

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
NATIONAL INSTITUTES OF HEALTH

FY 2022 CONGRESSIONAL JUSTIFICATION

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## 7q11.23 Duplication Syndrome

The agreement directs NIH to include updates on the following research, projects, and programs in the fiscal year 2022 Congressional Justification: gastric cancer; psycho-social distress in cancer research; the Office of Cancer Survivorship; progress in treating rare cancers; the Surveillance, Epidemiology, and End Results [SEER] Registry; Temporomandibular Disorders; diabetes, Rapid Acceleration of Diagnostics; 7q11.23 Duplication Syndrome; and Hereditary Spastic Paraparesis 49 (TECPR2). (Joint Explanatory Statement, p. 45)

### **Action Taken or to be Taken**

The National Center for Advancing Translational Sciences (NCATS) is working to find treatments for rare diseases, most of which are inherited disorders caused by changes (mutations) to a patient's genetic material (genes and chromosomes) that are present at birth, including 7q11.23 duplication syndrome. With over 7,000 different rare diseases, the approach of tackling one disease at a time will take too long. One NCATS goal is to move from investigating one disease at a time to investigating many diseases at a time, and thus speed the development of treatments for multiple diseases simultaneously and ultimately help more patients more quickly.

Many rare diseases are caused by genetic abnormalities, some of which, such as 7q11.23 duplication syndrome, are due to a small amount of additional (duplicated) genetic material from a chromosome (chromosome 7 in the case of 7q11.23 duplication syndrome). In other genetic diseases, parts of chromosomes may be missing (deletions), have changes (mutations) in individual genes leading to too much ("dominant" or "gain of function" mutations) or too little (deficiency syndromes) activity, or a variety of other changes in the patients' DNA. NCATS is working to expand research on rare genetic and chromosomal abnormalities by developing new and improved tools needed to conduct such research. Genetic therapies, such as gene replacement, gene silencing, and gene editing, are particularly relevant to rare disease patients, as more than 80 percent of rare diseases have a known monogenic (single gene) cause, and genetic therapies have the potential to correct or ameliorate the underlying genetic defects. For larger genetic abnormalities, such as 7q11.23 duplication syndrome, that affect many genes, gene editing may also be a relevant treatment strategy. A major challenge with gene editing is to find better ways to deliver genome editors into the relevant cell type(s). NCATS is coordinating an National Institutes of Health (NIH) Common Fund program on Somatic Cell Genome Editing (SCGE),<sup>1</sup> an effort that involves staff from several other NIH Institutes and Centers as well. Notably, 20 of the projects supported by the SCGE program focus on gene-based delivery technologies.

For a disease that has developmental consequences, early diagnosis is important. To explore this issue further, NCATS is planning to host a workshop focused on early diagnostic strategies for rare genetic diseases in Spring 2021. In addition, NCATS is currently supporting a project titled "Precision Medicine in the Diagnosis of Genetic Disorders in Neonates" that is examining the use of whole genome sequencing to rapidly diagnose newborns with undiagnosed diseases in neonatal intensive care units. The overarching goal is to examine the clinical utility and

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<sup>1</sup> [commonfund.nih.gov/editing](https://commonfund.nih.gov/editing)

operational infrastructure of a neonatal gene panel in high-risk neonates in order to determine if it will provide earlier diagnosis and better clinical care than standard diagnostic care.

## **Academic and Non-Profit Institutional Research Using Human Ocular Tissue from Not-for-Profit Eye Banks**

Macular degeneration is the leading cause of blindness and impacts some 15 million people in the U.S., with an estimated 200,000 new cases annually. The Committee is aware that, due to the high cost of human ocular tissue, many academic researchers resort to using animal tissue when studying diseases and conditions of the eye. This is problematic as animal tissue is not a perfect equivalent to human tissue, and certain diseases, such as macular degeneration, are not present in animal tissue. The Committee encourages NEI to consider establishing an ocular tissue program to achieve cost savings and facilitate critical ocular research utilizing tissue provided by non-profit organizations to academic and other not-for-profit research entities. Such a program could facilitate critical research to eradicate the debilitating impact of macular degeneration and other ocular disorders (House Report, p. 114).

### **Action Taken or To Be Taken**

The National Eye Institute (NEI) has been meeting with key stakeholders to assess the challenges vision scientists encounter in obtaining human ocular (eye) tissue for research. In the U.S., a network of non-profit eye banks obtain and distribute donor eye tissues for use in patients (typically corneal transplantation) or for research. In October 2018, results of a 407-participant survey conducted by the Association for Research in Vision and Ophthalmology found that many vision scientists reported difficulty in accessing enough quality human eye tissue for their research.<sup>2</sup> For example, despite organized procurement systems, some have had to rely on personal networks to acquire tissue. Depending on the type of research being conducted, researchers typically have specific eye tissue requirements including age-matched normal and diseased tissue, clinical documentation, and customized preparation methods. These specifications introduce procurement challenges (e.g., lack of supply from donor networks, complex recovery methods, timing of delivery for fresh tissue, cost, differing standards to procure high quality tissue).

NEI is taking several approaches to expand access to human eye tissue for the vision research community. Along with other NIH Institutes and Centers, NEI currently co-funds the Human Tissue and Organ Research Resource (HTORR), a division of the National Disease Research Interchange, the only not-for-profit NIH-funded organization providing human tissues for research.<sup>3</sup> HTORR offers a customized service to researchers seeking high quality human samples by collaborating with tissue source sites throughout the U.S. Separately, NEI researchers are preparing a small-scale pilot study to compare the output and utility of RNA extracted from human ocular tissue preserved using different methods: 1) Formalin-fixed paraffin-embedded method, a common preservation and preparation technique for biological specimens, versus 2) Freshly frozen ocular tissue samples. The latter are more costly and sensitive than fixed tissues. In comparing tissue types, fixed tissue has generated similar RNA results as frozen tissue. This study will inform the utility and effectiveness of these methods and

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<sup>2</sup> Stamer, W. Daniel, Andrew M. Williams, Stephen Pflugfelder, and Sarah E. Coupland. "Accessibility to and quality of human eye tissue for research: A cross-sectional survey of ARVO members." *Investigative Ophthalmology & Visual Science* 59, no. 12 (2018): 4783-4792. [iovs.arvojournals.org/article.aspx?articleid=2705713](https://iovs.arvojournals.org/article.aspx?articleid=2705713).

<sup>3</sup> "NIH HTORR." National Disease Research Interchange. Accessed October 13, 2020. [ndriresource.org/nihhtorr](https://ndriresource.org/nihhtorr).

may help alleviate some of the demand for fresh ocular tissue for vision research. Acknowledging that not all barriers have been resolved, NEI will continue assessing the needs of the vision research community through collaborating with external stakeholders, exploring ways to improve existing efforts, and establishing best practices to access and utilize eye tissue for research.

## Addressing Maternal Mortality Disparities

The Committee encourages NICHD to continue its support of research into the leading causes of maternal morbidity and mortality. As Black women experience maternal mortality at nearly four times the rate of white women, the Committee strongly urges NICHD to support research that investigates factors contributing to this disparity, and test evidence-based interventions to address this disparity. The Committee also encourages NICHD to collaborate with the National Institute for Minority Health and Health Disparities (NIMHD) as appropriate to develop targeted funding opportunities (House Report, p. 110).

### **Action taken or to be taken**

In the United States, women who are members of some racial or ethnic minorities face higher rates of maternal morbidity and mortality compared to White women. The pregnancy-related mortality ratios per 100,000 live births during the period of 2011-2016<sup>4</sup> were 42.4 deaths among African American women, 30.4 for American Indian/Alaska Native women, 14.1 for Asian/Pacific Islander women, 13 for White women, and 11.3 for Hispanic or Latina women. NIH is continuing its longstanding research efforts to improve maternal health and prevent maternal mortality and morbidity, with 22 Institutes and Centers (ICs) supporting over \$334 million in research projects in FY 2019; over 50 percent of the projects were funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD).

NICHD is committed to supporting research to understand the causes of and to develop potential interventions for preventing maternal mortality and treating maternal morbidity. NICHD-supported investigators have shown that pregnancy-related health outcomes are influenced by a woman's underlying health and other factors such as race, ethnicity, geography, age, income, and potential complications of co-occurring conditions such as obesity. For example, one NICHD-funded study indicated that differences in hospital quality can significantly contribute to racial and ethnic disparities in health outcomes. Another study found a reduction in the risk of severe maternal morbidity from obstetric hemorrhage when hospitals implemented evidence-based recommendations to improve clinical practice. The reduction was more dramatic for Black women than for White women.

As requested by Congress, NICHD, contracted with the National Academies of Sciences, Engineering, and Medicine, to conduct a study on the factors that may affect the choice of birth setting, examining risk factors and social determinants related to birth settings that influence maternal health outcomes. The report,<sup>5</sup> released in 2020, concluded that improvements to the maternity workforce and insurance policies, such as involvement of a wider range of health care professionals and better insurance coverage for non-hospital births, could help minimize risks regardless of the birth setting. It also suggested ways to improve childbirth services in hospital settings, birthing centers, and home births.

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<sup>4</sup> [www.cdc.gov/reproductivehealth/maternal-mortality/pregnancy-mortality-surveillance-system.htm#:~:text=During%202011%E2%80%932016%2C%20the%20pregnancy,for%20black%20non%20Hispanic%20women.](https://www.cdc.gov/reproductivehealth/maternal-mortality/pregnancy-mortality-surveillance-system.htm#:~:text=During%202011%E2%80%932016%2C%20the%20pregnancy,for%20black%20non%20Hispanic%20women.)

<sup>5</sup> [www.nationalacademies.org/our-work/assessing-health-outcomes-by-birth-settings](https://www.nationalacademies.org/our-work/assessing-health-outcomes-by-birth-settings)



NICHD regularly collaborates with other NIH ICs that support research on maternal mortality and morbidity. In FY 2020, the National Institute on Minority Health and Health Disparities (NIMHD) launched *Addressing Racial Disparities in Maternal Mortality and Morbidity* (Request For Applications (RFA) MD-20-008), an initiative designed to support multidisciplinary research examining the efficacy and/or effectiveness of multi-level interventions to reduce health and health care disparities in maternal morbidity and mortality experienced by racial and ethnic minority women. NIMHD supported five grants through this initiative, covering topics such as hospital quality, participation of doulas throughout continuum of care, and a specific focus on postpartum health. NIMHD is also supporting research to test the effectiveness and cost-effectiveness of an intervention that expands access to enhanced prenatal and postnatal services to address maternal morbidity and mortality in Black women.

NIH recently launched the initiative *Implementing a Maternal Health and Pregnancy Outcomes Vision for Everyone* (IMPROVE) by awarding over \$7 million in grants through a Notice of Special Interest on Maternal Mortality.<sup>6,7</sup> This initiative is supported by multiple NIH ICOs and co-led by NICHD, the NIH Office of the Director, and the NIH Office of Research on Women's Health. The goal of the IMPROVE initiative is to address the health disparities in women disproportionately affected by maternal mortality and morbidity, including geographic disparities and social determinants of health. The COVID-19 pandemic has added even more urgency to this work, as researchers move quickly to recognize how this disease affects maternal, fetal, and newborn health outcomes. NICHD's *Gestational Research Assessments of coVID (GRAVID)* study is leveraging its Maternal Fetal Medicine Units Network to analyze the medical records of a diverse group of 24,500 women to evaluate whether changes to healthcare delivery implemented as a result of the pandemic have led to higher rates of pregnancy-related complications and cesarean deliveries. Understanding the underlying social, economic, and structural factors are critical if we are to improve maternal health and prevent maternal mortality and severe morbidity.

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<sup>6</sup> [grants.nih.gov/grants/guide/notice-files/NOT-OD-20-104.html](https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-104.html)

<sup>7</sup> [www.nih.gov/improve-initiative](https://www.nih.gov/improve-initiative)

## **Addressing Youth Mental Health Disparities**

The Committee is encouraged by the work of NIMH to support research on issues related to youth mental health, including suicide among youth. The Committee is further encouraged by NIMH efforts to address mental health disparities among underrepresented and underserved youth. To guide this continuing work, the Committee requests within 180 days of enactment of this Act, a 10-year strategic plan with long-term plan with short-term goals from NIMH with a goal of eliminating racial mental health disparities in youth by 2030. This plan should include, but is not limited to: (1) convening a consensus conference, which could be used to guide strategic plan development; (2) identifying and/or creating funding mechanisms that actively support the development of evidence-based practices for racial mental health disparities populations; (3) developing targeted funding opportunities for projects in communities with disparities starting in fiscal year 2021; and (4) developing structures to solicit wide-ranging community input on barriers to addressing mental health disparities. This may include quarterly workshops to solicit community input. The Committee requests an update in the fiscal year 2022 Congressional Justification on progress towards achieving goals in this strategic plan. The Committee further encourages the Institute to convene a consensus conference that includes: leading extramural experts on health disparities; representatives from other relevant NIH Institutes and Centers like the HHS Office of Minority Health, NICHD, NIMHD; and public stakeholders to discuss research opportunities and gaps, as well as evidence-based solutions and therapeutic interventions. At the conclusion of the conference, the Committee requests a report which should include priority areas for additional study to advance research in addressing mental health disparities in youth (House Report, p. 122).

### **Action Taken or To Be Taken**

Striking disparities exist in the prevalence and outcomes of mental illnesses within the United States and worldwide. Individuals from underserved communities frequently experience reduced access to evidence-based mental health services and lower levels of treatment engagement, and they experience fewer follow-ups in a variety of provider settings. To support mental health equity, the National Institute of Mental Health (NIMH) supports research that addresses the needs of individuals and communities across age, race, ethnicity, culture, language, gender identity, sexual orientation, geography, insurance status, socioeconomic status, and other social determinants of health.

NIMH is invested in understanding and reducing mental health disparities, particularly in vulnerable youth. To drive these efforts, NIMH is developing a 10-year strategic framework with the goal of reducing racial mental health disparities in youth by 2030. This framework will include both short-term and long-term goals, in an effort to pursue short-range gains and take advantage of future advancements to reduce or eliminate these disparities.

To guide strategic framework development, NIMH will convene leading extramural experts on health disparities; representatives from other relevant NIH Institutes and Centers like the U.S. Department of Health and Human Services Office of Minority Health, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and National Institute on Minority Health and Health Disparities (NIMHD); and, public stakeholders. This representative

group will discuss research opportunities and gaps, as well as evidence-based solutions and therapeutic interventions. Using this expert guidance, NIMH plans to produce a report identifying priority areas for additional study to advance research in addressing mental health disparities in youth. In addition to this conference, NIMH plans to regularly engage and solicit community input on barriers to addressing mental health disparities. As an example, one of the Institute's first efforts, prompted by a Congressional Black Caucus report,<sup>8</sup> community input, and building on a NIMH-hosted virtual roundtable,<sup>9</sup> will be to strengthen research on the alarming rise in suicide rates amongst Black youth.

As part of the strategic framework, NIMH will identify funding mechanisms that support the development of evidence-based mental health practices for racial and ethnic health disparities populations. As an example of our recent efforts on this front, NIMH published a Notice of Special Interest (NOSI) in Research on Risk and Prevention of Black Youth Suicide.<sup>10</sup> NIMH will continue to consider the development of targeted funding opportunities for projects in communities with health disparities based on future funding availability. For example, NIMH launched an initiative supporting projects aimed at implementing and sustaining evidence-based mental health practices in low-resource settings to achieve equity in patient outcomes.<sup>11</sup> Under this initiative, NIMH is supporting innovative approaches to remediate barriers to provision, receipt, and/or benefit from evidence-based practices.<sup>12,13,14,15</sup> These studies may also generate new information about factors integral to achieving equity in mental health outcomes, with due consideration for the needs of individuals across the life span, including youth. Another recent initiative aims to establish Practice-Based Suicide Prevention Research Centers, which, in part, are designed to support transdisciplinary programs of research in vulnerable populations and address health disparities that may affect at-risk youth.<sup>16</sup>

With the 10-year strategic framework described above, NIMH hopes to demonstrate its commitment to research aimed at understanding and eliminating the inequalities that lead to poorer mental health outcomes in underserved and underrepresented youth. The Institute will continue to encourage and support research to develop and increase the reach of effective, culturally- and age-appropriate interventions to reduce the burden of mental illnesses and promote prevention and resilience among our nation's youth.

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<sup>8</sup> [www.stevelfund.org/wp-content/uploads/2019/12/FULL-TASKFORCE-REPORT.pdf](http://www.stevelfund.org/wp-content/uploads/2019/12/FULL-TASKFORCE-REPORT.pdf)

<sup>9</sup> [www.nimh.nih.gov/news/media/2020/responding-to-the-alarm-addressing-black-youth-suicide.shtml](http://www.nimh.nih.gov/news/media/2020/responding-to-the-alarm-addressing-black-youth-suicide.shtml)

<sup>10</sup> [grants.nih.gov/grants/guide/notice-files/NOT-MH-20-055.html](https://grants.nih.gov/grants/guide/notice-files/NOT-MH-20-055.html)

<sup>11</sup> [grants.nih.gov/grants/guide/rfa-files/rfa-mh-20-400.html](https://grants.nih.gov/grants/guide/rfa-files/rfa-mh-20-400.html)

<sup>12</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=10112643](https://projectreporter.nih.gov/project_info_description.cfm?aid=10112643)

<sup>13</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=10113786](https://projectreporter.nih.gov/project_info_description.cfm?aid=10113786)

<sup>14</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=10114092](https://projectreporter.nih.gov/project_info_description.cfm?aid=10114092)

<sup>15</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=10247224](https://projectreporter.nih.gov/project_info_description.cfm?aid=10247224)

<sup>16</sup> [grants.nih.gov/grants/guide/pa-files/PAR-20-286.html](https://grants.nih.gov/grants/guide/pa-files/PAR-20-286.html)

## **Alzheimer’s Disease and Dementia Screening Tools**

The Committee remains very interested in opportunities to detect cognitive impairment that may be caused by Alzheimer’s disease and related dementias as early as possible. The Committee directs NIH to update its analysis of validated screening tools, including digital screening tools, that are able to reliably detect mild cognitive impairment (MCI). This review should focus on identifying tools that have been developed in the time since the last assessment was conducted and on providing information to assist healthcare providers in regularly using such tools to assess the cognitive health of their patients (House Report, p. 117).

### **Action Taken or To Be Taken**

The National Institute on Aging (NIA) provides links to a range of cognitive screening tools on its “Alzheimer’s and Dementia Resources for Professionals” and “Assessing Cognitive Impairment in Older Patients” web pages<sup>17,18</sup>; these tools may be used to detect mild cognitive impairment (MCI) in addition to more significant cognitive decline. NIA subject matter experts (SMEs) have provided guidance on which tools should be listed as options for healthcare providers, based on the scientific information available for each individual tool. NIA last reviewed and updated this information in March 2020. NIA will review the list of cognitive screening tools, including those for MCI, with its SMEs on an annual basis. However, the institute anticipates that future consideration of available cognitive screening tools may be most substantively informed by the output of the Consortium for Detecting Cognitive Impairment, Including Dementia (DetectCID),<sup>19</sup> a national consortium funded by the National Institute of Neurological Disorders and Stroke to test and validate assessment paradigms for cognitive impairment that can be used in primary health care and other everyday clinical settings. Three research teams across the U.S. are focusing on validating experimental paradigms that are simple to use, standardized, and take 10 minutes or less to administer. With phase 1 completed, the research sites have developed three different clinical paradigms based on a range of approaches and tools, from traditional pen and paper testing complemented with gait assessment to sophisticated user-friendly electronic platforms, while at the same time ensuring interoperability across various sites. Now in phase 2, DetectCID is conducting cohort and population testing, optimization, and validation, with significant testing in primary care and other everyday clinical settings. Preliminary data suggest that these are promising assessment approaches, but it will likely take several more years to complete validation testing (funding is planned through 2022).

NIA also anticipates that research funded in response to a June 2017 Funding Opportunity Announcement (FOA) , entitled Mobile Monitoring of Cognitive Change, will also be informative to healthcare providers in the future.<sup>20</sup> This FOA was developed to address the need for new measures of cognitive change and MCI, and therefore, invited applications to design and implement research infrastructure that will enable the monitoring of cognitive abilities and age, state, context, or health condition-related changes in cognitive abilities on mobile devices. This effort will include the development (or support for development) of apps on the Android and iOS

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<sup>17</sup> [www.nia.nih.gov/health/alzheimers-dementia-resources-for-professionals](http://www.nia.nih.gov/health/alzheimers-dementia-resources-for-professionals)

<sup>18</sup> [www.nia.nih.gov/health/assessing-cognitive-impairment-older-patients](http://www.nia.nih.gov/health/assessing-cognitive-impairment-older-patients)

<sup>19</sup> [www.detectcid.org/](http://www.detectcid.org/)

<sup>20</sup> [grants.nih.gov/grants/guide/rfa-files/rfa-ag-18-012.html](http://grants.nih.gov/grants/guide/rfa-files/rfa-ag-18-012.html)

platforms, the validation of tests and items to be used on the two leading smartphone platforms in age groups ranging from 20 to 85, and the norming of successfully validated measures to nationally representative U.S. population samples that will also receive gold standard measures, including the NIH Toolbox® for Assessment of Behavioral and Neurological Function. A goal of this project is to also support data collection efforts from participants enrolled in projects awarded through this FOA, as well as other NIH-funded studies through FY 2022, and enable the widespread sharing of both the collected data and the test instruments. Two awards were made in response to this FOA, and research is currently underway.

In addition, other ongoing research includes the development of other novel measures, including digital biomarkers, collected unobtrusively, that may help clinicians identify who is at higher risk, as well as brief measures that can be used by primary care or given to a close associate/spouse of the affected person. These have been studied in more diverse populations to help identify people with not only MCI and AD, but also other dementias.

## Amyloidosis

The Committee encourages NIH to continue its expansion of research efforts in amyloidosis, a group of rare diseases characterized by abnormally folded protein deposits in tissues. Amyloidosis is often fatal, and there is no known cure. Current methods of treatment are risky and unsuitable for many patients. Average survival without treatment is in months. The Committee directs NIH to inform the Committee on the steps NIH has taken to understand the causes of amyloidosis and the measures taken to improve the diagnosis and treatment of this devastating group of diseases in the fiscal year 2022 Congressional Justification (House Report, p. 129).

