorously testing its safety and ability to protect against infection. Other vaccines are still being tested.[39] Recent outbreaks of the Ebola virus spurred the development of multiple vaccine candidates for EVD, including the rVSV-ZEBOV vaccine, which through significant federal government support was brought to market by the private sector, licensed in 2019, and is now widely available.[40] Preliminary data from an outbreak in the Democratic Republic of the Congo (DRC) has shown that this vaccine is highly effective in preventing disease and death.[41] In the U.S., seasonal influenza causes 12,000–61,000 deaths annually,[42] and emerging influenza strains pose a pandemic risk. A key focus of the NIH influenza research program is developing a universal vaccine[43] that provides robust, long-lasting protection against multiple subtypes of influenza (Figure 8), eliminating the need for a seasonal flu vaccine each year and providing protection against newly emerging strains with pandemic potential. Several flu vaccine clinical trials are being conducted, including an NIH-sponsored trial of a universal vaccine candidate that uses a nanoparticle technology to display portions of the influenza virus that are the same or very similar among different influenza strains.[44]

Figure 8. Universal Flu Vaccine

A healthy volunteer receives an experimental universal influenza vaccine known as H1ssF_3928 as part of a Phase 1 clinical trial at the NIH Clinical Center in Bethesda, Maryland. Scientists at the Vaccine Research Center developed the vaccine.

Credit: NIAID, NIH.

In addition to furthering the development of vaccines against specific pathogens, NIH supports the development of technologies that enable scientists to apply a standardized manufacturing process to develop candidate vaccines against various pathogens and create a collective database with information on their safety. This streamlined approach can shorten the preclinical development period from years to months and is important for rapid response to emerging infectious disease threats.

Addressing Risk and Burden of Disease

NIH is committed to supporting research to reduce the impact of disease by identifying and improving understanding of risk factors (e.g., inadequate nutrition, low physical activity, built environment, tobacco use, alcohol or drug misuse) and protective factors (e.g., weight management, regular exercise, daily tooth brushing and flossing) alone and in combination with genetic factors. An important goal of prevention is to alter the balance between risk and protective factors so that protective factors outweigh risk factors. Screening, health promotion, counseling, behavioral change, stress management, and preventive medications are all potential strategies for reducing individual risk. NIH investments have helped lead to advances in screening for cardiovascular disease, lung cancer, abnormal blood glucose, type 2 diabetes, oral cancer, and intimate partner violence, as well as interventions to address obesity and tobacco use in children and adolescents.

One example of NIH's investments in risk identification is in suicide prevention (Figure 9). Suicide remains one of the top 10 leading causes of death in the U.S., claiming the lives of more than 48,000 people each year.[45] Although it impacts all ages and in all parts of the country, some specific groups are disproportionately affected, such as sexual and gender minority (SGM) populations (especially transgender and gender non-conforming youth) and American Indian or Alaska Native populations (who have the highest suicide rates of any racial or ethnic group in the U.S.[46]). NIH-supported suicide prevention research illustrates how improvements in care can save lives. Universal screening for suicide risk in emergency departments has been shown to be effective and feasible.[47] Building on these findings, NIH-supported researchers are testing brief interventions and follow-up care to prevent recurring self-harm and related comorbidities, such as substance use disorder.

NIH-supported studies have demonstrated how long-term, multigenerational studies of chronic diseases can give rise to innovative prevention and intervention strategies. For example, the Framingham Heart Study,[48] launched in 1948, continues to inform tobacco cessation, nutrition, physical activity, and blood pressure control strategies that are used all over the world to reduce the risk of chronic disease. High blood pressure, or hypertension, is common over the age of 50 years and is a leading risk factor for cardiovascular diseases like heart disease and stroke. It may also increase the risk of dementia later in life. Data from several NIH-funded observational studies suggested that cardiovascular disease risk increases when systolic blood pressure rises beyond a certain level. NIH's Systolic Blood Pressure Intervention Trial (SPRINT)[49] assessed whether aggressively lowering blood pressure can prevent these conditions. SPRINT found that maintaining systolic blood pressure at less than 120 mm Hg reduced the combined risk of heart attack, heart failure, and stroke by 25 percent and reduced the risk of death by 27 percent compared to the standard blood pressure target at the time (140 mm Hg).[50] These findings helped change the national guidelines for treating hypertension, which now use 120 mm Hg as the standard blood pressure target.[51] If successfully adopted into clinical practice across the U.S., these guidelines are expected to prevent about 107,500 deaths per year among people at high risk for fatal cardiovascular disease.[52]

Figure 9. Suicide Prevention

"Five action steps for helping someone in emotional pain": Infographic.

Credit: NIMH, NIH.

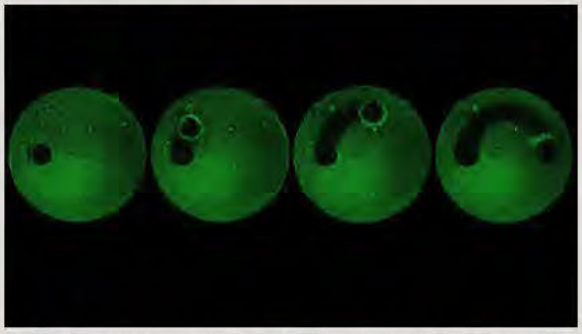
Harnessing Technology to Inform Decision-Making

NIH supports the development of new or improved interventions and technologies along with repurposing existing technologies to monitor and reduce disease risk, enhance protective factors, and restore health (Figure 10). Coupled with advances in data science that enhance analytical capacity and speed, these technologies and tools will help aid decision-making by patients and providers and improve disease prevention and health promotion strategies at the individual, family, community, and population health levels.

Most information used to make decisions in current medical practice is collected at a specific moment in time and in a clinical setting, such as taking blood pressure, providing a limited view of an individual's health and disease risk. Heart rate and motion sensors in smart watches and other wearable devices are examples of consumer technologies that can provide continuous feedback to help people improve their health. These devices detect underlying signs of illness and response to interventions, including medications and lifestyle changes, faster than conventional methods that often require weeks or months to provide actionable feedback. NIH-supported researchers have developed a wearable sensor made of stretchable microelectronics that uses ultrasound to measure blood pressure continuously, whether the wearer is resting or active. Such devices may help identify people at risk of stroke and heart disease by

Figure 10. Nanorobots for Dental Health

NIH supported a collaboration among biomedical researchers and engineers to build microscopic nanorobots to target, destroy, and remove dental plaque, a harmful community of bacteria that grow on teeth. The nanorobots, which contain an antibacterial compound, are controlled using tiny magnets to perform micro-scale precision cleaning, including hard-to-reach spaces. This technology could be used to prevent dental caries and periodontal disease, in addition to cleaning other surfaces susceptible to biofilms, such as metal implants and catheters or hospital equipment.



Credit: Geelsu Hwang and Edward Steager, University of Pennsylvania.

providing patients and physicians with more frequent and accessible information on blood pressure, including fluctuations that occur during the wide variety of activities that people engage in every day.[53]

Designing Research for Everyone

NIH prioritizes research that addresses the needs of underserved populations to address the factors that contribute to health disparities. NIH-wide efforts will continue to focus on developing and testing interventions to reduce health disparities, identifying key gaps in prevention science related to health disparities, and promoting targeted research on appropriately tailored public health, clinical, and community preventive services in diverse settings and contexts. For example, the NIH *All of Us* Research Program[54] has been designed to reflect the diversity of the U.S., with a special focus on including participants from groups that have been underrepresented in health research (Figure 11).

The Collaborative Minority Health and Health Disparities Research with Tribal Epidemiology Centers initiative supports research on topics related to minority health and health disparities in American Indian or Alaska Native populations, with emphasis on areas where there are significant gaps in data and knowledge. Current research projects include examining the impact of the Navajo Nation Tax on Junk Food on health outcomes, identifying the incidence and prevalence of arthritis and autoimmune disease among Alaska Natives, and understanding determinants of motor vehicle injuries and deaths among the Northwest Tribes.[55]

Sex and gender also influence health and disease. *Sex* refers to biological differences between females and males, including chromosomes, sex organs, and endogenous hormonal profiles. *Gender* refers to socially constructed and enacted roles and behaviors, which occur in a historical and cultural context and vary across societies and over time.[56] Considering the effects of sex and gender in study design, data collection and analysis, and dissemination of findings will help to inform the development of prevention strategies and interventions for everyone.

Developing and Optimizing Treatments, Interventions, and Cures

Building on the solid foundation of fundamental discoveries in biology, health and disease, and behavior, as well as innovations in data science and emerging technologies, NIH-supported scientists continue to develop new and improved treatments and cures, including for diseases that were considered intractable even a decade ago.

The path to a new treatment often begins not in the clinic or community but in the laboratory, where basic researchers refine our understanding of disease and identify aspects of disease causation or progression

Figure 11. *All of Us* Research Program

The NIH *All of Us* Research Program is a historic effort to collect and study data from 1 million or more people living in the U.S. The program's goal is better health for all of us, and its aim is to gather data on genetics, lifestyle, and environmental exposures. The *All of Us* Research Program is unique because it is disease agnostic, meaning that it will not focus on one disease, risk factor, or group of people, instead enabling researchers to evaluate multiple risk factors that are associated with outcomes across different diseases. This unprecedented scientific resource will enable research on numerous diseases and conditions across populations and the lifespan, with a special focus on outreach to groups that have been underrepresented in health research, to reflect the diversity of the U.S. The *All of Us* Research Program has already begun to make an early, non-finalized version of its Researcher Workbench available, an important milestone toward creating a publicly accessible platform to increase research on understudied areas, including wellness and resilience.

Credit: NIH.

that could be targeted therapeutically. Investigators use this information to design candidate treatment approaches using cell or tissue samples, animal models, or computer simulations. If the candidate approaches appear to be safe and effective in this preclinical setting, they are moved into human trials, where they are tested for safety and efficacy. Finally, new and improved methods to promote the adoption of effective and proven interventions are identified and refined through implementation research. This process is rarely straightforward. In fact, sometimes the process even circles back on itself in a "virtuous cycle," with applied research informing new ideas in basic research.

To illustrate, NIH-supported basic science was a springboard for the development of a ground-breaking new cystic fibrosis treatment. Cystic fibrosis is an inherited disorder that causes mucus to accumulate in the airways and digestive tract. The identification of the *CFTR* gene, which is mutated in affected individuals, along with additional discoveries over several decades, has enabled a variety of progressively more effective drug therapies for the disease. Recent NIH-supported clinical trials demonstrated that a novel triple-drug therapy could compensate for the effects of a *CFTR* mutation that occurs in 90 percent of affected individuals.[57] Now, instead of being a fatal disease, there is promise that cystic fibrosis in many individuals could soon be a chronic condition that can be managed over a long lifetime.

NIH supports randomized controlled clinical trials—studies conducted under "ideal" research conditions in which participants are randomly placed into one of two or more groups that receive different interventions or a placebo (i.e., a treatment with no therapeutic effect). Outcomes from each group are then analyzed and compared. Such studies are considered the gold standard by which clinical researchers determine the safety and effectiveness of interventions. NIH also supports pragmatic trials, which are designed to evaluate interventions in real-world settings and situations. To support and facilitate pragmatic trials, NIH established a Health Care Systems Research Collaboratory[58] under the NIH Common Fund to engage with health care delivery organizations as key research partners. The Collaboratory disseminates best research practices, provides education and coordination, and supports pilot projects involving a variety of diseases and conditions in community settings.

Giving the Right Treatment to the Right Patient at the Right Time

Advances in molecular medicine have allowed health professionals to move toward a precision medicine approach for targeted treatment and prevention that considers an individual's genes, environment, and lifestyle. In contrast to a one-size-fits-all approach, in which disease treatment and prevention strategies are developed for the average person, precision medicine will allow doctors and researchers to predict more accurately which treatment and prevention strategies will work best in an individual. Unlike research studies that focus on one disease, risk factor, or group of people, the *All of Us* Research Program is building an unprecedented scientific resource that will enable research on numerous diseases and conditions across populations and the lifespan.

Patients with certain types of cancer are already benefiting from precision medicine approaches. For example, an NIH-supported clinical trial showed that a molecular test for the expression of 21 genes associated with breast cancer recurrence could determine whether patients with the most common type of breast cancer would benefit from chemotherapy in addition to surgery.[59,60] The researchers found that most of these women can safely avoid chemotherapy and its toxic side effects.

The promise of precision medicine is exemplified by the development, built on decades of research, of new therapies that harness patients' own immune systems to attack their cancer. Among them are chimeric antigen receptor (CAR) T-cell therapies that are made by genetically engineering a patient's own immune cells so they will bind to specific proteins on cancer cells and kill them. Approved by the FDA in 2017, these biologic products have resulted in remarkable benefits to children and adults with certain types of leukemia and lymphoma.[61] Unfortunately, some patients initially respond to these treatments but then relapse, some patients' cancers do not respond at all, and the treatments can cause serious side effects. Scientists are working to understand the mechanisms underlying these challenges and to develop additional approaches for patients. Hundreds of clinical trials for new CAR T-cell therapies are ongoing, signaling the continued promise of this innovative new treatment for patients with cancer and HIV/AIDS.

Another area of NIH-supported research on personalized approaches to medical treatment has been to develop artificial pancreas technologies to automatically link individualized glucose monitoring and insulin delivery to improve the health and quality of life of people with type 1 diabetes (Figure 12). In the 1.6 million Americans estimated to have type 1 diabetes, the immune system destroys the pancreatic insulin-producing cells, leaving the body unable to absorb or use glucose. Significant progress toward artificial pancreas technologies—which consist of a continuous glucose monitor, an insulin pump, and a computer algorithm that, in some cases, can be run from the user's smartphone—has been made through extensive collaboration among NIH ICs, other federal agencies, private funders, academic investigators, and industry. In 2016, the FDA approved the first commercial hybrid artificial pancreas device[62] and in 2019, the FDA approved the first interoperable system[63] that could give patients the ability to choose the individual components that work best for them. Studies have shown that these technologies result in better control of blood glucose levels compared to standard treatment, potentially lowering the risk of diabetic complications.[64] NIH continues to support research to develop next-generation and novel devices that are smaller, easier to use, and available to all.

Figure 12. Artificial Pancreas

The Control-IQ artificial pancreas system was derived from research done at the Center for Diabetes Technology at the University of Virginia.

Catalyzing Cell Engineering, Bioengineering, and Regenerative Medicine

NIH is at the forefront of remarkable technological advances, such as innovations in cell engineering, bioengineering, and regenerative medicine. These advances are not only accelerating research but also creating the possibility of new treatments that previous generations of clinicians could only imagine. For example, scientists supported by the NIH BRAIN Initiative®[65] have pioneered a new technology that converts brain signals into audible speech—a potentially life-altering breakthrough for individuals who are unable to speak due to a stroke, injury, or other neurological condition. Next, researchers will design a clinical trial involving paralyzed, speech-impaired participants to determine how to best gather brain signal data, which can then be used to refine the previously trained computer algorithm.

Biotechnology is bringing us closer to a cure for AMD, a leading cause of visual impairment among older Americans. By 2050, the estimated number of people with AMD is expected to more than double from 2 million to 5 million.[66] The discovery of induced pluripotent stem cells (iPSCs)—adult cells that have been genetically reprogrammed to a developmental stage such that they can be turned into any cell type in the body—opened the door for transformative regenerative medicine therapies. Researchers at NIH were able to derive iPSCs from participants with advanced AMD and convert them into healthy retinal tissue. The newly developed tissue replaced damaged tissue and prevented blindness in animal models.[67] NIH received FDA approval to begin the first-ever clinical trial using replacement tissue derived from iPSCs in humans.[68]

Therapeutic development for many human diseases and conditions could become faster and more accurate due to the expanding use of tissue chips, or "organs-on-chips." These devices consist of 3-D platforms that support living human tissues or cells to model the structure and function of human organs, such as the lung, liver, and heart. Working closely with the pharmaceutical industry and FDA, the Tissue Chip for Drug Screening program[69] supports research using tissue chips to test new drugs and predict whether they will be safe and effective in humans. In collaboration with the International Space Station National Laboratory (ISS-NL) and the National Aeronautics and Space Administration (NASA), NIH is funding nine tissue chip projects in which different types of tissues are being sent to the ISS-NL to determine how human tissues behave in space when

exposed to reduced gravity,[70] which models aging in an accelerated manner (Figure 13). Researchers are also developing interconnected tissue chips that could model the entire human body's response to candidate therapeutics and are being deployed to address emerging health challenges, such as the opioid crisis and COVID-19 pandemic. In addition, current efforts are focused on the use of tissue chips to inform the implementation of clinical trials.

Figure 13. Tissue Chips in Space

An astronaut in a National Aeronautics and Space Administration spacesuit is shown with a kidney tissue chip in hand. When traveling in space, astronauts experience physiological changes normally associated with aging, such as bone loss, muscle deterioration, and altered immune systems. When the astronauts return to Earth, the changes often reverse. To better understand the relevance of the astronauts' experience to human health—both on the ground and in space—NIH partnered with the International Space Station U.S. National Laboratory to send tissue chips, a research technology that reflects the human body, into space.

Credit: NASA.

Meeting Emerging Public Health Needs

A critical focus of the NIH mission is readiness to address new and emerging public health needs rapidly, comprehensively, and efficiently. From the emergence of HIV/AIDS in the 1980s to the more recent outbreaks of infectious diseases—such as Zika virus disease, EVD, and COVID-19—to conducting research during an unfolding disaster like the Deepwater Horizon oil spill, NIH has been at the forefront of the global research response. NIH's role in combatting emerging threats involves identifying and understanding the responsible pathogens and their effects on the body, treating affected patients in the NIH Clinical Center as part of research studies, and conducting and supporting clinical trials throughout the nation and around the world.

The NIH Clinical Center is specially equipped with high-level respiratory isolation capabilities to handle patients with highly infectious diseases. In addition, the staff includes infectious disease and critical care specialists who have received training in strict infection control practices to prevent the spread of potentially transmissible agents. The Special Clinical Studies Unit is used for cutting-edge investigational clinical studies and treatments, ranging from EVD to universal influenza vaccine studies to treating patients affected by the COVID-19 pandemic.[71]

NIH can also swiftly mobilize its flexible infrastructure and collaborative research partnerships to help advance new and promising treatments, even in areas of armed conflict and tenuous security. NIH and the Institute of Biomedical Research in the DRC conducted the Pamoja Tulinde Maisha (PALM) clinical trial, meaning "Together Save Lives," in Kiswahili. The preliminary results were so compelling that the trial was halted, and the results were promptly made public to help save lives and stem the latest EVD outbreak.[72] All EVD patients in the DRC treatment centers are now treated with one of two treatment options based on the PALM trial results. Through this collaborative research conducted in a region of civil unrest during an ongoing outbreak, the U.S. and its partners have provided the world with two new effective treatments for an emerging disease. Additionally, this experience demonstrated the efficacy of promising therapeutics to treat EVD and serves as a potential guide for conducting future clinical trials in outbreak settings.

NIH's role in safeguarding the public health extends beyond infectious disease. For example, at this writing, opioid misuse and addiction continues to be a rapidly evolving U.S. public health crisis. Although more than 50 million Americans suffer from chronic pain, safe non-opioid options for pain management are unavailable.[73] In 2018, more than 46,000 Americans died of opioid overdose, making it one of the most common causes of non-disease-related deaths for adolescents and young adults.[74] More than 2 million Americans live with an opioid use disorder. To address this national crisis, NIH launched the Helping to End Addiction Long-term℠ (HEAL) Initiative,[75] an aggressive, NIH-wide effort to provide scientific solutions and offer new hope for individuals, families, and communities affected by this devastating crisis (Figure 14).

Figure 14. HEAL Initiative℠

The NIH Helping to End Addiction Long-term℠ Initiative, or NIH HEAL Initiative℠, launched in April 2018, is an aggressive NIH-wide effort to provide scientific solutions to the national opioid overdose crisis, including improved treatment strategies for both pain and opioid use disorder. Notably, a series of highly focused studies has been launched to accelerate the development of new medications to treat all aspects of opioid use disorder, from new formulations of existing drugs to creating new therapies aimed at novel targets to novel devices for the treatment of substance use disorder and pain. Working across scientific disciplines and care settings, the NIH HEAL Initiative seeks to match the seriousness of the crisis and offers new hope for individuals, families, and communities affected by this devastating crisis. In partnership with the Substance Abuse and Mental Health Services Administration (SAMHSA), in 2019 NIH launched the HEALing Communities Study to investigate how tools for preventing and treating opioid misuse and opioid use disorder are most effective at the local level.

Credit: NIH.

Partnering to Advance Treatments and Cures

Collaboration is essential to accelerating progress in developing effective prevention and treatment interventions, as well as ensuring that the benefits of research are available to all Americans. For example, the Partnership for Access to Clinical Trials is a collaborative effort that connects health care providers and their patients in the Washington, D.C., metropolitan area to NIH researchers conducting clinical trials at the NIH Clinical Center.[76] By serving as a bridge between research participants, their health care providers, and NIH researchers, this program serves as a successful model for increasing diversity in research participation, particularly among those who are underrepresented in clinical trials, and expanding access to the benefits of NIH research.

NIH facilitates collaboration with industry and federal partners to advance treatment science. In 2017, in collaboration with 12 leading biopharmaceutical companies and advocacy organizations, NIH launched the Partnership for Accelerating Cancer Therapies,[77] a 5-year public–private research collaboration, as part of Cancer Moonshot℠. The initial focus of the partnership is the development, validation, and standardization of biomarkers to better predict response to immunotherapy—a type of biological therapy that turns on or off the immune system to help the body fight cancer, infection, and other diseases. Immunotherapies have resulted in dramatic clinical benefit in certain types of cancer; however, existing immunotherapies do not work for all patients and are associated with substantial toxicity in some individuals.[78] A better understanding of why immunotherapies work in some patients and not others is needed to help target this treatment to the people most likely to benefit.

NIH is also transforming treatment of sickle cell disease (SCD) through collaborations (Figure 15). SCD is a group of inherited disorders characterized by the buildup of an abnormal protein in red blood cells. It can cause pain, fatigue, and damage to organs throughout the body. People of African ancestry have the highest prevalence of SCD; it is estimated that the disease affects up to 100,000 Americans.[79] Although treatments are available to relieve symptoms and extend lifespan, a bone marrow transplant is currently the only cure for SCD.[80] Unfortunately, a transplant is not feasible for most patients, because it requires bone marrow from an immune-matched sibling.

In 2016, NIH established the Sickle Cell Disease Implementation Consortium (SCDIC), the first

Figure 15. Sickle Cell Disease

In sickle cell disease, red blood cells make an abnormal protein that causes them to take on a sickle shape. These cells are inflexible and can stick to blood vessel walls, interrupting blood flow.

Credit: Janice Haney Carr and the CDC Public Health Image Library.

research program to use implementation science—the scientific study of how best to ensure the uptake of evidence-based practice—to identify and address barriers to quality care in SCD.[81] The SCDIC has created a registry of more than 2,400 patients. In 2018, NIH established the Cure Sickle Cell Initiative, an innovative collaboration among researchers in academia and industry, clinicians, patients, and advocates to identify and support the most promising genetic therapies for SCD.[82] Their goal is to bring new therapies to the point of FDA approval within the next 5–10 years.

NIH facilitates collaboration on complex scientific questions requiring the intersection of disciplines, methodologies, and knowledge by supporting a variety of funding mechanisms that are focused on collaborative or team-based work. Such opportunities for investigator-initiated research extend from serving as co-primary investigators on a grant award to participating in highly complex networks of investigators and institutions charged with advancing science in new directions. NIH looks forward to reaping the scientific benefits of continuing and expanding its partnerships in the next 5 years.

OBJECTIVE 2 Developing, Maintaining, and Renewing Scientific Research Capacity

NIH not only funds innovative biomedical and behavioral research but also pursues its mission by ensuring that the biomedical research workforce is well trained and diverse and conducts its work within an infrastructure that enables groundbreaking results at a rapid pace. Over the next 5 years, NIH is poised to enhance its support of research capacity to maximize the potential of the research that the agency sustains.

Enhancing the Biomedical and Behavioral Research Workforce

NIH recognizes that its mission will be met only through the continued efforts of a talented and dedicated biomedical research workforce. The strength of the NIH workforce depends on its sustainability and diversity (Figure 16), which NIH supports through both intramural and extramural focused training programs.

Sustainability is achieved by maintaining an appropriate balance of researchers at different career stages, ensuring that investigators early in their careers are given every opportunity to excel, even in times of limited funding. Intense competition for funding can pose a challenge for researchers trying to embark upon and sustain independent research careers. NIH's Next Generation Researchers Initiative (NGRI) aims to enhance opportunities for early-stage researchers by prioritizing funding of independent research applications for investigators who are within 10 years of completing postgraduate clinical training or their highest advanced research degree.[83] Through this initiative, NIH has more than doubled the number of early-stage researchers supported—from less than 600 in 2013 to 1,316 in 2019. Moving forward, NIH will continue to explore novel approaches to expand pathways for funding early-stage researchers and assess how NGRI policies affect women and individuals from groups that are underrepresented in biomedical and behavioral sciences.

To encourage early-stage researchers to explore new research avenues, NIH recently created the Stephen

Figure 16. Minority Women in Science

Alma Levant Hayden was one of the first minority women scientists in the federal government and worked at NIH as a biochemist. Photo taken around 1952.

Credit: NIH.

Ira Katz Award, in memory of the longtime director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases. This award is designed to support earlystage researchers who propose innovative and unique ideas that represent a significant change in research direction from their past research or training experience.

Ground-breaking, impactful biomedical and behavioral research depends upon a diverse workforce, composed of people trained in multiple disciplines and from different backgrounds, who can provide a richness of perspectives necessary to inspire new ideas. Recognizing the need to advance talent in muchneeded fields of study, NIH supports training programs in a wide variety of areas, such as bioinformatics, scientific rigor and reproducibility, and data science. To illustrate, NIH supports 16 University-based Biomedical Informatics and Data Science Training Programs,[84] including more than 200 Ph.D.- and postdoctoral-level researchers. Notably, NIH also partners with high schools, minority-serving institutions, and others to support bioinformatics training.

Given the role that interdisciplinary approaches and team science play in fostering innovation, NIH has developed a number of initiatives to encourage collaborative research. One such example is NIH's Building Interdisciplinary Research Careers in Women's Health (BIRCWH), which connects junior and senior faculty with shared interests in interdisciplinary research on women's health.[85] Since 2000, BIRCWH has helped more than 700 junior faculty pursue their career goals, thereby expanding the pipeline of women's health researchers and benefiting the health of women.

NIH supports numerous programs designed to foster research environments that encourage participation from a full and diverse range of talent. NIH's Maximizing Opportunities for Scientific and Academic Independent Careers (MOSAIC) program[86] facilitates the transition of promising postdoctoral researchers from diverse backgrounds, including those from underrepresented groups, to academic faculty positions at institutions throughout the country. The Native American Research Internship (NARI) program supports diverse student researchers, including American Indian and Alaskan Native students, from across the country in paid summer research internships. NARI researchers benefit from cultural and professional mentorship from American Indian or Alaskan Native elders, community organizations, and renowned faculty scientists.

Reflective of the high priority that NIH places on workforce diversity, the NIH Common Fund manages several training programs targeted on diversity. Launched in 2014, the Enhancing the Diversity of the NIHFunded Workforce Program[87] (also called the Diversity Program Consortium or DPC) encourages the inclusion of talent across the career span. Through integrated initiatives, DPC has supported thousands of trainees in biomedical and behavioral research careers by providing funding for institutional infrastructure, student support, and research mentoring. Within 4 years of launch, 1,116 students were appointed to research-training positions through DPC's Building Infrastructure Leading to Diversity (BUILD) program, with 68 percent of BUILD students from underrepresented groups.[88] Moreover, half of DPC member institutions (59 of 113) are either historically Black colleges and universities or institutions with a track record of training Hispanic or Latinx students. BUILD funding enables supported scientists to pursue research focused on understanding health disparities within and across underrepresented groups.

Plans are in place to launch the Faculty Institutional Recruitment for Sustainable Transformation (FIRST) initiative.[89,90] Modeled on the NIH's Distinguished Scholars Program,[91] FIRST aims to transform culture at NIH-funded institutions through the recruitment of faculty cohorts who have a demonstrated commitment to diversity and inclusion. As it enters Phase II of its 10-year program, the DPC will continue to closely monitor the impact of these programs on the careers of individuals from backgrounds underrepresented in NIH-funded research.

NIH recognizes that women scientists often face institutional and environmental barriers that restrict their potential to advance their careers. The NIH Working Group on Women in Biomedical Careers aims to identify and remove barriers to the entry, recruitment, retention, and career development of women biomedical and behavioral scientists.[92] The working group contributed to such recommendations as extended periods for the consideration of tenure and parental leave, a grant program for research on causal factors and interventions that affect the careers of women in science and engineering, and workshops on mentoring women and best practices for women's career success. The Women of Color Committee within the

working group ensures that the unique career barriers faced by women of color are addressed.

Public health needs extend far beyond geographical borders. For example, deadly infectious diseases, such as EVD and COVID-19, can spread rapidly across international borders and continents. Recognizing that scientific research capacity is not equally distributed across the globe, potentially hampering the ability to combat such challenges, NIH develops international training programs. One such program, the Global Infectious Disease Research Training Program, builds infectious disease expertise and research capacity across the world and has prepared more than 1,200 researchers to conduct independent and locally relevant infectious disease research in their home countries.[93] The program connects U.S. institutions with institutions in low- and middle-income countries to provide degree programs, trainings, workshops, and mentoring on topics related to infectious diseases.

The COVID-19 pandemic has also shown the need for local epidemiological modeling capability to provide actionable information for policy makers to make public health decisions during outbreaks. NIH builds capacity for in-country analysis of COVID-19 in low- and middle-income countries by training modelers to track and analyze the progress of the pandemic. These activities include longstanding NIH partners who have well-established epidemiological and surveillance sites in Africa, South America, and South Asia, but lack analytical capacity.

Supporting Research Resources and Infrastructure

For the biomedical research workforce to succeed in moving discovery forward, it requires a scientific infrastructure that is expansive, durable, and capable of quickly integrating state-of-the-art resources that are available to all. To achieve this goal, NIH develops a number of programs and policies designed to provide the biomedical research workforce with stability and flexibility, broad access to innovations in tools and technologies, materials, and knowledge repositories necessary for the design of impactful research programs (Figure 17).

NIH's support of modern technology platforms and high-performance computing capabilities enables innovation in scientific research in several areas, particularly genomics, computational chemistry, and cryo-electron microscopy imaging. Cryo-electron microscopy is a cutting-edge technology that enables researchers to determine the structures of biological molecules to identify therapeutic targets for vaccines and drugs. NIH Common Fund's Transformative High Resolution Cryo-Electron Microscopy program[94] aims to broaden access to cryo-electron microscopy through the support of national service centers, improvement of technology, and training.

NIH is also investing in the data infrastructure necessary to accommodate rapid advances in biomedical and behavioral research. Research progress has produced an explosion of human health data that exceeds current abilities to capture and interpret them (Figure 18). To promote data sharing in high-priority research areas, NIH creates a number of different data repositories. For example, NIH has built a data repository to maximize publication availability and data sharing for NIH HEAL Initiative℠ research projects.[95] This effort promotes dissemination of new knowledge, enhances reproducibility, and will accelerate the ability of researchers to build upon research to make new discoveries. In addition, the Data and Biospecimen Hub (DASH) is a centralized resource that allows researchers to share and access deidentified data, and for many studies, linked biospecimens are available to researchers.[96]

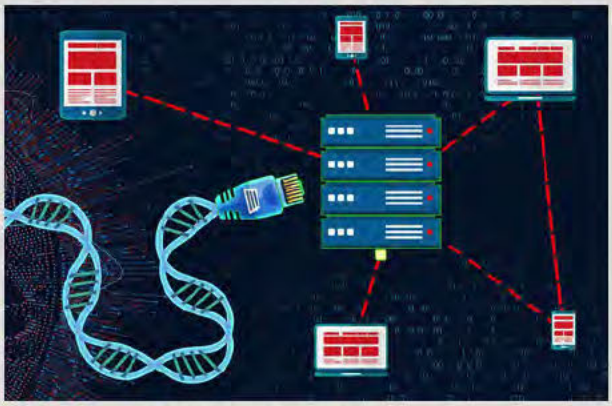
Figure 17. Zebrafish Facility

At the largest zebrafish facility on NIH's campus, Kevin Bishop, NIH Zebrafish Core staff member, holds up a tank of zebrafish to observe their behavior and physiology. Using molecular techniques, researchers alter the zebrafish's genome to mimic what is seen in human patients in the clinic.

Credit: Ernesto del Aguila III, NHGRI, NIH.

Figure 18. Modern Data Environments to Accelerate Research

Rapid advances in data generation and computing power provide extraordinary potential for accelerating biomedical research. However, researchers face technical hurdles to accessing, sharing, and analyzing within and across large biomedical datasets. NIH is tackling this challenge through multiple initiatives to build modern technology platforms, collaborative workspaces, tools, and applications necessary for researchers to securely find, access, share, store, and analyze data across diverse datasets. Two examples are the Genomic Data Science Analysis, Visualization, and Informatics Lab-space and the Cancer Research Data Commons. These platforms enable researchers to efficiently combine and analyze diverse data types, which can lead to new discoveries in disease prevention, diagnosis, and treatment. Several programs seek to provide researchers with state-of-the-art, high-performance computing, such as the Biowulf cluster, which is the world's most powerful supercomputer completely dedicated to advancing biomedical and behavioral research.



Credit: Ernesto del Aguila III, NHGRI, NIH.

Much of NIH's efforts in resource building focuses on providing researchers with the underlying evidence needed to design impactful research programs. These efforts include the development of resources for understanding public health needs of the general population and specific populations, resources that will assist in providing access to patient populations, and resources for better understanding the factors affecting such health conditions as Alzheimer's disease and related dementias (Figure 19).

A widely available tool in which NIH invests to help guide prevention and treatment efforts is the Global Burden of Disease (GBD) enterprise.[97] GBD is the world's largest scientific effort to systematically quantify health loss from all diseases, injuries, and risk factors by age, sex, and geographic location over time. NIH and GBD collaborated to improve the way that disease causes and risk factors are identified. As a result of this collaboration, NIH and the research community can identify and track the causes and risk factors of premature death and disability in the U.S. over time (both historically and projecting up to 25 years in the future). Because premature death is often preventable, the availability of these data not only improves understanding of the burden of disease and key health outcomes in the U.S., but also enhances the ability to focus on the most pressing health challenges facing the nation.

The ability to monitor cancer in the U.S. is an important step toward determining how best to prevent and treat cancer in specific, disproportionately affected populations. The NIH Surveillance, Epidemiology, and End Results (SEER)[98] Program provides information on cancer statistics based on race, gender, and geography to guide efforts to reduce the cancer burden among the U.S. population. SEER currently reflects 35 percent of the U.S. population, and NIH

Figure 19. Alzheimer's Disease Research Infrastructure

More than 5.8 million Americans age 65 and older are living with Alzheimer's disease (AD), the most common form of dementia. Many others younger than age 65 have developed the less common early-onset form of AD. Still more are affected by AD-related dementias (ADRDs). Although the underlying pathology may differ among these conditions, their ultimate outcome is the same: the inexorable, relentless loss of memory, thought, and function. At present, no intervention has been reliably proven to prevent, slow, or reverse the effects of AD/ADRD. Under the auspices of the National Plan to Address Alzheimer's and Related Dementias, NIH develops and supports a robust infrastructure for discovery that supports activity across the full spectrum of AD/ADRD research, including, but not limited to, the Dominantly Inherited Alzheimer's Network, an international consortium of researchers who are working with individuals from families with a rare form of the disease to identify the sequence of brain changes before symptoms appear; the NIH Blueprint Neurotherapeutics Network, NIH's preclinical/early clinical drug development program that provides support for drug discovery and development; and the Alzheimer's Disease Education and Referral Center, NIH's primary source for consumer information on AD/ADRD research and care.

will expand the program to cover 50 percent of the U.S. population.

The medical advances and new technologies that have allowed Americans to live longer and healthier lives have not helped everyone equally. To build capacity at institutions with a historical and current commitment to educating underrepresented students and providing health care in underserved communities, NIH created the Research Centers in Minority Institutions (RCMI) Program.[99] The goals of RCMIs are to enhance institutional research capacity, enable investigators to become more successful in obtaining competitive funding, foster environments conducive to career enhancement, promote research on minority health and health disparities, and establish sustainable relationships with community-based organizations.[100]

NIH is also working to promote health equity in rural populations. NIH's Clinical and Translational Science Awards (CTSA) Program[101,102,103] is engaging with patients, community members, and nonprofit organizations to develop and disseminate best practices for patient-focused research in rural health.[104] Project areas include improving access to clinical trials for rural communities, harnessing technology to deliver effective care, and enhancing rural community outreach. The CTSA Program is also partnering with other NIH ICs and federal agencies to support rural health.

To further support rural communities, NIH is harnessing the Institutional Development Award (IDeA) Program, which aims to broaden the geographic distribution of NIH funding and to build research capacity in states that historically have had low levels of NIH funding. NIH is building on the research capacity within IDeA states to help address the medical needs of children living in rural and underserved areas. Similarly, the Environmental influences on Child Health Outcomes (ECHO) Program also leverages IDeA to expand pediatric research capacity in the IDeA States Pediatric Clinical Trials Network.[105] Beginning in 2018, IDeA also collaborated with NIH's Shared Instrumentation Grant (SIG) Programs to improve access to modern technologies for researchers in underresourced institutions in IDeA-eligible states. SIG supports the acquisition of modern scientific instruments that must be used on a shared basis.[106]

Many NIH Common Fund projects focus on developing resources that can be useful for research communities focused on a particular topic. The NIH Common Fund Molecular Transducers of Physical Activity Consortium (MoTrPAC)[107,108] is building a map of the molecular responses to exercise, both immediate and over the long term. Data are being made widely available to the entire research community so that investigators from anywhere can use this map to develop and test hypotheses about how exercise improves health and ameliorates disease. The program is scheduled to run through 2023 and released its first dataset through the MoTrPAC Data Hub in 2019.

Another valuable resource for the research community includes improved understanding of the biological and behavioral mechanisms of symptoms, which can improve patient outcomes. The NIH Intramural Research Program launched the Symptom Science Center (SSC)[109] to address the need for a more comprehensive approach to understanding the complex mechanisms underlying symptoms. Increased knowledge in this area can help develop precision health interventions to treat patients more effectively. Furthermore, the SSC serves as a nexus for collaboration among investigators from multiple ICs and is committed to training scientists and clinicians in symptom science.

OBJECTIVE 3 Exemplifying and Promoting the Highest Level of Scientific Integrity, Public Accountability, and Social Responsibility in the Conduct of Science

As a steward of public resources, NIH has a responsibility to uphold public trust and confidence in the agency. In addition to fostering innovative research, NIH must endeavor to ensure that all of its operations and the research it supports are conducted efficiently, responsibly, ethically, and with integrity. Over the next

5 years, NIH is committed to taking additional steps to maintain and strengthen the processes by which it governs the conduct of science.

Fostering a Culture of Good Scientific Stewardship

This *NIH-Wide Strategic Plan* positions the agency to meet its mission by pursuing scientific opportunities when they arise, responding to ongoing and emerging public health needs, and addressing rare diseases. NIH research efforts also align with and reflect HHS's priority goals.[110] The agency promotes policies and programs that foster and ensure a strong foundation and culture of good scientific stewardship. As critical research needs arise, NIH will respond by ensuring that the scientific community has flexibility to quickly adapt to and address urgent public health issues.

Setting Priorities

Scientific priority setting at NIH encourages input from a range of sources, including the research community; public forums; the Advisory Committee to the NIH Director; U.S. Congress; Administration objectives; and consultation with advocacy groups, professional societies, and research participants. The NIH Director provides overall leadership to the ICs and OD offices, especially on efforts involving several components of the agency. Strategic plans developed by individual ICs and OD offices, committees composed of representatives from multiple ICs, and interagency working groups describe a multitude of scientific priorities and themes of interest to the agency.[111]

NIH demonstrates effective stewardship by supporting the most meritorious biomedical and behavioral research possible. The NIH peer review process assesses research grant applications for overall scientific and technical merit and ensures that applications receive fair, independent, expert, and timely reviews.[112] Scientific review panels are strategically formed to include reviewers who possess both broad and specialized expertise and who can address stability and recent trends in the field. NIH makes efforts to ensure that review panels reflect diversity in career stage, geographic region, and demographic characteristics. NIH staff seek input from a variety of sources to identify reviewers for panels, including NIH program staff and advisory councils, as well as scientific literature, meetings, and professional organizations.

The relative merit of applications as determined through peer review, in conjunction with input on mission relevance from IC Advisory Councils, informs IC Directors as they make funding decisions that consider mission focus, portfolio balance, scientific opportunity, emerging and ongoing public health needs, and stakeholder priorities. Balancing research with training and infrastructure—as well as distribution across basic, translational, and clinical research—are key factors taken into consideration in maintaining a diverse portfolio. NIH also considers the vital role of rare diseases research, through which unique biological insights are possible. This research is less likely to be supported by private funders than research into more prevalent disorders.

To maintain a peer review process of the highest caliber, NIH has developed an ongoing systematic multimethod evaluation that will objectively assess most peer review study sections over a 5-year cycle.[113] The aims of the system are to keep study sections aligned with the current state of the science, confirm NIH is attracting applications that propose cuttingedge science, and ensure that study sections are functioning efficiently with a balanced workload. Additional programs, such as the Early Career Reviewer Program,[114] help NIH refresh and diversify its pool of reviewers, while also helping investigators improve their grant-writing skills, develop research evaluation capacity, and strengthen critique-writing skills.

NIH proactively pursues scientific opportunities through a variety of programs that promote innovative research concepts and exploration of scientific hypotheses that could steer science in new directions. Additionally, NIH encourages team science and cross-disciplinary collaboration to propel research progress. NIH will continue to look for additional ways to capitalize on the intersection of scientific fields to further scientific progress and improve human health.

Monitoring Expenditures and Scientific Progress

NIH requires regular reporting from grant and contract award recipients on research progress, spending, and findings. NIH staff review these reports to ensure proper stewardship of federal funds and that supported research is fulfilling all terms of the funding agreement.

Another aspect of NIH stewardship is to provide the public with transparent and easily accessible information about NIH research awards and allow interested individuals to monitor NIH's support of research. The *NIH Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER)*[115] tool, for example, provides public access to information on the grants, contracts, and intramural research that NIH supports. Additionally, the *NIH Data Book*[116] provides quick access to key annual statistics, such as application success rates, workforce and training trends, the peer review process, and small business awardees. NIH will continue enhancing these and other tools in the suite of *NIH RePORTER* tools[117] to better meet information and communication needs in the coming years.

Making Evidence-Informed Decisions

NIH is committed to enhancing scientific stewardship by optimizing approaches that generate evidence used to inform programmatic, operational, and policy decisions. To further these efforts, NIH has developed several tools, available to its staff and to the broader scientific community, that can identify and analyze current and emerging areas of research that will advance NIH's mission. For example, the *iCite*[118] suite of tools is a public resource that enables users to examine validated metrics regarding the impact of NIH-funded research articles (Figure 20). These tools, which are informed by the judgment of subject-matter experts, help users examine the NIH portfolio's productivity, balance, and priorities across the spectrum of research—from basic to clinical and across the diverse areas of biomedical and behavioral research.

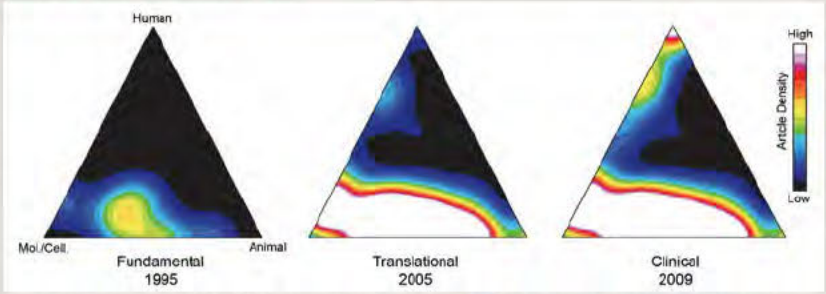
NIH shares common interests with many agencies across the federal government and often coordinates with other science agencies to promote collaboration among researchers and manage research portfolios. NIH supports *Federal RePORTER*,[119] a collaborative effort among federal funders to provide a central database for certain grant information. In addition, NIH is partnering with the National Science Foundation and the General Services Administration to develop and implement computational tools to identify overlap between grant proposals across agencies in real-time, reducing the risk of unnecessarily duplicative research.[120] Collectively, these efforts promote transparency and enable efficiency through data-driven decision-making.

Assessing Programs, Processes, Outcomes, and Impact

The NIH *Report on Approaches to Assess the Value of Biomedical Research by NIH*[121] found that a better understanding of all aspects of NIH's work is key to increasing the efficiency and effectiveness of the agency. NIH uses a variety of approaches—including monitoring, performance measurement, analysis, and evaluation—to assess the progress and effectiveness of its programs, policies, and operations and to generate information for decision-making. To increase the use of these tools, NIH is enhancing the quality of administrative data, making it an increasingly strategic source of information that, when coupled with other tools, could improve the agency's

Figure 20. Predicting Translational Progress of Research

Fundamental research can take decades to translate into clinical outcomes. To capture the translational potential of publications, NIH researchers created a machine learning model that maps papers on a trilinear graph using three Medical Subject Heading (MeSH) terms: Human, Animal, and Molecular/Cellular. Almost all NIH-funded papers (> 96 percent) are assigned at least one of the MeSH terms and can be plotted somewhere on "the triangle of biomedicine." The graph pictured depicts the accumulation of fundamental, translational, and clinical research that led to cancer immunotherapy drugs like Opdivo (nivolumab). This visualization was generated using the *iCite* web tool developed by NIH.



Credit: Hutchins BI, Davis MT, Meseroll RA, Santangelo GM. Predicting translational progress in biomedical research. PLOS Biol *2019;17(10):e3000416.* https://doi.org/10.1371/journal.pbio.3000416.

effectiveness. Under HHS's guidance, NIH will engage in capacity- and evidence-building activities to support the Department's implementation of the *Foundations for Evidence-Based Policymaking Act of 2018*[122] and further develop its data-driven, results-oriented culture.

Communicating Results

NIH fosters scientific stewardship by ensuring that the products and processes of scientific research, such as research data and scientific publications, are available in accord with the FAIR principles that all research data should be findable, accessible, interoperable, and reusable (Figure 21). NIH communicates research findings to the public in numerous ways, including through press releases on recent scientific advances on the *NIH News & Events*[123] website, the *NIH Director's Blog*,[124] and the *Impact of NIH Research* pages,[125] which have examples illustrating the downstream impact of NIH research on public health and society. Additionally, NIH ICs and OD offices develop and disseminate a range of publicfriendly health- and disease-specific educational materials on a host of topics. NIH provides evidence-based and authoritative biomedical information in highly expeditious and proactive ways. This vital function is especially important during public health emergencies, such as infectious disease or foodborne illness outbreaks.

Figure 21. FAIR Principles

NIH is working to align the research that it supports with the FAIR principles (findable, accessible, reusable, interoperable) to ensure that the results of NIH investments can be leveraged by the entire research enterprise. NIH organizes its data science efforts around five themes: advancing data infrastructure to increase connectivity across systems and platforms; defining strategies to help researchers better store and share their data; adopting and adapting data science tools to enhance research; engaging with stakeholder communities and enabling citizen scientists to support the biomedical data enterprise; and increasing the capacity of computational and data science workers in biomedical research through new and existing workforce programs.

Credit: Office of Data Science Strategy, NIH.

Research results are also communicated through such NIH resources as *PubMed* and *ClinicalTrials.gov*. In 2020, NIH launched the new *PubMed*,[126,127] the most heavily used biomedical literature citation database in the world, which enables the communication and discovery of scientific literature around the world. NIH's *PubMed Central* (PMC)[128] provides public access to the full text of more than 6 million peer-reviewed research articles (Figure 22). PMC facilitates linking between articles and associated data; supports discovery of these data by aggregating data citations, data availability statements, and supplementary materials; and contains a subset of about 3 million articles available for bulk retrieval for text mining and other research purposes.

Reports from clinical studies are made available through *ClinicalTrials.gov*, the largest public clinical research registry and results database in the world. This NIH resource provides patients and their caregivers, health care providers, and researchers with information on more than 330,000 active and complete registered studies, including studies with summary results, many of which are not otherwise available through published literature. A multiyear effort is underway to modernize *ClinicalTrials.gov* to deliver an improved user experience on an updated platform that will accommodate growth and improve efficiency.

In response to the COVID-19 pandemic, NIH partnered with researchers and leaders from universities and industry to rapidly mobilize and create the *COVID-19 Open Research Dataset* (CORD-19)[129] of scholarly literature about COVID-19, SARS-CoV-2, and other coronaviruses. *CORD-19* provides immediate, machinereadable access to the full text of pre-print and peer-reviewed articles to assist researchers worldwide in finding answers to high-priority scientific questions related to the COVID-19 response. NIH also developed the COVID-19 portfolio tool[130] as a complement to *CORD-19*. This tool provides powerful search functionality and interactive

Figure 22. PubMed Central

As a free archive of full-text biomedical and life sciences journal literature, *PubMed Central* is an authoritative source of scholarly information that ensures the insights gained through biomedical discovery are made openly available to research and clinical care communities, as well as to the public at large.

Credit: National Library of Medicine, NIH.

visualizations to support cutting-edge analytics of the literature to identify gaps and opportunities in COVID-19-related research. In addition, to assist researchers working on the genomics of the novel coronavirus, the COVID-19 Genome Sequence Dataset on Registry of Open Data on Amazon Web Services[131] is a centralized sequence repository for strains of SARS-CoV-2.

Leveraging Partnerships

Expanding fundamental knowledge of biological systems and applying that knowledge to the advancement of health requires strategic partnerships with a range of organizations, including other federal agencies, international governments, the private sector, and the public. These partnerships bring enhanced coordination, critical expertise, pooled resources, and novel stakeholder connections to augment NIH efforts.

Federal Partnerships

NIH values collaboration with its federal partners and partners extensively with other federal agencies. Interagency collaborations address critical public health needs and facilitate coordination, communication, and resource-sharing. For instance, the Tobacco Regulatory Science Program (TRSP),[132] a partnership between NIH and FDA, funded research on youth tobacco use; toxins and nicotine concentration in e-cigarettes; and the Population Assessment of Tobacco and Health (PATH) Study, a longitudinal examination of tobacco product use.[133] Data from TRSP studies provide valuable evidence to inform government-wide policymaking. Research results from the Tobacco Centers of Regulatory Science, a centerpiece of TRSP, will provide further insight into who is using these products, what health outcomes result from product use, and how to implement interventions to target health outcomes.[134]

Another key federal collaboration is the Interagency Pain Research Coordinating Committee (IPRCC),[135] chaired by NIH with members from several agencies within HHS, including FDA, Centers for Disease Control and Prevention (CDC), Agency for Healthcare Research and Quality (AHRQ), Department of Defense (DoD), and U.S. Department of Veterans Affairs (VA). IPRCC coordinates federal activities to enhance pain research efforts and promote collaboration across the government, with the ultimate goals of advancing the fundamental understanding of pain and improving pain-related treatment strategies. NIH also partners with DoD and VA on the NIH-DoD-VA Pain Management Collaboratory, which supports the development, implementation, and testing of cost-effective, large-scale, real-world research on nonpharmacologic approaches for pain management and related conditions in military and veteran health care delivery organizations.[136]

The *21st Century Cures Act* established the HHS Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) to advise the HHS Secretary regarding gaps in knowledge and research on safe and effective therapies for pregnant women and lactating women (Figure 23).[137] Led by NIH, other

Figure 23. Research for Pregnant and Lactating Women

The *21st Century Cures Act* established the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) to advise the Secretary of Health and Human Services regarding gaps in knowledge and research on safe and effective therapies for pregnant women and lactating women. PRGLAC was tasked with identifying these gaps and reporting its findings to the Secretary.