### **Action Taken or To Be Taken**

NIH supports research on the pathogenesis, diagnosis, and treatment of systemic amyloidosis. For example, investigators supported by the National Institute on Aging (NIA) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) are working to determine why<sup>21</sup> and how misfolded proteins<sup>22</sup> clump together to cause disease. NIDDK intramural scientists are also investigating how various “chaperones”<sup>23</sup> (proteins that assist in the folding or unfolding of other proteins) may affect amyloid formation and/or propagation in a yeast model system, and are studying the biology of chaperones in the hope of one day manipulating their activities as a potential therapeutic strategy.

Elsewhere, NIA-supported researchers have elucidated the structures of transthyretin (TTR) and immunoglobulin light chain fibrils—proteins associated with different forms of amyloidosis—and developed compounds<sup>24</sup> that cap the ends of the developing fibrils, preventing their further growth. Some of these compounds have advanced to preclinical testing in model systems. Other NIA-supported investigators are developing small-molecule activators<sup>25</sup> of a cellular pathway involved in protein maintenance; these compounds could potentially be used to treat a range of conditions including amyloidosis, cardiovascular disease, diabetes, and Alzheimer’s disease. Still, other investigators are developing monoclonal antibodies<sup>26</sup> that can efficiently target and clear amyloid from cells. In addition, NIDDK-supported researchers are working to develop potential new therapeutics<sup>27</sup> for the treatment of immunoglobulin light chain amyloidosis.

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<sup>21</sup>[projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9986748&icde=52441963&ddparam=&ddvalue=&ddsueb=&cr=11&csb=default&cs=ASC&pball=](https://projectreporter.nih.gov/project_info_description.cfm?aid=9986748&icde=52441963&ddparam=&ddvalue=&ddsueb=&cr=11&csb=default&cs=ASC&pball=)

<sup>22</sup>[projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9923528&icde=52441763&ddparam=&ddvalue=&ddsueb=&cr=1&csb=default&cs=ASC&pball=](https://projectreporter.nih.gov/project_info_description.cfm?aid=9923528&icde=52441763&ddparam=&ddvalue=&ddsueb=&cr=1&csb=default&cs=ASC&pball=)

<sup>23</sup>[projectreporter.nih.gov/project\\_info\\_description.cfm?aid=10008651&icde=52441963&ddparam=&ddvalue=&ddsueb=&cr=12&csb=default&cs=ASC&pball=](https://projectreporter.nih.gov/project_info_description.cfm?aid=10008651&icde=52441963&ddparam=&ddvalue=&ddsueb=&cr=12&csb=default&cs=ASC&pball=)

<sup>24</sup>[projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9852939&icde=52441832&ddparam=&ddvalue=&ddsueb=&cr=1&csb=default&cs=ASC&pball=](https://projectreporter.nih.gov/project_info_description.cfm?aid=9852939&icde=52441832&ddparam=&ddvalue=&ddsueb=&cr=1&csb=default&cs=ASC&pball=)

<sup>25</sup>[projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9904304&icde=52441854&ddparam=&ddvalue=&ddsueb=&cr=1&csb=default&cs=ASC&pball=](https://projectreporter.nih.gov/project_info_description.cfm?aid=9904304&icde=52441854&ddparam=&ddvalue=&ddsueb=&cr=1&csb=default&cs=ASC&pball=)

<sup>26</sup>[projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9854083&icde=52441876&ddparam=&ddvalue=&ddsueb=&cr=1&csb=default&cs=ASC&pball=](https://projectreporter.nih.gov/project_info_description.cfm?aid=9854083&icde=52441876&ddparam=&ddvalue=&ddsueb=&cr=1&csb=default&cs=ASC&pball=)

<sup>27</sup>[projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9941866&icde=52441963&ddparam=&ddvalue=&ddsueb=&cr=17&csb=default&cs=ASC&pball=](https://projectreporter.nih.gov/project_info_description.cfm?aid=9941866&icde=52441963&ddparam=&ddvalue=&ddsueb=&cr=17&csb=default&cs=ASC&pball=)

Research on the genetics of amyloidosis is also ongoing. A recent NIDDK-supported study reported a significant association of the hereditary TTR amyloid-causing genetic variant V122I with heart failure in those of African or Hispanic/Latino ancestry.

Finally, early and accurate diagnosis of systemic amyloidosis remains an active area of study. For example, individuals with smoldering multiple myeloma (SMM) or monoclonal gammopathy of unknown significance (MGUS) often go on to develop light chain amyloidosis (AL). However, diagnosis in these cases is often delayed, and patients older than 60 are often too sick at diagnosis to undergo intensive life-extending therapy. NIA-supported investigators have established the Screening to Improve Survival in AL Amyloidosis<sup>28</sup> study, in which genetic screening is used to identify AL-related light chain genes among individuals with SMM or MGUS, enabling diagnosis of AL before significant organ damage occurs. In a separate study<sup>29</sup>, investigators are binding the molecules in some potentially therapeutic compounds to nanoparticles that enable visualization by magnetic resonance imaging, facilitating diagnosis of these diseases.

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<sup>28</sup>[projectreporter.nih.gov/project\\_info\\_description.cfm?aid=10110939&icde=52441904&ddparam=&ddvalue=&dds ub=&cr=1&csb=default&cs=ASC&pbll=](http://projectreporter.nih.gov/project_info_description.cfm?aid=10110939&icde=52441904&ddparam=&ddvalue=&dds ub=&cr=1&csb=default&cs=ASC&pbll=)

<sup>29</sup>[projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9740794&icde=52441929&ddparam=&ddvalue=&dds ub=&cr=1&csb=default&cs=ASC&pbll=](http://projectreporter.nih.gov/project_info_description.cfm?aid=9740794&icde=52441929&ddparam=&ddvalue=&dds ub=&cr=1&csb=default&cs=ASC&pbll=)

## **Amyotrophic Lateral Sclerosis**

The Committee strongly supports the Transformative Research Award program for ALS and directs the Director to continue to fund this critical initiative in fiscal year 2021 (House Report, p. 129).

### **Action taken or to be taken**

NIH appreciates the Committee's encouragement and support for advancing ALS research. In June 2020, NIH announced the launch of the Accelerating Leading-edge Science in ALS (ALS<sup>2</sup>) program to spur innovative research into the basic biology and underlying causes of ALS.<sup>30</sup> This \$25 million NIH Common Fund Initiative is in collaboration with the National Institute of Neurological Disorders and Stroke (NINDS), National Institute of General Medical Sciences (NIGMS), National Institute of Environmental Health Sciences (NIEHS), and National Institute on Aging (NIA), and will encourage scientists to pursue exceptionally innovative, interdisciplinary, and/or unconventional research that could dramatically change our understanding of the biological basis of ALS and further pave the way for effective therapy development and clinical application. NIH has received 58 applications in response to this announcement. As of February 2021, the peer review process of these grant applications is ongoing, and awards will be funded through the FY 2021 Transformative Research Award (TRA) program as part of the NIH Common Fund's High-Risk, High-Reward Research program.

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<sup>30</sup> [commonfund.nih.gov/tra/als2](https://commonfund.nih.gov/tra/als2)



## **Antimicrobial Resistance**

The Committee recommendation includes \$511,000,000 within NIAID to support research related to combatting antimicrobial resistance. The Committee remains concerned by the growing threat posed by antimicrobial resistant pathogens. While antibiotics are necessary to treat secondary infections, their expanded usage is causing concern that a lasting consequence of the virus could be increased global antibiotic resistance rates. The Committee supports NIAID's efforts to encourage innovative approaches to AMR, and directs NIH to brief the House and Senate Committees on Appropriations no later than 30 days after the enactment of this act, detailing the focus of its initiatives for fiscal years 2021–2022. The Committee also requests an update on AMR-related research activities in the fiscal year 2022 CJ (Senate Report, p. 95).

### **Action Taken or To Be Taken**

The National Institute of Allergy and Infectious Diseases (NIAID) is the lead Institute for antimicrobial resistance (AMR) research at the National Institutes of Health (NIH). NIAID released its *Antibiotic Resistance Research Framework: Current Status and Future Directions* in December 2019. This framework describes NIAID's AMR research portfolio and outlines innovative approaches to address AMR, including the development of diagnostics, therapeutics, vaccines, and alternatives to traditional antimicrobials. These efforts also are a critical component of the *National Action Plan for Combating Antibiotic-Resistant Bacteria 2020-2025*.

NIAID has invested in the development of rapid point-of-need diagnostics to identify drug-resistant infections, inform appropriate treatment strategies, and improve antibiotic stewardship. NIAID supported the development of six novel diagnostics recently cleared by the U.S. Food and Drug Administration, including tests for sepsis, urinary tract infections, pneumonia, chlamydia, and gonorrhea. NIH also partnered with the Biomedical Advanced Research and Development Authority (BARDA) to support the Antimicrobial Resistance Diagnostic Challenge competition to identify innovative and rapid point-of-need diagnostic tests. On August 5, 2020, Visby Medical, Inc., was awarded \$19 million in prize funding for its novel gonorrhea diagnostic test that may allow for rapid diagnosis and identification of the appropriate antibiotic treatment.

NIAID has supported the development of several novel therapeutics that are currently in late-stage clinical trials to treat complicated urinary tract infections, uncomplicated gonorrhea, and multidrug-resistant tuberculosis. In FY 2020, NIAID renewed funding for the Antibacterial Resistance Leadership Group, which oversees clinical research on AMR, including optimization and development of novel therapeutics, treatment strategies, and diagnostics. NIAID also provides in-kind and technical support for the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), a public-private partnership led by BARDA that invests in innovative approaches to combat drug-resistant bacteria. In addition, NIAID is soliciting proposals to create a chemistry center, which will synthesize and deliver rationally designed compound libraries to the scientific community for AMR drug discovery. In FY 2021, NIAID plans to launch an interdisciplinary research program focused on stimulating fundamental research to inform the development of new approaches to combat AMR.

NIAID supports research on non-traditional approaches to AMR, including vaccines for AMR pathogens and the use of bacteriophage therapy, beneficial bacteria, and fecal microbiota transplants to prevent and treat infections. NIAID scientists and grantees are studying the use of antibodies to help boost the human immune response to *Klebsiella pneumoniae* and other pathogens. NIAID has supported the development of the vaccine candidate, NDV-3, which has demonstrated efficacy in preventing recurrent vaginal yeast infections in humans and infections caused by *Staphylococcus aureus* and *Candida auris* in animal models. NIAID recently released a funding opportunity announcement to support the preclinical development of countermeasures against drug-resistant and other select pathogens, including non-traditional therapeutics. In FY 2021, NIAID will launch a program to support basic and translational research on bacteriophages to address knowledge gaps that hinder the development of phage-based products for AMR.

NIAID will continue to support innovative approaches to combating AMR including the development of improved strategies to identify, prevent, and treat drug-resistant infections.

## **Biomedical Research Facilities**

The bill provides \$50,000,000, the same as the fiscal year 2020 enacted level and \$50,000,000 above the fiscal year 2021 budget request, for grants to public and/or not-for-profit entities to expand, remodel, renovate, or alter existing research facilities or construct new research facilities as authorized under 42 U.S.C. section 283k. The Committee urges NIH to consider recommendations made by the NIH Working Group on Construction of Research Facilities, including making awards that are large enough to underwrite the cost of a significant portion of newly constructed or renovated facilities, as well as applicants that demonstrate innovative solutions and cost savings to meet safety and scientific requirements of facilities for basic, translational, and clinical research. The Committee also directs NIH to allocate no less than 25 percent of funding for this program to institutions that serve underrepresented and underprivileged populations and to institutions in the geographical areas with deficits in research resources, access to advanced technologies, and health-related services to ensure geographic and institutional diversity (House Report, p. 130).

### **Action Taken or To Be Taken**

The Office of Research Infrastructure Programs (ORIP), located in the Division of Program Coordination Planning and Strategic Initiatives (DPCPSI) within the National Institutes of Health (NIH) Office of the Director, is authorized to issue and manage construction awards to biomedical extramural research institutions, when funds for such awards are appropriated by Congress pursuant to authorities in 42 U.S.C. Section 283k.

In 2001 the NIH Working Group on Construction of Research Facilities of the Advisory Committee to the Director (ACD), NIH produced a report and recommendations on factors that limit the construction and renovation of biomedical research facilities. NIH has reviewed and considered the Working Group's recommendations and has subsequently implemented several of these recommendations. We did not require matching funds for construction grants and made awards that are large enough to underwrite the cost of a significant portion of constructing or renovating facilities. In aligning with the report, construction award considerations will include research intensive, and minority and emerging institutions, designated as Centers of Excellence. Other factors will include the broad geographic distribution of awards, including awards to Institutional Development Award-eligible states. In FY 2019 and FY 2020, NIH allocated no less than 25 percent of funding for this program to institutions that serve underrepresented and underprivileged populations and to institutions in the geographical areas with deficits in research resources, access to advanced technologies, and health-related services to ensure geographic and institutional diversity and the distribution of funds throughout the nation's biomedical research enterprise. NIH will continue that approach for construction fund allocations in FY 2021.

Consistent with Federal regulations, NIH submits all construction grant applications to a two-level peer review process. The first level of review considers scientific and technical merit and is conducted by the Scientific and Technical Review Board on Biomedical and Behavioral Research Facilities authorized by 42 U.S.C. Section 283k; the second level of review is carried out by the Council of Councils. Following funding decisions and issuing of the Notice of Award, applicants are required to submit design construction documents; these documents are

reviewed by the NIH Office of Research Facilities (ORF) Division of Technical Resources (DTR) to ensure compliance with the NIH Design Requirements Manual. Grant recipients are allowed to proceed with construction only after the design documents have been accepted by DTR. This formal review process ensures optimal stewardship and that taxpayers receive the full value of investments in biomedical research construction.

Finally, in accordance with Federal regulations, NIH provides construction surveillance to ensure that construction is compliant with the approved design documents. NIH monitors the long-term use of the facility for its intended functions under the Notice of Federal Interest.

## **BRAIN Initiative**

The Committee directs NIH to transfer \$50,000,000 from the NIH Innovation Account to NINDS to support the BRAIN Initiative. These funds were authorized in the 21st Century Cures Act (P.L. 114–255). This collaborative effort is revolutionizing the understanding of how neural components and their dynamic interactions result in complex behaviors, cognition, and disease, while accelerating the development of transformative tools to explore the brain in unprecedented ways, making information previously beyond reach accessible. To achieve this goal, two specific projects outlined in a recent BRAIN 2.0 Initiative Advisory Committee report stand out for their importance to human health and technical viability: the Human Brain Cell Atlas and the Human Brain Projectome. Both projects are separate transformative projects that will culminate in a body of data that will provide the clearest view possible of the human brain. To be successful, these projects will require a focused, large-scale effort with multidisciplinary teams with open platforms for dissemination of the tools and knowledge realized. The Committee requests an update on this effort in the fiscal year 2022 Congressional Justification (House Report, p. 104).

### **Action taken or to be taken**

The Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative is an ambitious program to develop and apply new technologies to answer fundamental questions about the brain and, ultimately, to understand and treat brain diseases. The BRAIN 2025 report, which a stellar interdisciplinary team of scientists and engineers developed in consultation with the research community, provided an overarching vision and specific objectives for this multi-faceted program.<sup>31</sup> The report included the recommendation that NIH monitor progress because of the unpredictable path of science and technology. The Advisory Committee to the NIH Director (ACD) charged the “BRAIN 2.0” Working Group (WG) with this task. After extensive evaluation and consultation with the scientific community, the BRAIN 2.0 WG reported to the ACD in 2019 that the Initiative was advancing on all major priorities of the plan, with many milestones already accomplished.<sup>32</sup> They also recommended that the Initiative continue on its productive path, developing technology while increasing application of the new methods to understand brain circuits while continuing to balance individual-investigator research with team science, both of which are vital to advance our understanding of the brain.

Because of the remarkable early progress of the Initiative, the BRAIN 2.0 WG also suggested that opportunities have emerged to invest in larger scale, transformative projects that might advance neuroscience far into the future. Transformative projects on three major themes are moving forward, with extensive internal and external discussions, pilot projects, and scientific workshops as appropriate to developing focused, large scale programs at the frontiers of science and technology. The major themes are: 1) Developing a comprehensive Human Brain Cell Atlas or “parts list” of cell types in the human brain, to serve as a foundation for understanding the brain and developing tools to target specific cell types; 2) Mapping connections to create a “wiring diagram” of the mammalian brain beginning with the nanometer connectome in the mouse and proceeding to the “projectome” of long range pathways in human (the Human Brain

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<sup>31</sup> [braininitiative.nih.gov/strategic-planning/brain-2025-report](https://braininitiative.nih.gov/strategic-planning/brain-2025-report)

<sup>32</sup> [acd.od.nih.gov/working-groups/brain2.0.html](https://acd.od.nih.gov/working-groups/brain2.0.html)

Projectome) and non-human primate brains; and 3) Developing an armamentarium of tools and resources to precisely access and modulate specific brain cell types and circuits, with the ultimate goal of revolutionary precision medicine applications in humans.

As these, and other aspects of the BRAIN Initiative move forward, ensuring that researchers across all of neuroscience have access to the knowledge and tools as they emerge is a high priority. Although the initial focus of the Initiative has been on basic research, enabling researchers to harness the emerging opportunities to develop new diagnostics and therapeutics is also a high priority for the future, with some notable successes already achieved in early stage human clinical trials. Certainly, the single cell technologies from the BRAIN Initiative have already revolutionized the study of brain tissue in a host of neurological and mental health disorders.

## **Building and Facilities (B&F)**

Last year, the National Academies of Sciences, Engineering, and Medicine [NASEM] released a report that stated there is a \$1,300,000,000 backlog in capital needs at NIH's Bethesda Campus. In the fiscal year 2020 bill, the Committee provided \$225,000,000 from HHS' Nonrecurring Expenses Fund for buildings and facilities at NIH. In fiscal year 2021, the Committee provides \$229,000,000 from HHS' Nonrecurring Expenses Fund to finish the Clinical Center's Surgery, Radiology, and Laboratory Medicine project. In addition, the Committee has included new bill language to allow the Institutes and Centers (ICs) of NIH to use up to 1 percent of IC funding for facility maintenance and construction. All 27 IC Directors have agreed to this funding structure.

The Committee directs NIH to provide a report with the fiscal year 2022 CJ describing the steps it has and will take to continue implementation of NASEM's recommendations. In addition, the Committee directs NIH to provide biannual updates of its Buildings and Facilities maintenance and construction plans, including specific milestones for advancing projects, status of the project, cost, and priorities. These updates should also highlight and explain any potential cost and schedule changes affecting projects (Senate Report, p. 124).

### **Action taken or to be taken**

The 2019 National Academies of Sciences, Engineering, and Medicine (NASEM) report included 14 recommendations: Two relate to increased resources for the National Institutes of Health (NIH) and 12 deal with procedural and governance improvements. NIH concurs with all 14 recommendations and has made substantial progress in implementing the 12 procedural and governance improvements within its control. Following are several key illustrations of implementation of the recommendations:

- NASEM Recommendation 5.1 is that NIH revise its Buildings and Facilities (B&F) prioritization model so no less than one-third of the total points are assigned to Condition Index (CI) and Mission Dependency. In response to this recommendation, NIH revised its prioritization model such that of 1000 potential points, 800 are assigned to CI and Mission Dependency. NIH has begun using this model and it has received positive feedback from the NIH Facilities Working Group and its subordinate committee, the Research Facilities Advisory Committee.
- NASEM Recommendation 6.1 is that NIH should integrate its research strategic plan with its capital facility asset management plans, with explicit prioritization aimed at relating the long-term research strategy to the long-term campus Master Plan. These plans should undergo annual review at the highest levels of NIH. In response to this recommendation, for the first time ever, the new NIH Strategic Plan will incorporate facilities into the document. The NIH Strategic Plan is scheduled to be published later in 2021.
- NASEM Recommendation 6.3 is that NIH should establish processes and a system that ensure third-party, expert peer review of all adopted Office of Research Facilities (ORF) preplanning programs of requirements (PORs) and total project capital cost models. In response to this recommendation, NIH has reached an agreement with the Federal Facilities Council (FFC) that Members of the FFC will conduct third-party, expert peer reviews of PORs and total project capital cost models.

- NASEM Recommendation 7.1 is that NIH should study non-NIH federal research programs and adopt functionally similar assessment, prioritization, and funding strategies to better meet facilities and infrastructure investment needs. In response to this recommendation, NIH consulted with seven other large facility organizations: the Centers for Disease Control and Prevention (CDC), the U.S. Food and Drug Administration (FDA), the National Aeronautics and Space Administration (NASA), the National Institute of Standards and Technology (NIST), the Smithsonian Institution, the U.S. Department of Agriculture (USDA), and the Naval Research Laboratories.
- NASEM Recommendation 7.3 is that NIH should convene an annual capital facilities planning workshop or similar forum with other federal agencies and academic research institutions to assess NIH capital asset management program processes and identify improvements. In response to this recommendation, NIH conducted two capital facilities planning workshops. The first was conducted on October 22, 2020 and included (in addition to NIH) 223 representatives from NIST, NASEM, NASA, Architect of the Capital, the Department of Energy (DOE), the Department of Homeland Security (DHS), USDA, Lawrence Livermore National Laboratory, Accruent, and Johns Hopkins Medicine. The topics covered were: Project Prioritization Model; benefits of conducting renovations and/or construction on a larger scale; use of Artificial Intelligence and Machine Learning to optimize the performance of Central Utilities Plants; and the use of Archibus for tracking facilities-related emergencies. The second forum was conducted on November 5, 2020 and included (in addition to NIH) 228 representatives from Architect of the Capital, DOE, DHS, NASA, NASEM, USDA, John Hopkins University, SmithGroup, University of Texas at Austin, Accruent, Catholic Diocese of Arlington, Sharif University of Technology, and Lawrence Livermore National Laboratory.
- NASEM Recommendation 7.4 is that NIH align its organizational structure with scientific research and capital assets management strategies and plans. In doing so, NIH should consider assigning a senior organizational leader with such responsibilities and empowering that person with commensurate authority. In response to this recommendation, on January 31, 2020, the NIH Director appointed Alfred Johnson, Ph.D., the Deputy Director for Management, as the NIH Senior Real Property Officer. This appointment of a senior organizational leader is a logical choice given that the Deputy Director for Management oversees (among other functions) the Office of Budget, the Office of Financial Management, and ORF.