Credit: NICHD, NIH.

federal members include CDC, FDA, AHRQ, Health Resources and Services Administration (HRSA), VA, and HHS Office on Women's Health. Non-federal members include representatives from medical societies, nonprofit organizations, and industry. More than 6 million women are pregnant in the U.S. each year, many taking medications or dietary supplements. PRGLAC identified the lack of scientific evidence on the safety and efficacy of these compounds during pregnancy or breastfeeding as a substantial knowledge gap in maternal health.

Public-Private Partnerships

Public–private partnerships (PPPs) provide a mechanism to strategically accelerate advances and accomplish goals that NIH cannot readily achieve by acting alone. For example, to hasten the development of interventions for COVID-19, NIH is leading the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)[138] PPP (Figure 24). PPP activities focus on the shared goals and mandates of the partners and leverage knowledge, skills, resources, and services to achieve synergy. For example, NIH—together with FDA, biopharmaceutical companies, and nonprofit organizations—launched the Accelerating Medicines Partnership (AMP).[139] The goal of AMP is to increase the number of new diagnostics and therapies and reduce the time and cost of developing them. Four AMP initiatives are underway: AMPAlzheimer's Disease (AMP-AD), AMP-Parkinson's Disease (AMP-PD), AMP-Rheumatoid Arthritis/Lupus (AMP-RA/Lupus), and AMP-type 2 diabetes (AMP-T2D). After successfully meeting program milestones, AMP-AD and AMP-T2D are finalizing research plans for the next phase of the program. New AMP initiatives have been launched for schizophrenia[140] and are in development for gene therapy.

To capitalize on dramatic advances in genetics, NIH and the Bill and Melinda Gates Foundation have expanded their cooperation toward an audacious goal: to develop affordable, gene-based cures for SCD and HIV within a decade. The intention is for these cures to be made globally available, especially in lowresource settings where people are most affected by these conditions.

Figure 24. ACTIV: An Unprecedented Partnership for Unprecedented Times

In April 2020, NIH launched the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public–private partnership to develop a coordinated research strategy for prioritizing and speeding the clinical evaluation of the most promising vaccines for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and treatments for coronavirus disease 2019 (COVID-19). Through ACTIV, NIH has partnered with more than 15 biopharmaceutical companies, as well as its sibling agencies and offices within the U.S. Department of Health and Human Services, other government agencies, the European Medicines Agency, and representatives from academia and philanthropic organizations. Through the ACTIV partnership, NIH is pursuing four fast-track focus areas most ripe for opportunity: (1) developing a collaborative, streamlined forum to standardize and share evaluation methods and testing of preclinical therapeutics and vaccines; (2) prioritizing and accelerating clinical testing of the most promising treatments for all stages of the disease; (3) leveraging clinical trial capacity and effectiveness; and (4) accelerating the evaluation of vaccine candidates to enable rapid authorization or approval.

Credit: NIH.

The NIH Science and Technology Research Infrastructure for Discovery, Experimentation, and Sustainability (STRIDES) Initiative[141]—one of many NIH-wide efforts underway to implement the *NIH Strategic Plan for Data Science*—provides NIH and its funded researchers with cost-effective access to state-of-the-art cloud-based data storage and computational capabilities, tools, and expertise. Through STRIDES, NIH has established PPPs with commercial providers, such as Amazon Web Services and Google Cloud. NIH anticipates forming additional industry partnerships through STRIDES to broaden access to services and tools, including training and professional services for researchers on how to use the latest cloud tools and technologies. These partnerships will allow academic researchers and industry to come together to create a data ecosystem that maximizes the use of NIH-supported biomedical and behavioral research data for the greatest benefit to human health.

During the next 5 years, NIH will continue to expand partnership opportunities focused on increasing diagnostics and therapies for particular conditions, curing intractable diseases, and making the vast amount of data generated by biomedical research accessible to as many researchers as possible.

International Partnerships

As the world grows increasingly connected, NIH remains committed to developing and sustaining relationships with partners around the globe. Recent events, including the COVID-19 pandemic, have illuminated the importance of a coordinated approach to global health aligned with humanitarian and scientific values. Geographic boundaries do not prevent infectious disease spread, nor should they prevent the advancement of research on such diseases. For this reason, NIH collaborates internationally with foreign governments and organizations.

In collaboration with the Office of the U.S. Global AIDS Coordinator and Health Diplomacy, NIH supports the African Forum for Research and Education in Health (AFREhealth)[142,143] Program and the Health-professional Education Partnership Initiative,[144] both of which are designed to enhance the quality, quantity, retention, research engagement, and networking of an interprofessional health workforce across Africa. NIH also supports the Human Heredity and Health in Africa Consortium (H3Africa) via the NIH Common Fund.[145] This partnership includes the Wellcome Trust and the African Academy of Sciences and seeks to build African research capacity in the genomic sciences and contribute to improving understanding of health and disease in underrepresented and underserved populations.

NIH participates in the Global Alliance for Chronic Diseases (GACD),[146] a consortium of the world's largest public research funding agencies. GACD's mission is to reduce the burden of chronic noncommunicable diseases (NCDs) in low- and middle-income countries and in populations facing conditions of vulnerability in high-income countries, by building evidence to inform national and international NCD policies. NIH funds GACD research in the areas of cancer prevention, mental health, lung disease, type 2 diabetes, hypertension, and scaling-up evidence-based interventions.

In addition to working with international partners on disease, NIH also supports other types of international health initiatives. For example, the NIH Disaster Research Response (DR2) Program, which supports research to inform disaster and public health emergency preparedness, response, and recovery, serves as a compelling model for addressing crises. DR2 has partnered with Japan's National Institute for Environmental Studies and Health Canada to begin developing similar programs in those countries.[147] Early outcomes include translation of data collection tools to Japanese, using DR2 tools in response to Typhoon Hagibis, collaboration on DR2 workshops and training exercises, and international outreach.

Public Engagement

Public engagement is vital to NIH research. Patients, research participants, disease advocacy organizations, and local, state, and cultural communities have a leading role to play in the research enterprise. During study design, these groups can highlight important knowledge gaps impeding community-level programs, policies, and practices. During data collection and analysis, they advise researchers on the challenges of applying new knowledge in different local and cultural contexts.

As part of its commitment to public engagement, NIH will continue providing underrepresented groups with equal access to research in an ethical and responsible manner that protects privacy and respects cultural sensitivities. NIH facilitated a data sharing and use agreement between the Navajo Nation

and NIH grantees of the ECHO Program.[148] The agreement was created to advance the Navajo Birth Cohort Study while respecting Navajo Nation cultural beliefs, Tribal sovereignty, and community values.[149] It is the first Tribal data-sharing agreement for a large-scale database as part of a nationwide research consortium. This achievement lays the groundwork for discussion of similar agreements with other Tribal Nations considering participation in biomedical and behavioral research programs.

Public engagement is also key to NIH's maternal health efforts. The NIH Task Force on Maternal Mortality developed Implementing a Maternal health and PRegnancy Outcomes Vision for Everyone (IMPROVE), an NIH-wide research initiative. IMPROVE was informed by input from a variety of sources, including the public and NIH-convened meetings for scientists and clinicians to solicit recommendations on health disparities underlying maternal mortality, as well as gaps and opportunities for future research. IMPROVE will focus on women beginning in pregnancy and continuing up to 1 year postpartum and will include community-focused social and biobehavioral research, as well as research to accelerate discovery and advance technologies to reduce maternal health risks.

Ensuring Accountability and Confidence in Biomedical and Behavioral Sciences

To foster confidence in NIH-funded research and results, NIH must ensure that both its operations and its supported research are conducted efficiently, responsibly, ethically, and with integrity. NIH is committed to taking steps to maintain and strengthen the processes by which it governs the conduct of science, continuing to be accountable for the public funds it invests in research.

Enhancing Reproducibility Through Rigorous and Transparent Research

Two cornerstones of scientific research are rigor in the design and conduct of experiments and the ability to reproduce research findings. The application of scientific rigor ensures robust and unbiased experimental design, methodology, analysis, interpretation, and reporting of results. When a result can be reproduced by multiple scientists working independently, it validates the original result and indicates readiness to progress to the next phase.

NIH has collaborated with scientific journal publishers to identify shared opportunities to enhance transparency, rigor, and reproducibility in published literature. NIH has also convened working groups and workshops focused on rigor, developed training modules for the research community on good experimental design, enhanced requirements for the content and review of grant applications, and developed specific funding opportunities aimed at improving rigor and reproducibility. Moving forward, NIH will continue working closely with researchers, publishers, and federal partners to develop and share recommendations and best practices. Along these lines, NIH has convened a working group of the Advisory Committee to the Director to explore ways to enhance reproducibility and rigor in laboratory animal research.[150]

Improving Stewardship of Clinical Trials

NIH invests more than $3 billion each year in clinical trials. NIH must ensure these trials investigate high-priority questions, do not needlessly duplicate previous trials, recruit and maintain sufficient participants, are completed in a timely manner, and are likely to advance knowledge and improve health. NIH has launched a series of efforts to enhance accountability and transparency in clinical research,[151] as well as address challenges and shortcomings in the design, efficiency, and timeliness of reporting clinical trial results. These efforts included dedicated funding opportunities, Good Clinical Practice training, a single Institutional Review Board for multisite research policy, and an optional template that guides investigators through the systematic development of a comprehensive clinical protocol and required registration and reporting of clinical trial results. In addition, by ensuring that summaries of results of NIH-supported clinical trials are widely and freely available, *ClinicalTrials.gov* promotes transparency and helps ensure that research findings are contributing to the advancement of public health.

Assuring Ethical and Equitable Conduct of Research Through Inclusion

More women and underrepresented and underserved groups are participating in clinical research than ever before, in large part thanks to NIH policy. NIH's goal is to ensure that these trends continue so that

the knowledge gained from research is applicable to everyone affected by the disease or condition under study (Figure 25). To this end, NIH has taken critical steps to ensure the scientifically appropriate enrollment of women and underrepresented and underserved groups in clinical research and is engaged in efforts to increase inclusion of children, older adults, pregnant and lactating women, and individuals with disabilities as appropriate. NIH requires researchers who propose research involving human subjects to include plans for how participants from these groups will be enrolled, unless there is a scientific or ethical justification for their exclusion. Once a grant is awarded, researchers must annually report deidentified individual-level demographic data so that NIH can continue to monitor inclusion.

Figure 25. Clinical Center Research

An NIH researcher examines a pediatric patient in the NIH Clinical Center.

Credit: Richard Clark, NIAMS, NIH.

NIH will continue its focus on challenges to recruiting and retaining underrepresented populations in clinical studies and will add data on the age at enrollment of participants to the Research, Condition, and Disease Classification (RCDC) *Inclusion Statistics Report*, which allows users to view trends over time. In addition, NIH will train researchers to include women, underrepresented and underserved populations, and individuals of all ages in studies as part of its efforts to increase the diversity of study populations.

Maintaining Transparency Through Data Access and Sharing

NIH is committed to making findings from the research that it funds accessible and available in a timely manner, while also providing safeguards for privacy, intellectual property, security, and data management. For instance, NIH-funded investigators are expected to make the results and accomplishments of their activities freely available within 12 months of publication. NIH also encourages investigators to share results prior to peer review, such as through preprints, to speed the dissemination of their findings and enhance the rigor of their work through informal peer review.

A robust culture of data sharing is critical to continued progress in science, maximizing NIH's investment in research, and assurance of the highest levels of transparency and rigor. To this end, NIH will continue to promote opportunities for data management and sharing while allowing flexibility for various data types, sharing platforms, and strategies. Additionally, NIH is implementing a policy requiring that all applications include data sharing and management plans that consider input from stakeholders.[152,153]

Fostering a Safe and Harassment-Free Work Environment

NIH has an imperative to transform the culture of science to prevent harassment (sexual, gender, and other) and mitigate its detrimental impacts, whether it is in the agency or anywhere NIH-funded activities are conducted. In 2019, NIH established the Advisory Committee to the NIH Director Working Group on Changing the Culture to End Sexual Harassment.[154] Following this group's recommendations, NIH is taking actions within the agency's authority to change the scientific workplace to make it safer and more welcoming (Figure 26). NIH issued several new policies, guidelines, and requirements on this topic and communicated them widely to make expectations clear to NIH-funded organizations and the workforce at NIH.[155]

NIH expects recipients of federal funds to have policies and practices in place that foster a safe and harassment-free environment.[156] For instance, NIH must be notified if a principal investigator or other key personnel named on an NIH grant award is unable to

Figure 26. NIH *Harassment Does Not Work Here* Campaign

An image stating "Harassment Doesn't Work Here" as part of NIH's campaign to create a safe and civil workplace wherever NIH-funded research is conducted.

Credit: NIH Civil Program.

fulfill their obligations to conduct research because they are under investigation or have been removed from the workplace because of sexual harassment concerns. NIH expects recipients requesting changes in investigator, key personnel, or recipient institution to mention whether these requests are related to concerns about the safety and/or work environment, including issues related to sexual harassment or bullying.[157] Internally, NIH has undergone a workplace climate and harassment survey to inform policy and practice and has expanded its human resources program to foster civility throughout the NIH community.[158]

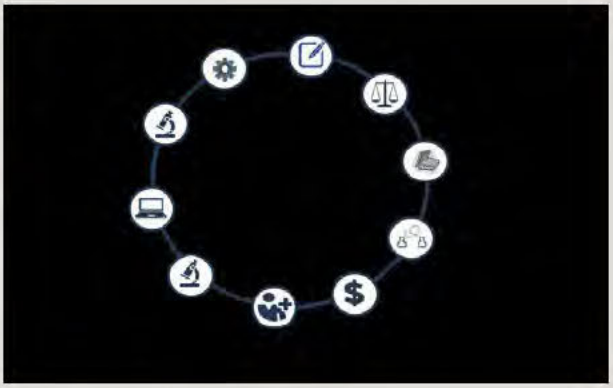
NIH's efforts have led to increased scrutiny and awareness of harassment, centralized mechanisms for reporting harassment, and new anti-harassment policies. NIH will continue working with its partners and exploring policymaking options based on recommendations from the Advisory Committee to the NIH Director and findings from internal studies to change the scientific culture, prevent sexual harassment, and promote a civil, safe, and respectful workplace for everyone.

Managing Risks to the Research Enterprise

NIH is committed to proactively managing risks that may impede the NIH mission. Such risks have the potential to affect patient and laboratory safety, the peer review process, laboratory animal welfare, conflict of interest disclosures, closeout of grant awards, data security, and more. Understanding the need to identify and manage risks, NIH incorporated Enterprise Risk Management (ERM) capabilities into its strategic planning, performance management, and resource allocations (see Figure 27). Going forward, NIH is better prepared to respond to emerging risks that may undermine its research activities and are inconsistent with its research values and principles.

Figure 27. Managing Risks to the Research Enterprise

The NIH Risk Management Program provides NIH with a framework for systematically identifying and addressing risks that might adversely affect NIH's ability to fulfill its mission. Risk management is a continuous process that requires all NIH staff and researchers to proactively identify and mitigate risk as part of their daily jobs. Understanding the need to identify and manage risk, NIH has incorporated Enterprise Risk Management (ERM) capabilities into its strategic planning, performance management, and resource allocations. ERM is a strategic discipline that seeks to deliberately and proactively understand the full spectrum of risks, including opportunities across an entire organization, and integrates them into an enterprise-wide, strategically aligned, and interrelated risk portfolio view. By incorporating ERM, NIH can proactively address emerging threats and opportunities and deliver results to the public in a transparent and accountable manner, all in an effort to further support NIH's mission.



Credit: NIH Risk Management Program.

As a part of its commitment to a culture of health and safety for people conducting NIH-funded research, and to mitigating the effects of emergencies on the research enterprise, the NIH Extramural Response to Natural Disasters and Other Emergencies policy allows NIH to provide resources and assistance to those in the NIH community affected by public health emergencies.[159] Under such circumstances, NIH will provide administrative flexibilities and additional funding using a number of mechanisms to support the continuation of research, as demonstrated during the COVID-19 pandemic.[160]

NIH and the research community have a vested interest in mitigating any breaches of trust and confidentiality that undermine the integrity of U.S. biomedical research, while continuing the tradition of scientific collaboration, including international collaboration. NIH recognizes the importance of these collaborations to advancing its mission. However, some researchers at NIH-funded institutions have taken advantage of these collaborations through failing to disclose contributions of resources from foreign organizations, diverting proprietary information to foreign governments, and sharing confidential information obtained from NIH peer review meetings or otherwise trying to influence the peer review process.

NIH works with other federal agencies to take strong actions in response to these breaches of integrity which appear to be, at least partly, instigated by foreign governments.[161] NIH has increased the visibility of this issue and reminds grant recipients to be transparent and disclose all affiliations, financial conflicts of interest, and other support (including from foreign entities) and contacts recipient institutions about any concerns.[162] NIH has also bolstered its internal processes and systems and increased awareness among its own staff.

Looking to the future, NIH will continue careful monitoring and extensive outreach with academia, professional societies, and federal partners to reinforce the importance of research security and integrity, as well as to hold people and institutions accountable for inappropriate actions.[163] NIH will continue to work closely with federal partners to protect the safety, integrity, and inclusivity of U.S. research and looks forward to continuing to work with institutions and researchers to strengthen values that underpin research integrity and protect the nation's biomedical innovations.[164]

Reducing Administrative Costs and Work Throughout the Grants Process

Reducing administrative burden increases the amount of time that investigators can spend on research and that administrators can spend supporting the research enterprise. NIH works to streamline grants policies and processes to reduce administrative work and costs. Recent changes include automating the issuance of certificates of confidentiality that protect participants in NIH-funded research, creating the Application Submission System & Interface for Submission Tracking (ASSIST) as an option for preparing and submitting applications, developing a tool that reduces the need to develop clinical trial protocol text de novo, simplifying the appendix and other material in grant applications to help during the review process, and reducing the need for multiple biographic profiles across different systems to help people find information and simplify reporting and analysis.[165] NIH will continue to work with stakeholders to further streamline the grant application process, while promoting rigor and fostering compliance.

Optimizing Operations

NIH seeks to continually optimize operations across an array of business, administrative, and scientific functions, as well as to improve its physical and technological infrastructures. Increasing coordination and engagement throughout the agency and managing risk while fostering innovation are critical to the stewardship of the nation's biomedical and behavioral research ecosystem. Over the next 5 years, NIH will implement strategies to excel as a federal science agency dedicated to protecting and improving public health.

NIH will continue implementing its *Optimize NIH* efforts, which were established as part of the *Reimagine HHS* effort to improve performance across the Department's divisions. Through the *Optimize NIH* initiative, the agency is focusing on administrative areas that could be made more efficient and effective if managed centrally, or better harmonized across ICs and OD offices. Using a combination of process mapping, surveys, and focus groups, the agency will carefully evaluate which approach or combination of approaches would yield the greatest improvements in each area. NIH's optimization efforts are guided in a data-driven and scientific manner, using teams led

by NIH experts in administrative operations with full engagement by employees.

Examples of functional areas that have already seen substantial improvement through *Optimize NIH* include management of federal advisory committees, employee ethics requirements, and *Freedom of Information Act (FOIA)* requests. NIH has adopted a unified system to standardize and streamline management of FOIA requests across the agency and has launched a public-facing portal, FOIAXpress, to improve the FOIA requestor experience. The launch of this portal increased information request processing speed by 83 percent, decreased the backlog by 11 percent, and offered solutions that can be leveraged across HHS. The lessons learned through the optimization of initial functional areas will inform NIH's approach to other business practice enhancements, such as information technology security, acquisitions, appointment of employees via a specialized hiring mechanism, travel management, and property management.

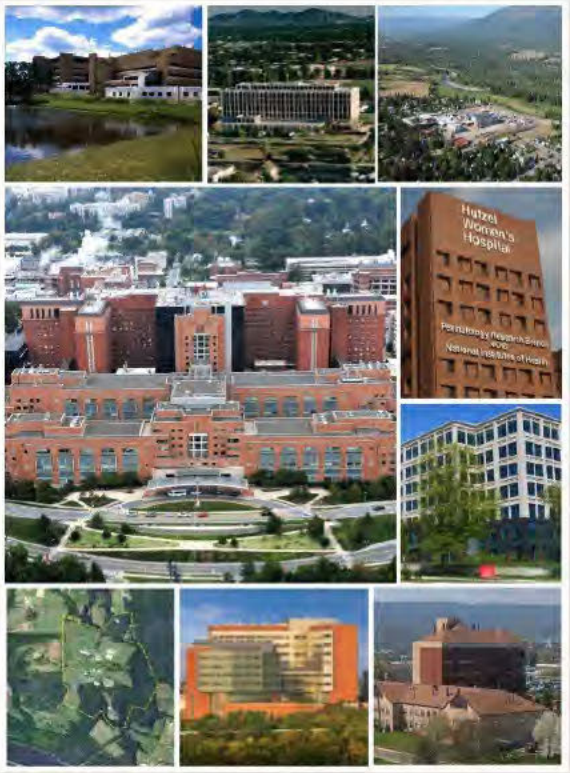
Optimize NIH will also continue to establish best practices for evaluating employee workload to improve the management of resources, inform hiring decisions, and reduce workload inequities. Workload harmonization across ICs and OD offices is already underway for scientific review, grants management, and program management, with additional areas identified for future improvement. NIH will also continue to harmonize and align each IC's strategic plan with a common template derived from the *NIH-Wide Strategic Plan*. Taken together, *Optimize NIH* projects will improve organizational effectiveness and performance and maximize the investment made by American taxpayers.

In alignment with the *Reimagine HHS* and *Optimize NIH* initiatives and in response to NIH community feedback, the NIH OD launched the OD Strategic Engagement Agenda to foster a unified and coordinated OD, which engages seamlessly with the ICs to advance the mission of the agency. This data- and participant-driven initiative will solicit and incorporate employee input through listening tours, working groups, and an online ideation campaign to improve communication and functionality within the OD through coordination and engagement with the ICs. By working toward these goals and improving on the use of OD operating principles of transparency, accountability, strategy, coordination, and decisionmaking, NIH will increase the efficiency and effectiveness of collaboration across NIH.

Meeting the goal of increased efficiency and effectiveness of operations across the agency requires the systematic assessment and management of risk in NIH's administrative and scientific programs, processes, and procedures. NIH is committed to integrating an ERM framework into its organizational culture to help prevent surprises, avoid operational failures, and allow quicker recovery when the unexpected happens. For example, NIH evaluated the extramural grant program using a fraud risk framework to identify vulnerabilities and develop mitigation strategies, including a staff fraud awareness and training program, to reduce the risk

Figure 28. NIH Campuses

Aerial views and photos of various building on NIH campuses showing a portfolio of biomedical research, administrative, and infrastructure-supporting facilities. From left to right and top to bottom: Research Triangle Park, North Carolina; Phoenix Epidemiology and Clinical Research Branch, Phoenix, Arizona; Rocky Mountain Laboratories, Hamilton, Montana; NIH Main Campus, Bethesda, Maryland; Pregnancy and Perinatology Branch, Detroit, Michigan; National Cancer Institute at Shady Grove, Rockville, Maryland; NIH Animal Center, Poolesville, Maryland; Bayview Campus, Baltimore, Maryland; and Frederick National Laboratory for Cancer Research, Frederick, Maryland.



Credit: Office of Research Facilities Development and Operations, NIH.

of fraud in the NIH extramural program and protect public funds. By conducting risk assessments and leveraging data collected within the ERM framework, NIH will improve information sharing and leadership decisionmaking and will prioritize corrective actions for identified risks. Incorporating ERM practices into daily operations also supports NIH in taking risks intelligently and prudently to achieve desired mission outcomes and enhances the agency's transparency and accountability to the public.

Underpinning NIH efforts to optimize its administrative and scientific operations are efforts to advance the agency's physical and technological infrastructures. For example, many of the agency's research and supporting facilities were constructed more than 50 years ago and require significant operating and maintenance costs, repairs, and upgrades to remain competitive in a global research environment. As resources become available, NIH will make strategic investments in building, expanding, and modernizing infrastructure on all its campuses.

It is critical that NIH provide, maintain, and operate its physical infrastructure—buildings and facilities capable of fulfilling and responding to the complex, collaborative, and changing nature of biomedical and behavioral science (Figure 28). The conduct of scientific discovery is enabled through safe and reliable facilities that can be adapted to support research on existing and emerging public health challenges, such as Alzheimer's disease and viral pandemics. NIH will closely link its strategic research goals to the availability, suitability, and capability of existing facilities and will plan, program, and budget for redeveloped and new facilities using planning and space utilization principles consistent with recognized business practices and the National Academies of Sciences, Engineering, and Medicine recommendations.[166] This integration of strategic research and infrastructure planning will enhance the oversight, prioritization, and delivery of facilities to meet the changing scientific needs over time.

CROSSCUTTING T

Many scientific challenges and opportunities are not unique to any one Objective in this Strategic Plan. To emphasize this, NIH has identified five key Crosscutting Themes that span all aspects of NIH's Strategy.

Minority Health and Health Disparities

Improving Minority Health and Reducing Health Disparities

Underserved groups—including Black, Latinx, and Indigenous and Native American persons, Asian Americans and Pacific Islanders, and other persons of color; members of religious minorities; lesbian, gay, bisexual, transgender, and queer (LGBTQ+) persons; persons with disabilities; persons who live in rural areas; or persons otherwise adversely affected by persistent poverty or inequality—have distinct health needs and often experience disparities in health outcomes. NIH maintains that racial and ethnic minorities, rural residents, people with low incomes, SGM, and other populations experiencing health disparities should be included in all relevant research, such that there is sufficient representation of each population to conduct relevant analyses. Inclusivity in research generates more broadly applicable information and improves scientific understanding of the health and well-being of specific population groups.