In summary, NIH has made substantial progress in implementation of 12 of the 14 recommendations made by the NASEM Consensus Study and continues to collaborate with Congress, the Office of Management and Budget (OMB), and the U.S. Department of Health and Human Services (HHS) regarding the two recommendations associated with funding. It should also be added that in addition to the resource requirements associated with the Bethesda campus, NIH has responsibilities for facilities in Frederick, MD; Poolesville, MD; Research Triangle Park, NC; and Rocky Mountain Laboratories, Hamilton, MT. The NIH Budget request continues to take into account the requirements of all sites where NIH owns facilities. With respect to quarterly updates to Congress, NIH has provided to Congress quarterly updates on April 15, 2020; August 12, 2020; November 18, 2020; and March 30, 2021 and will continue to do so as long as Congress requests these updates.



## Cancer Immunotherapy

The Committee recognizes that cancer immunotherapies hold enormous promise to cure a number of cancers. Patients with certain hematologic malignancies have already benefited from the development of chimeric antigen receptor T-cell (CAR-T), an immunotherapy. Additional innovative and life-saving therapies for different types of cancers, some with few treatment options, will only be available from additional research in this field. The Committee is encouraged by the research NCI has already supported in this field, but urges the Institute to continue to prioritize research on new immunotherapies. The Committee requests that NCI provide an update in the fiscal year 2022 Congressional Justification on progress being made in this area and the gaps in research that remain (House Report, p. 93).

### Action Taken or To Be Taken

A major role for the National Cancer Institute (NCI) is supporting the basic and translational research necessary for positioning new immunotherapy agents for development. This research includes studies to understand the interaction between the immune system and cancer, identifying new immunotherapy targets, and studying the adverse effects of immunotherapy agents.

An important research need includes understanding why some cancer types do not respond to current immunotherapies and investigating potential immune-based approaches for them. For example, NCI-funded researchers are identifying mechanisms underlying the immunosuppressive pancreatic cancer microenvironment. In one recent study, scientists described the complex interplay between certain T cells and fibroblasts in pancreatic tumors uncovering a potential new approach to relieve immunosuppression.<sup>33</sup>

Another factor that affects response to immunotherapy is tumor mutational burden (TMB), a measure of the total number of mutations (changes) found in the DNA of cancer cells. Tumors that have a high TMB appear to be more likely to respond to certain types of immunotherapy, while those with low TMB often do not respond to current immune checkpoint inhibitors. Therefore, NCI-funded researchers are testing ways to increase the ability of the immune system to recognize and kill cancer cells in these tumors. For example, NCI-funded researchers recently reported making cancer cells susceptible to killing by T cells found naturally in the body after a common viral infection (cytomegalovirus or CMV).<sup>34</sup>

New frontiers in immunotherapy include leveraging the innate (nonspecific) immune system against cancer and understanding the role of the microbiome in the immune response against cancer. NCI is funding a variety of research in these areas.<sup>35</sup> While many patients with certain blood cancers have benefited from CAR T-cell therapies, CAR T-cells have not yet been successful in solid tumors. Research is focused on identifying suitable CAR T-cell targets, overcoming mechanisms that hinder their effectiveness, and minimizing toxicities. For example, NCI-funded research is supporting the development of CAR T-cell therapies against targets such

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<sup>33</sup> [pubmed.ncbi.nlm.nih.gov/31911451/](https://pubmed.ncbi.nlm.nih.gov/31911451/)

<sup>34</sup> [pubmed.ncbi.nlm.nih.gov/32042168/](https://pubmed.ncbi.nlm.nih.gov/32042168/)

<sup>35</sup> [www.cancer.gov/about-nci/budget/plan/2021-annual-plan-budget-proposal.pdf](https://www.cancer.gov/about-nci/budget/plan/2021-annual-plan-budget-proposal.pdf) (page 24)

as a protein called, GD2, for neuroblastoma and osteosarcoma<sup>36</sup> and B7-H3 for a variety of pediatric solid tumors and brain tumors.<sup>37,38</sup> Many potential targets for CAR-T cells in solid tumors are expressed in some normal tissues, making toxicity a major risk of therapy. Therefore, NCI-supported studies are developing innovative ways to minimize this type of toxicity. For example, researchers recently reported a preclinical study using an approach to CAR T-cell therapy against tumors expressing a target called ROR1, which is relevant in a variety of cancer types including breast cancer. The researchers engineered the T-cells to regulate their function and minimize toxicity to normal tissue.<sup>39</sup>

The Cancer Moonshot is supporting a large number of ongoing projects in adult immunotherapy, immunoprevention, and immuno-engineering to accelerate translation of basic discoveries to clinical applications to improve immunotherapy outcomes through the Immuno-Oncology Translational Science Network (IOTN).<sup>40</sup> In addition, the Pediatric Immunotherapy Discovery and Development Network (PI-DDN) is working to develop new, more-effective immune-based therapeutic regimens for high-risk pediatric cancers. In FY 2020 both networks expanded their scope to focus on immune-related adverse effects of immunotherapy. The overall goal is to accelerate research to improve immunotherapy outcomes by specifically promoting strategies that will predict, prevent, or ameliorate immune-related adverse effects.

NCI also supports immunotherapy research for rare cancers, including numerous clinical trials to test the efficacy of immunotherapy agents for patients with rare cancers. *See the Rare Cancer Therapeutics Research and Development Significant Item response for additional details.*

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<sup>36</sup> [clinicaltrials.gov/ct2/show/NCT04539366](https://clinicaltrials.gov/ct2/show/NCT04539366)

<sup>37</sup> [pubmed.ncbi.nlm.nih.gov/30655315/](https://pubmed.ncbi.nlm.nih.gov/30655315/)

<sup>38</sup> [pubmed.ncbi.nlm.nih.gov/32341579/](https://pubmed.ncbi.nlm.nih.gov/32341579/)

<sup>39</sup> [pubmed.ncbi.nlm.nih.gov/30889382/](https://pubmed.ncbi.nlm.nih.gov/30889382/)

<sup>40</sup> [www.iotnmoonshot.org/en/](https://www.iotnmoonshot.org/en/)

## Celiac Disease

The Committee supports NIH research on celiac disease, including the autoimmune causation underpinning the affliction. Today, the only known treatment for this disease is a gluten-free diet, but recent research reveals that this strategy is insufficient for many who suffer from celiac disease. The Committee urges NIAID to support new research and to better coordinate existing research with NIDDK and the other Institutes and Centers. The Committee requests that NIAID report back in the fiscal year 2022 Congressional Justification on the progress made towards promoting, recruiting, and supporting additional celiac-focused research (House Report, p. 106).

### **Action Taken or To Be Taken**

The National Institute of Allergy and Infectious Diseases (NIAID) supports a broad research portfolio that spans basic immunological research on the underlying pathogenesis of celiac and other autoimmune diseases, as well as clinical trials of immune modulating and tolerance inducing therapies that could be used to treat celiac disease. NIAID also supports several collaborative autoimmune disease research programs that support efforts to address celiac disease such as the Autoimmunity Centers for Excellence, the Immune Tolerance Network, and the NIAID Mucosal Immunology Studies Team.<sup>41,42,43</sup> In addition, NIAID chairs the NIH Autoimmune Disease Coordinating Committee (ADCC).<sup>44</sup> The ADCC aims to increase collaboration and facilitate coordination of autoimmune diseases research among NIH Institutes and Centers (ICs), other Federal agencies, and private health and patient advocacy groups.

One of the FY 2020 NIAID-supported studies is focused on identifying biomarkers that are specifically associated with different stages or presentations of celiac disease. In addition, NIAID is supporting a Phase 2 clinical trial evaluating the use of a candidate therapeutic intervention, latiglutenase, in patients with celiac disease who remain symptomatic despite adhering to a gluten-free diet.<sup>45</sup> This investigational therapy degrades gluten proteins and, if demonstrated to be safe and effective, could improve quality of life for individuals with celiac disease when a gluten-free diet is insufficient.

In addition to the activities described above, NIAID is actively working with the celiac and autoimmune disease research communities to identify additional research needs. On May 29, 2020, NIAID hosted an ADCC meeting focused on the unmet needs, emerging opportunities, and patient perspectives on the diagnosis, prevention, and treatment of celiac disease. In response to this meeting, NIH plans to develop a *Research, Condition, and Disease Category* (RCDC) report for celiac disease within the NIH Research Portfolio Online Reporting Tools (RePORT) website.<sup>46</sup> The establishment of a celiac disease RCDC category would result in a complete list of all NIH-funded projects related to celiac disease in a publicly accessible format. In FY 2021,

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<sup>41</sup> [www.niaid.nih.gov/research/autoimmunity-centers-excellence](http://www.niaid.nih.gov/research/autoimmunity-centers-excellence)

<sup>42</sup> [www.immunetolerance.org/](http://www.immunetolerance.org/)

<sup>43</sup> [mucosal.org/](http://mucosal.org/)

<sup>44</sup> [www.niaid.nih.gov/about/autoimmune-diseases-coordinating-committee-members](http://www.niaid.nih.gov/about/autoimmune-diseases-coordinating-committee-members)

<sup>45</sup> [linicaltrials.gov/ct2/show/NCT04243551](https://clinicaltrials.gov/ct2/show/NCT04243551)

<sup>46</sup> [report.nih.gov/categorical\\_spending.aspx](https://report.nih.gov/categorical_spending.aspx)

NIAID will be developing a *Notice of Special Interest* to encourage investigator-initiated celiac disease research.

NIAID will continue to support research on celiac disease and welcomes research applications to increase understanding of celiac disease and to develop effective therapies for the disease. In addition, NIAID will continue to work with other NIH ICs as well as other partners in the celiac disease research community to coordinate efforts to address this important disease.

## **Childhood Cancer Data Initiative (CCDI)**

The Committee includes \$50,000,000 for the second year of the CCDI, as proposed in the fiscal year 2021 budget request. The development of new therapies is important to finding a cure for childhood cancers, many of which have not seen new therapies in decades (House Report, p. 94).

### **Action Taken or To Be Taken**

In 2019, the National Cancer Institute (NCI) launched the Childhood Cancer Data Initiative (CCDI) in alignment with the Presidentially proposed federal investment of \$500 million over ten years to make progress against childhood cancers. FY 2020 appropriations provided the first \$50 million of this 10-year investment and NCI looks forward to continuing this initiative with a second year of investment as provided in FY 2021 appropriations.

The CCDI provides a blueprint for the bold vision of learning from every child with cancer while providing each of them state-of-the-art clinical care and ultimately changing the course of cancer in all children. Through the CCDI, NCI will connect data repositories and registries, collect standardized, high-quality data on childhood and adolescent cancers, and promote efficient data sharing to accelerate research and stimulate discovery. Increasing data use and sharing among the pediatric cancer research community will improve our understanding of childhood cancers and advance research to develop new and innovative treatments.

Since the initiative's launch in July 2019, NCI has undertaken a range of research activities to lay the foundation for developing and supporting the CCDI, including:

- Conducting a comprehensive review of existing childhood and adolescent cancer data, data repositories, and analytic tools that can be connected under the CCDI
- Developing the National Childhood Cancer Registry, as part of the CCDI data ecosystem, to enhance access to patient-linked childhood and adolescent cancer and survivorship data
- Building the technical infrastructure of the data ecosystem, which will connect various types of cancer and clinical care data and tools
- Developing a preclinical data commons—a platform for submitting, sharing, and analyzing data from studies involving cancer models (e.g., cell lines or animal research), that can help to prioritize which agents to pursue in human clinical trials for childhood and adolescent cancer
- Expanding comprehensive data collection to include more institutions engaged in childhood and adolescent cancer and survivorship research
- Continuing to enhance data sharing to promote open access to data

In addition, NCI convened a working group of its Board of Scientific Advisors (BSA) to provide guidance regarding future priorities for CCDI. In June 2020, at a joint meeting of the BSA and the National Cancer Advisory Board, the working group presented its report, which included recommendations for implementing the CCDI that could lead to transformative discoveries in pediatric and adolescent cancer treatment and survivorship.

NCI continues to take actions to realize the bold vision of the CCDI. These include carefully reviewing the recommendations of the BSA working group and planning how and when to implement this guidance to best advance CCDI. The CCDI will not only be a foundational component of the NCI childhood cancer program, it will also complement and inform other, ongoing pediatric cancer research.

## Childhood Cancer Survival Metrics

A recent study determined that childhood cancer diagnoses are on the rise by approximately 0.8 percent per year. Worldwide, there are 400,000 new childhood cancer diagnoses annually. However, childhood cancer death rates are described as being on the decline. The Committee is concerned that the current metric used to determine mortality and survival statistics for childhood cancer does not fully capture the long-term morbidity and mortality of these diseases. Currently, a child or adult that lives five years from the date of diagnosis is considered a survivor. Yet, children are not small adults and their potential life span after diagnosis is much longer than an adult. Using the five-year survival metric does not capture children who die prematurely as a result of their cancer or its treatment when they are past the five-year point. The Committee directs NCI to establish a task force composed of childhood cancer researchers and advocates to determine the most appropriate survivorship metric for childhood cancer. In addition, the Committee recognizes a critical goal of the CCDI is to collect comprehensive data about every child diagnosed with cancer in the U.S., including data on survival and mortality, such as death due to late effects of cancer and its treatment. The Committee requests an update from NCI in the fiscal year 2022 Congressional Justification focusing on how CCDI efforts will address this need to more accurately capture childhood cancer mortality beyond the current five-year survival metric (House Report, p. 94).

### **Action Taken or To Be Taken**

The 2020 Annual Report to the Nation on the Status of Cancer did report childhood cancer incidence rates increased on average 0.8 percent per year during 2012 through 2016.<sup>47</sup> The report states that factors potentially influencing childhood cancer incidence trends include changes over time in diagnostic technology, disease classification, and registry completeness as well as changes in risk factors, such as increasing maternal age. However, reasons for increasing incidence rates for cancer overall and for the most common types among children are largely unknown. The American Cancer Society's Cancer Facts & Figures 2020 notes that cancer death rates are the best measure of progress against cancer because they are less affected by detection practices than cancer incidence and survival rates.<sup>48</sup> Childhood cancer death rates for children ages 0-14 years old continue to decline, decreasing an average of 1.4 percent per year during 2013 through 2017. The National Cancer Institute (NCI) recognizes these declines are not distributed evenly across all types of childhood cancer and remains committed to supporting research to reduce all childhood cancer mortality, particularly for those childhood cancers for which effective treatments do not currently exist.

Cancer survival rates are statistics that provide a benchmark for the percentage of people alive at some point subsequent to their diagnosis of cancer. Five-year survival rate is a historic statistic that allows for comparisons to be made between groups in a study. It is the percentage of people in a study or treatment group who are alive five years after their diagnosis or the start of treatment for a disease, such as cancer. Use of this metric allows researchers to compare outcomes from standard of care treatment protocols with newer treatments and provides a

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<sup>47</sup> [seer.cancer.gov/report\\_to\\_nation/](https://seer.cancer.gov/report_to_nation/)

<sup>48</sup> [www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf](https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf)

standard measure of survival as a clinical endpoint. Generally, relative 5-year survival rates are population statistics which are adjusted for normal life expectancy by comparing survival among cancer patients to survival in people of the same age, race, and sex who were not diagnosed with cancer.

The NCI defines a cancer survivor as an individual living after a cancer diagnosis, through the balance of their life. Survivors include those living with cancer and those free of cancer. NCI has an Office of Cancer Survivorship (OCS)<sup>49</sup> and supports a robust research portfolio focusing on survivorship issues for children and adults with a history of cancer. NCI is pleased to announce that it recently welcomed a new Director for the OCS, Dr. Emily Tonorezos, MD, MPH. Dr. Tonorezos has extensive research and clinical experience in caring for adult survivors of childhood cancer. Under her leadership, OCS will be seeking engagement from the extramural research and childhood cancer advocacy communities to discuss opportunities and priorities that span NCI's childhood cancer survivorship research efforts supported through the Childhood Cancer Survivorship, Treatment, Access, and Research (STAR) Act, the Childhood Cancer Data Initiative (CCDI) and the broader investigator-initiated research portfolio. This will include engaging the community regarding how survivorship metrics are defined and utilized in survivorship research and determining clinical endpoints.

In addition, the longstanding, NCI-funded Childhood Cancer Survivor Study (CCSS) is focused on studying the long-term outcomes for childhood cancer survivors. CCSS studies the quality of life and long-term effects that survivors experience 10-, 20-, 30-years, and beyond their cancer diagnosis. One research metric that the CCSS uses is conditional survival.<sup>50</sup> This is the likelihood of continued survival for a specified interval of time after having already survived for a specific time interval (e.g., 5 years) after a cancer diagnosis. This measurement of survival is clinically relevant because the likelihood of survival changes with increasing duration of follow-up from initial cancer diagnosis. Studies like these, including those also conducted by the NCI supported St. Jude Lifetime Cohort, capture and report on the long-term morbidity and mortality experienced by childhood cancer survivors beyond the traditional 5-year survival metric.

More research is needed to understand long-term morbidity and mortality to improve the length and quality of life for childhood cancer survivors. As part of the Institute's STAR Act implementation efforts, NCI is working to improve the care and quality of life for those diagnosed during childhood, adolescence, and young adulthood by supporting research across multiple domains. NCI is also working to expand childhood cancer biobanking in alignment with the STAR Act to aid the biological understanding of long-term effects of treatments for childhood cancers (*See the STAR Act Significant Item response for additional details*). Finally, the Childhood Cancer Data Initiative (CCDI)<sup>51</sup>, which includes the development of a National Childhood Cancer Registry, will collect, store, analyze, and share data to learn from every child with cancer. The registry will build upon and complement existing cancer registry efforts led by both NCI and the Centers for Disease Control and Prevention and enhance access to patient-linked data collected throughout the life of a childhood cancer survivor (*See the CCDI Significant Item response for additional details*).

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<sup>49</sup> [cancercontrol.cancer.gov/ocs](https://cancercontrol.cancer.gov/ocs)

<sup>50</sup> [pubmed.ncbi.nlm.nih.gov/25557134/](https://pubmed.ncbi.nlm.nih.gov/25557134/)

<sup>51</sup> [www.cancer.gov/research/areas/childhood/childhood-cancer-data-initiative](https://www.cancer.gov/research/areas/childhood/childhood-cancer-data-initiative)



## **Childhood Post-Infectious Autoimmune Disorders**

The Committee continues to be concerned that children, following streptococcal and other infections, are experiencing the onset of neuropsychiatric and behavioral disorders. These auto-inflammatory encephalopathic conditions, including Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and Pediatric Acute-onset Neuropsychiatric Syndrome (PANS), are often misdiagnosed. Delays in diagnosis and lack of developed avenues of treatment result in a devastating escalation of mental health symptoms and associated costs. The Committee encourages NIH to explore cross-disciplinary research in this area, including neurobiology, neurology, immunology, infectious disease, and mental health, and report to the Committee in the fiscal year 2022 Congressional Justification on the understanding of the incidence, causes, diagnostic criteria, and treatment of these conditions (House Report, p. 131).

### **Action Taken or To Be Taken**

Pediatric Acute Onset Neuropsychiatric Syndrome (PANS) and its subset PAN Disorder Associated with Streptococcal infection (PANDAS) are auto-inflammatory encephalopathic conditions characterized by a sudden onset of obsessive-compulsive disorder (OCD) and/or severe eating restrictions. For over two decades, the National Institute of Mental Health (NIMH) has supported a robust research portfolio on the full range of mental and neurodevelopmental disorders that emerge during childhood and adolescence. Collectively, this portfolio aims to identify the mechanisms leading to mental illnesses, including neuroimmune mechanisms relevant to PANS and PANDAS, and to identify potential targets for the development of new and improved interventions.

Findings from NIMH-supported research have led to the development of new treatments to improve outcomes for individuals with these diagnoses. For example, the NIMH Intramural Research Program was instrumental in identifying immune mechanisms that lead to brain dysfunction in PANS and PANDAS.<sup>52</sup> In the case of PANDAS, this immune response is associated specifically with Group A streptococcal (strep) infections, such as strep throat and scarlet fever. Researchers found that strep-related PANDAS episodes can be treated by prescribing antibiotics to eliminate the strep infection and ameliorate symptoms. Children with PANS- or PANDAS-related OCD symptoms may also benefit from standard OCD treatment, which includes medication and behavioral therapy.

NIMH continues to support multidisciplinary approaches in which teams of researchers from multiple fields, including neurobiology, molecular biology, psychiatry, pediatrics, and clinical research, are exploring the biological pathways and mechanisms underlying PANS and PANDAS, which may lead to new therapies. For example, in one NIMH-funded project, scientists are investigating how T-helper cells – critical components of a typical immune response – contribute to brain inflammation and dysfunction following strep infection.<sup>53</sup> Another NIMH-funded investigator recently discovered that children with PANDAS produce antibodies that bind to and alter the activity of a specific type of neuron, providing a possible

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<sup>52</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9790789&icde=46937455](https://projectreporter.nih.gov/project_info_description.cfm?aid=9790789&icde=46937455)

<sup>53</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9775457&icde=46891708](https://projectreporter.nih.gov/project_info_description.cfm?aid=9775457&icde=46891708)

mechanistic explanation for PANDAS symptoms.<sup>54</sup> Building on the finding from this initial small clinical study, the research team is now studying a larger cohort of patients to determine whether their PANDAS symptoms correlate with the binding of immune proteins to this type of neuron.<sup>55</sup> These multidisciplinary approaches aim to provide a more precise understanding of the link between autoimmune processes and PANS/PANDAS, and may identify new targets for treatment to ultimately improve outcomes for individuals with these conditions.