To promote health equity, NIH remains committed to supporting a robust program of research examining how biological, behavioral, environmental, sociocultural, and other factors interact with and shape individuals' health trajectories across the lifespan. The science of minority health and health disparities is founded on the principle that the social construct of individual race and ethnicity and socioeconomic status influence behavior, biology, and health outcomes in many defined and undefined ways. These individual factors interact with structural social determinants that may promote cumulative adversity that leads to worsened health outcomes through biological mechanisms.

Racism and discrimination are increasingly recognized as contributing to poorer health outcomes for

racial and ethnic minorities and other disproportionately affected populations. There is also a growing societal recognition that racism and discrimination extend beyond the behavior of individuals and are embedded in social, institutional, organizational, and governmental structures, processes, procedures, and practices that limit opportunities and resources to segments of the population.[167] NIH understands that health research needs to routinely incorporate constructs and measurement of structural racism or discrimination across multiple domains and levels of influence if minority health is to be optimized, health equity achieved, and health disparities eliminated.[168]

Understanding why underrepresented groups experience specific health outcomes is at the core of minority health science. It is essential to identify contributing factors to minority health conditions independent of whether a health disparity exists or is identified. Minority health research is the scientific investigation of distinctive health characteristics and attributes of minority racial and/or ethnic groups that are usually underrepresented in biomedical research to understand health outcomes in these populations and develop interventions to reduce disparities in health outcomes The *NIH Minority Health and Health Disparities Strategic Plan*[169] sets the direction and goals for NIH research in this area. Several NIH ICs and OD offices have core missions to address the health of underserved and underrepresented populations and to ensure they are adequately included in all NIH research. In addition, NIH-wide strategic plans identify efforts specific to the needs of underrepresented populations to develop synergy and facilitate collaborations across NIH.[170,171,172]

Promoting the recruitment, retention, and advancement of scientists from underserved groups will also have a significant influence on workforce development and will provide opportunities for individual scientists to achieve their full potential, thereby improving research on minority health and reducing health disparities.

Women's Health

Enhancing Women's Health

Women's health is a wide-ranging topic that goes beyond reproductive health to address a broader spectrum of diseases and conditions experienced by women throughout their lifespan. To advance science for the health of women, the *Trans-NIH Strategic Plan for Women's Health Research*[173] established NIH priorities across the research continuum and emphasized the importance of interdisciplinary partnerships. The NIH policy on *Sex as a Biological Variable,*[174] along with the expanded *NIH Inclusion Policy*[175] that requires investigators to report Phase III clinical trial results by sex or gender, race, and ethnicity to *ClinicalTrials.gov,*[176] will build foundational knowledge, accelerate translational research, and ultimately enable women to receive evidence-based interventions specific to their needs.

Promoting the recruitment, retention, and advancement of women scientists will also have a significant influence on workforce development, as well as provide opportunities for individual scientists to achieve their full potential, thereby improving research on the health of women.

Public Health Challenges Across the Lifespan

Addressing Public Health Challenges Across the Lifespan

NIH supports biomedical and behavioral research applicable to the full spectrum of public health challenges and needs, such as acute and chronic diseases, persistent and emerging infectious diseases, cancers, substance use disorders, disordered eating, Alzheimer's disease and related dementias, the health impacts of environmental exposures, and many more.[177] NIH research must address the prevention, treatment, and management of public health challenges; meet new challenges with fundamental research; and be ready to mobilize cutting-edge science in emergent situations.

Many public health challenges affect people of various ages and populations differently. To promote health across the lifespan, NIH efforts include targeted studies of specific age groups; studies of diseases that are unique to, or more common in, certain age groups; longitudinal cohort studies that follow the health outcomes of groups of individuals over long periods of time (including across generations); and studies that examine how early exposures, adversity, and positive experiences affect later health outcomes. The critical issue of maternal mortality and morbidity in the U.S. is one example of a public health challenge that requires multifaceted approaches at different points in the lifespan. Risks include not only complications at the time of pregnancy, birth, and

postpartum, but also cumulative and intergenerational impacts and exposures.

In addition to these programmatic approaches, NIH policies set the expectation that all supported studies will be designed to include children and older adults unless there is a scientific or ethical reason to exclude them. This policy ensures that the scientific findings for a given disease or condition are applicable to all those affected.[178]

Collaborative Science

Promoting Collaborative Science

Complex public health challenges and scientific questions require collaborative, team-driven research involving experts working together across multiple scientific fields, resulting in innovations that exceed the capacity of a single laboratory or discipline. NIH promotes opportunities that bring together scientists and clinicians and recognizes patients and research participants as partners and collaborators to generate outcomes that address the public health challenges that communities face. NIH partners with a wide array of other federal agencies, and domestic and international organizations in the public and private sectors to leverage their respective expertise and translate NIH research findings into new therapies, technologies, and evidence-based practices for improving health. For example, efforts to accelerate COVID-19 diagnostics, therapeutic interventions, and vaccine development are being conducted alongside sister agencies within HHS and representatives from academic, nonprofit, and commercial organizations.[179]

Scientific progress also benefits from collaboration across NIH ICs and OD offices. These NIH collaborations occur at every level of NIH operation, resulting in innovative scientific programs that address a wide range of health conditions. For example, the Pediatric Research Consortium brings together staff from across NIH to discuss issues in pediatric research for a range of health conditions. NIH also cultivates strategic partnerships across HHS to strengthen the public health ecosystem. For example, NIH plays a key role in the Department-wide implementation and dissemination of the HHS Secretary's evidence-based initiative to combat opioid use disorder.

Data Science

Leveraging Data Science for Biomedical Discovery

An immense amount of data is generated throughout the research enterprise, from fundamental experiments using cells and model organisms to human clinical studies and community-level epidemiological research. The exponential growth of data has resulted from the development of advanced biomedical technologies and computational processing unavailable a decade ago, including advanced AI and virtual reality technologies. These transformative changes require innovative approaches and business practices to address opportunities and challenges in data science. Storing, managing, standardizing, analyzing, sharing, and disseminating vast amounts of data are therefore critical priorities for NIH.

The *NIH Strategic Plan for Data Science*[180] provides a roadmap for modernizing and integrating the NIHfunded biomedical data ecosystem, which comprises the universe of data infrastructure, resources, tools, and workforce. Combining existing strengths with new strategic partnerships, NIH works to ensure that data resources are guided by the FAIR principles (Figure 21).[181,182] Implementing the *NIH Strategic Plan for Data Science* will enhance the scientific community's ability to address new challenges, maximize the value of data generated, and accelerate discoveries that lead to better health outcomes. Woven into this plan is NIH's commitment to rapid, open sharing of data and greater harmonization of data science efforts across research domains, while respecting participant privacy, security of sensitive data, and Tribal sovereignty with respect to data.

Bold Predictions

In the previous iteration of the *NIH-Wide Strategic Plan*, NIH set out 14 ambitious goals, or "Bold Predictions," for the next 5 years. These short-term predictions were considered aspirational goals for biomedical and behavioral research that were potentially within reach, but by no means guaranteed outcomes. The 14 Bold Predictions were not an exhaustive list of all of the potential avenues of success for NIH but were designed to illustrate some of the potential achievements in a wide range of research fields that might be possible under NIH's stewardship. NIH has made significant progress on all 14 Bold Predictions, with four being fully realized within the ambitious 5-year timeframe. Despite the risks associated with making short-term predictions, it is important that NIH continue to place high hopes on the ability for NIH-supported research to push the boundaries of innovation faster than ever before. Below are some of the outcomes that NIH will strive to deliver over the next 5 years.

1. The *All of Us* Research Program will reach its goal of 1 million diverse participants and will have gathered the most diverse collection of data (e.g., deep phenotypic, -omic, EHR, digital health technology) on 1 million or more participants of any research resource in the world.
2. The regular use of genomic information will have transitioned from boutique to mainstream in all clinical settings, making genomic testing as routine as complete blood counts.
3. Human studies on type 1 diabetes will assess the long-term survival and function of encapsulated human islets, as well as their efficacy in preventing or delaying the onset of complications and increasing overall survival.
4. Incorporating novel genomics findings from clinical studies on congenital heart disease will help researchers move toward precision therapy and personalized counseling, leading to improved outcomes and longevity for affected children and adults.
5. The high burden of heart disease in communities of color and rural areas will be reduced, especially for major outcomes, such as maternal morbidity and mortality, hypertension, and heart failure.
6. A gene therapy for muscular dystrophy will restore the function of the mutated gene and improve patient outcomes.
7. Gene-based therapies for SCD will be evaluated and refined in large-scale clinical trials, offering a cure to the approximately 100,000 people in the U.S. and 20 million globally who suffer severe pain and premature death from this condition.
8. First-in-human clinical trials will demonstrate the efficacy of iPSC-derived products.
9. Engineered biological cells and scaffolds will be successfully used to repair and replace tissue damaged by chronic wounds or such disorders as osteoarthritis.
10. Insight will be gained into the ultimate ability to regenerate human limbs, using emerging technologies to activate the body's own growth pathways and processes.
11. Research on new approaches to cervical cancer screening will lead to the development of self-sampling for women, with the potential to substantially reduce the incidence and mortality of this disease.
12. At least one novel, non-hormonal pharmacologic treatment for endometriosis will be identified and moved to clinical trials.
13. The number of maternal deaths per year in the U.S. will be significantly decreased, particularly among Black and American Indian or Alaska Native women, by implementing results of research studies focusing on links between social determinants and biological risk factors.
14. Following PRGLAC Task Force findings that almost no data exist on medications in pregnant and lactating women, label changes will be facilitated by results of clinical trials for at least three therapeutics specific to (1) pregnant women and lactating women and (2) children.
15. NIH-wide research will lead to new implementation strategies for pre-exposure prophylaxis that will significantly reduce the number of new HIV infections and to new longacting therapies to improve viral load suppression among people with HIV to levels that prevent transmission.

Bold Predictions (continued)

16. At least one candidate universal influenza vaccine against groups 1 and 2 with 75 percent efficacy will be submitted to the FDA for consideration.
17. NIH-supported researchers will develop a universal coronavirus vaccine.
18. By actively engaging with underserved populations to reduce disparities for COVID-19, researchers will prevent and curb the spread of COVID-19 and save lives.
19. AI will reveal molecular signatures associated with the return to health after an acute illness (e.g., COVID-19).
20. Biomarkers will guide the choice of the most effective therapy for each individual rheumatoid arthritis patient.
21. NIH-supported research will lead to the development of a clinically actionable biomarker for precision psychiatry, using neuroimaging and/or additional physiological and psychological biomarkers.
22. Comprehensive atlases of cell types in the mouse and human brain will provide a deeper understanding of the circuits underlying behavior and a foundation for understanding the circuits affected in complex human brain disorders, including depression.
23. Invasive and noninvasive human brain recording and stimulation technologies will enable new paradigms for interventions in movement disorders and neuropsychiatric diseases, as well as the development of brain-machine interfaces for sensory and motor neural prostheses.
24. Preventive approaches targeting vascular risk factors will reduce the risk for dementia and promote healthy brain aging.
25. At least one promising lifestyle intervention to prevent Alzheimer's disease and related dementias will be rigorously demonstrated in the next 5 years.
26. The role of cellular senescence in aging and disease will be clarified and translated into interventions to improve health.
27. Infant survival will be optimized by synthesizing milk that captures all of the components and properties of human milk, even individualizing it to the characteristics of the infant's mother.
28. NIH research will discover how technology exposure and media use affect developmental trajectories, health and educational outcomes, and parent–child interactions in childhood in the post-COVID-19 era.
29. NIH research will lead to optimized treatment for infants with Neonatal Opioid Withdrawal Syndrome.
30. NIH research will identify one promising intervention to mitigate risks of altered brain development trajectories produced by exposure to alcohol and other drugs among adolescents.
31. Increasing evidence of the effectiveness of nonpharmacologic treatments for pain will transform the way pain is managed and decrease the need for opioids and other medications.
32. Effective screening based on a person's genetics, environmental exposures, and sociobehavioral factors will significantly decrease the 9 million lives lost each year to global air pollution by identifying those who are most vulnerable for early intervention.
33. NIH and NASA will spearhead the development of a space-based platform that will monitor species diversity and predict geographic areas of climate concern.
34. The number of NIH R01 awards that support principal investigators from underrepresented racial and ethnic groups will be increased by 50 percent, and the racial funding disparities gap for NIH R01 grants will be eliminated by fiscal year 2025.
35. New forms of scientific communications, such as preprints, will accelerate clinical research and shorten the evidence-to-practice cycle.

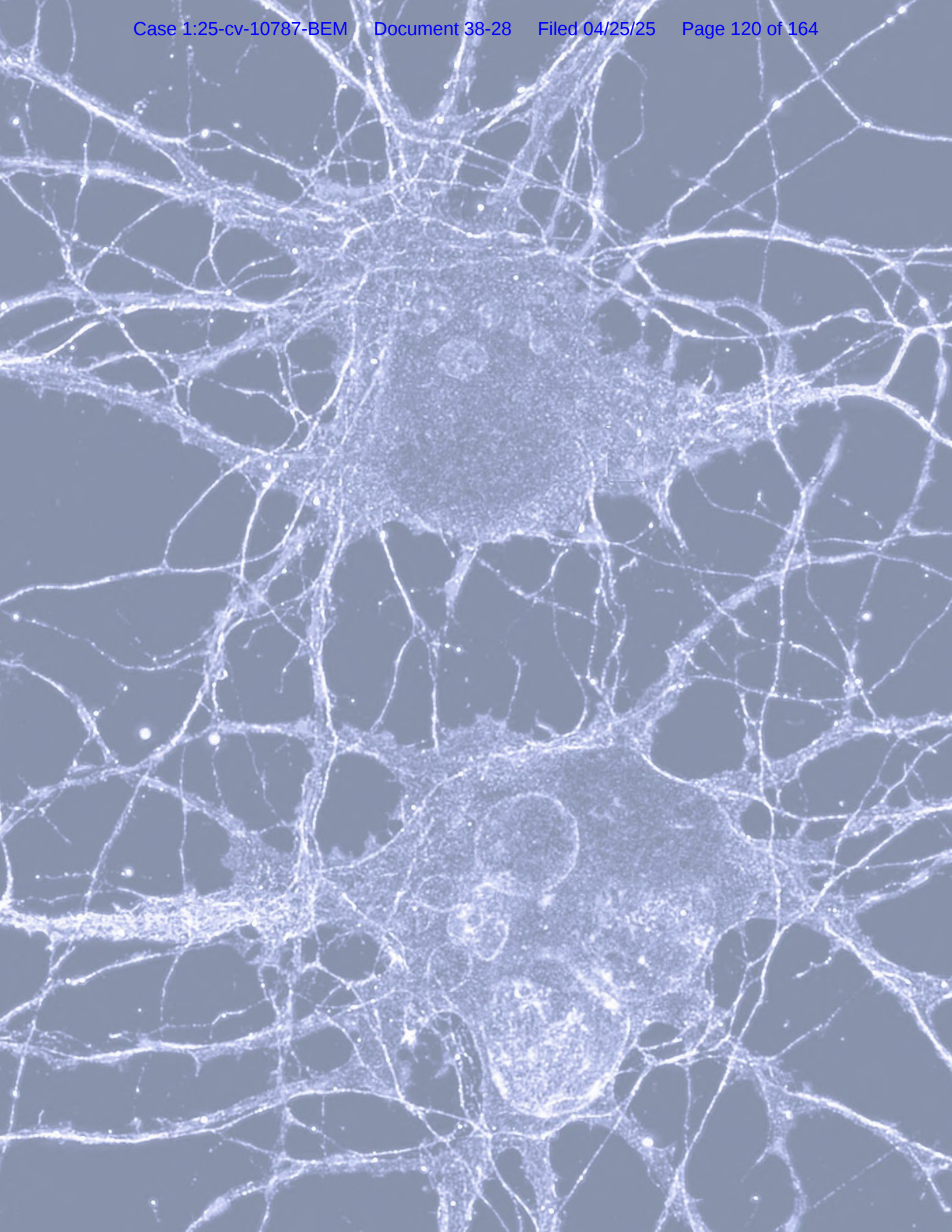
References

1 https://www.nih.gov/about-nih/what-we-do/mission-goals.
2 https://www.nih.gov/about-nih/who-we-are/organization.
3 https://www.nih.gov/about-nih/what-we-do/budget.
4 https://report.nih.gov/nihdatabook/category/10.
5 https://grants.nih.gov/grants/peer-review.htm.
6 https://grants.nih.gov/grants/peerreview22713webv2.pdf.
7 https://grants.nih.gov/funding/index.htm.
8 https://irp.nih.gov/about-us/what-is-the-irp.
9 https://irp.nih.gov/nih-clinical-center.
10 https://clinicalcenter.nih.gov/ocmr/research-discoveries.html.
11 Collins FS. NIH Basics. *Science*, 2012; 337:503. PMID: 22859455.
12 Moses H 3rd, et al. *JAMA*, 2015; 313(2):174-89. PMID: 25585329.
13 https://www.genome.gov/Funded-Programs-Projects/ENCODE-Project-ENCyclopedia-Of-DNA-Elements.
14 https://www.genome.gov/Funded-Programs-Projects/ClinGen-Clinical-Genome-Resource.
15 https://www.genome.gov/Funded-Programs-Projects/Human-Genome-Reference-Program#faq.
16 https://commonfund.nih.gov/hmp.
17 Elovitz MA, et al. *Nature Communications* 2019;10(1):1305. PMID 30899005.
18 Gehrig JL, et al. *Science* 2019;365(6449):eaau4732. PMID: 31296738.
19 Wilbert SA, et al. *Cell Rep*. 2020;30:4003-15.e3. PMID: 32209464.
20 https://www.cancer.gov/about-nci/budget/plan/immune-system-and-cancer.
21 Hand TW. et al. *Trends Endocrinol Metab* 2016;27(12):831-43. PMID: 27623245.
22 https://abcdstudy.org/about/.
23 Paulus MP, et al. *Neuroimage* 2019;185:140-53. PMID: 30339913.
24 Fine JD et al. *JAMA Psychiatry* 2019;76(7):762-4. PMID: 30916716.
25 Cheng W, et al. *Mol Psychiatry*, 2020. PMID: 32015467
26 https://braininitiative.nih.gov.
27 https://braininitiative.nih.gov/brain-programs/cell-census-network-biccn.
28 https://commonfund.nih.gov/singlecell.
29 https://commonfund.nih.gov/hubmap.
30 https://acd.od.nih.gov/documents/presentations/12132019AI.pdf.
31 Peng Y, et al. *Ophthalmology* 2019;126(4):565-75. PMID: 30471319.
32 Keenan TD, et al. *Ophthalmology* 2019;126(11):1533-40. PMID: 31358385.
33 https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-artificial-intelligence-based-device-detect-certain-diabetes-related-eye.
34 https://www.healthypeople.gov/2020/topics-objectives/topic/social-determinants-of-health.
35 Walsh JJ, et al. *Lancet Child Adolesc Health* 2018;2(11):783-91. PMID: 30268792.
36 Trinh MH, et al. *JAMA Pediatr* 2019;174(1):71-8. PMID: 31764966.
37 https://www.niaid.nih.gov/diseases-conditions/infographic-hiv-vaccine.
38 https://www.niaid.nih.gov/diseases-conditions/coronaviruses-therapeutics-vaccines.
39 https://www.nih.gov/news-events/news-releases/statement-nih-barda-fda-emergency-use-authorization-moderna-covid-19-vaccine.
40 Regules JA, et al. *N Engl J Med* 2017;376(4):330-41. PMID: 25830322.
41 https://www.who.int/csr/resources/publications/ebola/ebola-ring-vaccination-results-12-april-2019.pdf?ua=1.
42 https://www.cdc.gov/flu/about/burden/index.html.
43 https://www.niaid.nih.gov/diseases-conditions/universal-influenza-vaccine-research.
44 https://www.niaid.nih.gov/news-events/nih-begins-first-human-trial-universal-influenza-vaccine-candidate.
45 https://www.cdc.gov/nchs/data/nvsr/nvsr69/nvsr69-13-508.pdf.
46 https://www.cdc.gov/nchs/data/hestat/suicide/rates_1999_2017.pdf.
47 Boudreaux ED, et al. *Contemp. Clin. Trials* 2013;36(1):14-24. PMID: 23707435.
48 https://www.nhlbi.nih.gov/science/framingham-heart-study-fhs.
49 https://www.nhlbi.nih.gov/science/systolic-blood-pressure-intervention-trial-sprint-study.
50 SPRINT Research Group. *N Engl J Med* 2015;373(22):2103-16. PMID: 26551272.
51 Whelton PK, et al. *Hypertension* 2018;71(6):1269-324. PMID: 29133354.
52 Bress AP, et al. *Circulation* 2017;135(17):1617-28. PMID: 28193605.
53 Wang C, et al. *Nat Biomed Eng* 2018;2(9):687-95. PMID: 30906648.

54 https://allofus.nih.gov.
55 https://grants.nih.gov/grants/guide/pa-files/PAR-17-483.html.
56 https://orwh.od.nih.gov/sex-gender.
57 https://www.nih.gov/news-events/nih-research-matters/replacing-function-impaired-cystic-fibrosis-protein.
58 https://commonfund.nih.gov/hcscollaboratory.
59 https://pubmed.ncbi.nlm.nih.gov/29860917/.
60 https://www.cancer.gov/news-events/press-releases/2018/tailorx-breast-cancer-chemotherapy.
61 https://pubmed.ncbi.nlm.nih.gov/29385370/.
62 https://www.fda.gov/news-events/press-announcements/fda-approves-first-automated-insulin-delivery-device-type-1-diabetes.
63 https://www.fda.gov/news-events/press-announcements/fda-authorizes-first-interoperable-automated-insulin-dosing-controller-designed-allow-more-choices.
64 Bekiari E, et al. *BMJ* 2018; 361:k1310. PMID: 29669716.
65 http://www.braininitiative.nih.gov.
66 https://www.nei.nih.gov/learn-about-eye-health/resources-for-health-educators/eye-health-data-and-statistics/age-related-macular-degeneration-amd-data-and-statistics.
67 Sharma R, et al. *Sci Transl Med* 2019;11(475):eaat5580. PMID: 30651323.
68 https://www.nih.gov/news-events/news-releases/nih-launches-first-us-clinical-trial-patient-derived-stem-cell-therapy-replace-dying-cells-retina.
69 https://ncats.nih.gov/tissuechip/about/operations.
70 https://www.nih.gov/news-events/news-releases/nih-funded-tissue-chips-rocket-international-space-station.
71 https://www.niaid.nih.gov/clinical-trials/laboratory-infectious-diseases.
72 Mulangu S, et al. *N Engl J Med* 2019;381(24):2293-303. PMID: 31774950.
73 Dahlhamer J, et al. *MMWR Morb Mortal Wkly Rep* 2018;67(36):1001-6. PMID: 30212442.
74 https://www.cdc.gov/nchs/products/databriefs/db394.htm.
75 https://heal.nih.gov/.
76 https://www.niaid.nih.gov/clinical-trials/pact.
77 https://fnih.org/what-we-do/programs/partnership-for-accelerating-cancer-therapies.
78 Kennedy LB, Salama AKS. *CA Cancer J Clin* 2020;70(2):86-104. PMID: 31944278.
79 https://www.cdc.gov/ncbddd/sicklecell/data.html.
80 https://www.nih.gov/news-events/news-releases/nih-researchers-create-new-viral-vector-improved-gene-therapy-sickle-cell-disease.
81 https://scdic.rti.org/.
82 https://www.nhlbi.nih.gov/science/cure-sickle-cell-initiative.
83 https://grants.nih.gov/ngri.htm.
84 https://www.nlm.nih.gov/ep/GrantTrainInstitute.html.
85 https://orwh.od.nih.gov/career-development-education/building-interdisciplinary-research-careers-womens-health-bircwh.
86 https://www.nigms.nih.gov/training/careerdev/Pages/MOSAIC.aspx.
87 https://commonfund.nih.gov/diversity.
88 https://acd.od.nih.gov/documents/presentations/06132019Diversity.pdf.
89 https://dpcpsi.nih.gov/sites/default/files/CoC_Jan_2020_1115_FIRST_program_concept_clearance.pdf.
90 https://www.sciencemag.org/news/2020/01/nih-s-new-cluster-hiring-program-aims-help-schools-attract-diverse-faculty.
91 https://diversity.nih.gov/programs-partnerships/dsp.
92 https://womeninscience.nih.gov/.
93 https://www.fic.nih.gov/Programs/Pages/infectious-disease.aspx.
94 https://commonfund.nih.gov/CryoEM.
95 https://heal.nih.gov/about/public-access-data.
96 https://dash.nichd.nih.gov/.
97 https://vizhub.healthdata.org/gbd-compare/.
98 https://seer.cancer.gov/.
99 https://www.nimhd.nih.gov/programs/extramural/research-centers/rcmi/index.html.
100 https://grants.nih.gov/grants/guide/rfa-files/RFA-MD-20-006.html.
101 https://ncats.nih.gov/ctsa.
102 https://grants.nih.gov/grants/guide/notice-files/NOT-TR-19-015.html.
103 https://grants.nih.gov/grants/guide/notice-files/NOT-TR-19-016.html.
104 https://ncats.nih.gov/ctsa/projects/RuralHealth.
105 https://echochildren.org/idea-states-pediatric-clinical-trials-network.
106 https://orip.nih.gov/construction-and-instruments/s10-instrumentation-programs.
107 https://commonfund.nih.gov/moleculartransducers/overview.
108 https://motrpac-data.org/.