NIMH intramural researchers recently conducted clinical trials that include individuals diagnosed with PANS or PANDAS, with the aim of developing comprehensive clinical profiles of the disorders. For example, one trial is evaluating patient characteristics that are associated with symptom profiles and responses to standard interventions for a related variety of childhood behavioral, psychiatric, and developmental disorders.<sup>56</sup> The clinical, behavioral, and biological data collected in this trial may provide an invaluable resource for future investigations.

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<sup>54</sup> [pubmed.ncbi.nlm.nih.gov/32539528/](https://pubmed.ncbi.nlm.nih.gov/32539528/)

<sup>55</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9726837&icde=46891708](https://projectreporter.nih.gov/project_info_description.cfm?aid=9726837&icde=46891708)

<sup>56</sup> [clinicaltrials.gov/ct2/show/NCT01778504](https://clinicaltrials.gov/ct2/show/NCT01778504)

## **Clinical and Translational Science Awards (CTSA)**

The Committee directs NIH to fund the CTSA program at not less than the level provided in fiscal year 2020. The Committee reiterates its support for the CTSA program and notes the recent contributions of this critical infrastructure program towards community engagement and addressing health disparities. Because CTSA are uniquely positioned to help address physician workforce shortage issues, NCATS is encouraged to bolster the role of CTSA in workforce development activities with an emphasis on training and career development opportunities (House Report, p. 126).

### **Action Taken or To Be Taken**

The Clinical and Translational Science Awards (CTSA) Program comprises a dynamic suite of initiatives focused on fostering and improving clinical and translational research and science, with the aim of getting more treatments to more patients more quickly. The Program supports a nationwide network of institutions capable of addressing important roadblocks in clinical translation by working together locally, regionally, and nationally. The National Center for Advancing Translational Sciences (NCATS) continues to fund the CTSA Program at the levels provided in the annual appropriations acts. More information about the funded activities is available online.<sup>57</sup>

The CTSA Program supports biomedical research institutions to improve clinical translation and to develop a cadre of investigators trained to become translational scientists. Providing the resources to train, cultivate, and sustain future leaders of the biomedical research workforce is a key Program goal. The program enables a coordinated, national effort to help ensure that our nation will have a pipeline of trained investigators who can move basic research findings into application for improving health as novel therapies, diagnostics, and preventives. Scientists and clinicians gain practical research experience by working with interdisciplinary teams guided by experienced mentors. This team science approach helps prepare clinician-scientists to better address today's complex research challenges and opportunities. In addition, CTSA Program support enables open access to a wide variety of training resources and educational materials created by CTSA Program grantees and NIH.

**Translational Endeavors Core:** The CTSA hub award (UL1) includes support for continuing education in translational research for health care professionals and for the development of innovative online tools or training collaborations in translational research.

**Institutional Career Development Awards (KL2):** The KL2 awards support more than 350 scholars a year (around 50 percent of whom are MDs) and are required components of every CTSA Program hub award. The awards offer senior postdoctoral fellows and junior faculty scholars protected time and multidisciplinary, mentored research career development opportunities in clinical and translational science research. Programs engage scholars in flexible educational offerings to facilitate their transition to research independence.

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<sup>57</sup> [ncats.nih.gov/files/CTSA\\_Funding\\_Information\\_FY19\\_508\\_v2.pdf](https://ncats.nih.gov/files/CTSA_Funding_Information_FY19_508_v2.pdf)

**Institutional National Research Service Award (NRSA) Training Grants (TL1):** The TL1 awards support more than 500 trainees a year (with around 33 percent having acquired or are in training for a medical degree) and are optional components of every CTSA Program hub award. The awards offer predoctoral and postdoctoral fellows training in clinical and translational science research. In addition, short-term research training for students in health professional schools (includes medical school) can be offered. Programs engage multiple departments, schools, and clinical research institutes to support intensive research training, didactics leading to graduate degrees, team science, and optional experiential learning. Exposure to training in broad areas such as entrepreneurship, regulatory science, and community-engaged research is encouraged.

**Diversity and Re-Entry Research Supplements:** These supplements promote diversity in health-related research and re-entry into biomedical and behavioral research careers. The goal is to build the clinical and translational research workforce that is prepared to improve the quality, safety, efficiency, and speed of clinical and translational science research nationally. Since 2015, the CTSA Program has supported 43 awardees, of which 18 (42 percent) have a medical, nursing, or dental degree.

In 2014, an NIH Advisory Committee to the Director provided a report<sup>58</sup> on the Physician-Scientist Workforce. Among the recommendations was for NIH to leverage the existing resources of the CTSA Program to obtain maximum benefit for training and career development of early-career physician-scientists. The National Institute of Dental and Craniofacial Research, National Center for Complementary and Integrative Health, National Institute of Biomedical Imaging and Bioengineering, and the NIH INCLUDE (INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndrome) Project have supported 16 scholars leveraging the education, training, and mentoring provided through the CTSA Institutional Career Development Awards (KL2).

In late 2019, NCATS solicited comments from the public and several groups, including the CTSA Program grantees, on ways to enhance the CTSA Program. Multiple comments related to workforce development were received, including suggestions to expand training beyond the K and T programs, expand available funding mechanisms, increase flexibility of the programs, and share best practices and tools. NCATS is considering these suggestions as it develops ways to strengthen the CTSA Program and will keep the Appropriations Committees informed as it considers such updates.

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<sup>58</sup> [report.nih.gov/workforce/psw/psw-group.aspx](https://report.nih.gov/workforce/psw/psw-group.aspx)

## **Deadliest Cancers**

The Committee looks forward to seeing NCI's update on developing scientific frameworks for stomach and esophageal cancers as well as ways in which it is supporting research into all recalcitrant cancers, as directed in House Report 116–62. Further, the Committee notes that the Recalcitrant Cancer Research Act of 2012 directed NCI to develop a scientific framework for at least two cancer types that meet the definition of recalcitrant cancers as defined in the Act. The Committee directs NCI to outline other specific steps the NCI is taking to support research that aims to reduce the burden of disease from pancreatic, nonsmall cell lung, stomach, and esophageal cancers in the fiscal year 2022 Congressional Justification (House Report, p. 94).

### **Action Taken or To Be Taken**

The National Cancer Institute (NCI) is working on the development of a scientific framework for gastric, esophageal, and gastro-esophageal (GE) junction cancers, as these cancer types are closely related. Initial steps include a portfolio analysis to identify relevant research projects, and a comprehensive literature review to identify subject matter experts and to assess challenges and opportunities in the field, both of which are underway. NCI is in the process of forming a multi-disciplinary working group to guide the development of a scientific framework, a broad group of subject matter experts and patient advocates is being engaged and it is anticipated that this group will convene virtually within the first half of 2021.

NCI's commitment to basic research builds the foundation of knowledge that fuels progress across the cancer continuum, and this foundational work is especially important for cancers for which we have not made significant progress in identifying therapeutic targets and improving survival. Fundamental discoveries about cancer biology can lead to future clinical breakthroughs for any and all cancer types. For example, recent advances in the use of immunotherapy are providing effective treatment for many cancers including pancreatic, non-small cell lung, stomach, and esophageal cancers. There is at least one FDA-approved indication for the use of an immunotherapy agent for each of these cancer types, an advance that would not have been possible without NCI's decades long commitment to understanding the immune system and its role in cancer.

NCI maintains a robust research portfolio in pancreatic, non-small cell lung, stomach, and esophageal cancers. This includes investigator-initiated grants across the cancer continuum. Investigator-initiated grants support ideas from scientists who propose research projects based on their area of expertise and receive funding for those projects after they are deemed meritorious in a rigorous peer-review process. In addition to investigator-initiated research, NCI supports research and scientific infrastructure in a variety of ways, including specifically targeted networks and special programs. Again, pancreatic, non-small cell lung, stomach, and esophageal cancers are well-represented in these networks and programs. Selected examples are described below but are far from a complete list of NCI's portfolio in these areas.

NCI's portfolio for pancreatic cancer includes initiatives described in more detail in the pancreatic ductal adenocarcinoma (PDAC) framework such as the Pancreatic Cancer

Microenvironment Network<sup>59</sup> and the consortium to study Chronic Pancreatitis, Diabetes, and Pancreatic Cancer<sup>60</sup>, and initiatives outside the framework including the RAS initiative and the Early Detection Research Network.<sup>61</sup> The latter also supports research in lung, gastrointestinal and esophageal cancers. The Barrett's Esophagus Translational Research Network (BETRNet)<sup>62</sup> has been a cornerstone of NCI's esophageal cancer portfolio. Barrett's esophagus is the only known precursor lesion to esophageal cancer and research supported by the BETRNet lead to the development of a new, less invasive test to detect Barrett's esophagus and assess risk for esophageal cancer. As the BETRNet concludes its research efforts, NCI is actively planning next steps for continued progress. The Provocative Questions (PQ) Initiative<sup>63</sup>, which stimulates specific areas of cancer research, has a PQ focused on understanding the underlying causes of the unexplained rising incidence in early-onset gastric cancer. Additionally, several open funding opportunity announcements are supporting research to understand the link between obesity and cancer and the role of the microbiome in cancer. This research is relevant to gastric, pancreatic, and esophageal cancers.

The Specialized Programs of Research Excellence (SPOREs), a key component of NCI's Translational Research Program, also supports research on these four cancer types, among others.<sup>64</sup> There are currently five gastrointestinal SPORE programs which include projects in pancreatic, gastric, and esophageal cancers as well as one SPORE program dedicated solely to pancreatic cancer. Lung cancer was an early focus of the SPORE Program and the first Lung SPOREs were funded over 25 years ago. Presently, there are five lung cancer SPORE programs. In the past 3 years, NCI has also been supporting planning grants for future SPORE programs in cancer health disparities.<sup>65</sup> The aim is to build programs to improve the prevention, early detection, diagnosis, and treatment of cancers that disproportionately affect specific racial and ethnic minority populations that can compete for SPORE funding in future years. In FY 2020, Duke University was awarded a SPORE planning grant focusing on racial differences in gastric and non-small cell lung cancer.<sup>66</sup>

The Cancer Intervention and Surveillance Modeling Network (CISNET) uses simulation modeling to improve understanding of cancer control interventions such as screening and treatment. The CISNET supports research in esophageal cancer<sup>67</sup> to understand the natural history of the disease and research on the impact of tobacco control policies and screening in lung cancer.<sup>68</sup>

These four cancers are also represented in initiatives funded through the Cancer Moonshot. Selected examples include the Patient-Derived Xenograft (PDX) Models Network and the

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<sup>59</sup> [dctd.cancer.gov/NewsEvents/20200102\\_PaCMEN.htm](https://dctd.cancer.gov/NewsEvents/20200102_PaCMEN.htm)

<sup>60</sup> [cpdpc.mdanderson.org/index.html](https://cpdpc.mdanderson.org/index.html)

<sup>61</sup> [edrn.nci.nih.gov/](https://edrn.nci.nih.gov/)

<sup>62</sup> [prevention.cancer.gov/major-programs/barretts-esophagus-translational-research-network](https://prevention.cancer.gov/major-programs/barretts-esophagus-translational-research-network)

<sup>63</sup> [grants.nih.gov/grants/guide/rfa-files/RFA-CA-20-004.html](https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-20-004.html)

<sup>64</sup> [trp.cancer.gov/](https://trp.cancer.gov/)

<sup>65</sup> [grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-033.html](https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-033.html); [grants.nih.gov/grants/guide/rfa-files/RFA-CA-19-034.html](https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-19-034.html)

<sup>66</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=10037506&icde=52031787](https://projectreporter.nih.gov/project_info_description.cfm?aid=10037506&icde=52031787)

<sup>67</sup> [cisnet.cancer.gov/esophagus/](https://cisnet.cancer.gov/esophagus/)

<sup>68</sup> [cisnet.cancer.gov/lung/](https://cisnet.cancer.gov/lung/)

Human Tumor Atlas Network (HTAN). Specifically, the minority PDX Development and Trial Center at the University of California at Davis is establishing PDX models of gastric and lung cancer to help clinical decision-making in Hispanic/Latino American, Asian American/Native Hawaiian/Pacific Islander, and African American populations.<sup>69</sup> The HTAN research centers are constructing exemplary multi-dimensional atlases for five adult tumors including lung and pancreatic cancer. This work will provide a more comprehensive understanding of tumor biology and create a platform for modeling tumor behavior and predicting tumor evolution.

NCI has been committed to supporting research to reduce lung cancer mortality from smoking and other causes for many years. These investments have led to a sharp decrease in mortality rates, including 6.3 percent from 2013 to 2016, for non-small cell lung cancer as reported in a 2020 study in the *New England Journal of Medicine*.<sup>70</sup> The study found that advances in lung cancer treatment, particularly approvals for and use of targeted therapies, is likely to explain the reduction in mortality.

As the largest single funder of cancer research in the world, NCI is responsible for advancing progress in all cancers and supporting the infrastructure and training that enables cutting-edge research to succeed. NCI is committed to our mission of helping all people live longer, healthier lives.

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<sup>69</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?icde=0&aid=9627665](https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=9627665)

<sup>70</sup> [pubmed.ncbi.nlm.nih.gov/32786189/](https://pubmed.ncbi.nlm.nih.gov/32786189/)

## **Deadliest Cancers - Updates on Seven Deadliest Cancers**

For fiscal year 2020, Congress directed NCI to develop a scientific framework using the process outlined in the Recalcitrant Cancer Research Act of 2012 (Public Law 112–239) for stomach and esophageal cancers. The Committee expects that outlining the state of the science and foremost research questions for both of these diseases will provide a roadmap for future research. The Act defined “recalcitrant cancers” as those for which the 5 year survival rate is below 50 percent. According to NCI, the 5 year survival rates for stomach and esophageal cancers are 32 and 20 percent, respectively. The Committee expects to be kept informed of NCI’s efforts, alongside the research and advocacy communities, to convene working groups of experts to develop scientific frameworks for both cancers; and to be kept informed of ways in which NCI is supporting research into all recalcitrant cancers. The deadliest cancers, which also include cancers of the brain, liver, lung, ovary, pancreas, and mesothelioma, among others, account for nearly half of all U.S. cancer deaths. While steady advances have made it possible to reduce the overall rate of cancer deaths for more than 2 decades, there has been little progress reducing mortality for these diseases. The Committee recognizes that advances in treating what were once thought of as incurable diseases has previously occurred in unexpected ways, and is encouraged by NCI’s continued support for research related to the deadliest cancers. In particular, the Committee notes the promising focus on diagnostics to make earlier identification possible when successful treatment might still be possible. Given the toll all recalcitrant cancers exact on society and the lack of diagnostic and treatment resources currently available to help patients, the Committee directs NCI to provide an update on its work over the past year for each of the seven deadliest cancers in the fiscal year and to identify future goals for each in the fiscal year 2022 CJ (Senate Report, p. 85-86).

### **Action Taken or to be Taken**

The National Cancer Institute (NCI) is committed to supporting scientific research to advance knowledge about all cancers, prevent all cancers, and improve the lives of those affected by cancer. We share the Committee’s commitment to making progress for cancers that have high mortality rates. Brief, individual updates for gastric, esophageal, brain, liver, lung, ovarian, and pancreatic cancers are provided below as requested. Selected examples are described below but are far from a comprehensive list of NCI’s investments in research on these cancers. Also, see the House Deadliest Cancers Significant Item response for additional information.

Overall, advances in immunotherapy over the last 10 years have led to the U.S. Food and Drug Administration (FDA) approval of the use of immunotherapy agents for all of the cancers noted here. This would not have been possible without NCI’s decades-long commitment to understanding the immune system and its role in cancer. Likewise, NCI’s long-term support of discovery research led to the development of a liquid biopsy test called CancerSEEK that received Breakthrough Designation for the detection of genetic mutations and proteins associated with pancreatic and ovarian cancers. CancerSEEK also has the potential to non-invasively detect cancers of the stomach, esophagus, and liver.<sup>71</sup>

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<sup>71</sup> [pubmed.ncbi.nlm.nih.gov/29348365/](https://pubmed.ncbi.nlm.nih.gov/29348365/)



### *Gastric and Esophageal Cancers*

NCI continues to support a broad portfolio of gastric and esophageal research projects, including support for Specialized Programs of Research Excellence (SPORES) focusing on early detection and treatment of gastric cancer and esophageal cancers.<sup>72,73</sup> NCI also funded new projects in both of these cancers in FY 2020, including a Small Business Innovation Research (SBIR) grant to develop novel inhibitors of a key signaling pathway that is mutated in esophageal and many other cancers<sup>74</sup> and an investigator-initiated project to investigate how changes in gastric tumor cell biology affects tumor cell survival, anti-tumor immunity, and response to therapy.<sup>75</sup>

Currently, NCI is developing a scientific framework for gastric, esophageal, and gastro-esophageal (GE) junction cancers, a closely related group of cancers known collectively as “gastroesophageal cancers.” The initial steps include the development of a portfolio analysis to identify relevant research projects and an associated comprehensive literature review to identify subject matter experts to assess key challenges and opportunities in the field. NCI is in the process of forming a multi-disciplinary working group to guide the development of a scientific framework, a broad group of subject matter experts and patient advocates is being engaged and it is anticipated that this group will convene virtually within the first half of 2021.

In December 2020, the NCI Board of Scientific Advisors approved the launch of a new program to identify the origins of gastroesophageal cancers and to build on advances in our understanding of the molecular classification and genomics of gastric and esophageal cancers made possible by The Cancer Genome Atlas and other NCI-supported research. This new program, funded at \$20 million over a five-year period, will provide unprecedented opportunities to examine the earliest cellular changes in transformation that precede any manifestations of cancer to tackle these cancers at their foundation. This new program is built on and energized by new discoveries and discussions that took place at a recent NCI-sponsored think tank on the origins of gastrointestinal cancers. The think tank highlighted this promising research area and explored challenges faced by the research community.

Also, in 2020, the FDA awarded breakthrough designation to a new technology (EsoCheck™) and biomarker test (EsoGuard™) developed by researchers supported by NCI’s Barrett’s Esophagus Translational Research Network (BETRNet).<sup>76</sup> The device and test detect Barrett’s Esophagus, a precursor lesion of esophageal adenocarcinomas. Both are currently in clinical trials, giving patients timely access to a quick, accurate and less invasive way to identify risk of esophageal adenocarcinomas. These cancers are usually diagnosed at an advanced stage when difficult to treat however, detecting Barrett's esophagus could help patients by giving physicians a chance to intervene early.

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<sup>72</sup> [trp.cancer.gov/spores/abstracts/case\\_gi.htm](http://trp.cancer.gov/spores/abstracts/case_gi.htm) (Project 3)

<sup>73</sup> [trp.cancer.gov/spores/abstracts/dfhcc\\_gi.htm](http://trp.cancer.gov/spores/abstracts/dfhcc_gi.htm) (Project 4)

<sup>74</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=10010409&icde=0](http://projectreporter.nih.gov/project_info_description.cfm?aid=10010409&icde=0)

<sup>75</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?icde=0&aid=9972209](http://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=9972209)

<sup>76</sup> [prevention.cancer.gov/news-and-events/blog/new-technology-gives-patients](http://prevention.cancer.gov/news-and-events/blog/new-technology-gives-patients)

### *Brain Cancer*

In August of 2020, NCI initiated a new program focused on adult glioblastoma with the publication of a funding announcement for the Glioblastoma Therapeutics Network (GTN).<sup>77</sup> The goal of the network is to improve the treatment of adult GBM by developing novel and effective agents to overcome the blood-brain barrier and GBM heterogeneity and eventually evaluate drugs in Phase 3 clinical trials. The network will also work to improve and/or repurpose existing drugs and drug combinations for use in GBM. The GBM Therapeutics Network will consist of multi-institutional teams of researchers working in a collaborative manner and in conjunction with a Coordinating Center. The Coordinating Center will provide network harmonization on research activities, such as biobanking, and on clinical activities. Each team in the network will be expected to drive drug development of novel agents from pre-clinical development, through Investigational New Drug studies, and into clinical studies. Applications are now being accepted, and NCI expects to fund up to five awards in FY 2021.

New investigator-initiated projects were funded in FY 2020 that seek to improve imaging of tumors in the brain, improve delivery of therapies to the brain, and increase understanding of the development of cancer in the brain. In addition, NCI supported a number of new SBIR/Small Business Technology Transfer (STTR) projects to develop and/or test new treatments for brain cancers. This includes a Phase 2 clinical trial of a new agent for treatment of high-grade gliomas that follows the completion of a Phase 1 study from a previous award.<sup>78</sup>

NCI is also supporting an expansion of the Pediatric Brain Tumor Consortium (PBTC), which was recently approved for an additional five-year funding period. This expansion will allow the PBTC to add up to six additional sites and to increase its organizational capabilities so that it can support more clinical trials. An important part of this expansion includes several efforts focused specifically on the pediatric brain tumor Diffuse Intrinsic Pontine Glioma (DIPG). The expansion of the PBTC will enable the growth of the clinical research program for DIPG and other pediatric brain tumors, ultimately allowing for greater access to clinical trials for children and families throughout the country.

### *Liver Cancer*

While there are several FDA-approved targeted therapies for liver cancer, these current therapies usually extend patients' lives by just a few months, and the prognosis for this disease remains poor. NCI-supported researchers are working to develop better treatments. Examples include clinical trials to determine if an experimental cell therapy is effective in shrinking hepatobiliary tumors in patients whose cancer is resistant to standard treatment;<sup>79</sup> to evaluate efficacy of single or combination immune checkpoint inhibitors (nivolumab and ipilimumab) in treating patients with liver cancer that can be removed by surgery;<sup>80</sup> and testing a combination of the antibiotic vancomycin with other drugs that enhance antitumor immune responses.<sup>81</sup> See the House Liver Cancer Significant Item response for more information.