109 https://www.ninr.nih.gov/newsandinformation/pressreleases/press-release-symptom-science-center.
110 https://www.hhs.gov/about/strategic-plan/index.html.
111 https://report.nih.gov/reports/strategic-plans.
112 https://grants.nih.gov/grants/peer-review.htm.
113 https://public.csr.nih.gov/StudySections/CSREnquire.
114 https://public.csr.nih.gov/ForReviewers/BecomeAReviewer/ECR.
115 https://projectreporter.nih.gov/.
116 https://report.nih.gov/nihdatabook/.
117 https://report.nih.gov/.
118 https://icite.od.nih.gov/.
119 https://federalreporter.nih.gov/.
120 https://gcn.com/articles/2018/12/03/nsf-blockchain.aspx.
121 https://smrb.od.nih.gov/documents/reports/VOBR SMRB Report 2014.pdf.
122 https://www.congress.gov/bill/115th-congress/house-bill/4174.
123 https://www.nih.gov/news-events/news-releases.
124 https://directorsblog.nih.gov/.
125 https://www.nih.gov/about-nih/what-we-do/impact-nih-research/our-stories.
126 https://pubmed.ncbi.nlm.nih.gov/.
127 https://www.nlm.nih.gov/news/NLMAnnouncesNewPubMed_202002.html.
128 https://www.ncbi.nlm.nih.gov/pmc/.
129 https://www.semanticscholar.org/cord19.
130 https://icite.od.nih.gov/covid19/search/.
131 https://registry.opendata.aws/ncbi-covid-19/.
132 https://prevention.nih.gov/tobacco-regulatory-research.
133 https://pathstudyinfo.nih.gov/landing.
134 https://prevention.nih.gov/tobacco-regulatory-research/funded-research/funded-research-tobacco-centers-regulatory-science.
135 https://www.iprcc.nih.gov/.
136 http://painmanagementcollaboratory.org/.
137 https://www.nichd.nih.gov/about/advisory/PRGLAC.
138 https://www.nih.gov/research-training/medical-research-initiatives/activ.
139 https://www.nih.gov/research-training/accelerating-medicines-partnership-amp.
140 https://www.nih.gov/news-events/news-releases/nih-public-private-partnership-advance-early-interventions-schizophrenia.
141 https://cloud.nih.gov/.
142 https://www.afrehealth.org/.
143 https://www.fic.nih.gov/Programs/Pages/african-association-health-professions.aspx.
144 https://www.fic.nih.gov/Programs/Pages/health-professional-education-partnership-initiative-hepi.aspx.
145 https://h3africa.org/.
146 https://www.fic.nih.gov/Funding/Pages/collaborations-gacd.aspx.
147 https://www.niehs.nih.gov/research/programs/disaster/index.cfm.
148 https://www.nih.gov/news-events/news-releases/nih-facilitates-first-tribal-data-sharing-agreement-navajo-nation.
149 https://echochildren.org/nih-echo-and-the-navajo-nation-make-history-with-new-data-sharing-and-use-agreement/.
150 https://www.acd.od.nih.gov/working-groups/eprar.html.
151 https://grants.nih.gov/policy/clinical-trials.htm.
152 https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-final-nih-policy-data-management-sharing.
153 https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-013.html.
154 https://www.acd.od.nih.gov/working-groups/sexual-harassment.html.
155 https://www.nih.gov/anti-sexual-harassment.
156 https://grants.nih.gov/grants/policy/harassment.htm#:~:text=Anti-Sexual.
157 https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-124.html.
158 https://diversity.nih.gov/building-evidence/harassment-survey.
159 https://grants.nih.gov/policy/natural-disasters.htm.
160 https://grants.nih.gov/policy/natural-disasters/corona-virus.htm.
161 https://grants.nih.gov/policy/protecting-innovation.htm.
162 https://nexus.od.nih.gov/all/2019/07/11/clarifying-long-standing-nih-policies-on-disclosing-other-support/.
163 https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-protecting-integrity-us-biomedical-research.
164 https://nexus.od.nih.gov/all/2020/07/08/addressing-foreign-interference-and-associated-risks-to-the-integrity-of-biomedical-research-and-how-you-can-help/.

165 https://nexus.od.nih.gov/all/2019/08/05/linking-orcid-identifiers-to-era-profiles-to-streamline-application-processes-and-to-enhance-tracking-of-career-outcomes/.
166 https://www.nap.edu/read/25483/.
167 https://www.healthypeople.gov/2020/topics-objectives/topic/social-determinants-health/interventions-resources/discrimination.
168 https://www.nimhd.nih.gov/about/overview/research-framework.html.
169 https://www.nimhd.nih.gov/about/overview/strategic-plan.html.
170 https://www.nimhd.nih.gov/about/overview/strategic-plan.html.
171 https://dpcpsi.nih.gov/file/sgm-strategic-plan-2021-2025.
172 https://orwh.od.nih.gov/sites/orwh/files/docs/ORWH_Strategic_Plan_2019_02_21_19_V2_508C.pdf.
173 https://orwh.od.nih.gov/about/trans-nih-strategic-plan-womens-health-research.
174 https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-102.html.
175 https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-014.html.
176 https://clinicaltrials.gov/.
177 https://report.nih.gov/categorical_spending.aspx.
178 https://grants.nih.gov/policy/inclusion/lifespan.htm.
179 https://covid19.nih.gov/nih-strategic-response-covid-19.
180 https://datascience.nih.gov/strategicplan.
181 https://www.go-fair.org/fair-principles/.
182 Wilkinson MD, et al. *Sci. Data* 2016;3:19. PMID: 26978244.



Appendix I: NIH Statutory Authority

Begun as a one-room Laboratory of Hygiene in 1887 (renamed the Hygienic Library in 1891), the National Institutes of Health (NIH) today is one of the world's foremost medical research centers. An agency of the U.S. Department of Health and Human Services, NIH is the federal focal point for health research. The Statutory Authority granted to NIH generally appears in Title IV of the *Public Health Service (PHS) Act*, 42 U.S.C. 281 et seq. This authority has a long history with many revisions and additions granted by new legislation over the years. Below are several highlights from the legislative history of NIH.

The Ransdell Act, P.L. 71–251

On May 26, 1930, the *Ransdell Act* reorganized, expanded, and redesignated the Hygienic Laboratory of the Public Health Service as the National Institute of Health (NIH), authorizing $750,000 for construction of two buildings for NIH and creating a system of fellowships.

The Public Health Service Act, P.L. 78–410

On July 1, 1944, the *PHS Act* (P.L. 78—410) consolidated and revised existing public health legislation, dividing the PHS into the Office of the Surgeon General, the Bureau of Medical Services, the Bureau of State Services, and NIH. The *PHS Act* gave NIH the legislative basis for its postwar program, with general authority to conduct and support research into the diseases and impairments of man, authorized research projects and fellowships, and made the National Cancer Institute a division of NIH.

The National Heart Act of 1948, P.L. 80–655

On June 16, 1948, the *National Heart Act of 1948* amended the *PHS Act* and authorized the National Heart Institute and changed the name of the National Institute of Health to National Institutes of Health.

The Public Health Improvement Act, P.L. 106–505

On November 13, 2000, the *Public Health Improvement Act* amended the *PHS Act* and provided new authorities to NIH and other PHS agencies and placed ongoing activities or programs in statute.

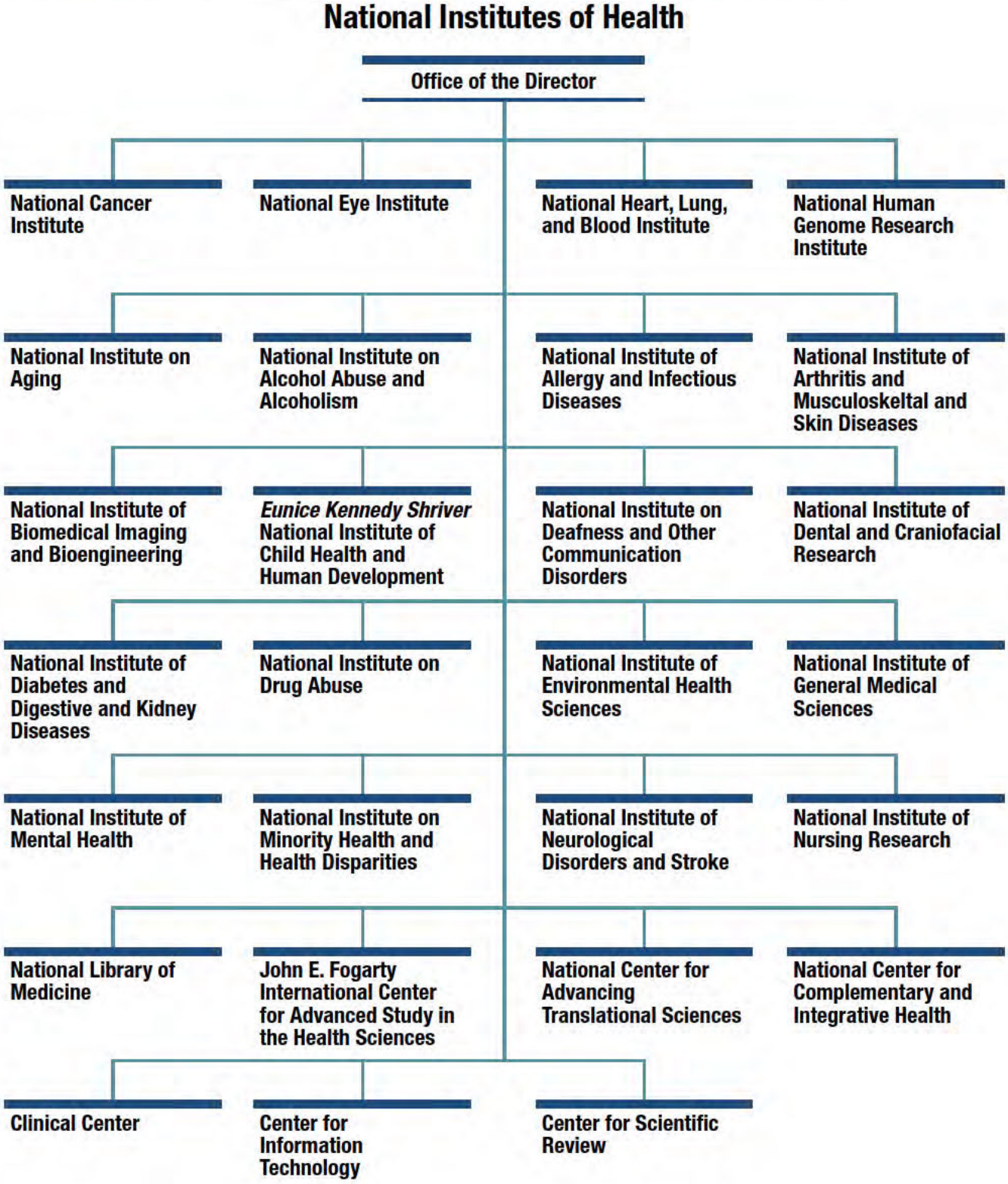
The National Institutes of Health Reform Act of 2006, P.L. 109–482

On January 15, 2007, the *NIH Reform Act of 2006* affirmed the importance of NIH and its vital role in advancing biomedical research to improve the health of the nation. The law reinforced how NIH's 27 Institutes and Centers, along with various other NIH components, work together on the nation's largest medical research enterprise. Among its provisions, the *NIH Reform Act* revised Title IV of the *PHS Act* to create the Division of Program Coordination, Planning, and Strategic Initiatives, to be supported by a Common Fund.

The 21st Century Cures Act, P.L. 114–255

On December 13, 2016, the *21st Century Cures Act* provided NIH with critical tools and resources to advance biomedical research across the spectrum, from foundational basic research studies to advanced clinical trials of promising new therapies. The Cures Act provided NIH with important new authorities that could be employed to hasten its mission to improve the health of Americans.

Appendix II: NIH Organizational Chart



Appendix III: Strategic Planning Process

The National Institutes of Health (NIH)-Wide Strategic Plan outlines NIH's research priorities and how these priorities align with the agency's mission and goals in an evolving research landscape. It represents one facet of NIH's stewardship of federal dollars and contributes to maintaining transparency and accountability to its many stakeholders.

Biomedical and behavioral science is progressing rapidly. To keep pace and capitalize on scientific advances while addressing evolving public health needs, NIH updates the NIH-Wide Strategic Plan every 5 years. The NIH-Wide Strategic Plan is a living document, with each iteration building off the foundation of the previous plan and aligning with the agency's near-, mid-, and long-range goals. This latest iteration of the NIH-Wide Strategic Plan, covering fiscal years 2021–2025, retains many of the core elements of the NIH-Wide Strategic Plan for fiscal years 2016–2020. However, the Strategic Plan has been revised, updated, and expanded in response to the many discoveries and changes in the field made during the past 5 years. As part of this process, the Framework around which the Strategic Plan is organized has also been revised.

In September 2019, NIH began updating the NIH-Wide Strategic Plan to cover fiscal years 2021–2025. The goal was to follow a process that was transparent, focused on science and good stewardship of research, guided by evidence, and informed by NIH's many stakeholders.

The strategic planning process entailed four phases: (1) pre-planning, (2) gathering internal input and development of the Strategic Plan framework, (3) gathering input from external stakeholders, and (4) drafting and publishing the Strategic Plan. The following are key activities undertaken during these four phases.

Pre-Planning

The NIH Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) within the Office of the Director (OD), coordinated the development of the NIH-Wide Strategic Plan for fiscal years 2021–2025. At the initiation of this process, DPCPSI developed a timeline for the strategic planning process and established an internal NIH-Wide Strategic Plan Working Group, composed of staff from each Institute and Center (IC) and OD Office, representing the range of NIH's activities and research portfolio. The first Working Group meeting was held at the end of September 2019.

Gathering Internal Input and Development of the Strategic Plan Framework

From October to December 2019, the Working Group met biweekly to develop the Framework for the Strategic Plan, which outlines, at a high level, NIH's priorities for biomedical and behavioral research that will be addressed over the next five years. The Framework of the NIH-Wide Strategic Plan for fiscal years 2016-2020 was used as a starting point, and the Framework for the new Strategic Plan evolved over several meetings. The proposed framework was reviewed by the IC Directors at the end of October, the Advisory Committee to the NIH Director in December, and the DPCPSI Council of Councils in January 2020. The final Framework was approved by NIH Leadership.

In parallel with development of the Framework, ICs and OD Offices were asked to provide information on biomedical and behavioral research advances that have been made under the NIH-Wide Strategic Plan for fiscal years 2016–2020 and proposed activities that will be conducted during the next 5 years. The Working Group reviewed the content provided and, through an iterative process of voting and deliberation, proposed for NIH Leadership's approval the top NIH-wide accomplishments and priorities for each section of the Framework.

Gathering Input from External Stakeholders

NIH recognizes that input from external stakeholders—including members of the scientific and health care communities, professional societies, advocacy organizations, industry, other federal agencies, and

the general public—provides valuable insight to be considered during its strategic planning process.

To solicit comments on the proposed Framework from external stakeholders, the Working Group developed a Request for Information (RFI) in the NIH Guide (NOT-OD-20-064[1]) and the *Federal Register* (FRN 2020-02919[2]), which was advertised broadly. Comments were accepted online from February 12, 2020, to April 1, 2020. NIH received 160 responses to the RFI from external stakeholders. In addition, NIH hosted two webinars on March 9 and 16, 2020, to provide the opportunity for stakeholders to ask questions on the Strategic Plan development process and comment on the Framework. A summary of RFI responses, the webinar slides, and transcript, will be made available on the NIH-Wide Strategic plan webpage.[3]

Drafting and Publishing the Strategic Plan

In January 2020, the Working Group began drafting the Strategic Plan based on the Framework and the prioritized content approved by NIH Leadership. As it became available from the RFI and webinars, the Working Group reviewed public feedback on the Framework and adjusted the draft Strategic Plan in response to this input.

Finalizing and Publishing the Strategic Plan

The draft Strategic Plan was finalized through an iterative review process with NIH Leadership. Beginning in July 2020, the draft Strategic Plan was reviewed by IC and OD Office Directors, and subsequently by the NIH Director and Deputy Director. It was then reviewed by the DPCPSI Council of Councils and the Advisory Committee to the NIH Director. Following final review and approval by the NIH Director and Deputy Director, and subsequent sign off by the U.S. Department of Health and Human Services, the final version of the NIH-Wide Strategic Plan for fiscal years 2021–2025 was posted publicly on NIH's website and widely disseminated to NIH stakeholders.

Endnotes

1 https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-064.html
2 https://www.federalregister.gov/documents/2020/02/13/2020-02919/request-for-information-rfi-inviting-comments-and-suggestions-on-a-framework-for-the-nih-wide
3 https://www.nih.gov/about-nih/nih-wide-strategic-plan

Appendix IV: NIH Common Fund Strategic Plan Report

About the NIH Common Fund

The National Institutes of Health (NIH) Common Fund[1] programs represent time-limited, strategic investments in biomedical and behavioral research (collectively referred to as *biomedical research* in the remainder of this appendix) designed to achieve high-impact goals and catalyze discovery. Approximately 30 multidisciplinary scientific programs are supported by the NIH Common Fund, spanning NIH's mission and addressing challenges and opportunities that are of high priority for NIH as a whole. These bold scientific programs often accelerate emerging science, enhance the biomedical research workforce, remove research roadblocks, or support high-risk, high-reward science. NIH Common Fund programs frequently produce resources—such as datasets, tools, technologies, or methods—that are designed to spur subsequent biomedical advances often not possible otherwise. The work supported by the NIH Common Fund is inherently risky, but this risk is embraced because of the potential for transformative impact in advancing science and, ultimately, improving human health.

The origins of the NIH Common Fund lie in the NIH Roadmap for Medical Research, which was launched in 2004. The *NIH Reform Act of 2006* created the NIH Common Fund as a source of support for these transformative, NIH-wide programs within the NIH Office of the Director (OD). This established a novel approach to support crosscutting, NIH-wide programs in areas of emerging scientific opportunities, rising public health challenges, and knowledge gaps that deserved special emphasis or would otherwise benefit from strategic planning and coordination. The Act also mandated an emphasis on goals and milestones in NIH Common Fund programs and directed NIH to encourage participation by early-career researchers.

The Office of Strategic Coordination (OSC) within the NIH Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) is responsible for managing the NIH Common Fund. OSC coordinates teams across NIH who collectively plan, implement, and oversee each program to ensure broad impact. Individual awards supported through the NIH Common Fund are administered in partnership with NIH Institutes and Centers (ICs).

About the NIH Common Fund Strategic Plan Report

The *Public Health Service Act* requires, as part of the NIH-Wide Strategic Plan, that the NIH Director submit a report to Congress containing a strategic plan for funding research "that represents important areas of emerging scientific opportunities, rising public health challenges, or knowledge gaps that deserve special emphasis and would benefit from conducting or supporting additional research that involves collaboration between two or more national research institutes or national centers, or would otherwise benefit from strategic coordination and planning" through the NIH Common Fund (42 U.S.C. §282a(c)(1)(C); 282(b)(7)(A)(i)).

NIH Common Fund Program Lifecycle

The congressional mandate to support goal- and milestone-driven programs underlies a critical feature of NIH Common Fund programs: Each program establishes high-impact goals that are expected to be achieved within a maximum of 10 years. This program enables new needs or opportunities to be supported as they emerge. The NIH Common Fund supports research programs that transcend the scientific boundaries of the individual ICs, are synergistic with current IC-funded research, and would benefit from limited-term NIH Common Fund investment. These programs are identified through a strategic planning process that includes input from many stakeholders who first identify broad scientific areas that are priorities for NIH as a whole and subsequently establish a focused strategy for scientific initiatives that will catalyze progress within that area. This process ensures that the programs provide maximum utility to the

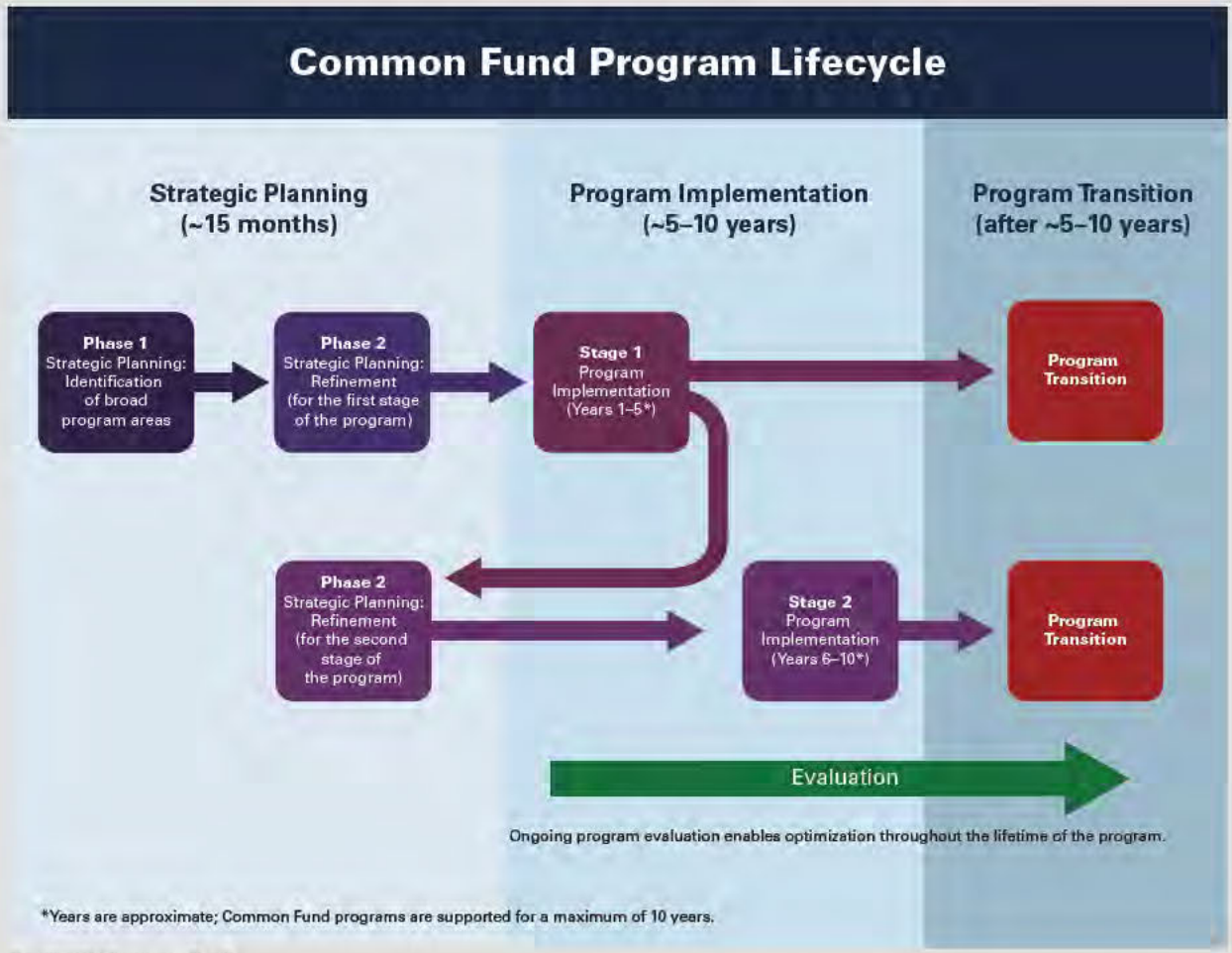
broad biomedical community and that they address major roadblocks to research progress. At the completion of each program, the tools, technologies, and data produced by the program are taken up and used by the community at large, and the infrastructure that the NIH Common Fund has built transitions to other sources of support. The lifecycle of a NIH Common Fund program is shown in Figure 29.

NIH Common Fund strategic planning is a two-phase process. Phase 1 of strategic planning identifies broad areas that are high priorities for NIH and for which transformational progress can be envisioned. Phase 2 of strategic planning involves analysis of the scientific landscape within a given field to identify the specific challenges and opportunities for progress. Programmatic goals are established, with a series of funding initiatives collectively designed to achieve those goals. The strategic planning process is described in more detail in the next section, "NIH Common Fund Strategic Planning Process."

Following strategic planning and selection of new program areas, research projects addressing goals and milestones identified during the planning process are supported through a variety of funding mechanisms. Awards are often implemented as partnerships among the many scientific investigators supported by a program and expert NIH staff, collaboratively working together to achieve defined goals. NIH Common Fund programs are actively managed to ensure that the output of each program is maximally useful to the broader scientific community. Assessment of the utility of the program to the community is emphasized and is achieved through a variety of evaluative processes.

Figure 29. Lifecycle of NIH Common Fund Programs

"Common Fund Program Lifecycle": Infographic. Note that not all programs follow this exact timeline.



Credit: NIH Common Fund.

Evaluation is an ongoing activity throughout the lifecycle of the program and includes both formal and informal evaluative activities. Informal evaluation involves convening grantees and NIH-wide teams to review progress, discuss new challenges, and develop strategies to adapt as part of routine program management. It also involves gathering input from external consultants and using their input, together with internal analysis, to help guide the implementation of the program. Formal evaluations involve the development of baseline data for new programs and the development of multiple metrics of outcomes. The utility of data, resources, technologies, and other program outputs is assessed through surveys, expert opinion, and the analysis of bibliometric data, such as citation analyses. Challenges and opportunities to strengthen each program are considered continuously, but this assessment is also done systematically for every program on an annual basis. This management process ensures that the programs stay on track toward their stated goals while also allowing adjustments to ensure that the impact of each program is maximized.

Another ongoing activity for the NIH Common Fund is the support of infrastructure designed to maximize the accessibility and utility of NIH Common Fund datasets and digital resources. To this end, the NIH Common Fund Data Ecosystem (CFDE)[2] is working to ensure all NIH Common Fund datasets are findable, accessible, interoperable, and reusable (FAIR), providing training for users to operate on data in a cloud environment and ensuring that NIH Common Fund data continue to be available after individual programs are completed. For more information on the CFDE, see Figure 30.

The final stage of NIH Common Fund support involves the transition of mature programs to other sources of support or use within the scientific community.

Although represented as sequential activities, the management of each program has an iterative nature. Plans for implementation and transition are considered early in the lifecycle but may be adapted in response to the science. Similarly, scientific progress may demand changes in the strategic plan, as new opportunities or challenges are identified. Nevertheless, early consideration of implementation and transition ensures that program goals and milestones are established to meet the needs identified during strategic planning and to provide a sustainable model for continued use by the scientific community when NIH Common Fund support for a program has ended.

Figure 30. NIH Common Fund Data Ecosystem

NIH Common Fund programs are intended to provide resources that accelerate discovery across many different biomedical research fields. Often these resources include large datasets and associated digital tools needed to mine and analyze the data. To maximize impact, these datasets and tools must be leveraged by researchers from different disciplines, using varying expertise in bioinformatics and large-scale data analysis. Additionally, these datasets must be usable together across interoperable platforms. However, current approaches to data storage, management, and analysis mean that data are often not findable, accessible, interoperable, and reusable (FAIR).

To address this challenge, the NIH Common Fund is supporting the NIH Common Fund Data Ecosystem (CFDE), an ongoing investment in data management infrastructure that will support past, current, and future NIH Common Fund datasets.

The CFDE includes several integrated efforts:

- **CFDE Coordinating Center**—The Coordinating Center will manage and organize CFDE activities, engage with participating NIH Common Fund programs, connect with user communities, support training, develop tools and standards, and provide technical expertise.
- **Participating NIH Common Fund Data Coordinating Centers**—These Centers will work with the CFDE Coordinating Center to understand its program's unique requirements for data storage and analysis, adopt/adapt guidelines and best practices, share resources and tools, establish and enable use cases for cross-data analyses, and provide training.
- **Leveraging NIH-wide cloud service provider partnerships**—Using the Science and Technology Research Infrastructure for Discovery, Experimentation, and Sustainability (STRIDES) will ensure that data are onboarded to the cloud in a consistent manner and provide favorable pricing for cloud data storage and use.

Ultimately, the CFDE is intended to amplify the impact of many NIH Common Fund programs by enabling researchers to interrogate multiple disparate datasets and thereby make new kinds of scientific discoveries that were not possible before.

NIH Common Fund Strategic Planning Process

Strategic planning for the NIH Common Fund involves the identification of NIH-wide challenges and opportunities that meet NIH Common Fund program criteria[3] (Figure 31). It is designed to be flexible from year to year to adapt to emerging opportunities, the changing needs of the scientific community, and the availability of funds. Broad topics identified in Phase 1 are refined into well-defined programs and initiatives in Phase 2.

Figure 31. NIH Common Fund Program Criteria

Transformative: **Programs must have high potential to dramatically affect biomedical research.**

Catalytic: **Programs must achieve a defined set of high-impact goals within a defined period of time.**

Synergistic: **Outcomes must synergistically promote and advance individual missions of ICs to benefit health.**

Crosscutting: **Program areas must cut across missions of multiple ICs, be relevant to multiple diseases or conditions, and require a coordinated approach across NIH.**

Unique: **Programs must be something no other entity is likely or able to do.**

Phase 1 identifies broad scientific needs and opportunities, focusing on the greatest challenges to research discovery and translation, as well as on the most promising emerging opportunities to catalyze research across a variety of scientific disciplines and disease conditions. Although specific Phase 1 activities vary, ideas may be gathered through meetings with external scientific experts, solicitation of ideas from ICs, discussions with NIH Leadership and Advisory Committees, and engagement with the broader scientific community.

To effectively evaluate the responsiveness of the proposed idea to NIH Common Fund criteria, as well as the potential impact of the program, the following questions are typically posed:

- What is the greatest opportunity in biomedical research today? How can this opportunity be realized?
- Why is now the right time for this idea (i.e., why is this idea timely)?
- What would be the goals of the program, and what initiatives or activities are envisioned to achieve these goals?

Generally, Phase 1 strategic planning activities generate many more ideas than can be supported. Ideas are prioritized by the NIH Director, with input from the OSC, DPCPSI, and Principal Deputy Directors. IC Directors may also provide input to the NIH Director on prioritization of concepts. A small subset of prioritized ideas then moves into Phase 2 planning.

Phase 2 refines the prioritized set of broad ideas identified in Phase 1 into specific, well-defined initiatives. An NIH-wide Working Group representing a broad range of interested scientific communities is formed to continue the planning process and, if the program is approved, lead program implementation. Phase 2 strategic planning also occurs before decisions are made to provide a second stage of support for existing programs. OSC assesses the progress of NIH Common Fund programs at the end of the first stage of funding to determine whether a second stage of funding (up to a limit of 10 years total) is necessary to reap maximum benefit from the program. The Phase 2 refinement process includes analysis of NIH and external scientific research portfolios (Figure 32), solicitation of input from subject-matter experts, and input from IC Directors.

During Phase 2 planning, the DPCPSI Council of Councils (CoC)[4] provides input about whether the proposed idea addresses the NIH Common Fund criteria and, if so, whether the proposed program initiatives are likely to achieve the program goals and produce the highest possible impact. When the concept for a potential new program is cleared by the CoC, the Working Group develops a program proposal that clearly describes scientific needs, gaps, and opportunities; goals and milestones of the proposed program; description of program management; and a budget for all years of the program. Program proposals are presented to the NIH Director for a final decision about program approval.

Figure 32. Portfolio Analysis: Focusing Scope and Identifying Opportunities

Portfolio analysis occurs during Phase 2 of the strategic planning process. It is a vital part of strategic planning that provides critical information concerning ongoing efforts in areas being considered as potential NIH Common Fund programs. Portfolio analysis helps identify specific areas where strategic investment by the NIH Common Fund could support unique and potentially transformative research.

The Somatic Cell Genome Editing (SCGE) program, launched in fiscal year 2018, included a robust portfolio analysis during the planning process to identify specific activities in support of the program's overall goal to advance therapeutic use of precision genome editing approaches to treat or cure numerous diseases caused by genetic mutations. With the discovery of CRISPR and similar tools that can precisely change genetic sequences, this field experienced an explosion of interest. However, remaining gaps in research investment were holding back the translation of genome editing approaches into the clinic, especially for rare or uncommon diseases. Information on private-sector and other government agency investment was provided by consultation with experts, complementing the SCGE portfolio analysis that assessed NIH investment in genome editing tools and technologies in fiscal year 2016. This analysis identified critical gap areas, including gene editing reporter systems and in vitro models for testing efficacy and safety. Additionally, the analysis demonstrated a pressing need to develop new genome editing tools that were less likely to produce adverse or off-target effects. Furthermore, the analysis revealed that current investment in genome editing delivery vehicles was highly focused on a single viral vector (adeno-associated virus, or AAV) with inherent limitations. Other delivery systems—such as nanoparticles, alternative viruses, ribonucleoprotein complexes, and exosomes—were largely overlooked, despite representing potentially transformative approaches to overcoming limitations associated with AAVs.

The results of this portfolio analysis, combined with expert input, identified areas of scientific opportunity that became the basis of the SCGE program initiatives. These initiatives include (1) developing animal models for testing genome editing tools; (2) generating assays and models to test the efficacy and safety of genome editing tools; (3) improving genome editing delivery systems—including a wide range of delivery systems beyond AAVs—to target specific cells and tissues; (4) expanding the number and types of genome editing complexes; and (5) distributing the knowledge and resources developed through this program to the scientific community.

A follow-up analysis conducted in 2020 confirmed that the SCGE program is stimulating research in gap areas identified in the baseline portfolio analysis. This analysis showed that the SCGE program is filling an important niche by supporting research on exploring the use of exosomes, nanoparticles, and ribonucleoproteins as delivery vehicles. The analysis also revealed that the SCGE program is developing genome editing tools that target a wide range of tissues and organs, including one organ system (the gastrointestinal tract) that is not targeted by any other NIH-supported genome editing projects, as well as other several tissues or organs for which SCGE projects are the only ones using non-AAV delivery systems for targeted delivery.

Strategic Planning Activities Since 2015

Prior to the passage of the *21st Century Cures Act*,[5] the NIH Common Fund developed a biennial strategic planning report. With the passage of this Act, the NIH Common Fund Strategic Planning Report is now included within the NIH-Wide Strategic Plan. Described here are the strategic planning activities that have taken place since the last NIH Common Fund Strategic Planning Report in 2015.[6]

Strategic Planning 2015–2016

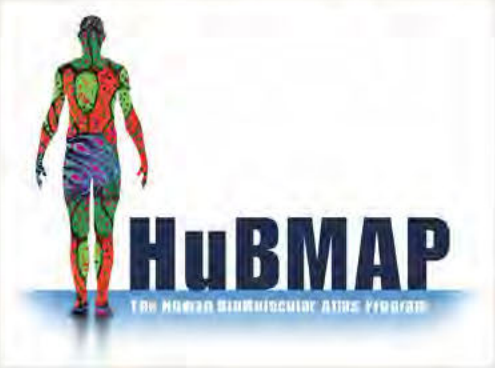
In 2015, OSC held the "Innovate to Accelerate" 2-day strategic planning workshop that brought together more than 20 innovative thinkers representing diverse areas of expertise to brainstorm ideas for potential new NIH Common Fund programs beginning in fiscal year 2018 or later. Following the workshop, all ideas that emerged from the workshop were posted in an online discussion forum, where an additional cohort of approximately 300 selected scientific experts were invited to view ideas, provide comments and suggestions, and submit one original idea for inclusion in the online discussion. All ideas and associated discussions were considered along with ideas submitted by IC Directors.

From these activities, two ideas were prioritized for further planning and ultimately were launched in fiscal year 2018:

- Human BioMolecular Atlas Program (HuBMAP)[7] (Figure 33)—The planning process that led to the HuBMAP program identified understanding human physiology and disease at the level of individual cells as a challenge that we now have the technologies to address. Because the cell is the fundamental unit of the human body, an understanding of normal and disease processes at this level is anticipated to lead to more specific and effective therapies. In recent years, technologies that enable the analysis of single

Figure 33. Human BioMolecular Atlas Program

The Human BioMolecular Atlas Program is a collaborative effort to develop an open and global platform to map healthy cells in the human body.



Credit: NIH Common Fund.

cells within the context of the tissues have made the goals of HuBMAP feasible. However, this challenge is enormous, given that the human body has approximately 37 trillion cells. HuBMAP is developing an open and global platform to map healthy cells in the human body, coordinating with other international efforts. Capitalizing in part upon the foundation laid by the NIH Common Fund's Single-Cell Analysis Program,[8] HuBMAP is building the framework needed to construct cell atlases, tools, and resources to understand the function of and relationship among all the cells in the human body. This understanding is expected to lead to new insights into human health, growth, development, aging, and disease.

- Transformative High Resolution Cryo-Electron Microscopy (CryoEM)[9]—Improvements in cryoEM technologies and new computational methods to analyze the associated data have created a transformative opportunity in structural biology. With these new methods, investigators can analyze protein structures more easily than ever before, providing the basis for smart drug design and fundamental biological insights. However, the high cost of required equipment and limited workforce proficient in this technology represent a substantial challenge. The CryoEM program addresses this challenge. It is broadening access to high-resolution cryoEM for biomedical researchers by creating national service centers and cultivating a skilled cryoEM workforce by developing and implementing cryoEM training materials. By expanding access and training for cryoEM, this program aims to enable research and accelerate development of drugs and vaccines to combat many diseases and conditions.

In addition to launching new programs, several existing NIH Common Fund programs underwent planning for a second stage of support that began in fiscal year 2018. These programs are described below:

- Illuminating the Druggable Genome (IDG)[10] (Figure 34)—Most drugs target proteins within four families: G protein–coupled receptors, nuclear receptors, ion channels, and protein kinases. However, only a small number of proteins within each of these families are well studied, and these proteins typically are present in many cells throughout the body. Therefore, drugs that target these proteins may cause widespread adverse effects in cells and tissues that are not affected by disease. However, the lesser known members of these protein families may be present in fewer tissues and thus have potential as specific drug targets leading to fewer side effects. Technological advances in genomics, protein characterization, and computational methods provide an opportunity to identify and study large numbers of unknown proteins. IDG originally launched a pilot stage in fiscal year 2014 to compile data about the uncharacterized proteins within the four protein classes that are most frequently targeted by drugs. In the second stage, implementation, IDG is capitalizing on the information gathered and technologies developed in the pilot to further elucidate the

Figure 34. Illuminating the Druggable Genome Program

The goal of the Illuminating the Druggable Genome program is to compile data about the uncharacterized proteins within the four protein classes that are most frequently targeted by drugs.

Credit: NIH Common Fund.

function of uncharacterized proteins within three key families: G protein–coupled receptors, ion channels, and protein kinases. IDG is also expanding the informatics tools developed in the pilot stage and disseminating the IDG-generated resources to the biomedical research community.

- Metabolomics[11]—Chemical reactions in the body produce small molecules, called metabolites, that can provide important information about diet, environmental exposures, and drug metabolism. The study of all of the metabolites in a given sample, or metabolomics, therefore provides a powerful tool for researchers and clinicians to understand an individual's current physiological state and possibly to develop personalized diagnoses and treatment approaches. The NIH Common Fund's Metabolomics program was established to support broader use of metabolomic analysis in basic research and in the clinic. The first stage of the Metabolomics program contributed to wider use of metabolomic approaches in the biomedical research community and enhanced researchers' ability to conduct metabolic analyses. In the second stage, the Metabolomics program aims to enhance metabolomics data sharing; develop novel tools to facilitate data analysis; and generate standards, guidelines, and resources to enable metabolomics research.

- Undiagnosed Diseases Network (UDN)[12] (Figure 35)—Rare diseases collectively affect approximately 25 million Americans,[13] many of whom face a long and frustrating process to arrive at a diagnosis. The NIH Intramural Research Program launched the Undiagnosed Diseases Program (UDP) in 2008 with the goal of diagnosing, understanding, and treating rare disorders. This program leveraged revolutionary genomic sequencing technologies to aid in the diagnosis of rare diseases and developed a robust interdisciplinary approach to disease diagnosis that proved successful. However, the overwhelming patient need far exceeded the capacity of the UDP. In 2013, the NIH Common Fund launched UDN with the goal of expanding the proven approach of UDP to academic health centers across the county, working through challenges associated with implementing this approach in different clinical and economic models. UDN promotes the use of genomic data in disease diagnosis and engages basic researchers to uncover underlying disease mechanisms so that treatments can be identified. UDN accepted 601 participants undiagnosed by traditional medical practices in the first 20 months of operation. Of those who completed their UDN evaluation during this time, 35 percent were given a diagnosis. Many of these diagnoses were rare genetic diseases, including 31 previously unknown syndromes. In the second stage, UDN is focusing on forming a sustainable national resource to diagnose both rare and new diseases, advancing laboratory and clinical research, enhancing global coordination and collaboration among laboratory and clinical researchers, and sharing resulting data and approaches throughout the scientific and clinical communities.

Figure 35. Undiagnosed Diseases Network

The Undiagnosed Diseases Network is a research study to improve the level of diagnosis of rare and undiagnosed conditions.

Credit: NIH Common Fund.

Strategic Planning 2016–2017

Anticipated budget limitations led to a scaled-down strategic planning process in 2016–2017, focused on two existing NIH Common Fund programs requesting a second stage of support in fiscal year 2019:

- Diversity Program Consortium (DPC): Enhancing the Diversity of the NIH-Funded Workforce[14] (Figure 36)—In 2012, The Advisory Committee to the NIH Director Working Group on Diversity in the Biomedical Research Workforce issued a report[15] acknowledging NIH's longstanding recognition that diversity in the biomedical research workforce is critical to ensuring the most creative minds have the opportunity to contribute to our research and health goals. However, despite ongoing investment by NIH and others to increase the number of scientists from underrepresented groups, unacceptable disparities in the biomedical workforce remain. The DPC was established to develop, implement, assess, and disseminate innovative and effective training and mentoring approaches to enhance the participation and persistence of individuals from underrepresented backgrounds

in biomedical research careers so that future programs may be more effective at recruiting and retaining a diverse workforce. Launched with planning grants in 2013, the first stage of the program had three initiatives: (1) Building Infrastructure Leading to Diversity (BUILD), which is developing approaches to determine the most effective ways to engage and retain students from diverse backgrounds in biomedical research and to prepare students to become future contributors to the NIH-funded research enterprise; (2) the National Research Mentoring Network, a national network of mentors and mentees providing mentorship, professional development, training, networking, and resources; and (3) the Coordination and Evaluation Center, which is coordinating and evaluating DPC activities. In the second stage of the program, two additional initiatives are being supported. The Sponsored Programs Administration Development program aims to increase the productivity of sponsored programs offices (or similar entities) at academic institutions to enhance biomedical research and research training. The DPC Dissemination and Translation Awards (DPC DaTA) supports non-DPC institutions to employ DPC methods to evaluate the effectiveness of a biomedical research training, mentoring, or research capacity-building intervention.

Figure 36. Diversity Program Consortium

The Diversity Program Consortium was established to develop, implement, assess, and disseminate innovative and effective training and mentoring approaches to enhance the participation and persistence of individuals from underrepresented backgrounds in biomedical research careers so that future programs may be more effective at recruiting and retaining a diverse workforce.

Credit: NIH Common Fund.

- Extracellular RNA Communication (ERC)[16]—Once thought to exist only inside cells, RNA is now known to travel outside cells and play a role in communication among cells throughout the body. When the ERC program was launched in 2013, researchers understood that RNA was exported from cells, but fundamental questions about the function of these extracellular RNAs (exRNAs), how exRNAs are targeted to deliver messages to other cells, and how exRNAs are regulated had yet to be fully explored. Additionally, a lack of standards, protocols, and data infrastructure was a significant roadblock that hindered research progress and prevented comparison of experiments between different laboratories. The ERC program aimed to enable researchers to tackle fundamental questions about exRNAs in a coordinated way, thereby establishing new biological paradigms and accelerating development of exRNAs as potential therapeutics or in diagnostics. The first stage of this program catalogued exRNA molecules found in human biofluids from more than 2,000 healthy donors; established data standards, created a data portal, and developed novel tools and reagents; and identified potential exRNA biomarkers for nearly 30 diseases. In the second stage of the program, ERC is focusing on tool and technology development addressing major roadblocks to understanding exRNAs, including better understanding of the larger complexes, like extracellular vesicles that carry exRNAs through the body.

Strategic Planning 2017–2018

In 2017, NIH leadership identified two timely, high-priority research areas suitable for NIH Common Fund support. Due to the pressing public health needs that these programs are intended to address, both programs were planned and launched on an accelerated timeline.

- Acute to Chronic Pain Signatures (A2CPS)[17]—As part of NIH's response to the growing opioid crisis, the A2CPS program aims to further our understanding of the transition from acute to chronic pain. Acute pain following injury resolves in many patients, but for a large number of people, the pain becomes chronic, even after the injury itself has healed. This transition is poorly understood and therefore prevention or treatment is difficult. The A2CPS program is addressing this challenge

by developing a set of objective biomarkers (i.e., a "signature") to predict susceptibility for transitioning to chronic pain after an acute pain event. The A2CPS program enhances the objectives of the NIH Helping to End Addiction Long-term℠ (HEAL) Initiative,[18] a transagency effort to speed scientific solutions to end the opioid public health crisis. A2CPS will benefit the HEAL℠ research priority to enhance pain management. Building upon previous efforts by the NIH Pain Consortium and others, this program was well positioned to rapidly launch in advance of HEAL℠ but is now fully coordinated with HEAL℠ initiatives. It began a planning stage in fiscal year 2019, scaling up to implementation in fiscal year 2020.

- Somatic Cell Genome Editing (SCGE)[19] (Figure 37)—The development of tools and approaches to precisely change genomic sequences, including CRISPR, have raised the possibility of a fundamentally new approach to treat an enormous number of genetic diseases. Capitalizing on the rapidly expanding field of precision genome editing tools, planning for the SCGE program identified several critical areas in need of strategic investment to accelerate development of new genome editing–based therapies. Significant ongoing investments were advancing this nascent field but were largely focused on ex vivo genome editing approaches, in which cells are edited outside of the body and then reintroduced; in vivo approaches involving editing cells within the body were lagging behind, despite applicability to a larger number of diseases. Additionally, a significant technological challenge was targeting the editing machinery to the appropriate cells and avoiding off-target effects. Building upon these opportunities and challenges, the SCGE program aims to improve the efficacy and specificity of gene editing approaches to help reduce the burden of common and rare diseases caused by genetic changes. SCGE is developing tools to perform and assess effective and safe genome editing in nonreproductive (i.e., somatic) cells of the body, including approaches to ensure genome editing tools are delivered specifically to the targeted cell type within the body. By sharing these resources with the entire research community, SCGE aims to reduce the time and cost required to develop new therapies. An accelerated planning process that brought together thought leaders from academia, industry, and government allowed this program to be quickly launched in fiscal year 2018.

Figure 37. Somatic Cell Genome Editing Program

The Somatic Cell Genome Editing program is working to improve the efficacy and specificity of gene editing approaches to help reduce the burden of common and rare diseases caused by genetic changes.

Credit: NIH Common Fund.

Additionally, discussions between NIH leadership and IC Directors revealed enthusiasm for developing high-priority initiatives that extend from existing NIH Common Fund programs and leverage previous investments. Within the CryoEM program, a new effort was developed to increase access to cryo-electron tomography, a related technology that enables improved imaging of molecules within intact cells and tissues in 3-D. Additional efforts to address the opioid public health crisis were supported through an expansion of the Stimulating Peripheral Activity to Relieve Conditions (SPARC)[20] program, launching a new initiative to generate anatomical and functional data from neural circuits mediating visceral pain.

Strategic Planning 2018–2019

To plan for new NIH Common Fund programs for potential launch in fiscal year 2021 or later, OSC hosted a series of web-based workshops[21] with editors from a diverse array of biomedical and behavioral research journals. The objective of these workshops was to learn about new scientific trends, emerging areas of research, and crosscutting challenges that may contribute to planning for new NIH Common Fund programs. Journal editors, with the exposure to and assessment of new scientific advances, are in a good position to understand the current scientific landscape. One prominent theme articulated in these

workshops was the emerging opportunities presented by integration of artificial intelligence (AI) and machine learning approaches into biomedical research. Independently, in recognition of the opportunity and challenges posed by AI in biomedicine, NIH organized a workshop in July 2018, Harnessing Artificial Intelligence and Machine Learning to Advance Biomedical Research.[22] These initial discussions contributed to additional planning activities and, ultimately, a new NIH Common Fund program in AI (see the next section, "Strategic Planning 2019–2020," for more details).

In addition to input gathered through the journal editor workshops, OSC also solicited ideas from IC Directors. From this process, three ideas emerged that are now being pursued as potential NIH Common Fund programs.

- **Harnessing Data Science for Health Discovery and Innovation in Africa**[23]—This program will leverage data science technologies and prior NIH investments to develop solutions to Africa's most pressing public health problems through a robust ecosystem of new partners from academic, government, and private sectors. Extensive mobile phone coverage in Africa provides an opportunity to rapidly advance health care delivery systems through mobile health applications, point-of-care technologies, and self-management systems. Additionally, this program leverages and builds upon substantial investment in African research and research training by NIH ICs, the NIH Common Fund, and other organizations. For example, the Data Science in Africa program will build on and translate the resources and expertise developed through the Human Heredity and Health in Africa[24] program into products and policies impacting health in Africa and around the world. The program aims to promote sustainability of the African health research enterprise by encouraging robust partnerships with African governmental, private, and academic partners and will also consider ethical, legal, and social issues for data science research and its applications to public health in Africa. This program was approved by the NIH Director and is anticipated to launch in fiscal year 2021.
- **Faculty Institutional Recruitment for Sustainable Transformation (FIRST)**[25]—Despite ongoing investment in programs designed to enhance the diversity of the biomedical workforce, underrepresentation of some racial and ethnic groups, particularly at the faculty level, remains a persistent challenge. Many previous efforts have focused on individuals; however, substantial evidence suggests that targeting institutional culture change is needed to achieve the desired results. Early success of the NIH Distinguished Scholars Program[26] and other cohort-based recruitment programs indicates that recruitment of a critical mass of investigators committed to diversity and inclusion may foster the institutional changes needed to create meaningful changes in diversity at the faculty level. The FIRST program aims to create cultures of inclusive excellence at NIH-funded institutions, establishing and maintaining scientific environments that can cultivate and benefit from a full range of talent. It will establish a faculty cohort model for hiring, mentoring, and professional development; integrated, institution-wide approaches to address bias, faculty equity, mentoring, and work-life issues; and a coordination and evaluation center to conduct independent evaluations of program impacts. This program was approved by the NIH Director and is anticipated to launch in fiscal year 2021.
- **Nutrition for Precision Health, powered by the NIH *All of Us* Research Program**—Current dietary recommendations are often confusing, sometimes contradictory, and generally do not consider individual differences. Rapidly advancing technologies—including high-throughput *-omics* (e.g., genomics, epigenomics, proteomics, metabolomics) and AI—combined with the growing emphasis on personalized medicine approaches present an opportunity to develop more precise and dynamic nutritional recommendations. The program, still in development, would aim to understand individual responses to diet, enabling tailored dietary recommendations to be provided by physicians and the development of tools to allow individuals to make more informed decisions about healthy food choices. This program is anticipated to launch in fiscal year 2021.

Strategic Planning 2019–2020

To plan for new NIH Common Fund programs to begin in fiscal year 2022 or beyond, OSC used an online crowdsourcing platform to solicit ideas from

the NIH community for bold investments that could become future NIH Common Fund programs. The community was also encouraged to provide constructive comments on ideas submitted by others, so that each idea could benefit from the collective expertise of the NIH community. In addition to gathering ideas through the crowdsourcing site, IC Directors were also invited to submit ideas.

From this process, one idea focused on exploring transposable elements and somatic mosaicism was selected for further development. This potential program, Somatic Mosaicism and Retrotranspositions (SMaRt), would investigate genetic elements that make up approximately half of the human genome and which, in some cases, have the ability to move within the genome and thereby create genetically distinct cells within a single individual. This mobility can result in genomic damage and disease, but the extent to which this process happens and how it is regulated is largely unknown. If approved, the SMaRT program would aim to deliver new paradigms concerning the regulation of these elements and how their transposition contributes to normal biology and disease. Pending approval, this program is anticipated to launch in fiscal year 2022.

In addition to the strategic planning process above, several other NIH-wide efforts contributed to development of new NIH Common Fund programs. At the NIH Leadership Forum, NIH leadership and IC Directors identified cellular senescence as a high-priority research area. Cellular senescence refers to a highly stable state of cell cycle arrest in which cells stop dividing, often in response to various stressors, such as aging and inflammation. A better understanding of the mechanisms of cellular senescence and how this process affects tissue and organ function may lead to new approaches for addressing the deleterious effects of aging and of numerous diseases and conditions. If approved, this program is planned to launch in fiscal year 2022.