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<sup>77</sup> [grants.nih.gov/grants/guide/rfa-files/RFA-CA-20-047.html](https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-20-047.html)

<sup>78</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?icde=0&aid=9989552](https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=9989552)

<sup>79</sup> [clinicaltrials.gov/ct2/show/NCT01174121](https://clinicaltrials.gov/ct2/show/NCT01174121)

<sup>80</sup> [clinicaltrials.gov/ct2/show/NCT03222076](https://clinicaltrials.gov/ct2/show/NCT03222076)

<sup>81</sup> [clinicaltrials.gov/ct2/show/NCT03785210](https://clinicaltrials.gov/ct2/show/NCT03785210)

### *Lung Cancer*

A study published in the *New England Journal of Medicine* in August of 2020 revealed that mortality rates from the most common lung cancer, non-small cell lung cancer, have fallen sharply in the U.S. in recent years, and that this decline is primarily due to advances in treatments.<sup>82</sup> This development is a testament to NCI's long commitment to supporting research to reduce lung cancer mortality. For lung cancer, as for all the cancers detailed herein, NCI supports investigator-initiated grants across the cancer continuum, as well as research and scientific infrastructure in a variety of other ways, including specifically targeted networks and special programs such as the Specialized Programs for Research Excellence.<sup>83</sup> More than 50 new investigator-initiated R01 projects in lung cancer were awarded in FY 2020 adding to NCI's portfolio.

In addition, researchers in NCI's Division of Epidemiology and Genetics embarked on a major effort to evaluate factors influencing lung cancer risk among never-smokers. The Sherlock-lung study is a comprehensive genomic epidemiologic study of lung cancer in never-smokers.<sup>84</sup> It aims to identify processes involved in lung tumor growth to develop a more refined classification of lung cancer in never-smokers and provide insights into prognosis and treatment strategies. Preliminary data is beginning to emerge, highlighting the large differences in the molecular landscape of lung cancer in never-smokers from that of smokers. The study will collect data from 2,500 never-smokers.

### *Ovarian Cancer*

NCI supports a robust research program in women's cancers including breast, cervical, endometrial and ovarian cancers, and including research aimed at addressing disparities for women from certain racial/ethnic and underserved populations. Recently three new studies launched to better understand why certain groups of patients with ovarian cancer do worse than others.<sup>85</sup> One of the studies is using a comprehensive approach to examine the interplay among patient, health care, social contextual, and biological factors from data collected on approximately 4,500 women to understand racial disparities in ovarian cancer survival.<sup>86</sup> Similarly, a second study is focusing on factors that contribute to poor ovarian cancer survival in African American women.<sup>87</sup> The third study is surveying women who recently completed initial treatment for ovarian cancer to determine barriers to access to quality cancer care.<sup>88</sup> Women with pathogenic mutations in the BRCA1/2 gene have an increased risk for developing breast and ovarian cancers; however, only a small percentage of women at risk of carrying these mutations undergo genetic testing. In FY 2020, NCI funded three collaborative pilot projects using a "Traceback" approach to genetic testing for women with a personal or family history of ovarian cancer and reaching out to family members to identify unaffected individuals at

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<sup>82</sup> [pubmed.ncbi.nlm.nih.gov/32786189/](https://pubmed.ncbi.nlm.nih.gov/32786189/)

<sup>83</sup> [trp.cancer.gov/spores/lung.htm](https://trp.cancer.gov/spores/lung.htm)

<sup>84</sup> [dceg.cancer.gov/research/cancer-types/lung/sherlock-lung-study](https://dceg.cancer.gov/research/cancer-types/lung/sherlock-lung-study)

<sup>85</sup> [cancer.gov/news-events/cancer-currents-blog/2020/ovarian-cancer-racial-disparities-studies](https://cancer.gov/news-events/cancer-currents-blog/2020/ovarian-cancer-racial-disparities-studies)

<sup>86</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?icde=0&aid=9998465](https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=9998465)

<sup>87</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?icde=0&aid=9887475](https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=9887475)

<sup>88</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9831150](https://projectreporter.nih.gov/project_info_description.cfm?aid=9831150)

increased risk for cancer.<sup>89,90,91</sup> Traceback testing is a framework for identifying and genetically testing previously diagnosed but unreferred patients with ovarian cancer and other unrecognized mutation carriers to improve the detection of families at risk for breast or ovarian cancer. Identifying and caring for individuals with inherited cancer syndromes is also a focus of the Cancer Moonshot. One Moonshot project is assessing the effectiveness of population scale testing for hereditary breast and ovarian cancers and for Lynch syndrome, which is associated with an increased risk of several cancers, including ovarian cancer.<sup>92</sup>

### *Pancreatic Cancer*

In response to the Recalcitrant Cancer Research Act (RCRA), and in collaboration with the extramural research community and advocacy groups, NCI developed a Scientific Framework for Pancreatic Ductal Adenocarcinoma (PDAC) in 2014,<sup>93</sup> which sought to leverage decades of NCI-funded research and identify the most promising scientific opportunities in this field. NCI has since provided several updates to Congress through reports and other requests for information, and the Institute continues to establish, and support research opportunities identified through the PDAC framework and to fund meritorious grant proposals in all areas of pancreatic cancer.

One of the recommendations from the PDAC framework was to study the connection between diabetes and pancreatic cancer. The National Institute of Diabetes and Digestive and Kidney Diseases and NCI developed the Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer Clinical Centers, which was renewed in 2020.<sup>94</sup> Nine centers were renewed, and one new center was funded in FY 2020. The consortium is focused on translational research to understand the origins of and interactions between chronic pancreatitis, diabetes, and pancreatic cancer in children and adults.<sup>95</sup>

In FY 2018, NCI introduced the R37 Method to Extend Research in Time (MERIT) Award, to provide longer term grant support to Early-Stage Investigators (ESIs).<sup>96</sup> In FY 2020, four R37 to ESIs are focused on pancreatic cancer. These projects are seeking to improve response to treatment by targeting cancer stem cells<sup>97</sup> and the immune response,<sup>98</sup> developing novel combination therapies to target a cellular process that feeds the cancer cells<sup>99</sup> and increase understanding of how metabolic alterations support tumor cell growth.<sup>100</sup>

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<sup>89</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9972625](https://projectreporter.nih.gov/project_info_description.cfm?aid=9972625)

<sup>90</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9863850](https://projectreporter.nih.gov/project_info_description.cfm?aid=9863850)

<sup>91</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9969941](https://projectreporter.nih.gov/project_info_description.cfm?aid=9969941)

<sup>92</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9848432](https://projectreporter.nih.gov/project_info_description.cfm?aid=9848432)

<sup>93</sup> [deainfo.nci.nih.gov/advisory/ctac/workgroup/pc/pdacframework.pdf](https://deainfo.nci.nih.gov/advisory/ctac/workgroup/pc/pdacframework.pdf)

<sup>94</sup> [grants.nih.gov/grants/guide/rfa-files/RFA-DK-19-009.html](https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-19-009.html)

<sup>95</sup> [cpdpc.mdanderson.org/about-cpdpc.html](https://cpdpc.mdanderson.org/about-cpdpc.html)

<sup>96</sup> Investigators who have completed their education within the past decade and have not yet received their first substantial independent NIH research grant

<sup>97</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?icde=0&aid=9866478](https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=9866478)

<sup>98</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?icde=0&aid=10051259](https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=10051259)

<sup>99</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?icde=0&aid=10033575](https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=10033575)

<sup>100</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?icde=0&aid=10033018](https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=10033018)

## Diabetes

The agreement directs NIH to include updates on the following research, projects, and programs in the fiscal year 2022 Congressional Justification: gastric cancer; psycho-social distress in cancer research; the Office of Cancer Survivorship; progress in treating rare cancers; the Surveillance, Epidemiology, and End Results [SEER] Registry; Temporomandibular Disorders; diabetes, Rapid Acceleration of Diagnostics; 7q1 1.23 Duplication Syndrome; and Hereditary Spastic Paraparesis 49 (TECPR2). (Joint Explanatory Statement, p. 45).

### **Action taken or to be taken**

Diabetes and obesity are two of the diseases most frequently associated with severe cases of COVID-19. In July 2020, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) released a Funding Opportunity Announcement (FOA) to support research into the interactions between coronavirus disease 2019 (COVID-19) and these as well as other diseases in the NIDDK mission, and to improve treatment for vulnerable populations. Through another mechanism, the NIDDK has already provided funding supplements to grantees who proposed revisions to ongoing projects aimed at achieving insights into the relationship between COVID-19 and preexisting or new-onset diseases, including diabetes, in hopes of mitigating the impact of COVID-19 on people with these diseases. At the same time, NIDDK-supported research has led to significant recent progress toward prevention, treatment, and cure of various forms of diabetes.

For example, NIDDK-supported research contributed to several U.S. Food and Drug Administration-approved technologies, giving people with type 1 diabetes new options for managing their disease with less burden. Continuous glucose monitors now alleviate the need for fingerstick calibration or are implantable. Artificial pancreas devices automate insulin administration in response to blood glucose levels in ways that more closely mimic normal physiologic insulin secretion; and ready-to-use glucagon formulations offer a simpler way to treat hypoglycemia. These innovations are making a real and positive impact on the lives of people with type 1 diabetes. The National Institutes of Health (NIH) continues to support research to develop and test next-generation devices that are smaller, easy to use, and available to all people, including groups for which glycemic control remains a challenge. Diabetes doubles the risk of many devastating conditions in the body, and NIDDK research strives to prevent, delay, and treat these complications as well. For example, NIDDK established the Diabetic Foot Consortium to validate biomarkers for diabetic foot ulcers through a network of clinical and biomarker measurement sites and, in partnership with the National Heart, Lung, and Blood Institute (NHLBI) will issue an FOA in 2021 to investigate the excess burden of cardiovascular disease faced by those with type 1 diabetes.

Research is also progressing toward curing diabetes. The Human Islet Research Network (HIRN) is conducting multiple avenues of research to determine how beta cells are lost in diabetes and to identify strategies to protect or replace them in people. For example, HIRN's Human Pancreas Analysis Program is analyzing human pancreata at the single-cell level, providing knowledge that is changing our understanding of diabetes. Researchers have also developed the first functional, lab-generated islets capable of evading immune attack in pre-

clinical models. The NIDDK's Longitudinal Assessment of Bariatric Surgery-2 study showed that Roux-en-Y gastric bypass achieves a higher likelihood of type 2 diabetes remission in obese patients with the disease than does laparoscopic gastric banding, even when controlling for weight loss, providing clues as to the mechanism that may lead to improved treatment or even reverse the disease.

The Accelerating Medicines Partnership T2D Project Knowledge Portal is leveraging the dramatic NIH-led progress in understanding type 2 diabetes genetics to identify and validate the most promising biological targets for new diagnostic and drug development. Recent research has shown how one rare genetic variant may be protecting against type 2 diabetes, which may lead to important advances in treatment and prevention of the disease, while a meta-analysis of older data has revealed hundreds of new potential targets for intervention. The Rare and Atypical Diabetes Network seeks to understand how best to classify diabetes subtypes, which could bring more precision to diabetes treatment. The NIDDK is also supporting a research consortium to better define the development and impact of elevated maternal glucose levels and diabetes at early stages and longitudinally over the course of pregnancy, so that we might better predict who may develop gestational diabetes and continue efforts to improve short- and long-term health outcomes in infants and mothers.

## Dystonia

The Committee notes the recommendations from the conference on dystonia held by NINDS to revitalize the dystonia research portfolio were recently released. The Committee requests an update in the fiscal year 2022 Congressional Justification on the release of the recommendations and new research and therapeutic needs that the conference identified. The Committee encourages NINDS to work with other dystonia research related Institutes such as the National Institute on Deafness and Other Communication Disorders (NIDCD) and the National Eye Institute (NEI) on research that will lead to a better understanding of dystonia etiology and evaluation of the current status of translational research that may lead to more treatment options for those affected by dystonia (House Report, p. 105).

### **Action taken or to be taken**

As the Committee notes, NINDS, working together with other parts of NIH and patient groups, convened a scientific workshop to identify opportunities for research to advance the understanding and treatment of dystonia. Researchers in dystonia and other relevant fields of science, clinicians who treat dystonia, representatives of NGOs focused on dystonia, and scientific staff from NIH discussed existing data and resources, as well as new tools and techniques that might be brought to bear on dystonia. Topics included the underlying neurobiology, animal models that mimic aspects of the disease, genetics, natural history, neuropathology, and therapeutic approaches. In February 2020, the journal *Neurology* published “Defining research priorities in dystonia” which reported to the research and patient community on opportunities for research and collaboration that emerged from the discussion<sup>101</sup>.

The report noted that the heterogeneity of dystonia, which takes many forms, poses challenges to research and treatment. The types of dystonia can be conceptualized according to clinical characteristics, etiology (causes), and pathophysiology (underlying mechanisms). Therefore, much can be learned from studying specific genetic subtypes. Overall research priorities include generation of high-quality data on the clinical characteristics and genetics of dystonia, reproducing key features in cellular and animal models, leveraging new research technologies, and targeting brain circuit dysfunction with specific therapies. The report also emphasized the importance of collaboration for collecting data and integration of different research methods and strategies.

As for all diseases, NIH relies heavily on investigators at universities, medical centers, and small companies throughout the U.S. to propose research, while taking into account guidance such as was proposed during this workshop. Rigorous scientific peer review informs selection of the most meritorious proposals. NIH offers a variety of grant mechanisms designed for small- and large-scale projects in individual laboratories and collaborative teams. The Dystonia Coalition, for example, is a large consortium of investigators and patient advocacy groups throughout the U.S. supported by NINDS and the NIH Office of Rare Diseases Research to pursue a broad mission to advance clinical and translational research on the dystonias to find better treatments and a cure. NIH continues to support a broad range of extramural research on dystonia, from genetic studies to neuro-engineering approaches, that addresses priorities from the workshop.

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<sup>101</sup> [www.ncbi.nlm.nih.gov/pmc/articles/PMC7274927/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC7274927/)

This includes continuing research and several new projects launched since the workshop on high priority topics such as new technologies for monitoring dystonia, model systems, genetic subtypes, and brain circuit mechanisms.

The NIH Intramural Research Program also continues a longstanding research program on dystonia. Looking forward, as the workshop discussed, the NIH's Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative is likely to have a major impact on dystonia research in the future. Dystonia is a prime example of a disease in which symptoms arise from malfunction of the brain circuits -- in dystonia, circuits that control movement are dysfunctional. The BRAIN Initiative is providing new insights about how brain circuits work, developing new methods to study these circuits, and exploring new therapies to intervene precisely when circuits malfunction. In 2003, the FDA approved electrical stimulation of deep brain circuits under a humanitarian device exemption for the treatment of dystonia. Furthermore, the BRAIN Initiative is providing new technologies to map brain circuits, monitor the firing of millions of neurons that give rise to movements, and more precisely modulate activity in circuits.



## Eating Disorder Research

The Committee commends NIH for supporting multi-Institute research on the chronic, fatal, and serious mental illnesses encompassing eating disorders that affect 30 million Americans during their lifetimes, and its association with other conditions such as diabetes, infertility, heart disease, PTSD, substance use, co-morbid mental illnesses, and tooth decay. The Committee recognizes that eating disorders are a deadly bio-psycho-social illness and that multiple research topics must be explored to understand, prevent, and treat eating disorders, including psychosocial issues; health disparities and food insecurity; environmental factors such as weight stigma; the complex interplay of metabolic processes; and maternal health. The Committee encourages NIH to increase support for eating disorders research and explore these and other research questions through multiple Institutes and Centers, including NIMH, NIDDK, NIMHD, and NIDA. The Committee directs NIH to inform the Committee on the steps taken to increase support for eating disorders and measures taken to improve prevention, diagnosis, and treatment of eating disorders in the fiscal year 2022 Congressional Justification (House Report, p. 133).

### **Action Taken or To Be Taken**

Approximately 30 million individuals are diagnosed with an eating disorder (ED) in their lifetime, making this a high priority research area for the National Institute of Mental Health (NIMH). NIMH supports a diverse research portfolio that aims to improve clinical care for individuals with EDs and inform future treatments and interventions. NIMH funds ED research across the spectrum from basic to applied research; such funding has increased in recent years. In FY 2019, NIMH invested approximately \$23 million dollars in ED research, up from \$15 million dollars in FY 2016.<sup>102</sup> Further, NIMH continues to support ED research, such as the funding opportunity announced in April 2020 to encourage researchers to develop pilot projects that evaluate the preliminary effectiveness of interventions targeting sustained and enhanced treatment response following acute treatment for anorexia nervosa (AN).<sup>103</sup>

NIMH is investing in research that may help clarify the basic biological mechanisms, including genetic factors and neural circuitry associated with eating, reward, and impulsivity, that underlie the behavioral dysregulation found among individuals with EDs.<sup>104</sup> NIMH is also supporting studies in clinical neuroscience to improve our understanding of potential brain circuitry impairments that contribute to EDs. For example, a current NIMH supported project is examining the role of the neural reward systems in individuals with AN and how these systems may be contributing to ED-related behaviors. This project, which is using sophisticated neuropharmacology and neuroimaging methods, may be important in the development of neurotransmitter-specific pharmacological treatments for individuals with AN.<sup>105</sup>

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<sup>102</sup> [report.nih.gov/categorical\\_spending.aspx](https://report.nih.gov/categorical_spending.aspx)

<sup>103</sup> [grants.nih.gov/grants/guide/rfa-files/RFA-MH-20-500.html](https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-20-500.html)

<sup>104</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9799476&icde=52052691](https://projectreporter.nih.gov/project_info_description.cfm?aid=9799476&icde=52052691)

<sup>105</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9805065&icde=52052756](https://projectreporter.nih.gov/project_info_description.cfm?aid=9805065&icde=52052756)

NIMH is also supporting research on interventions and service delivery.<sup>106,107</sup> One current study is focused on refining and testing targeted approaches for individuals who are not likely to respond to Family Based Treatment (FBT), a commonly utilized intervention for AN.<sup>108,109</sup> Two related projects include a clinical trial that employs intensive parent coaching for families of adolescents who exhibit a poor early response to standard FBT, and another study that targets problematic aspects of the family's emotional climate that have been associated with poorer outcomes.<sup>6,7</sup> NIMH is supporting research that leverages technology to improve access to and engagement in evidence-supported interventions and services. For example, researchers are using social media to identify teens with EDs and connect them to a low-cost mobile health intervention that may be adapted to their preferred treatment delivery mechanism to support and motivate ED recovery.<sup>110</sup>

NIMH is committed to collaborating with other NIH Institutes and Centers, and professional organizations such as the Academy for Eating Disorders and the National Eating Disorders Association (NEDA), to advance our understanding of the biological and psychological underpinnings of EDs.<sup>111</sup> NIMH remains committed to improving practices known to be effective by working collaboratively with stakeholders invested in ED research and treatment. For example, NIMH is supporting researchers who are aiming to extend the impact of NEDA's online screening tool by developing a chatbot feature that aims to increase engagement by providing personalized recommendations to those who screen positive on the website.<sup>112</sup> This tool may help increase mental health service utilization and treatment engagement.

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<sup>106</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9883335&icde=52052918](https://projectreporter.nih.gov/project_info_description.cfm?aid=9883335&icde=52052918)

<sup>107</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=10044077&icde=52052963](https://projectreporter.nih.gov/project_info_description.cfm?aid=10044077&icde=52052963)

<sup>108</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9297942&icde=52052802](https://projectreporter.nih.gov/project_info_description.cfm?aid=9297942&icde=52052802)

<sup>109</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9647884&icde=52052841](https://projectreporter.nih.gov/project_info_description.cfm?aid=9647884&icde=52052841)

<sup>110</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9719997&icde=52053024](https://projectreporter.nih.gov/project_info_description.cfm?aid=9719997&icde=52053024)

<sup>111</sup> [www.ncbi.nlm.nih.gov/pmc/articles/PMC2228330/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2228330/)

<sup>112</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9955368&icde=52062768](https://projectreporter.nih.gov/project_info_description.cfm?aid=9955368&icde=52062768)

## **Environmental influences on Child Health Outcomes (ECHO)**

The Committee provides \$180,000,000, the same level as fiscal year 2020, for the ECHO Program. The OD is directed to provide an update in the fiscal year 2022 CJ on progress made by ECHO-funded research (Joint Explanatory Statement, p. 64).

### **Action Taken or to be Taken**

ECHO aims to enhance the health of children for generations to come. Research conducted through ECHO focuses on five key pediatric outcomes: pre-, peri- and postnatal outcomes; upper and lower airway health; obesity; neurodevelopment; and positive health. ECHO has two major components, the ECHO cohorts – for observational research, and the ECHO IDeA States Pediatric Clinical Trials Network (ISPCTN) – for interventional research. The ECHO Program has developed a strategic plan to assess the program’s overall direction and to focus its priorities. This strategic plan<sup>113</sup> articulates the mission and vision of the Program Office and will be its roadmap for success over the next five years.

**ECHO Cohorts.** ECHO has created a sophisticated data collection protocol for all 72-participating mother–child cohort studies, whose collective data form the ECHO–wide Cohort. Cohort teams have uploaded, to the ECHO–wide Cohort data platform, existing cohort-specific data that map to the ECHO protocol. They are now beginning to populate the data platform with standardized newly collected data from pregnant women and children. The platform features data from approximately 50,000 children and their families. This platform allows ECHO investigators, and soon thereafter the wider scientific community, to address solution–oriented questions that no single cohort could accomplish alone.

The ECHO cohorts have published approximately ~600 manuscripts.<sup>114</sup> Some examples that leverage data from multiple ECHO cohorts include: a recent article<sup>115</sup> on childhood obesity in the US that details results from an ECHO study of more than 37,000 babies and kids from 70 ECHO cohorts, noting that obesity rates are higher among older than younger children, and rates are higher in non–White races/ethnicities; an article published in *Quality of Life Research*<sup>116</sup> identified that better sleep quality in school-age children was associated with lower psychological stress and better general health status, which in turn, predicted better life satisfaction; and an article published in *Pediatrics*<sup>117</sup> from a study that found while children with chronic illnesses have worse health overall, their life satisfaction was comparable with that of their peers without chronic illnesses, suggesting that children with chronic illnesses may still lead happy lives.

**Supporting Diversity Supplements in ECHO Cohorts.** The ECHO Program is committed to fostering a diverse workforce, including individuals from groups identified as underrepresented, and is well poised to support talented individuals from diverse backgrounds. In response to a

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<sup>113</sup> [www.nih.gov/echo/echo-strategic-plan](http://www.nih.gov/echo/echo-strategic-plan)

<sup>114</sup> [echochildren.org/echo-program-publications](http://echochildren.org/echo-program-publications)

<sup>115</sup> [www.nature.com/articles/s41366-019-0470-5](http://www.nature.com/articles/s41366-019-0470-5)

<sup>116</sup> [link.springer.com/article/10.1007/s11136-020-02491-9](https://link.springer.com/article/10.1007/s11136-020-02491-9)

<sup>117</sup> [pediatrics.aappublications.org/content/early/2019/05/02/peds.2018-2988](https://pediatrics.aappublications.org/content/early/2019/05/02/peds.2018-2988)

Notice of Special Interest (NOSI),<sup>118</sup> the ECHO Program awarded a total of eight diversity supplements to existing grantees. Five of the supplements were for pre-doctoral awardees and three for postdocs, who will gain experience in child health research through collaboration with ECHO investigators.

**ECHO IDeA States Pediatric Clinical Trials Network (ISPCTN).** The ECHO ISPCTN consists of interventional research sites in 18 states historically underrepresented in biomedical research. This program, renewed in 2020, aims to include children and infants from rural areas in clinical research while building capacity by supporting professional development and infrastructure. During the first cycle of the ISPCTN, the Network participated in the National Institute of Child Health and Development (NICHD) Pediatric Trials Network study of pharmacokinetics of medications routinely used in, but not U.S. Food and Drug Administration–approved for, pediatrics. The second cycle of the ECHO ISPCTN includes 1) two Advancing Clinical Trials in Neonatal Opioid Withdrawal<sup>119</sup> (ACT NOW) Clinical Trials—in collaboration with the NICHD as part of the Helping to End Addiction Long-term (HEAL) Initiative<sup>120</sup>—to build evidence for best practices to care for newborns with opioid withdrawal syndrome, and 2) two ISPCTN–initiated clinical trials: VODRA,<sup>121</sup> a pharmacokinetic trial of vitamin D supplementation in children with obesity–related asthma, and iAmHealthy,<sup>122</sup> a pilot study of a mobile–health healthy weight intervention in children from rural or underserved populations.

**ECHO’s Contribution to COVID–19 Research.** ECHO researchers are focused on understanding how the coronavirus disease 2019 (COVID–19) pandemic affects pregnant women and children. The ISPCTN COVID–19 task force is identifying specific COVID–19–related intervention trials that this network of rural and underserved children could mount, and several ISPCTN sites are participating in national COVID–19 vaccine trials. The ECHO cohorts rapidly produced COVID–19 measures that are now part of the ECHO–wide Cohort data collection protocol and are publicly available on NIH websites.<sup>123,124</sup> The Cohort COVID–19 Working Group facilitated collaborative responses to a NOSI<sup>125</sup> for ECHO COVID–19–related research. The ECHO Program awarded 12 administrative supplements to support time–sensitive data collection and analyses during the pandemic.

**ECHO Opportunities and Infrastructure Fund (OIF).** The OIF seeks to develop *early career scientists* and foster their transition to research independence. OIF supports innovative projects for new research, tools, and technologies in the ECHO Program. It also promotes collaborations to produce transdisciplinary research via team science. Since its establishment in 2018, ECHO has funded 30 early career scientists on projects such as integration of technology–based measures; innovations in biomarkers of key exposures and pathways; analysis of complex data; improved characterization of pathways to multiple outcomes or to positive health; and innovative ways to leverage extant ECHO–wide Cohort data. This year’s OIF will also fund projects related

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<sup>118</sup> [grants.nih.gov/grants/guide/notice-files/NOT-OD-20-098.html](https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-098.html)

<sup>119</sup> [heal.nih.gov/news/stories/ACTing-Now](https://heal.nih.gov/news/stories/ACTing-Now)

<sup>120</sup> [heal.nih.gov/](https://heal.nih.gov/)

<sup>121</sup> [www.clinicaltrials.gov/ct2/show/NCT03686150?term=VDORA&draw=2&rank=1](https://www.clinicaltrials.gov/ct2/show/NCT03686150?term=VDORA&draw=2&rank=1)

<sup>122</sup> [www.clinicaltrials.gov/ct2/show/NCT04142034?term=iAmHealthy&draw=2&rank=1](https://www.clinicaltrials.gov/ct2/show/NCT04142034?term=iAmHealthy&draw=2&rank=1)

<sup>123</sup> [dr2.nlm.nih.gov/](https://dr2.nlm.nih.gov/)

<sup>124</sup> [www.phenxtoolkit.org/covid19](https://www.phenxtoolkit.org/covid19)

<sup>125</sup> [grants.nih.gov/grants/guide/notice-files/NOT-OD-20-107.html](https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-107.html)

to health disparities; interactions among exposures; strategies for remote recruitment, informed consent, and data and biospecimen collection; and machine learning approaches to data analysis.

## E-Cigarette Research

The Committee encourages NIH to prioritize research into the understanding of the biological changes that occur due to use of electronic nicotine delivery systems (ENDS) among adolescents (House Report, p. 133).

### Action Taken or To Be Taken

The National Institutes of Health (NIH) is committed to research aimed at understanding how electronic nicotine delivery systems (ENDS), such as e-cigarettes and vaping devices, affect human health and biology, particularly among young Americans. E-cigarettes became available to U.S. consumers in 2007 and became quickly popular with adolescents such that by 2019, one in four 12th graders reported having vaped in the past 30 days.<sup>126</sup> Years before the surge in popularity of e-cigarettes, the National Heart, Lung, and Blood Institute (NHLBI) organized a two-day workshop on the cardiovascular and pulmonary health effects of ENDS, which helped inform NHLBI's growing portfolio of research in this area.<sup>127</sup>

The acute risks of vaping became dramatically evident with an outbreak of e-cig/vaping-associated lung injury (EVALI) in March 2019, which caused 2,807 hospitalizations and 68 deaths by February 2020.<sup>128</sup> In October 2019, NHLBI convened investigators and federal health agency officials to identify the most urgent research questions related to EVALI and to guide a funding opportunity that invited researchers to study vaping-related illness.<sup>129,130</sup> The NHLBI research community quickly answered this call, and made significant contributions to understanding EVALI. For example, researchers found that inhalation of vitamin E acetate—a chemical in vaping products—causes acute lung injury in mice<sup>131</sup>; this chemical was also found in the lungs of EVALI patients but not in e-cigarette users without EVALI.<sup>132</sup> In response to NHLBI's funding announcement in fall 2019, other researchers modified an ongoing study of children in intensive care for lung injury. In addition to general medical histories, the researchers are now collecting detailed e-cigarette and cigarette exposure history from all participants and have identified some cases of EVALI; these cases will help us learn more about EVALI risk factors and outcomes.<sup>133</sup>

NHLBI also continues to support research to understand the potential health effects of vaping in the absence of acute illness. One recent NIH-supported study found that just one vaping session—even without nicotine—can produce acute stiffening in the blood vessels of healthy

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<sup>126</sup> [pubmed.ncbi.nlm.nih.gov/31532955/](https://pubmed.ncbi.nlm.nih.gov/31532955/)

<sup>127</sup> RFA-HL-17-008, “Pulmonary and Cardiovascular Consequences of Inhaled Nicotine (R01)” and RFA-HL-17-021 (reissued as RFA-HL-18-024), “Cardiovascular and Pulmonary Research on E-Cigarettes (R01).

<sup>128</sup> [www.cdc.gov/tobacco/basic\\_information/e-cigarettes/severe-lung-disease.html](https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html)

<sup>129</sup> [www.nhlbi.nih.gov/events/2019/nih-workshop-e-cigarette-or-vaping-product-use-associated-lung-injury-evali-developing](https://www.nhlbi.nih.gov/events/2019/nih-workshop-e-cigarette-or-vaping-product-use-associated-lung-injury-evali-developing)

<sup>130</sup> [grants.nih.gov/grants/guide/notice-files/NOT-HL-19-724.html](https://grants.nih.gov/grants/guide/notice-files/NOT-HL-19-724.html)

<sup>131</sup> [pubmed.ncbi.nlm.nih.gov/32822237/](https://pubmed.ncbi.nlm.nih.gov/32822237/)

<sup>132</sup> [pubmed.ncbi.nlm.nih.gov/32101656/](https://pubmed.ncbi.nlm.nih.gov/32101656/)

<sup>133</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=10115413](https://projectreporter.nih.gov/project_info_description.cfm?aid=10115413)

young nonsmokers.<sup>134</sup> Other studies using animal models indicate that e-cigarette use may increase susceptibility to bacterial<sup>135</sup> and viral infections.<sup>136</sup>

In 2019, NHLBI also launched two epidemiological studies that are expected to help reveal long-term health effects of vaping. The Lung Health Cohort will follow 4,000 healthy young adults (aged 25-35) to identify early risk factors and signs of lung disease; the Risk Underlying Rural Areas Longitudinal (RURAL) Cohort will examine long-term cardiopulmonary health outcomes by following 4,000 young to middle-aged adults (aged 25-64) in 10 rural counties in Alabama, Kentucky, Louisiana, and Mississippi. Collection of e-cigarette exposure history in these studies will help shed light on the risk of long-term health effects that might linger in early adulthood.

In March 2020, NHLBI convened stakeholders from across NIH, the U.S. Food and Drug Administration, public health organizations, and the research community for a workshop to discuss the gaps, barriers, and research opportunities related to prevention and cessation of e-cigarette use in youth and young adults.<sup>137</sup>

The National Institute on Drug Abuse (NIDA) also supports research to examine the impact of tobacco products, including ENDS, on the developing adolescent brain. For example, the Adolescent Brain Cognitive Development (ABCD) study, which is the largest long-term study of brain development and child health in the United States, will assess the impact of substance use—including e-cigarettes—and on brain development and other outcomes from about age 10 to age 20.<sup>138</sup> NIDA-supported researchers have also examined whether nicotine exposure from ENDS is a risk factor for increased nicotine use and dependence.<sup>139</sup> They found that adolescents who regularly used e-cigarettes had higher levels of nicotine in their bodies than previously associated with conventional cigarettes. These findings raise key concerns about the potential for earlier and more significant nicotine addiction in teens.<sup>140</sup>

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<sup>134</sup> [pubmed.ncbi.nlm.nih.gov/31429679/](https://pubmed.ncbi.nlm.nih.gov/31429679/)

<sup>135</sup> [pubmed.ncbi.nlm.nih.gov/31664858/](https://pubmed.ncbi.nlm.nih.gov/31664858/)

<sup>136</sup> [pubmed.ncbi.nlm.nih.gov/31483291/](https://pubmed.ncbi.nlm.nih.gov/31483291/)

<sup>137</sup> [www.nhlbi.nih.gov/events/2020/e-cigarette-prevention-and-cessation-youth-and-young-adults](https://www.nhlbi.nih.gov/events/2020/e-cigarette-prevention-and-cessation-youth-and-young-adults)

<sup>138</sup> [abcdstudy.org/about/](https://abcdstudy.org/about/)

<sup>139</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9332356&icde=52043412](https://projectreporter.nih.gov/project_info_description.cfm?aid=9332356&icde=52043412)

<sup>140</sup> [pubmed.ncbi.nlm.nih.gov/31122507/](https://pubmed.ncbi.nlm.nih.gov/31122507/)

## Endometrial Cancer

The Committee is concerned that both the incidence and mortality rates for endometrial cancer are rising, with a survival disparity for Black women. The Committee believes that a renewed emphasis by NCI on endometrial cancer research is needed to facilitate early detection and optimal treatments and outcomes for all women, including minority populations. The Committee urges NCI to study endometrial cancer disparities, including biologic differences in tumor type, molecular mechanisms, pathogenesis, and tumor microenvironment, and to conduct clinical trials to better define appropriate therapy for a precision medicine approach to endometrial cancer. The Committee requests an update on NCI's activities regarding endometrial cancer in the fiscal year 2022 Congressional Justification, including progress made in incidence and survival rates by ethnicity (House Report, p. 94-95).

### **Action Taken or To Be Taken**

Endometrial cancer is the most common gynecologic cancer in the United States, with an estimated 65,620 new cases and 12,950 deaths in 2020.<sup>141</sup> The National Cancer Institute (NCI) remains dedicated to improving outcomes for all women with endometrial cancers and to better understanding endometrial cancer disparities.

A recent study led by NCI intramural researchers used population data from NCI's Surveillance, Epidemiology, and End Results (SEER) database to evaluate trends of hysterectomy-corrected uterine cancer incidence rates for women overall and by race and ethnicity, geographic region, and histologic subtype.<sup>142</sup> Correct estimation of these rates requires accounting for hysterectomy prevalence, which varies by race, ethnicity, and region. The researchers found that incidence rates of common subtypes of uterine cancer were stable in non-Hispanic white women over the study period and increased in women of other racial/ethnic groups. By contrast, incidence rates of aggressive subtypes have been increasing dramatically over time in all racial/ethnic groups, in particular much higher rates of these aggressive subtypes were observed in black women than in other racial/ethnic groups. The researchers also observed that survival rate was lower among all women with aggressive subtypes than among women with common subtypes, and black women had the lowest survival rates, within each stage at diagnosis or histologic subtype.

NCI supports research to understand underlying causes of endometrial cancer, in order to help better predict risk and work toward prevention and early detection of this cancer. For example, the Epidemiology of Endometrial Cancer Consortium (E2C2) is an NCI-supported consortium dedicated to studying the etiology of endometrial cancer through collaboration among investigators.<sup>143</sup> E2C2 researchers recently showed that the use of aspirin, other nonsteroidal anti-inflammatory drugs, and acetaminophen may reduce risk of endometrial cancer among overweight and obese women.<sup>144</sup> In a separate NCI-funded study, researchers have shown that an experimental screening test can detect some endometrial cancers at their early, more

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<sup>141</sup> [seer.cancer.gov/statfacts/html/corp.html](https://seer.cancer.gov/statfacts/html/corp.html)

<sup>142</sup> [pubmed.ncbi.nlm.nih.gov/31116674/](https://pubmed.ncbi.nlm.nih.gov/31116674/); [dceg.cancer.gov/news-events/news/2019/uterine-cancer-rate-rising](https://dceg.cancer.gov/news-events/news/2019/uterine-cancer-rate-rising)

<sup>143</sup> [epi.grants.cancer.gov/eccc/](https://epi.grants.cancer.gov/eccc/)

<sup>144</sup> [pubmed.ncbi.nlm.nih.gov/30566587/](https://pubmed.ncbi.nlm.nih.gov/30566587/)



treatable stages.<sup>145</sup> The test, called PapSEEK, is a type of liquid biopsy that identifies cancer-related alterations in DNA obtained from fluids collected during a routine Pap test.

Uterine serous carcinoma (USC) is a rare but aggressive type of endometrial cancer. In about one-third of women with USC, their tumor cells overproduce HER2 protein (HER2 positive), which is associated with poor prognosis in women with endometrial cancer. Black women are more likely than white women to be diagnosed with USC and are more likely than women of other races/ethnicities to have HER2-positive USC tumors. NCI clinical studies for patients that have HER2-positive uterine serous cancer and carcinosarcoma are currently in development.<sup>146</sup>

NCI conducts numerous preclinical and clinical studies to identify more effective treatments for endometrial cancer progression and recurrence. For example, an early career scientist from the University of North Carolina is studying the use of Metformin in the treatment of endometrial cancer in obese compared to non-obese women both in an animal model and an ongoing clinical trial.<sup>147</sup> Other examples of ongoing clinical studies include: testing an aromatase inhibitor as a preventative agent for patients with complex atypical hyperplasia of the endometrium/endometrial intraepithelial neoplasia or low grade endometrial cancer; evaluating a combination of immunotherapy and radiation treatment in women with newly diagnosed, early stages of endometrial cancer; evaluating an investigational drug in advanced endometrial cancer that, in laboratory studies, has been shown to kill endometrial cancer cells; and testing new delivery techniques for radiation to minimize treatment side effects in patients, including women with endometrial cancer.<sup>148</sup> In addition, recent findings from an NCI study indicated that combining a chemotherapy drug with immunotherapy could enhance antitumor responses in women with recurrent endometrial cancer.<sup>149</sup>

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<sup>145</sup> [pubmed.ncbi.nlm.nih.gov/29563323/](https://pubmed.ncbi.nlm.nih.gov/29563323/)

<sup>146</sup> [www.cancer.gov/news-events/cancer-currents-blog/2020/endometrial-cancer-usc-her2-trastuzumab](https://www.cancer.gov/news-events/cancer-currents-blog/2020/endometrial-cancer-usc-her2-trastuzumab)

<sup>147</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9869698&icde](https://projectreporter.nih.gov/project_info_description.cfm?aid=9869698&icde)

<sup>148</sup> [clinicaltrials.gov/ct2/show/study/NCT03300557](https://clinicaltrials.gov/ct2/show/study/NCT03300557); [clinicaltrials.gov/ct2/show/NCT04214067](https://clinicaltrials.gov/ct2/show/NCT04214067);  
[clinicaltrials.gov/ct2/show/NCT03394027](https://clinicaltrials.gov/ct2/show/NCT03394027); [clinicaltrials.gov/ct2/show/NCT00924027](https://clinicaltrials.gov/ct2/show/NCT00924027)

<sup>149</sup> [ascopubs.org/doi/abs/10.1200/JCO.2020.38.15\\_suppl.6010](https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.6010); [clinicaltrials.gov/ct2/show/NCT03367741](https://clinicaltrials.gov/ct2/show/NCT03367741)

## **Federal Advisory Committees Transparency Initiative**

The Committee recognizes that Federal advisory committees established as part NIH pursuant to 42 U.S.C. 282(b)(6) fill an important role in advising NIH on major decisions on plans and policies. However, to guarantee due process, it is vital that all NIH Federal advisory committees operate in a transparent way. As such, the Committee directs all NIH Federal advisory committees, including in particular the Literature Selection Technical Review Committee (LSTRC), to make public their standards of review, decision-making methodologies, and processes by which to appeal a recommendation. Moreover, the LSTRC and all other NIH Federal advisory committees shall ensure that they are operating in accordance with the provisions of the Federal Advisory Committee Act, as amended (5 U.S.C., Appendix 2). (House Report, p. 133-134).

### **Action Taken or To Be Taken**

The National Institutes of Health (NIH) recognizes the importance of transparent operations of the agency's Federal advisory committees. NIH utilizes several types of committees to advise on specific programs, research needs and opportunities, management policy issues, future initiatives, and research funding.

NIH's advisory committees operate in accordance with the requirements of the Federal Advisory Committee Act (FACA), such as announcing establishment of committees and upcoming meetings in the Federal Register, providing public access to committee information, and maintaining records such as costs, membership, meeting minutes, and any reports. Much of this information is maintained in the FACA database overseen by the General Services Administration (GSA) and verified by the Annual Comprehensive Review, an additional oversight activity required by FACA. Information on all of NIH's committees is located on the Office of Federal Advisory Committee Policy's website,<sup>150</sup> which include a complete listing of the agency's committees, meeting schedules, membership rosters as well as links to current statute, regulations, and guidelines governing FACA committees. Further information can be found on dedicated Institute/Center committee websites.

The Literature Selection Technical Review Committee (LSTRC) is a Federal Advisory Committee that advises the National Library of Medicine (NLM) on the selection of journals to be indexed for MEDLINE, NLM's database of citations to the biomedical journal literature. The LSTRC is comprised of authorities knowledgeable in the field of biomedicine such as physicians, researchers, educators, editors, and health science librarians. In making a recommendation to NLM as to whether or not a journal should be indexed in MEDLINE, the committee conducts an appraisal of a journal's scope and coverage, editorial policies and processes, scientific rigor of article content, production and administration, and impact. NLM considers the LSTRC recommendations in making its decisions about indexing a journal for MEDLINE. Both LSTRC and NLM take seriously the need to operate in a transparent manner. Information about the LSTRC, including its membership and minutes of its meetings are

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<sup>150</sup> [ofacp.od.nih.gov/index.asp](http://ofacp.od.nih.gov/index.asp)

available online.<sup>151</sup> Details of its selection procedures and critical elements of its reviews of journals are also available online.<sup>152</sup>

In the last year, NLM has taken steps to improve and further enhance the transparency of MEDLINE processes. NLM consolidated into a single platform the application system for several of its literature services, including MEDLINE. The new platform provides applicants (publishers, editors) with regular status updates throughout the review process. NLM notifies applicants if a preliminary staff screening determines that a journal does not meet minimum eligibility criteria for inclusion in the NLM collection. NLM also completed pilot testing of a new report for LSTRC members to use when completing their evaluation of a journal, to more clearly delineate the primary considerations used for assessment and provide more opportunity for a narrative summary of the review. NLM systematically shares these summary reports with applicants when notifying them of NLM's decision. Preliminary feedback from publishers has been extremely positive, and NLM plans to adopt the new approach in future reviews. Building on this experience, NLM is developing a process that could be used for appeals in the event a concern arises about an NLM decision for journal selection for MEDLINE. Under current procedures described on NLM's website, NLM decisions for journal selection for MEDLINE are final. Journals not deemed acceptable by the NLM for MEDLINE indexing may apply for re-review two years after their initial LSTRC review.<sup>153</sup>

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<sup>151</sup> [www.nlm.nih.gov/lstrccommittee/index.html](http://www.nlm.nih.gov/lstrccommittee/index.html)

<sup>152</sup> [www.nlm.nih.gov/lstrc/jsel.html](http://www.nlm.nih.gov/lstrc/jsel.html)

<sup>153</sup> [www.nlm.nih.gov/lstrc/j\\_sel\\_faq.html#a9](http://www.nlm.nih.gov/lstrc/j_sel_faq.html#a9)

## Fetal Tissue

The Committee directs OD to provide an update in the fiscal year 2022 CJ detailing how alternatives to fetal tissue acquired after an elective abortion can be used in fetal tissue research. Specifically, the CJ should detail how the use of donated tissue from a spontaneous abortion (miscarriage) or stillbirth would impact fetal tissue research (Senate Report, p.116).