Finally, the Advisory Committee to the NIH Director Working Group on Artificial Intelligence provided NIH-wide recommendations[27] on how NIH could leverage and promote AI to advance research across many biomedical topics and have positive effects across diverse fields. Several of these recommendations formed the basis for a new potential NIH Common Fund program, Artificial Intelligence for BiomedicaL Excellence (AIBLE).[28] This program aims to generate new biomedically relevant datasets amenable to machine learning analysis at scale. This program is anticipated to launch in fiscal year 2021. For more details, see Figure 38.

Figure 38. Artificial Intelligence for BiomedicaL Excellence Program

Following a 2018 NIH workshop on artificial intelligence (AI) and machine learning in biomedical research, the NIH Director formed the Advisory Committee to the NIH Director (ACD) Working Group on Artificial Intelligence. This group was charged with determining opportunities for NIH-wide efforts in AI and ways these efforts could cross biomedical topics to positively affect diverse fields, identifying ways for NIH to build connections between the data science and biomedical research communities, defining approaches to cross-training computer scientists and biomedical researchers, and identifying ethical consideration for biomedical research and AI.

This working group delivered its final recommendations in December 2019. Several of these recommendations fit well with the criteria for NIH Common Fund programs, whereas other recommendations were within the mandate of the NIH's Office of Data Science Strategy. An NIH-wide working group convened and conducted planning activities to determine how an NIH Common Fund program could effectively address the relevant recommendations, leading to development of the Artificial Intelligence for BiomedicaL Excellence (AIBLE) program. The overall goal of this program is to generate new biomedically relevant datasets amenable to machine learning analysis at scale, achieved through the following initiatives:

- Support data design centers to generate rubrics of amenability to machine learning approaches that allow the evaluation of datasets and plans to generate datasets, create infrastructure to disseminate tools, and host and promote datasets.
- Develop software and firmware tools to accelerate AI readiness.
- Enhance existing data generation efforts to improve AI readiness.
- Generate gold-standard, multimodal human datasets that adhere to the rubrics established by the program.
- Use the rubrics to evaluate and update select existing public biomedical research data.

Because this potential program leveraged the carefully developed recommendations from the ACD working group, it is anticipated to launch on an accelerated timeline in fiscal year 2021.

Strategic Planning 2020–2021

OSC is currently beginning a new round of strategic planning in 2020. Still in the early stages of development, this round of strategic planning is intended to leverage existing community-generated white papers (i.e., assessments of scientific opportunities and needs in a given scientific area). By reviewing these thoughtful analyses from many scientific societies or other groups, NIH may obtain well-considered input that reflects consensus views and that may reveal overlapping challenges and opportunities affecting multiple communities. Potential program concepts will also be solicited from the IC Directors and may arise from discussions involving NIH leadership, Advisory Councils, or other entities providing input to NIH.

Planning for Transition from NIH Common Fund Support

NIH Common Fund programs are designed to achieve a set of high-impact goals within a defined time frame. At the conclusion of each program, deliverables will either stimulate IC-funded research or will transition to support by ICs or other entities that find the resources generated by the program useful.

Transition plans are considered early in the lifecycle of an NIH Common Fund program, and these plans are reconsidered throughout the lifecycle to ensure the transition accommodates the changing needs of both the program and the external scientific community. A detailed description of the NIH Common Fund's Human Microbiome Project[29] transition is provided as an example in Figure 39.

Figure 39. Transition of the Human Microbiome Project

The Human Microbiome Project (HMP), supported by the NIH Common Fund from 2007 to 2016, developed numerous research resources to enable the study of the microbial communities that live in and on the human body and the roles these communities play in health and disease. The first stage of HMP developed DNA sequence datasets and computational tools for characterizing the microbiome in healthy adults and in people with microbiome-associated diseases. The second stage of HMP created integrated datasets of multiple biological properties from both the microbiome and the host over time in people with specific microbiome-associated diseases.

HMP was an extremely successful program. Some of its major accomplishments include sequencing approximately 3,000 reference bacterial genomes isolated from the human body; generating a comprehensive profile of the healthy human microbiome; developing integrated datasets of metagenomic, transcript, protein, and metabolite profiles from microbiome and host in multiple human cohorts; developing software and online resources to enable studies of the microbiome; and publication of more than 700 scientific papers.

HMP helped catalyze the nascent field of microbiome research, laying the foundation for continued NIH investment through the Institutes and Centers (ICs) after the program ended. NIH investment in microbiome research outside of HMP has increased more than 40-fold since the inception of HMP and now spans more than 20 ICs. The Trans-NIH Microbiome Working Group was established in 2012 to provide a forum for coordinating NIH research activities related to the human microbiome. Ongoing access to critical HMP resources, including datasets and digital tools, will be accomplished through the Common Fund Data Ecosystem (CFDE). Inclusion of these resources within the CFDE ensures that the biomedical research community continues to benefit from HMP and that investment in HMP is leveraged for maximum possible impact.

The NIH Common Fund Budget

The NIH Common Fund budget for fiscal years 2018–2021 is shown in Table 1. Although NIH Common Fund programs are planned in advance, the specific activities funded in each program depend on the budget made available through annual appropriations. As programs end, funds are freed to support new programs and planned expansions of ongoing programs.

Table 1: The NIH Common Fund Budget, Fiscal Years 2018–2021

	Fiscal Year 2018 Actual	Fiscal Year 2019 Actual	Fiscal Year 2020 Actual	Fiscal Year 2021 President's Budget Request[a]
NIH Common Fund (dollars in millions)	$600.7	$619.2	$639.1	$596.5
NIH Common Fund Percentage of NIH Labor/U.S. Department of Health and Human Services Funding[b]	1.62%	1.59%	1.54%	1.54%

[a] Includes March 17, 2020, budget amendment of $439.584 million for the National Institute of Allergy and Infectious Diseases.
[b] Excludes mandatory funding for the Type 1 Diabetes Research program and funding appropriated through the Interior, Environment, and Related Agencies Appropriations Act for the National Institute of Environmental Health Sciences Superfund Research Program. Includes program evaluation financing resources.

The *Public Health Service Act* requires that the NIH Common Fund Strategic Plan Report include an estimate of amounts needed for (i) maximizing the potential of the Common Fund research under 42 U.S.C. 282(b)(7)(A)(i); (ii) to be sufficient only for continuing to fund research activities previously identified by the Division of Program Coordination, Planning, and Strategic Initiatives; and (iii) to be necessary to fund research described in 42 U.S.C. 282(b)(7)(A)(i) that (1) is in addition to the research activities described in clause (ii) and (2) for which there is the most substantial need. See 42 U.S.C. 282a(c)(1)(C).

Budgets for ongoing NIH Common Fund programs are planned in advance to maximize the potential of all programs. Therefore, the amounts described in (i) and (ii) are the same and are equal to the total budget for all NIH Common Fund programs. In addition to the amount for ongoing NIH Common Fund programs, funds are available for new initiatives each year. These new initiatives are identified by the strategic planning principles outlined in this report, thus ensuring they address research areas of substantial need. Within each of the programmatic areas identified through strategic planning, the NIH peer review process also identifies specific research proposals addressing areas of substantial need. Therefore, the amounts described in (iii) are equal to the amount reserved for new NIH Common Fund initiatives.

Each year, as part of the President's Budget Request, the NIH Common Fund describes both the amounts estimated for each ongoing program (i and ii) and the amounts budgeted for new initiatives (iii). Table 2 shows the estimates presented in the Fiscal Year 2021 President's Budget Request; prior years' Requests can be found at https://commonfund.nih.gov/about/budgetrequests.

Table 2: NIH Common Fund President's Budget Request, Fiscal Year 2021

NIH Common Fund Program (Dollars in Thousands)	Fiscal Year 2019 Final	Fiscal Year 2020 Enacted	Fiscal Year 2021 President's Budget Request
4D Nucleome	27,997	28,860	27,485
Acute to Chronic Pain Signatures	2,094	16,636	14,648
Big Data to Knowledge (BD2K)	2,605	0	0
Enhancing the Diversity of the NIH-Funded Workforce	52,656	53,713	47,401
Extracellular RNA Communication	6,728	5,846	10,497
Gabriella Miller Kids First Pediatric Research	13,482	13,000	13,000
Genotype-Tissue Expression (GTEx) Resources	772	0	0
Global Health	15,569	11,565	9,261
Glycoscience	19,435	13,362	5,191
Health Care Systems Research Collaboratory	1,988	1,750	1,694
High-Risk Research	206,110	193,100	186,001
NIH Director's Pioneer Award	*45,446*	*54,265*	*51,293*
NIH Director's New Innovator Award Program	*102,692*	*77,815*	*79,795*
Transformative Research Award	*35,149*	*38,402*	*34,659*
NIH Director's Early Independence Award Program	*22,823*	*22,618*	*20,255*
Human BioMolecular Atlas Project (HuBMAP)	15,005	27,031	31,040
Illuminating the Druggable Genome	12,970	13,390	12,971
Knockout Mouse Phenotyping Program	13,757	11,000	0
Library of Integrated Network-Based Cellular Signatures (LINCS)	9,946	87	0
Metabolomics	12,403	12,401	12,000
Molecular Transducers of Physical Activity	44,744	46,126	42,609
New Models of Data Stewardship	199	0	0
NIH Center for Regenerative Medicine (NCRM)	7,597	5,700	0
Protein Capture	1,334	0	0
Science of Behavior Change	12,674	222	0
Somatic Cell Genome Editing	33,324	38,937	44,232
S.P.A.R.C. - Stimulating Peripheral Activity to Relieve Conditions	51,559	47,268	41,883
Strengthening the Biomedical Research Workforce	56	0	0
Transformative High Resolution Cryo-Electron Microscopy (CryoEM)	14,895	51,800	36,290
Undiagnosed Diseases Network	29,207	24,401	21,683
Strategic Planning, Evaluation, and Infrastructure	10,061	22,917	21,129
Subtotal NIH Common Fund	619,166	639,111	579,017
New Initiatives in NIH Common Fund	0	0	17,450
Total NIH Common Fund	**619,166**	**639,111**	**596,467**

Endnotes

1 https://commonfund.nih.gov.
2 https://commonfund.nih.gov/dataecosystem.
3 https://commonfund.nih.gov/sites/default/files/Initiatives_6-28-11.pdf.
4 https://dpcpsi.nih.gov/council.
5 https://www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf.
6 https://commonfund.nih.gov/sites/default/files/2015%20Common%20Fund%20Strategic%20Planning%20Report_final%20-%20508.pdf.
7 https://commonfund.nih.gov/HuBMAP.
8 https://commonfund.nih.gov/Singlecell.
9 https://commonfund.nih.gov/CryoEM.
10 https://commonfund.nih.gov/IDG.
11 https://commonfund.nih.gov/metabolomics.
12 https://commonfund.nih.gov/Diseases.
13 https://archives.nih.gov/asites/report/09-09-2019/report.nih.gov/nihfactsheets/ViewFactSheete790.html?c-sid=126&key=R#R.
14 https://commonfund.nih.gov/diversity.
15 https://acd.od.nih.gov/documents/reports/DiversityBiomedicalResearchWorkforceReport.pdf.
16 https://commonfund.nih.gov/exrna.
17 https://commonfund.nih.gov/pain.
18 https://heal.nih.gov.
19 https://commonfund.nih.gov/editing.
20 https://commonfund.nih.gov/sparc.
21 https://commonfund.nih.gov/sites/default/files/Journal_Editors_Workshop_Exec_Summary_508.pdf.
22 https://datascience.nih.gov/community/2018biomedAI.
23 https://commonfund.nih.gov/AfricaData.
24 https://h3africa.org.
25 https://commonfund.nih.gov/first.
26 https://diversity.nih.gov/programs-partnerships/dsp.
27 https://acd.od.nih.gov/documents/presentations/12132019AI.pdf.
28 https://dpcpsi.nih.gov/sites/default/files/CoC_May_2020_1.05PM_Concept_Clearance_AIBLE_Brennan_508.pdf.
29 https://commonfund.nih.gov/hmp.

Appendix V: Acronyms

3-D	three-dimensional
A2CPS	Acute to Chronic Pain Signatures
ABCD	Adolescent Brain Cognitive Development
ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines
AFREhealth	African Forum for Research and Education in Health
AHRQ	Agency for Healthcare Research and Quality
AI	artificial intelligence
AIBLE	Artificial Intelligence for BiomedicaL Excellence
AMD	age-related macular degeneration
AMP	Accelerating Medicines Partnership
AMP-AD	AMP-Alzheimer's Disease
AMP-PD	AMP-Parkinson's Disease
AMP-RA/Lupus	AMP-Rheumatoid Arthritis/Lupus
AMP-T2D	AMP-Type 2 Diabetes
ASSIST	Application Submission System & Interface for Submission Tracking
BIRCWH	Building Interdisciplinary Research Careers in Women's Health
BRAIN	Brain Research through Advancing Innovative Neurotechnologies®
BUILD	Building Infrastructure Leading to Diversity
CAR	chimeric antigen receptor
CC	NIH Clinical Center
CDC	Centers for Disease Control and Prevention
CFDE	Common Fund Data Ecosystem
CIT	Center for Information Technology
ClinGen	Clinical Genome
CoC	Council of Councils
CORD-19	COVID-19 Open Research Dataset
COVID-19	coronavirus disease 2019
cryoEM	cryo-electron microscopy
CSR	Center for Scientific Review
CTSA	Clinical and Translational Science Awards
DASH	Data and Biospecimen Hub
DoD	U.S. Department of Defense
DPC	Diversity Program Consortium
DPC DaTA	DPC Dissemination and Translation Awards
DPCPSI	Division of Program Coordination, Planning, and Strategic Initiatives
DR2	Disaster Research Response
DRC	Democratic Republic of the Congo
ECHO	Environmental influences on Child Health Outcomes
ENCODE	ENCyclopedia of DNA Elements
ERC	extracellular RNA communication
ERM	Enterprise Risk Management
EVD	Ebola virus disease
exRNA	extracellular RNA
FAIR	findable, accessible, interoperable, and reusable
FDA	U.S. Food and Drug Administration
FIC	Fogarty International Center
FIRST	Faculty Institutional Recruitment for Sustainable Transformation
FOIA	Freedom of Information Act
GACD	Global Alliance for Chronic Diseases
GBD	Global Burden of Disease
H3Africa	Human Heredity and Health in Africa Consortium

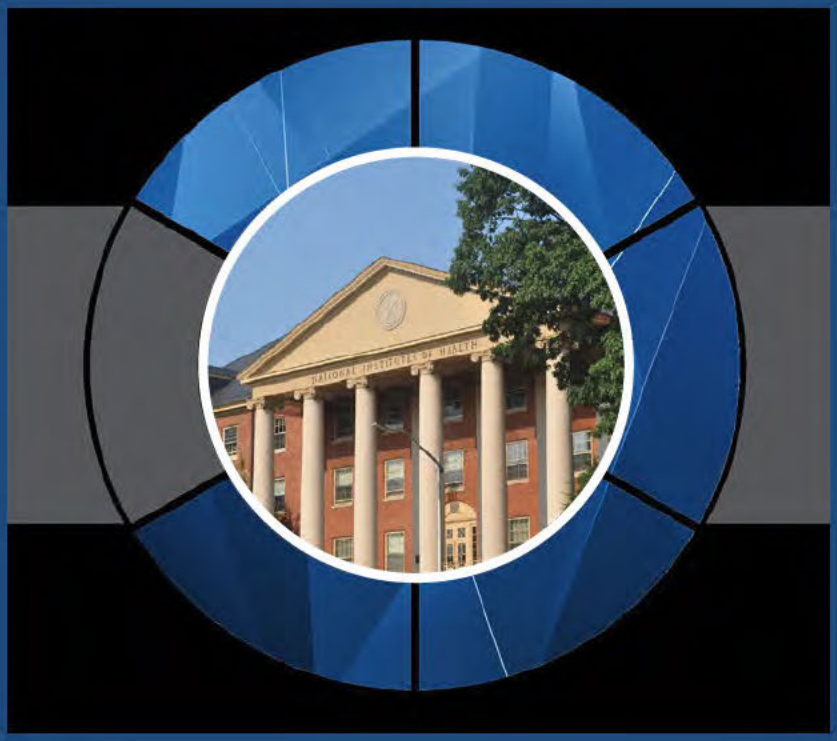
HEAL	Helping to End Addiction Long-term℠
HHS	U.S. Department of Health and Human Services
HMP	Human Microbiome Project
HRSA	Health Resources and Services Administration
HuBMAP	Human BioMolecular Atlas Program
IC	Institute and Center
IDeA	Institutional Development Award
IDG	Illuminating the Druggable Genome
IMPROVE	Implementing a Maternal health and PRegnancy Outcomes Vision for Everyone
INCLUDE	INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE
IPRCC	Interagency Pain Research Coordinating Committee
iPSC	induced pluripotent stem cell
ISS-NL	International Space Station U.S. National Laboratory
MOSAIC	Maximizing Opportunities for Scientific and Academic Independent Careers
MoTrPAC	Molecular Transducers of Physical Activity Consortium
NARI	Native American Research Internship
NASA	National Aeronautics and Space Administration
NCATS	National Center for Advancing Translational Sciences
NCCIH	National Center for Complementary and Integrative Health
NCD	noncommunicable diseases
NCI	National Cancer Institute
NEI	National Eye Institute
NGRI	Next Generation Researchers Initiative
NHGRI	National Human Genome Research Institute
NHLBI	National Heart, Lung, and Blood Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NIDA	National Institute on Drug Abuse
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIH	National Institutes of Health
NIH RePORTER	NIH *Research Portfolio Online Reporting Tools Expenditures and Results*
NIMH	National Institute of Mental Health
NIMHD	National Institute on Minority Health and Health Disparities
NINDS	National Institute of Neurological Disorders and Stroke
NINR	National Institute of Nursing Research
NLM	National Library of Medicine
OD	NIH Office of the Director
OSC	Office of Strategic Coordination
PALM	Pamoja Tulinde Maisha
PATH	Population Assessment of Tobacco and Health

PHS	Public Health Service
PMC	PubMed Central
PPP	public–private partnership
PRGLAC	Pregnant Women and Lactating Women
RCDC	Research, Condition, and Disease Classification
RCMI	Research Centers in Minority Institutions
RFI	Request for Information
SAMHSA	Substance Abuse and Mental Health Services Administration
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCAP	Single Cell Analysis Program
SCD	sickle cell disease
SCDIC	Sickle Cell Disease Implementation Consortium
SCGE	Somatic Cell Genome Editing
SEER	Surveillance, Epidemiology, and End Results
SGM	sexual and gender minority
SIG	Shared Instrumentation Grant
SMaRt	Somatic Mosaicism and Retrotranspositions
SPARC	Stimulating Peripheral Activity to Relieve Conditions
SPRINT	Systolic Blood Pressure Intervention Trial
SSC	Symptom Science Center
STRIDES	Science and Technology Research Infrastructure for Discovery, Experimentation, and Sustainability
TRSP	Tobacco Regulatory Science Program
UDN	Undiagnosed Diseases Network
UDP	Undiagnosed Diseases Program
VA	U.S. Department of Veterans Affairs

Acknowledgments

The *NIH-Wide Strategic Plan for Fiscal Years 2021–2025* is the product of many contributors. The NIH Director would like to thank the following stakeholders, committees, and staff for their time and effort in helping to develop this Strategic Plan.

- We would like to thank the **NIH-Wide Strategic Working Group,** whose enthusiasm, knowledge, and commitment made this document possible: Elizabeth Baden, Julie Frost Bellgowan, Michelle Bennett, Laura Berkson, David Bochner, Laura Brockway-Lunardi, Thomas Calder, Cindy Caughman, Mindy Chai, Stephanie Clipper, Laura Cole, Christine Cooper, Stephanie Courchesne-Schlink, Jessica Creery, Ned Culhane, Hope Cummings, Charles Dearolf, Clarence Dukes, Deborah Duran, Yvette Edghill Spano, Nicole Garbarini, Taylor Gilliland, Shefa Gordon, John Grason, Rebecca Hong, Cristina Kapustij, Edmund Keane, Mary Beth Kester, David Kosub, Ira Kukic, Erica Landis, Charlene Le Fauve, Issel Anne Lim, Ryan Mahon, Rebecca Meseroll, Wynn Meyer, Lara Miller, Kathryn Morris, Kate Nagy, Patty Newman, Sheila Newton, Rosanna Ng, Samia Noursi, Eileen Oni, Wilma Peterman Cross, Kamilah Rashid, Reaya Reuss, Sarah Rhodes, David Saeger, Leigh Samsel, Claire Schulkey, Paul Scott, Ching-Yi Shieh, Kelly Singel, Tyrone Spady, Erin Spaniol, Meredith Stein, Daniel Stimson, Nathaniel Stinson, Denise Stredrick, Rachel Sturke, Meredith D. Temple-O'Connor, Kimberly Thigpen Tart, Leslie Thompson, Valerie Virta, Marina Volkov, Julie Wallace, Elizabeth Walsh, Bridget Williams-Simmons, Nora Wong.
- In addition, we thank those across NIH who took the time to review the Framework and draft Strategic Plan and provide content. This includes **Institute, Center,** and **OD Office Directors** and **staff**.
- We would like to thank the **NIH Advisory Committee to the Director** and the **NIH Division of Program Coordination, Planning, and Strategic Initiatives Council of Councils** for their insightful feedback on the Framework and draft Strategic Plan.
- Finally, we are enormously appreciative of the robust input into the strategic planning process from **stakeholder communities,** including members of the scientific and health care communities, professional societies, advocacy organizations, industry, other federal agencies, and the general public. We look forward to your continued involvement as NIH works to implement the vision outlined here.


NATIONAL INSTITUTES OF HEALTH


DEPARTMENT OF HEALTH & HUMAN SERVICES · USA
NIH

EXHIBIT D

PRIVILEGED, CONFIDENTIAL, PRE-DECISIONAL

NIMHD
National Institute on Minority Health and Health Disparities

February 28, 2025

[redacted]

Dear Authorized Organization Representative:

Funding for Project Number [redacted] is hereby terminated pursuant to the 2022 National Institutes of Health ("NIH") Grants Policy Statement,[1] and 2 C.F.R. § 200.340(a)(2) (2023). This letter constitutes a notice of termination.[2]

The 2022 Policy Statement applies to your project because NIH approved your grant on January 22, 2023, and "obligations generally should be determined by reference to the law in effect when the grants were made."[3]

The 2022 Policy Statement "includes the terms and conditions of NIH grants and cooperative agreements and is incorporated by reference in all NIH grant and cooperative agreement awards."[4] According to the Policy Statement, "NIH may … terminate the grant in whole or in part as outlined in 2 CFR Part 200.340."[5] At the time your grant was issued, 2 C.F.R. § 200.340(a)(2) permitted termination "[b]y the Federal awarding agency or pass-through entity, to the greatest extent authorized by law, if an award no longer effectuates the program goals or agency priorities."

This award no longer effectuates agency priorities. NIH is obligated to carefully steward grant awards to ensure taxpayer dollars are used in ways that benefit the American people and improve their quality of life. Your project does not satisfy these criteria.

> DEI: Research programs based primarily on artificial and non-scientific categories, including amorphous equity objectives, are antithetical to the scientific inquiry, do nothing to expand our knowledge of living systems, provide low returns on investment, and ultimately do not enhance health, lengthen life, or reduce illness. Worse, so-called diversity, equity, and inclusion ("DEI") studies are often used to support unlawful discrimination on the basis of race and other protected characteristics, which harms the

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[1] https://grants.nih.gov/grants/policy/nihgps/nihgps_2022.pdf.
[2] 2 C.F.R. § 200.341(a); 45 C.F.R. § 75.373
[3] *Bennett v. New Jersey*, 470 U.S. 632, 638 (1985).
[4] 2022 Policy Statement at IIA-1.
[5] *Id.* at IIA-153.

health of Americans. Therefore, it is the policy of NIH not to prioritize such research programs.

Although "NIH generally will suspend (rather than immediately terminate) a grant and allow the recipient an opportunity to take appropriate corrective action before NIH makes a termination decision,"[6] no corrective action is possible here. The premise of Project Number [redacted] is incompatible with agency priorities, and no modification of the project could align the project with agency priorities.

Costs resulting from financial obligations incurred after termination are not allowable.[7] Nothing in this notice excuses either NIH or you from complying with the closeout obligations imposed by 2 C.F.R. §§ 75.381-75.390. NIH will provide any information required by the Federal Funding Accountability and Transparency Act or the Office of Management and Budget's regulations to *USAspending.gov*.[8]

Administrative Appeal

You may object and provide information and documentation challenging this termination.[9] NIH has established a first-level grant appeal procedure that must be exhausted before you may file an appeal with the Departmental Appeals Board.[10]

You must submit a request for such review to Matthew J. Memoli, MD, MS, Acting Director, National Institutes of Health, no later than 30 days after the written notification of the determination is received, except that if you show good cause why an extension of time should be granted, Dr. Memoli may grant an extension of time.[11]

The request for review must include a copy of the adverse determination, must identify the issue(s) in dispute, and must contain a full statement of your position with respect to such issue(s) and the pertinent facts and reasons in support of your position. In addition to the required written statement, you shall provide copies of any documents supporting your claim.[12]

Sincerely,

Priscilla Grant

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[6] 2022 Policy Statement at IIA-154.
[7] *See* 2 C.F.R. § 200.343 (2023).
[8] 2 C.F.R. § 200.341(c); 45 C.F.R. § 75.373(c)
[9] *See* 45 C.F.R. § 75.374.
[10] See 42 C.F.R. Part 50, Subpart D.
[11] *Id.* § 50.406(a).
[12] *Id.* § 50.406(b).

PRIVILEGED, CONFIDENTIAL, PRE-DECISIONAL

Priscilla Grant, JD
Chief Grants Management Officer

National Institute on Minority Health and Health Disparities
National Institutes of Health
Bethesda, MD 20892

EXHIBIT E

Department of Health and Human Services
National Institutes of Health
NATIONAL INSTITUTE ON MINORITY HEALTH AND HEALTH DISPARITIES

Notice of Award
[redacted]
Federal Award Date
02/28/2025

Recipient Information

1. Recipient Name
[redacted]

2. Congressional District of Recipient
[redacted]

3. Payment System Identifier (ID)
[redacted]

4. Employer Identification Number (EIN)
[redacted]

5. Data Universal Numbering System (DUNS)
[redacted]

6. Recipient's Unique Entity Identifier
[redacted]

7. Project Director or Principal Investigator
[redacted]

8. Authorized Official
[redacted]

Federal Agency Information

9. Awarding Agency Contact Information
Sy Shackleford

NATIONAL INSTITUTE ON MINORITY HEALTH AND HEALTH DISPARITIES
shacklefords@mail.nih.gov
301-402-1366

10. Program Official Contact Information
Nancy Lynne Jones
Health Scientist Administrator
NATIONAL INSTITUTE ON MINORITY HEALTH AND HEALTH DISPARITIES
jonesna@mail.nih.gov
301-594-8945

Federal Award Information

11. Award Number
[redacted]

12. Unique Federal Award Identification Number (FAIN)
[redacted]

13. Statutory Authority
42 USC 241 42 CFR 52

14. Federal Award Project Title
[redacted]

15. Assistance Listing Number
[redacted]

16. Assistance Listing Program Title
Minority Health and Health Disparities Research

17. Award Action Type
Non-Competing Continuation (REVISED)

18. Is the Award R&D?
Yes

Summary Federal Award Financial Information	
19. Budget Period Start Date 02/01/2023 – **End Date** 02/28/2025	
20. Total Amount of Federal Funds Obligated by this Action	$0
20 a. Direct Cost Amount	$0
20 b. Indirect Cost Amount	$0
21. Authorized Carryover	
22. Offset	
23. Total Amount of Federal Funds Obligated this budget period	$648,444
24. Total Approved Cost Sharing or Matching, where applicable	$0
25. Total Federal and Non-Federal Approved this Budget Period	$648,444
26. Project Period Start Date 06/19/2019 – **End Date** 02/28/2025	
27. Total Amount of the Federal Award including Approved Cost Sharing or Matching this Project Period	$3,324,899

28. Authorized Treatment of Program Income
Additional Costs

29. Grants Management Officer - Signature
[redacted]

30. Remarks

Acceptance of this award, including the "Terms and Conditions," is acknowledged by the recipient when funds are drawn down or otherwise requested from the grant payment system.

Notice of Award

RESEARCH
Department of Health and Human Services
National Institutes of Health

NATIONAL INSTITUTE ON MINORITY HEALTH AND HEALTH DISPARITIES

SECTION I – AWARD DATA – [redacted]

Principal Investigator(s):
[redacted]

Award e-mailed to: [redacted]

Dear Authorized Official:

The National Institutes of Health hereby revises this award (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to [redacted] in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award, including the "Terms and Conditions," is acknowledged by the recipient when funds are drawn down or otherwise requested from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Institute On Minority Health And Health Disparities of the National Institutes of Health under Award Number [redacted] The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please direct questions to the Federal Agency contacts.

Sincerely yours,

Priscilla Grant
Grants Management Officer
NATIONAL INSTITUTE ON MINORITY HEALTH AND HEALTH DISPARITIES

Additional information follows

Cumulative Award Calculations for this Budget Period (U.S. Dollars)

Salaries and Wages	$215,395
Fringe Benefits	$96,465
Personnel Costs (Subtotal)	$311,860
Travel	$7,225
Subawards/Consortium/Contractual Costs	$127,302
Publication Costs	$7,650
Federal Direct Costs	$454,037
Federal F&A Costs	$194,407
Approved Budget	$648,444
Total Amount of Federal Funds Authorized (Federal Share)	$648,444
TOTAL FEDERAL AWARD AMOUNT	$648,444
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$0

SUMMARY TOTALS FOR ALL YEARS (for this Document Number)		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
5	$648,444	$648,444

Fiscal Information:
Payment System Identifier: [redacted]
Document Number:
PMS Account Type:
Fiscal Year: 2023

IC	CAN	2023
[redacted]	[redacted]	$648,444

NIH Administrative Data:
PCC: [redacted] / **OC:** [redacted] / **Released**: 02/28/2025
Award Processed: 03/01/2025 12:01:42 AM

SECTION II – PAYMENT/HOTLINE INFORMATION – [redacted]

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – STANDARD TERMS AND CONDITIONS – [redacted]

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-

research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

An unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.

This grant is subject to Streamlined Noncompeting Award Procedures (SNAP).

This award is subject to the requirements of 2 CFR Part 25 for institutions to obtain a unique entity identifier (UEI) and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a UEI requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) [redacted]. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

This award represents the final year of the competitive segment for this grant. See the NIH Grants Policy Statement Section 8.6 Closeout for complete closeout requirements at: http://grants.nih.gov/grants/policy/policy.htm#gps.

A final expenditure Federal Financial Report (FFR) (SF 425) must be submitted through the Payment Management System (PMS) within 120 days of the period of performance end date; see the NIH Grants Policy Statement Section 8.6.1 Financial Reports, http://grants.nih.gov/grants/policy/policy.htm#gps, for additional information on this submission requirement. The final FFR must indicate the exact balance of unobligated funds and may not reflect any unliquidated obligations. There must be no discrepancies between the final FFR expenditure data and the real-time cash drawdown data in PMS. NIH will close the awards using the last recorded cash drawdown level in PMS for awards that do not require a final FFR on expenditures. It is important to note that for financial closeout, if a grantee fails to submit a required final expenditure FFR, NIH will close the grant using the last recorded cash drawdown level.

A Final Invention Statement and Certification form (HHS 568), (not applicable to training, construction, conference or cancer education grants) must be submitted within 120 days of the expiration date. The HHS 568 form may be downloaded at: http://grants.nih.gov/grants/forms.htm. This paragraph does not apply to Training grants, Fellowships, and certain other programs—i.e., activity codes C06, D42, D43, D71, DP7, G07, G08, G11, K12, K16, K30, P09, P40, P41, P51, R13, R25, R28, R30, R90, RL5, RL9, S10, S14, S15, U13, U14, U41, U42, U45, UC6, UC7, UR2, X01, X02.

Unless an application for competitive renewal is submitted, a Final Research Performance Progress Report (Final RPPR) must also be submitted within 120 days of the period of performance end date. If a competitive renewal application is submitted prior to that date, then an Interim RPPR must be submitted by that date as well. Instructions for preparing an Interim or Final RPPR are at: https://grants.nih.gov/grants/rppr/rppr_instruction_guide.pdf. Any other specific requirements set forth in the terms and conditions of the award must also be addressed in the Interim or Final RPPR. *Note that data reported within Section I of the Interim and Final RPPR forms will be made public and should be written for a lay person audience.*

NIH requires electronic submission of the final invention statement through the Closeout feature in the Commons.

NOTE: If this is the final year of a competitive segment due to the transfer of the grant to another institution, then a Final RPPR is not required. However, a final expenditure FFR is required and must be submitted electronically as noted above. If not already submitted, the Final Invention Statement is required and should be sent directly to the assigned Grants Management Specialist.

Recipients must administer the project in compliance with federal civil rights laws that prohibit discrimination on the basis of race, color, national origin, disability, age, and comply with applicable conscience protections. The recipient will comply with applicable laws that prohibit discrimination on the basis of sex, which includes discrimination on the basis of gender identity, sexual orientation, and pregnancy. Compliance with these laws requires taking reasonable steps to provide meaningful access to persons with limited English proficiency and providing programs that are accessible to and usable by persons with disabilities. The HHS Office for Civil Rights provides guidance on complying with civil rights laws enforced by HHS. See https://www.hhs.gov/civil-rights/for-providers/provider-obligations/index.html and https://www.hhs.gov/.

- Recipients of FFA must ensure that their programs are accessible to persons with limited English proficiency. For guidance on meeting the legal obligation to take reasonable steps to ensure meaningful access to programs or activities by limited English proficient individuals, see https://www.hhs.gov/civil-rights/for-individuals/special-topics/limited-english-proficiency/fact-sheet-guidance/index.html and https://www.lep.gov.
- For information on an institution's specific legal obligations for serving qualified individuals with disabilities, including providing program access, reasonable modifications, and to provide effective communication, see http://www.hhs.gov/ocr/civilrights/understanding/disability/index.html.
- HHS funded health and education programs must be administered in an environment free of sexual harassment; see https://www.hhs.gov/civil-rights/for-individuals/sex-discrimination/index.html. For information about NIH's commitment to supporting a safe and respectful work environment, who to contact with questions or concerns, and what NIH's expectations are for institutions and the individuals supported on NIH-funded awards, please see https://grants.nih.gov/grants/policy/harassment.htm.
- For guidance on administering programs in compliance with applicable federal religious nondiscrimination laws and applicable federal conscience protection and associated anti-discrimination laws, see https://www.hhs.gov/conscience/conscience-protections/index.html and https://www.hhs.gov/conscience/religious-freedom/index.html.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.

Treatment of Program Income:
Additional Costs

SECTION IV – [redacted]

Clinical Trial Indicator: No
This award does not support any NIH-defined Clinical Trials. See the NIH Grants Policy Statement Section 1.2 for NIH definition of Clinical Trial.

This project is suspended and therefore, no research activities may be carried out under this award and no funds may be obligated nor charged for any reason under this project. NIH is carrying out the suspension under NIH's independent authority under the Public Health Service Act to determine research priorities and ensure program integrity and is not being carried out under any of the Executive Orders.

THE FOLLOWING TERMS FROM THE PREVIOUS NOTICE OF AWARD LETTER ISSUED ON 11/28/2024 ALSO APPLY TO THIS AWARD:

INFORMATION: This revised award extends the 05-year budget period and project period 12 months, as requested in the awardee's letter dated 10/25/2024. The new budget and project period expiration date will

be 01/31/2026. Funds remaining in the 05- year may be used during the extension; however, no additional funds have been awarded.

THE FOLLOWING TERMS FROM THE PREVIOUS NOTICE OF AWARD LETTER ISSUED ON 1/22/2023 ALSO APPLY TO THIS AWARD:

REQUIREMENT: This award is subject to the conditions set forth in PAR-18-484, NIH Research Project Grant (Parent R01 Clinical Trial Not Allowed), NIH Guide to Grants and Contracts, 12/06/2017, which is hereby incorporated by reference as special terms and conditions of this award.

Copies of this RFA may be accessed at the following internet address:
https://grants.nih.gov/grants/guide/pa-files/PA-18-484.html

Copies may also be obtained from the Grants Management Contact indicated in the terms of award.

RESTRICTION: In addition to the PI, the following individuals are named as key personnel:

Kenneth Mayer

Written prior approval is required if any of the individual(s) named above withdraws from the project entirely, is absent from the project during any continuous period of 3 months or more, or reduces time devoted to the project below 0.39 person months.

REQUIREMENT: Use of humans and animals in any new activities must be requested prior to the start of the activity and must be approved in writing in advance by the NIMHD. See NOT-MD-08-002, "Guidance and Clarification on NCMHD Policy on Prior Approval for Subprojects and Pilot Projects Involving Human Subjects or Vertebrate Animals," NIH Guide to Grants and Contracts, April 29, 2008, which is hereby incorporated by reference as special terms and conditions of this award. See also NOT-OD-15-129, "**Prior NIH Approval of Human Subjects Research in Active Awards Initially Submitted without Definitive Plans for Human Subjects Involvement (Delayed Onset Awards): Updated Notice,"** and NIH-OD-15-128, "**Guidance on Changes That Involve Human Subjects in Active Awards and That Will Require Prior NIH Approval: Updated Notice."**

Copies of these Notices may be accessed at the following internet address:
http://www.nih.gov/grants/guide/index.html

Copies may also be obtained from the Grants Management Contact indicated in the terms of award.

INFORMATION: This award reflects the NIMHD's acceptance of the certification that all key personnel have completed education on the protection of human subjects, in accordance with NIH policy, "Required Education in the Protection of Human Research Participants," as announced in the June 5, 2000 NIH Guide (revised August 25, 2000) (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html).

Any individual involved in the design and conduct of the study that is not included in the certification must satisfy this requirement prior to participating in the project. Failure to comply can result in the suspension and/or termination of this award, withholding of support of the continuation award, audit disallowances, and/or other appropriate action.

INFORMATION: Unobligated balances may be used by the NIMHD to reduce or offset funding for a subsequent budget period.

SPREADSHEET SUMMARY
AWARD NUMBER: [redacted]

INSTITUTION: [redacted]

Budget	Year 5
Salaries and Wages	$215,395
Fringe Benefits	$96,465
Personnel Costs (Subtotal)	$311,860
Travel	$7,225
Subawards/Consortium/Contractual Costs	$127,302
Publication Costs	$7,650
TOTAL FEDERAL DC	$454,037
TOTAL FEDERAL F&A	$194,407
TOTAL COST	$648,444

Facilities and Administrative Costs	Year 5
F&A Cost Rate 1	59.5%
F&A Cost Base 1	$326,735
F&A Costs 1	$194,407

EXHIBIT F

Department of Health and Human Services
National Institutes of Health
NATIONAL INSTITUTE ON MINORITY HEALTH AND HEALTH DISPARITIES

Notice of Award
[redacted]
Federal Award Date
03/06/2025

Recipient Information

1. Recipient Name
[redacted]

2. Congressional District of Recipient
[redacted]

3. Payment System Identifier (ID)
[redacted]

4. Employer Identification Number (EIN)
[redacted]

5. Data Universal Numbering System (DUNS)
[redacted]

6. Recipient's Unique Entity Identifier
[redacted]

7. Project Director or Principal Investigator
[redacted]

8. Authorized Official
[redacted]

Federal Agency Information

9. Awarding Agency Contact Information
Sy Shackleford

NATIONAL INSTITUTE ON MINORITY HEALTH AND HEALTH DISPARITIES
shacklefords@mail.nih.gov
301-402-1366

10. Program Official Contact Information
Nancy Lynne Jones
Health Scientist Administrator
NATIONAL INSTITUTE ON MINORITY HEALTH AND HEALTH DISPARITIES
jonesna@mail.nih.gov
301-594-8945

Federal Award Information

11. Award Number
[redacted]

12. Unique Federal Award Identification Number (FAIN)
[redacted]

13. Statutory Authority
42 USC 241 42 CFR 52

14. Federal Award Project Title
[redacted]

15. Assistance Listing Number
[redacted]

16. Assistance Listing Program Title
Minority Health and Health Disparities Research

17. Award Action Type
Non-Competing Continuation (REVISED)

18. Is the Award R&D?
Yes

Summary Federal Award Financial Information

19. Budget Period Start Date 02/01/2023 – **End Date** 02/28/2025	
20. Total Amount of Federal Funds Obligated by this Action	$0
20 a. Direct Cost Amount	$0
20 b. Indirect Cost Amount	$0
21. Authorized Carryover	
22. Offset	
23. Total Amount of Federal Funds Obligated this budget period	$648,444
24. Total Approved Cost Sharing or Matching, where applicable	$0
25. Total Federal and Non-Federal Approved this Budget Period	$648,444
26. Project Period Start Date 06/19/2019 – **End Date** 02/28/2025	
27. Total Amount of the Federal Award including Approved Cost Sharing or Matching this Project Period	$3,324,899

28. Authorized Treatment of Program Income
Additional Costs

29. Grants Management Officer - Signature
[redacted]

30. Remarks

Acceptance of this award, including the "Terms and Conditions," is acknowledged by the recipient when funds are drawn down or otherwise requested from the grant payment system.

Notice of Award

RESEARCH
Department of Health and Human Services
National Institutes of Health

NATIONAL INSTITUTE ON MINORITY HEALTH AND HEALTH DISPARITIES

SECTION I – AWARD DATA – [redacted]

Principal Investigator(s):
[redacted]

Award e-mailed to: [redacted]

Dear Authorized Official:

The National Institutes of Health hereby revises this award (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to [redacted] in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award, including the "Terms and Conditions," is acknowledged by the recipient when funds are drawn down or otherwise requested from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Institute On Minority Health And Health Disparities of the National Institutes of Health under Award Number [redacted]. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please direct questions to the Federal Agency contacts.

Sincerely yours,

Priscilla Grant
Grants Management Officer
NATIONAL INSTITUTE ON MINORITY HEALTH AND HEALTH DISPARITIES

Additional information follows

Cumulative Award Calculations for this Budget Period (U.S. Dollars)

Salaries and Wages	$215,395
Fringe Benefits	$96,465
Personnel Costs (Subtotal)	$311,860
Travel	$7,225
Subawards/Consortium/Contractual Costs	$127,302
Publication Costs	$7,650
Federal Direct Costs	$454,037
Federal F&A Costs	$194,407
Approved Budget	$648,444
Total Amount of Federal Funds Authorized (Federal Share)	$648,444
TOTAL FEDERAL AWARD AMOUNT	$648,444
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$0

SUMMARY TOTALS FOR ALL YEARS (for this Document Number)		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
5	$648,444	$648,444

Fiscal Information:
Payment System Identifier:
Document Number: [redacted]
PMS Account Type:
Fiscal Year: 2023

IC	CAN	2023
MD	8472687	$648,444

NIH Administrative Data:
PCC: [redacted] / **OC:** [redacted] / **Released:** 03/06/2025
Award Processed: 03/07/2025 12:01:02 AM

SECTION II – PAYMENT/HOTLINE INFORMATION – [redacted]

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – STANDARD TERMS AND CONDITIONS – [redacted]

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-

research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

An unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.

This grant is subject to Streamlined Noncompeting Award Procedures (SNAP).

This award is subject to the requirements of 2 CFR Part 25 for institutions to obtain a unique entity identifier (UEI) and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a UEI requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) [redacted]. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

This award represents the final year of the competitive segment for this grant. See the NIH Grants Policy Statement Section 8.6 Closeout for complete closeout requirements at: http://grants.nih.gov/grants/policy/policy.htm#gps.

A final expenditure Federal Financial Report (FFR) (SF 425) must be submitted through the Payment Management System (PMS) within 120 days of the period of performance end date; see the NIH Grants Policy Statement Section 8.6.1 Financial Reports, http://grants.nih.gov/grants/policy/policy.htm#gps, for additional information on this submission requirement. The final FFR must indicate the exact balance of unobligated funds and may not reflect any unliquidated obligations. There must be no discrepancies between the final FFR expenditure data and the real-time cash drawdown data in PMS. NIH will close the awards using the last recorded cash drawdown level in PMS for awards that do not require a final FFR on expenditures. It is important to note that for financial closeout, if a grantee fails to submit a required final expenditure FFR, NIH will close the grant using the last recorded cash drawdown level.

A Final Invention Statement and Certification form (HHS 568), (not applicable to training, construction, conference or cancer education grants) must be submitted within 120 days of the expiration date. The HHS 568 form may be downloaded at: http://grants.nih.gov/grants/forms.htm. This paragraph does not apply to Training grants, Fellowships, and certain other programs—i.e., activity codes C06, D42, D43, D71, DP7, G07, G08, G11, K12, K16, K30, P09, P40, P41, P51, R13, R25, R28, R30, R90, RL5, RL9, S10, S14, S15, U13, U14, U41, U42, U45, UC6, UC7, UR2, X01, X02.

Unless an application for competitive renewal is submitted, a Final Research Performance Progress Report (Final RPPR) must also be submitted within 120 days of the period of performance end date. If a competitive renewal application is submitted prior to that date, then an Interim RPPR must be submitted by that date as well. Instructions for preparing an Interim or Final RPPR are at: https://grants.nih.gov/grants/rppr/rppr_instruction_guide.pdf. Any other specific requirements set forth in the terms and conditions of the award must also be addressed in the Interim or Final RPPR. *Note that data reported within Section I of the Interim and Final RPPR forms will be made public and should be written for a lay person audience*.

NIH requires electronic submission of the final invention statement through the Closeout feature in the Commons.

NOTE: If this is the final year of a competitive segment due to the transfer of the grant to another institution, then a Final RPPR is not required. However, a final expenditure FFR is required and must be submitted electronically as noted above. If not already submitted, the Final Invention Statement is required and should be sent directly to the assigned Grants Management Specialist.

Recipients must administer the project in compliance with federal civil rights laws that prohibit discrimination on the basis of race, color, national origin, disability, age, and comply with applicable conscience protections. The recipient will comply with applicable laws that prohibit discrimination on the basis of sex, which includes discrimination on the basis of gender identity, sexual orientation, and pregnancy. Compliance with these laws requires taking reasonable steps to provide meaningful access to persons with limited English proficiency and providing programs that are accessible to and usable by persons with disabilities. The HHS Office for Civil Rights provides guidance on complying with civil rights laws enforced by HHS. See https://www.hhs.gov/civil-rights/for-providers/provider-obligations/index.html and https://www.hhs.gov/.

- Recipients of FFA must ensure that their programs are accessible to persons with limited English proficiency. For guidance on meeting the legal obligation to take reasonable steps to ensure meaningful access to programs or activities by limited English proficient individuals, see https://www.hhs.gov/civil-rights/for-individuals/special-topics/limited-english-proficiency/fact-sheet-guidance/index.html and https://www.lep.gov.
- For information on an institution's specific legal obligations for serving qualified individuals with disabilities, including providing program access, reasonable modifications, and to provide effective communication, see http://www.hhs.gov/ocr/civilrights/understanding/disability/index.html.
- HHS funded health and education programs must be administered in an environment free of sexual harassment; see https://www.hhs.gov/civil-rights/for-individuals/sex-discrimination/index.html. For information about NIH's commitment to supporting a safe and respectful work environment, who to contact with questions or concerns, and what NIH's expectations are for institutions and the individuals supported on NIH-funded awards, please see https://grants.nih.gov/grants/policy/harassment.htm.
- For guidance on administering programs in compliance with applicable federal religious nondiscrimination laws and applicable federal conscience protection and associated anti-discrimination laws, see https://www.hhs.gov/conscience/conscience-protections/index.html and https://www.hhs.gov/conscience/religious-freedom/index.html.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.

Treatment of Program Income:
Additional Costs

SECTION IV – [redacted]

Clinical Trial Indicator: No
This award does not support any NIH-defined Clinical Trials. See the NIH Grants Policy Statement Section 1.2 for NIH definition of Clinical Trial.

This award related to DEI no longer effectuates agency priorities. It is the policy of NIH not to further prioritize these research programs. Therefore, the award is terminated. Please be advised that your organization, as part of the orderly closeout process will need to submit the necessary closeout documents (i.e., Final Research Performance Progress Report, Final Invention Statement, and the Final Federal Financial Report (FFR), as applicable) within 120 days of the end of this grant to avoid unilateral closeout.

With prior approval, a portion of funds may be used to support patient safety and orderly closeout of the project. Funds used to support any other research activities will be disallowed and recovered.

NIH is taking this enforcement action in accordance with 2 C.F.R. § 200.340 as implemented in NIH GPS Section 8.5.2. This letter represents the final decision of the
NIH. It shall be the final decision of the Department of Health and Human Services (HHS) unless within 30 days after receiving this decision you mail or email a written notice of
appeal to Dr. Matthew Memoli. Please include a copy of this decision, your appeal justification, total amount

in dispute, and any material or documentation that will support your position. Finally, the appeal must be signed by the institutional official authorized to sign award applications and must be postmarked no later than 30 days after the postmarked date of this notice.

THE FOLLOWING TERMS FROM THE PREVIOUS NOTICE OF AWARD LETTER ISSUED ON 2/28/2024 ALSO APPLY TO THIS AWARD:

This project is suspended and therefore, no research activities may be carried out under this award and no funds may be obligated nor charged for any reason under this project. NIH is carrying out the suspension under NIH's independent authority under the Public Health Service Act to determine research priorities and ensure program integrity and is not being carried out under any of the Executive Orders.

THE FOLLOWING TERMS FROM THE PREVIOUS NOTICE OF AWARD LETTER ISSUED ON 11/28/2024 ALSO APPLY TO THIS AWARD:

INFORMATION: This revised award extends the 05-year budget period and project period 12 months, as requested in the awardee's letter dated 10/25/2024. The new budget and project period expiration date will be 01/31/2026. Funds remaining in the 05- year may be used during the extension; however, no additional funds have been awarded.

THE FOLLOWING TERMS FROM THE PREVIOUS NOTICE OF AWARD LETTER ISSUED ON 1/22/2023 ALSO APPLY TO THIS AWARD:

REQUIREMENT: This award is subject to the conditions set forth in PAR-18-484, NIH Research Project Grant (Parent R01 Clinical Trial Not Allowed), NIH Guide to Grants and Contracts, 12/06/2017, which is hereby incorporated by reference as special terms and conditions of this award.

Copies of this RFA may be accessed at the following internet address:
https://grants.nih.gov/grants/guide/pa-files/PA-18-484.html

Copies may also be obtained from the Grants Management Contact indicated in the terms of award.

RESTRICTION: In addition to the PI, the following individuals are named as key personnel:

Kenneth Mayer

Written prior approval is required if any of the individual(s) named above withdraws from the project entirely, is absent from the project during any continuous period of 3 months or more, or reduces time devoted to the project below 0.39 person months.

REQUIREMENT: Use of humans and animals in any new activities must be requested prior to the start of the activity and must be approved in writing in advance by the NIMHD. See NOT-MD-08-002, "Guidance and Clarification on NCMHD Policy on Prior Approval for Subprojects and Pilot Projects Involving Human Subjects or Vertebrate Animals," NIH Guide to Grants and Contracts, April 29, 2008, which is hereby incorporated by reference as special terms and conditions of this award. See also NOT-OD-15-129, "**Prior NIH Approval of Human Subjects Research in Active Awards Initially Submitted without Definitive Plans for Human Subjects Involvement (Delayed Onset Awards): Updated Notice,**" and NIH-OD-15-128, "**Guidance on Changes That Involve Human Subjects in Active Awards and That Will Require Prior NIH Approval: Updated Notice.**"

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AWARD NUMBER: [redacted]

INSTITUTION: [redacted]

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