### **Action Taken or to be Taken**

The National Institutes of Health (NIH) has recently made a concerted effort to fund research specifically to develop, demonstrate, and validate experimental models that are alternatives to human fetal tissue (HFT). In 2019, NIH published a series of announcements of funding opportunities for research on alternatives to HFT. The notices covered scientific areas including creating mice with humanized immune systems, ocular research, oncology research, tissue chip programs, and developmental processes and disorders. NIH has issued close to 30 awards in connection with the funding announcements. Examples of the alternatives to human fetal tissue being examined by these awards include experimental models using human pluripotent cells, cord blood cells, and adult cells and tissues to develop animal models, organoids, tissue chips, and other research tools.

NIH is optimistic that this research to develop alternatives to HFT will result in more options for researchers for particular uses; however, HFT from miscarriages or still births has limited utility for research as compared to tissue from elective abortions. NIH funded a major study with five tissue bank programs to collect and examine tissue donated from women who had miscarriages or ectopic pregnancies, to determine whether the tissue would be suitable for use in transplantation research.<sup>154</sup> From over 22,000 obstetric admissions, tissue from 1,250 miscarriages and 247 ectopic pregnancies were obtained. Of these, less than 1 percent were useful for human transplantation; 71 percent of samples were degenerated; 79 percent had bacterial contamination (despite use of aseptic collection techniques); and 40 percent had chromosomal abnormalities.

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<sup>154</sup> Branch DW, Ducat L, Fantel A, et al. Suitability of Fetal Tissues from Spontaneous Abortions and From Ectopic Pregnancies for Transplantation. *JAMA*. 1995;273(1):66–68.

## Gastric Cancer

The agreement directs NIH to include updates on the following research, projects, and programs in the fiscal year 2022 Congressional Justification: gastric cancer; psycho-social distress in cancer research; the Office of Cancer Survivorship; progress in treating rare cancers; the Surveillance, Epidemiology, and End Results [SEER] Registry; Temporomandibular Disorders; diabetes, Rapid Acceleration of Diagnostics; 7q1 1.23 Duplication Syndrome; and Hereditary Spastic Paraparesis 49 (TECPR2). (Joint Explanatory Statement, p. 45)

### **Action Taken or to be Taken**

NCI continues to support a broad portfolio of gastric and esophageal research projects, including support for Specialized Programs of Research Excellence (SPORES) focusing on early detection and treatment of gastric cancer and esophageal cancers.<sup>155,156</sup> NCI also funded new projects in both of these cancers in FY 2020, including a Small Business Innovation Research (SBIR) grant to develop novel inhibitors of a key signaling pathway that is mutated in esophageal and many other cancers<sup>157</sup> and an investigator-initiated project to investigate how changes in gastric tumor cell biology affects tumor cell survival, anti-tumor immunity, and response to therapy.<sup>158</sup>

Currently, NCI is developing a scientific framework for gastric, esophageal, and gastro-esophageal (GE) junction cancers, a closely related group of cancers known collectively as “gastroesophageal cancers.” The initial steps include the development of a portfolio analysis to identify relevant research projects and an associated comprehensive literature review to identify subject matter experts to assess key challenges and opportunities in the field. NCI is in the process of forming a multi-disciplinary working group to guide the development of a scientific framework, a broad group of subject matter experts and patient advocates is being engaged and it is anticipated that this group will convene virtually within the first half of 2021.

In December 2020, the NCI Board of Scientific Advisors approved the launch of a new program to identify the origins of gastroesophageal cancers and to build on advances in our understanding of the molecular classification and genomics of gastric and esophageal cancers made possible by The Cancer Genome Atlas and other NCI-supported research. This new program, funded at \$20 million over a five-year period, will provide unprecedented opportunities to examine the earliest cellular changes in transformation that precede any manifestations of cancer to tackle these cancers at their foundation. This new program is built on and energized by new discoveries and discussions that took place at a recent NCI-sponsored think tank on the origins of gastrointestinal cancers. The think tank highlighted this promising research area and explored challenges faced by the research community.

Also, in 2020, the FDA awarded breakthrough designation to a new technology (EsoCheck™) and biomarker test (EsoGuard™) developed by researchers supported by NCI’s Barrett’s

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<sup>155</sup> [trp.cancer.gov/spores/abstracts/case\\_gi.htm](http://trp.cancer.gov/spores/abstracts/case_gi.htm) (Project 3)

<sup>156</sup> [trp.cancer.gov/spores/abstracts/dfhcc\\_gi.htm](http://trp.cancer.gov/spores/abstracts/dfhcc_gi.htm) (Project 4)

<sup>157</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=10010409&icde=0](http://projectreporter.nih.gov/project_info_description.cfm?aid=10010409&icde=0)

<sup>158</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?icde=0&aid=9972209](http://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=9972209)

Esophagus Translational Research Network (BETRNet).<sup>159</sup> The device and test detect Barrett's Esophagus, a precursor lesion of esophageal adenocarcinomas. Both are currently in clinical trials, giving patients timely access to a quick, accurate and less invasive way to identify risk of esophageal adenocarcinomas. These cancers are usually diagnosed at an advanced stage when difficult to treat however, detecting Barrett's esophagus could help patients by giving physicians a chance to intervene early.

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<sup>159</sup> [prevention.cancer.gov/news-and-events/blog/new-technology-gives-patients](http://prevention.cancer.gov/news-and-events/blog/new-technology-gives-patients)

## **Glioblastoma (GBM)**

The Committee recognizes that GBM is the most common, most deadly, and most difficult form of brain cancer to treat in adults. For the thousands of Americans facing this disease, the lack of progress is a devastating reality that trails behind the impressive progress made in research of other forms of cancer. The Committee strongly encourages NIH to support additional research on glioblastoma treatment (House Report, p. 95).

### **Action Taken or To Be Taken**

Because glioblastoma (GBM) remains an essentially incurable disease with a 5-year survival rate of approximately 3 percent, there is an urgent need to develop more effective therapies for this disease. The National Cancer Institute (NCI) and others have invested in basic, translational, and clinical research on GBM for decades. NCI's investment includes the Specialized Programs of Research Excellence (SPOREs) in brain cancers and an extensive intramural research program. Currently there are six brain cancer SPORE programs which have made advances in prognostic testing and immunotherapy for brain cancers.<sup>160</sup> The research and clinical trials program of the intramural Neuro-Oncology Branch, Center for Cancer Research, focuses on developing novel diagnostic and therapeutic agents for patients with all types of brain tumors.<sup>161</sup> The branch also runs the NCI-CONNECT (Comprehensive Oncology Network Evaluating Rare Central Nervous System Tumors) rare tumor patient engagement network.

The blood-brain barrier, a natural mechanism through which the body prevents viruses or toxins in the bloodstream from reaching the brain, presents a significant challenge in delivering drugs to GBM and all types of brain tumors. In addition, GBM tumors are heterogeneous at the genetic and molecular levels. These factors mean that current treatments generally have not had long-term success.

NCI is committed to making progress in GBM and all cancers. In consultation with an advisory group of external experts, NCI has developed a plan to advance research on the treatment of GBM more rapidly. The Institute is launching the GBM Therapeutics Network with a goal to improve the treatment of adult GBM by developing novel and effective agents to overcome the blood-brain barrier and GBM heterogeneity, and eventually evaluate the drugs in Phase 3 clinical trials. The network will also work to improve and/or repurpose existing drugs, and drug combinations for use in GBM. The GBM Therapeutics Network will consist of multi-institutional teams of researchers working in a collaborative manner and in conjunction with a Coordinating Center. The Coordinating Center will provide network harmonization on research activities, such as biobanking, and on clinical activities. Each team in the network will be expected to drive drug development of novel agents from pre-clinical development, through investigational new drug studies and into clinical studies. Applications for the GBM Therapeutics Network are now being accepted, and NCI expects to fund up to five awards in FY 2021.<sup>162</sup>

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<sup>160</sup> [trp.cancer.gov/spores/brain.htm](http://trp.cancer.gov/spores/brain.htm)

<sup>161</sup> [ccr.cancer.gov/neuro-oncology-branch](http://ccr.cancer.gov/neuro-oncology-branch)

<sup>162</sup> [grants.nih.gov/grants/guide/rfa-files/RFA-CA-20-047.html](http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-20-047.html)

## Government-wide Collaborations

NIH, VA, and DOD collaborate frequently and successfully on various research activities. The Committee looks forward to the report in the fiscal year 2022 CJ focusing on the cooperative and strategic approach the agencies take in areas of biomedical research that overlap to maximize the potential of the research (Senate Report, p. 117).

### **Action Taken or to be Taken**

In keeping with the National Institutes of Health's (NIH) strategic objective to capitalize on cross-cutting opportunities to advance biomedical research<sup>163</sup>, NIH continues to work closely with the Department of Defense (DoD) and the Department of Veterans Affairs (VA) on research activities that support the organizations' mutual scientific and clinical missions to address the needs of military personnel and veterans and to accelerate specific research areas through strategic partnerships.

The novel coronavirus disease 2019 (COVID-19) pandemic is an unprecedented global crisis that has been met with a swift and extraordinary response. On April 17, 2020, NIH announced the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership, including DoD and VA among its federal partners, to develop a coordinated research strategy for prioritizing and speeding development of the most promising treatments and vaccines.<sup>164</sup> ACTIV has built off of the success of prior NIH, DoD, and VA collaborations to leverage the expertise and resources of these agencies and provide military personnel, veterans, and civilians with more opportunities to participate in industry and federally sponsored clinical trials.

In addition, the NIH, DoD, and VA, as part of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria, are collaborating to enhance infection prevention and antibiotic stewardship in humans and animals. Released in October 2020, the National Action Plan for Combating Antibiotic-Resistant Bacteria outlines coordinated, strategic actions that the United States government will take in 2020-2025 to reduce the impact of antibiotic and antimicrobial resistance on the nation.<sup>165</sup>

To promote data sharing, NIH and DoD co-lead the Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System, which partners with other federal agencies, including the VA.<sup>166</sup> As of December 2020, data from the Concussion Assessment Research Education (CARE) Consortium on more than 79,000 subjects were submitted to FITBIR, including 28 studies with shared data available, to enable researchers to gain new insights on traumatic brain injury and treatments for military personnel, veterans, and other Americans.<sup>167</sup>

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<sup>163</sup> [www.nih.gov/sites/default/files/about-nih/strategic-plan-fy2016-2020-508.pdf](http://www.nih.gov/sites/default/files/about-nih/strategic-plan-fy2016-2020-508.pdf)

<sup>164</sup> [www.nih.gov/research-training/medical-research-initiatives/activ](http://www.nih.gov/research-training/medical-research-initiatives/activ)

<sup>165</sup> [www.hhs.gov/sites/default/files/carb-national-action-plan-2020-2025.pdf](http://www.hhs.gov/sites/default/files/carb-national-action-plan-2020-2025.pdf)

<sup>166</sup> [fitbir.nih.gov/](http://fitbir.nih.gov/)

<sup>167</sup> [fitbir.nih.gov/content/submitted-data](http://fitbir.nih.gov/content/submitted-data)



Building on a long-term history of collaboration between the NIH, DoD, and VA, the Pain Management Collaboratory (PMC) is comprised of 11 large-scale, multisite, pragmatic clinical trials that are studying nonpharmacological approaches for the management of pain and common co-occurring conditions in Military and Veterans healthcare systems. The PMC is designed to address key scientific knowledge and clinical practice gaps in the delivery of high-quality pain care in DoD and VA health systems and support improved patient outcomes.<sup>168</sup> Results from the trials are expected in six years.

NIH's collaborations with DoD and VA highlight the importance of tackling complex medical challenges through strategic partnerships. By creating and fostering cross-cutting research opportunities, NIH can help accelerate the search for effective treatments for cancer, chronic pain, and other diseases and conditions that affect military personnel, veterans, and other Americans.

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<sup>168</sup> [www.ncbi.nlm.nih.gov/pmc/articles/PMC6895460/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC6895460/)

## **Hereditary Spastic Paraparesis 49 (TECPR2)**

The agreement directs NIH to include updates on the following research, projects, and programs in the fiscal year 2022 Congressional Justification: gastric cancer; psycho-social distress in cancer research; the Office of Cancer Survivorship; progress in treating rare cancers; the Surveillance, Epidemiology, and End Results [SEER] Registry; Temporomandibular Disorders; diabetes, Rapid Acceleration of Diagnostics; 7q1 1.23 Duplication Syndrome; and Hereditary Spastic Paraparesis 49 (TECPR2). (Joint Explanatory Statement, p. 45).

### **Action taken or to be taken**

Hereditary spastic paraplegia/paraparesis (HSP) is a large group of inherited neurological disorders that share the primary symptom of progressive muscle weakness and stiffness (spasticity) and the development of complete (paraplegia) or partial paralysis (paraparesis) of the lower limbs. There are over 80 genetic mutations that have been discovered so far that are associated with HSP, but other genetic factors that cause almost half of HSP cases remain unknown. HSP type 49 is one of many types of HSP and is caused by mutations in the TECPR2 gene.

While the National Institutes of Health (NIH) does not currently support projects specifically focused on HSP type 49, NIH is funding clinical and genetic research grants on HSP, as well as projects that promote clinical trial readiness for HSP and related disorders. One project of note is a genetic study supported by the National Institute of Neurological Disorders and Stroke (NINDS) that uses advanced sequencing technologies to systematically analyze the largest collection of clinical samples of HSP in the world. The project aims to identify novel genetic factors that underlie HSP and make the genomic data shareable as a resource for the research community. Also, NINDS and the National Center for Advancing Translational Sciences are co-funding the Clinical Research in ALS and Related Disorders for Therapeutic Development (CReATe) Consortium<sup>169</sup> which enrolls and studies individuals with amyotrophic lateral sclerosis (ALS) and related disorders, including HSP. The goal of the CReATe Consortium is to support collaborative research on this group of rare diseases and promote clinical trial readiness through development and dissemination of research resources, lowering barriers to patient participation in clinical research, enhancing training of young scientists, and engaging various stakeholders in partnerships that foster therapeutic development.

Other related, on-going projects funded by NINDS include research grants that aim to investigate distinct disease mechanisms underlying specific genetic types of HSP and to identify disease mechanisms that are common across different types of HSP with the goal of understanding how unrelated genetic mutations lead to similar clinical outcomes. Findings from these studies will help discover novel treatment targets that may work for various types of HSP, including HSP type 49. In addition, several NINDS-funded projects investigate how dysfunction in cellular disposal pathways and defects in a cellular structure called endoplasmic reticulum (ER) ultimately result in HSP pathology. For instance, an intramural research team at NINDS has been developing animal models for HSP and using advanced molecular and cell biology approaches to examine the changes that occur in the ER due to genetic mutations that cause HSP.

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<sup>169</sup> [www.rarediseasesnetwork.org/cms/create/about](http://www.rarediseasesnetwork.org/cms/create/about)

All of these efforts will advance our understanding of biological mechanisms underlying various types of HSP, which will lead to identification of novel biomarkers or treatment targets that prevent or slow the progression of HSP and related disorders. As always, NIH is committed to supporting rigorous and innovative research grants on rare diseases such as HSP and continues to encourage the research community to submit applications for research grants.

## **Induced Pluripotent Stem Cell (iPSC) Technology**

The Committee continues to stress iPSC technology as a critical tool in the realm of personalized medicine. The Committee notes that iPSCs are derived from adult skin cells, providing increased opportunities to develop sources of cells with immense therapeutic value and potential for curing human diseases. The Committee recognizes that basic science leads to pre-clinical trials, cures, diagnostics, and treatments and encourages NIH to further explore additional basic science opportunities. In addition, the Committee understands that collaborative consortiums such as the Southeast Stem Cell Consortium (SESCC) leverages research capabilities to further advance scientific knowledge in the area of iPSC basic research. The Committee requests an update in the fiscal year 2022 Congressional Justification on NIH efforts to expand iPSC technology basic research through collaborative consortiums (House Report, p. 136-137).

### **Action Taken or To Be Taken**

The National Institutes of Health (NIH) has a large investment in all types of human induced pluripotent stem cell (iPSC) research—basic, translational, and clinical projects totaling \$563 million in FY 2019.<sup>170</sup> Some of these research projects are part of established consortiums, and others involve various degrees of collaboration between basic research scientists, translational scientists, and clinicians.

Collaborative research is of high value to NIH, and thus the agency has built several collaborative research programs that include conducting research with iPSCs. Examples include: The (Re)Building a Kidney consortium, funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), which coordinates studies to generate or repair kidney cells, including kidney cells from iPSCs.<sup>171</sup> The Progenitor Cell Translational Consortium at The National Heart Lung and Blood Institute (NHLBI), which aims to translate advances for the treatment of heart, lung, and blood diseases.<sup>172</sup> The Microphysiological Systems for Modeling Diabetes consortium supported by NIDDK and the National Center for Advancing Translational Sciences (NCATS) aims to develop human tissue chips to model diabetes.<sup>173</sup> In the 3-D Tissue Bioprinting program, NCATS researchers are collaborating with academic investigators in basic and clinical research and also with private-sector partners to advance the development of new medicines by developing new assay models that better predict the effects of drugs in humans.<sup>174</sup>

In the NIH Intramural Research Program (IRP), researchers coordinate and collaborate with each other to advance research with iPSCs through the various stages of development. Dr. Kapil Bharti's research team developed a new iPSC-derived investigational retinal pigment epithelial cell product to treat age-related macular generation and did the preclinical work. Dr. Bharti collaborated with Dr. Henry Wiley, a staff clinician and surgeon in the NIH IRP, for transplantation into research participants in a clinical trial being conducted at the NIH Clinical

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<sup>170</sup> [report.nih.gov/categorical\\_spending.aspx](https://report.nih.gov/categorical_spending.aspx)

<sup>171</sup> [www.rebuildingakidney.org/about/](https://www.rebuildingakidney.org/about/)

<sup>172</sup> [translationalcells.org/](https://translationalcells.org/)

<sup>173</sup> [ncats.nih.gov/tissuechip/projects/modeling](https://ncats.nih.gov/tissuechip/projects/modeling)

<sup>174</sup> [ncats.nih.gov/bioprinting/about](https://ncats.nih.gov/bioprinting/about)

Center.<sup>175</sup> In another IRP initiative, the Stem Cell Translation Laboratory (SCTL) in NCATS utilizes a collaborative model including scientists in academia, biotechnology, and industry to overcome hurdles to translating iPSCs research into treatments.<sup>176</sup>

Another major NIH initiative, authorized by the 21st Century Cures Act, is the Regenerative Medicine Innovation Project (RMIP). RMIP is a trans-NIH effort, in coordination with the U.S. Food and Drug Administration, to further advance and help develop safe and effective regenerative medicine products using adult stem cells.<sup>177</sup> NIH made awards in FY 2019 to support late-stage pre-clinical studies utilizing iPSCs to advance treatment of various diseases.<sup>178</sup> In addition, the NIH Regenerative Medicine Innovation Catalyst (RMIC) component of RMIP provides critical clinical services to support RMIP awardees. The RMIC facilitates source and product stem cell characterization services, regulatory support services, and manufacturing assistance for the development of clinical-grade products.<sup>179</sup>

Collaborations in research with iPSCs also develop naturally between NIH-funded investigators at different institutions, as reflected in their joint publications. Some notable recent collaborative accomplishments include the development of personalized human blood-brain barrier chips to model inheritable neurological disorders and use in drug screening; the development of insulin-producing organoids for treating type 1 diabetes; the development of human lung and brain organoids to study SARS-COV-2 infection and search for potential treatments; and the development of an anti-cancer immunotherapy to provide “off-the-shelf” cell therapy.

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<sup>175</sup> [clinicaltrials.gov/ct2/show/NCT04339764](https://clinicaltrials.gov/ct2/show/NCT04339764)

<sup>176</sup> [ncats.nih.gov/stemcell](https://ncats.nih.gov/stemcell)

<sup>177</sup> [www.nih.gov/rmi](https://www.nih.gov/rmi)

<sup>178</sup> [www.nih.gov/rmi/funded-awards](https://www.nih.gov/rmi/funded-awards)

<sup>179</sup> [rmiatahub.org/](https://rmiatahub.org/)

## **Inflammatory Bowel Diseases (IBD)**

The Committee recognizes NIDDK's leadership in supporting research into Crohn's disease and ulcerative colitis. The Committee also recognizes the importance of patient-centered, bedside-to-bench approaches to understand complex, chronic diseases such as IBD, and the need to better understand the impact of diet on IBD. The Committee directs NIDDK to pursue research on the interactions among food, the gut, and the brain/nervous system in people with IBD and other chronic gastrointestinal diseases. The Committee notes that this bedside-to-bench approach has been successful in other disease areas, including type 2 diabetes and oncology, and we encourage NIDDK to use a similar approach focused on IBD (House Report, p. 102).

### **Action Taken or To Be Taken**

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) continues to encourage research that could lead to new therapies for inflammatory bowel disease (IBD) such as Crohn's disease and ulcerative colitis, including bedside-to-bench approaches that take into consideration the clinical and physiological characteristics of individual patients when developing treatments. For example, recent results from the NIDDK-supported Predicting Response to Standardized Pediatric Colitis Therapy (PROTECT) study suggested that the best treatment approaches for pediatric ulcerative colitis are those that are tailored based upon patients' clinical, genetic, and microbial profiles.<sup>180</sup> The study also sets the stage for additional clinical studies that will further move ulcerative colitis therapy toward more personalized, and ultimately more effective, approaches. Another study identified a tell-tale combination of cells in people with Crohn's disease who do not respond to one of this disease's most effective treatments, shedding light on the complex nature of the disease and revealing potential new targets for therapy. This study and the PROTECT study could help clinicians predict which therapies would be most effective for individual patients, and could also lead to the development of potential new treatments for people with IBD.

The NIDDK will also continue to support research on the interactions among food, the gut, and the brain/nervous system in the context of IBD and other chronic gastrointestinal diseases. For example, NIDDK-sponsored research is investigating how food, such as a high-fiber diet, affects intestinal inflammation by shaping the microbiome—the diverse community of microorganisms that inhabit the gut. Other research is exploring the intimate connections between the nervous system and the gut, such as the cross-talk between nerves and the cells that line the intestinal wall, and how inflammation in the gut could affect these communications. NIDDK-sponsored research is also examining how cells in the gut interact directly with the types of nerves that send pain signals to the brain, thereby pointing to a mechanism for how chronic visceral pain develops and how it is sensed by the brain. These studies could lead to new ways for treating pain caused by IBD and other gastrointestinal diseases.

Other research supported by NIDDK, in conjunction with the NIH Office of Research on Women's Health, is investigating changes in the brain and the gut microbiome in response to cognitive behavioral therapy for irritable bowel syndrome, a gastrointestinal disorder that is strongly linked to interactions between the brain and the gut. A main goal of the study is to

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<sup>180</sup> [clinicaltrials.gov/ct2/show/NCT01536535](https://clinicaltrials.gov/ct2/show/NCT01536535)

identify who would be most likely to benefit from this type of therapy. The NIDDK is also sponsoring a workshop in March 2021 to evaluate brain-gut communication in neurodegenerative disorders and to explore partnership opportunities among NIDDK, the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute of Environmental Health Sciences (NIEHS) for brain-gut research. Staff from each of these institutes are on the workshop's organizing committee.

NIDDK continues to encourage research in all of these areas with the overall goal of improving the lives of people with complex, chronic conditions like IBD.

## Liver Cancer

The Committee notes that liver cancer is a devastating disease, with a five-year survival rate of only 20 percent. The Committee commends NCI for the creation of a Specialized Center of Research Excellence (SPORE) focused on liver cancer and encourages other new program projects, research, and contract opportunities for investigators that focus on a better understanding of the biology of liver cancer and new therapeutic targets. In addition, the Committee commends NCI for its support of the inter-institute effort to develop the NIH Strategic Plan to Cure Hepatitis B and encourages continued close collaboration with the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and active participation in the Director's Trans-NIH Hepatitis B Working Group. The Committee requests an update on NCI's activities in these areas in the fiscal year 2022 Congressional Justification (House Report, p. 95).

### **Action Taken or To Be Taken**

The National Cancer Institute (NCI) conducts and supports research to improve the prevention, detection, diagnosis, and treatment of liver cancer, or hepatocellular carcinoma (HCC), including research on viral hepatitis, caused by the hepatitis B and C viruses, and its link to liver cancer.

The NCI intramural Center for Cancer Research Liver Cancer Program is a multidisciplinary network that collaborates with extramural investigators to develop diverse approaches to the prevention, early detection, diagnosis, and treatment of liver cancer.<sup>181</sup> Recently, NCI researchers, who are also part of the NCI's Translational Liver Cancer Consortium (described below), in collaboration with researchers from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and several academic centers, developed a new diagnostic test that can help identify people who are likely to develop HCC.<sup>182</sup> The approach uses a blood test to check for the patient's previous exposure to certain viruses; the test can distinguish people who are likely to develop liver cancer from those with chronic liver disease and healthy livers. Together with existing screening tests, this test could play an important role in screening people who are at risk for developing HCC. The researchers are continuing to study their approach and plan to test it in clinical trials, in particular in a prospective surveillance study of people with risk factors for HCC.

NCI also supports several translation programs working to develop strategies to detect liver cancer early and improve treatments of liver cancer patients. The NCI's Translational Liver Cancer Consortium conducts studies to better stratify patients at risk of developing liver cancer, improve the surveillance of liver cancer in high-risk populations, and increase the fraction of liver cancer detected at an early stage.<sup>183</sup> The NCI-supported Specialized Program of Research Excellence (SPORE) supports research on hepatobiliary (liver, gallbladder, bile ducts) cancers and hepatocellular carcinoma and is developing translational strategies to improve the detection, diagnosis, and treatment of patients with these malignancies.<sup>184</sup> The Mayo Clinic Hepatobiliary

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<sup>181</sup> [ccr.cancer.gov/liver-cancer-program](http://ccr.cancer.gov/liver-cancer-program)

<sup>182</sup> [pubmed.ncbi.nlm.nih.gov/32526205/](http://pubmed.ncbi.nlm.nih.gov/32526205/)

<sup>183</sup> [prevention.cancer.gov/major-programs/translational-liver-cancer-tlc-consortium](http://prevention.cancer.gov/major-programs/translational-liver-cancer-tlc-consortium)

<sup>184</sup> [trp.cancer.gov/spores/hepatobiliary.htm](http://trp.cancer.gov/spores/hepatobiliary.htm)



SPORE focuses on new approaches to hepatobiliary cancer diagnosis and therapy. The MD Anderson Cancer Center Hepatocellular Carcinoma SPORE is conducting studies to determine the prognostic significance of a biomarker for postoperative recurrence, perform extensive screening for liver fibrosis in obese and diabetic Hispanics, and evaluate how well immunotherapy with monoclonal antibodies, such as nivolumab and ipilimumab in combination or alone, work in treating patients with liver cancer that can be removed by surgery.<sup>185</sup> Preliminary results from this clinical trial are promising and are anticipated to be published soon.

While several targeted treatments have been approved by the U.S. Food and Drug Administration for liver cancer, they usually extend patients' lives by just a few months, and the prognosis for the disease remains poor. NCI supported researchers are working to develop better treatments. For example, researchers have initiated clinical trials to determine if an experimental cell therapy is effective in shrinking several types of tumors, including for hepatobiliary tumors in patients whose cancer is resistant to standard treatment.<sup>186</sup>

Other examples of NCI initiatives in liver cancer include the release of funding opportunity announcements to enhance mechanistic and epidemiologic investigations addressing the role of co-infection and emerging risk factors and liver cancer susceptibility, respectively.<sup>187</sup>

NCI continues working with NIDDK, the National Institute of Allergy and Infectious Diseases (NIAID), and the National Institute on Minority Health and Health Disparities (NIMHD) on research related to hepatitis B and progression to liver cancer. In 2020, NCI and NIMHD released funding opportunity announcements to support multidisciplinary research to understand the underlying etiologic factors and mechanisms that contribute to population-level disparities in chronic liver diseases and liver cancer in the U.S.<sup>188</sup>

Intramural researchers at NCI, NIDDK, NIAID, and the NIH Clinical Center are conducting ongoing translational research studies on the molecular mechanisms of disease processes in acute and chronic liver disease aimed at investigating the role of hepatitis viruses in liver carcinogenesis. In addition, NCI, NIDDK, NIAID and others participate in the Trans-NIH Hepatitis B Cure Working Group, Trans-NIH Viral Hepatitis Committee, and the US Department of Health and Human Services (HHS) National Viral Hepatitis Action Plan to coordinate efforts on hepatitis B and related liver cancer across NIH and HHS. The Strategic Plan for Trans-NIH Research to Cure Hepatitis B that was developed by the Trans-NIH Hepatitis B Cure Working Group was recently released.<sup>189</sup> Cirrhosis research is also contributing to efforts to understand liver cancer disease processes, as HCC is a major complication of cirrhosis. In 2020, the NIDDK released funding opportunity announcements to establish a new Liver Cirrhosis Network to promote clinical and translational research on liver cirrhosis caused by a wide range of conditions, including chronic viral hepatitis, nonalcoholic steatohepatitis, and others.<sup>190</sup>

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<sup>185</sup> [clinicaltrials.gov/ct2/show/NCT03222076](https://clinicaltrials.gov/ct2/show/NCT03222076)

<sup>186</sup> [clinicaltrials.gov/ct2/show/NCT01174121](https://clinicaltrials.gov/ct2/show/NCT01174121)

<sup>187</sup> [grants.nih.gov/grants/guide/pa-files/par-20-062.html](https://grants.nih.gov/grants/guide/pa-files/par-20-062.html); [grants.nih.gov/grants/guide/pa-files/par-18-677.html](https://grants.nih.gov/grants/guide/pa-files/par-18-677.html)

<sup>188</sup> [grants.nih.gov/grants/guide/pa-files/par-20-088.html](https://grants.nih.gov/grants/guide/pa-files/par-20-088.html)

<sup>189</sup> [www.niaid.nih.gov/sites/default/files/Trans-NIH-Hep-B-Strategic-Plan-2019.pdf](https://www.niaid.nih.gov/sites/default/files/Trans-NIH-Hep-B-Strategic-Plan-2019.pdf)

<sup>190</sup> [grants.nih.gov/grants/guide/rfa-files/RFA-DK-20-003.html](https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-20-003.html); [grants.nih.gov/grants/guide/rfa-files/RFA-DK-20-004.html](https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-20-004.html)

## Macular Degeneration

The Committee is concerned with advanced age-related macular degeneration as the leading cause of irreversible blindness and vision impairment globally. At least 11 million people in the U.S. have some form of macular degeneration and that number is expected to double to 22 million by 2050. The Committee encourages NIH to fund research that will stem the growth of macular degeneration and requests an update on current research and future initiatives in the fiscal year 2022 Congressional Justification (House Report, p. 115).

### **Action Taken or To Be Taken**

The National Eye Institute (NEI) appreciates the opportunity to provide highlights of current and future research initiatives on macular degeneration. From 2008 to 2017, NEI spent more than \$1 billion (adjusted for inflation) to conduct studies that have played an instrumental role in understanding the causes and nature of age-related macular degeneration (AMD).<sup>191</sup> NEI-supported research established common clinical stages for AMD, demonstrated ways to prevent advanced disease progression, and provided groundwork for a comprehensive understanding of the genetics associated with AMD. There are two forms of AMD, a predominant non-neovascular or “dry” form and a neovascular or “wet” form. Due to the lack of preventive measures and effective treatments for dry AMD, the National Advisory Eye Council, the external committee that guides the NEI, charged an interdisciplinary working group of scientists to assess the current state of research on dry AMD and provide recommendations for research priorities to discover targeted therapies. In July 2019, the working group published a report that recommends prioritizing integrative research, which combines genes and molecular pathway research with animal and human cell disease models to expedite the discovery of dry AMD treatments. The report also recommended improving access to high-quality ocular (eye) tissue and identifying biological indicators to detect early-stage disease changes in AMD patients.<sup>192</sup>

In December 2019, NEI researchers launched the first U.S. Food and Drug Administration-approved clinical trial in the United States using replacement eye tissue derived from reprogramming patient stem cells to treat certain forms of AMD.<sup>193</sup> NEI is also building on previous advances, such as the NEI Age Related Eye Disease Studies (AREDS) and follow-on AREDS2 investments, to develop new projects aimed at integrating datasets and encouraging the use of innovative approaches by cross-disciplined researchers to overcome translational barriers and develop new therapies for AMD patients. To catalyze such projects, NEI recently launched the AMD Integrative Biology Initiative in partnership with the New York Stem Cell Foundation Research Institute, to provide a widely available resource for the research community to access

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<sup>191</sup> Wright, Charles, Anna E. Mazzucco, Steven M. Becker, Paul A. Sieving, and Santa J. Tumminia. "NEI-supported age-related macular degeneration research: past, present, and future." *Translational vision science & technology* 9, no. 7 (2020): 49-49. [tvst.arvojournals.org/article.aspx?articleid=2770229](https://www.tvst.arvojournals.org/article.aspx?articleid=2770229).

<sup>192</sup> Handa, James T., Cathy Bowes Rickman, Andrew D. Dick, Michael B. Gorin, Joan W. Miller, Cynthia A. Toth, Marius Ueffing, Marco Zarbin, and Lindsay A. Farrer. "A systems biology approach towards understanding and treating non-neovascular age-related macular degeneration." *Nature communications* 10, no. 1 (2019): 1-11. [www.nature.com/articles/s41467-019-11262-1#Sec19](https://www.nature.com/articles/s41467-019-11262-1#Sec19).

<sup>193</sup> "More Than Meets the Eye 2020." National Eye Institute. U.S. Department of Health and Human Services. Accessed October 6, 2020. [www.nei.nih.gov/learn-about-eye-health/resources-for-health-educators/more-meets-eye-2020](https://www.nei.nih.gov/learn-about-eye-health/resources-for-health-educators/more-meets-eye-2020).

AMD patient-derived stem cell lines and their associated genomic and clinical datasets. Researchers can share data with the community and also access consenting patients' deidentified genomic and ocular imaging data. The launch of this community-based resource will support efforts to help compare genetic, molecular, and clinical characteristics, allowing researchers to develop new targeted therapies for the disease.

## Male Reproductive Health

The Committee urges NICHD to support research on male mechanisms of infertility. In fiscal year 2020, the Committee encouraged NICHD to support research on male infertility and requests a report on progress in this area in the fiscal year 2022 Congressional Justification. Due to the gap in knowledge of how to diagnose and treat male infertility and abnormal embryo development, the Committee reiterates its priority interest. The Committee requests a report within 90 days of enactment of this Act detailing NICHD's existing collaborations and research to identify new proteins and sperm structures that are necessary for normal sperm foundation and, consequently, for fertility and embryo development (House Report, p.112).

### Action taken or to be taken

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) continues to support research to understand the causes and to treat male infertility and abnormal embryo development. The Centers for Disease Control and Prevention (CDC) estimates that 9.4 percent of males in the United States are infertile and accounts for 40 to 50 percent of infertility experienced by couples.

NICHD's Strategic Plan 2020 proposes several scientific and public health priorities to advance research that directly align with male reproductive health. The goal of one theme, *Promoting Gynecologic, Andrologic, and Reproductive Health*, is to enable men and women to manage their fertility and minimize the impact of andrologic and gynecologic conditions in support of lifelong reproductive health. NICHD continues to be interested in identifying genes/pathways involved in development of the male reproductive tract, which also aligns with the Strategic Plan. For example, NICHD-funded investigators recently identified a protein that is critical to ensure proper sperm processing in the epididymis, a convoluted duct in which sperm mature.

Nutrition is another cross-cutting topic woven throughout the research themes of the Strategic Plan. In a study conducted by NICHD's Division of Intramural Population Health Research, investigators found that dietary supplements containing zinc and folic acid, typically marketed as fertility supplements, do not appear to improve sperm counts, sperm function, or pregnancy rates. Similarly, investigators in NICHD's Reproductive Medicine Network,<sup>194</sup> which carries out large, multicenter clinical trials of diagnostic and therapeutic interventions for male and female infertility, showed that the use of antioxidants in the treatment of male factor infertility did not improve semen parameters, DNA integrity, or increase the probability of live birth.

NICHD has a significant interest in understanding the potential link(s) between fertility status and overall health. NICHD issued a Funding Opportunity Announcement (FOA) with other NIH Institutes and Centers to explore the premise that infertility is not necessarily a unique disease of the reproductive system, but is often physiologically or genetically linked with diseases and/or conditions that affect the entire body. Potentially, fertility evaluations can lead to early interventions in serious, chronic diseases, such as cancer, cystic fibrosis, diabetes, or cardiovascular disease. NICHD's National Centers for Translational Research in Reproduction and Infertility (NCTRI) program comprises a national network of centers that promote

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<sup>194</sup> [www.nichd.nih.gov/research/supported/rmn](http://www.nichd.nih.gov/research/supported/rmn)

multidisciplinary interactions between basic and clinical scientists interested in establishing high-quality translational research in the reproductive sciences.<sup>195</sup> Three of the eight active NCTRI centers are focused on studying various aspects of male fertility. Investigators from one NCTRI center showed in a recent study that the hormone kisspeptin is a promising tool for predicting pubertal outcomes for children with delayed puberty.

NICHD will continue to explore the role that sperm contribute to the oocyte at the time of fertilization that is critical for proper development of the embryo and the later health of the individual. In response to the COVID-19 pandemic, NICHD recently released a FOA on *Emerging Viral Infections and their Impact on the Male and Female Reproductive Tract*, and later in FY 2021, the institute will host a scientific workshop to discuss the role of the male partner in early pregnancy loss.

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<sup>195</sup> <http://www.nichd.nih.gov/research/supported/NCTRI>

## Maternal Mortality Research

The Committee supports NIH efforts to establish the Implementing a Maternal Health and Pregnancy Outcomes Vision for Everyone (IMPROVE) Initiative. The initiative will use an integrated approach to understand biological, behavioral, sociocultural, and structural factors that affect severe maternal mortality and maternal mortality (SMM/MM) by building an evidence base for improved care and outcomes in specific regions of the country. IMPROVE will target health disparities associated with SMM/MM by (1) implementing and evaluating community-based interventions for disproportionately affected women (e.g., African American, American Indian/Alaska Native, advanced maternal age, low socioeconomic status, and rural populations), and (2) identifying risk factors and the underlying biological mechanisms associated with leading causes of SMM/MM, including cardiovascular disease, infection and immunity, and mental health (House Report, p. 112).

### **Action Taken or To Be Taken**

The Centers for Diseases Control and Prevention estimates that approximately 700 women die each year in the United States from pregnancy-related complications. Disparities exist among Black and American Indian/Alaska Native women, who are about three times as likely to die from a pregnancy-related cause compared to White women. Over 50,000 women in the United States experience severe maternal morbidity (SMM). In response to this crisis, the NIH recently launched the initiative *Implementing a Maternal Health and Pregnancy Outcomes Vision for Everyone* (IMPROVE) by awarding over \$7 million in grants through a Notice of Special Interest on Maternal Mortality.<sup>196,197</sup> This initiative is supported by multiple NIH Institutes, Centers, and Offices (ICOs) and is co-led by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the NIH Office of the Director, and the NIH Office of Research on Women's Health. The goal of the IMPROVE initiative is to address health disparities in women disproportionately affected by MM/SMM, including geographic disparities and social determinants of health. These grants will address leading causes of maternal mortality in the United States—cardiovascular disease, infection, and immunity—as well as contributing health conditions or social factors, such as mental health disorders, diabetes, obesity, substance use disorders, and structural and healthcare system issues.

In addition to IMPROVE, NIH is continuing its longstanding research efforts to enhance maternal health and prevent maternal mortality and morbidity, with 22 ICOs supporting over \$334 million in research projects in FY 2019<sup>198</sup>. Recent findings from NICHD-funded grants demonstrate that a hospital quality improvement effort can reduce racial disparities in severe maternal morbidity, and that adverse pregnancy outcomes are more common among women who are deaf or hard of hearing. A new public-private partnership through the Foundation for the National Institutes of Health with support from the Bill & Melinda Gates Foundation is supporting a large clinical trial conducted by investigators in NICHD's Global Network. The trial will assess whether a single oral dose of the antibiotic azithromycin during labor reduces the risk of maternal and infant bacterial infection and death in seven low- and middle-income

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<sup>196</sup> [grants.nih.gov/grants/guide/notice-files/NOT-OD-20-104.html](https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-104.html)

<sup>197</sup> [www.nih.gov/improve-initiative](https://www.nih.gov/improve-initiative)

<sup>198</sup> [report.nih.gov/funding/categorical-spending/](https://report.nih.gov/funding/categorical-spending/)

countries. This study has been shown to be effective in a smaller study and, if successful, would be a low-cost intervention.

The COVID-19 pandemic has added even more urgency to NIH's work on maternal mortality and morbidity, as researchers try to move quickly to recognize how this disease affects maternal, fetal, and newborn health outcomes. NIH's Rapid Acceleration of Diagnostics – Underserved Populations (RADx-UP) initiative leverages existing community partnerships to understand the factors associated with disparities in COVID-19 morbidity and mortality, including pregnant and postpartum women.<sup>199</sup> NICHD's *Gestational Research Assessments of coVID (GRAVID)* study is leveraging its Maternal Fetal Medicine Units Network to analyze the medical records of a diverse group of 24,500 women to evaluate whether changes to healthcare delivery implemented as a result of the pandemic have led to higher rates of pregnancy-related complications and cesarean delivery. Combined with the IMPROVE initiative, NIH has the opportunity to improve health outcomes for pregnant women across the country.

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<sup>199</sup> [www.nih.gov/research-training/medical-research-initiatives/radx](http://www.nih.gov/research-training/medical-research-initiatives/radx)

## **Maternal-Fetal Medicine Units (MFMU) Network**

The Committee supports the critical work of the MFMU Network in improving health outcomes for pregnant women and their babies. Leveraging existing infrastructure to address maternal mortality and severe maternal morbidity in the U.S. is critical. The Committee understands that NICHD is considering several models of infrastructure for its networks and encourages NICHD to maintain the features that made the MFMU Network successful and cost-effective, including the renewal process that maximizes efficiency and ability to conduct multiple large trials with long term follow up over many years. Such an infrastructure is essential for maintaining a collective repository of knowledge and skills as well as a stable foundation for data sharing and workforce development. The Committee looks forward to reports about the process for restructuring and final outcomes once a final decision has been made with respect to the new infrastructure (House Report, p. 112).

### **Action Taken or To Be Taken**

The *Eunice Kennedy Shriver* National Institute of Health and Human Development (NICHD) remains committed to supporting clinical trials in pregnancy and lactation in response to public health needs. In 1986, NICHD created a multicenter obstetric research network, the Maternal-Fetal Medicine Units Network (MFMU).<sup>200</sup> The network was designed to investigate the efficacy and safety of treatment and management strategies used to care for pregnant women at risk of preterm birth and other perinatal complications. The MFMU has been instrumental in augmenting the field of maternal-fetal medicine by increasing the number of experienced clinical trialists capable of independently conducting the kind of rigorous trials needed to shape clinical practice.

Advances in science and health, as well as public health emergencies, not the least of which is the COVID-19 pandemic, provide opportunities to adapt to current research needs and to re-examine a clinical trials infrastructure for obstetric research. For example, when the serious nature of the COVID-19 pandemic became apparent, NICHD quickly launched a multipronged study, known as Gestational Research Assessments for coVID (GRAVID), to understand the effects of having COVID-19 during and after pregnancy. Researchers in the MFMU Network, a group of 12 U.S. clinical centers, are analyzing the medical records of over 24,500 women to evaluate whether changes to healthcare delivery that were implemented as a result of the pandemic have led to higher rates of pregnancy-related complications and cesarean deliveries. MFMU Network sites encompass more than 160,000 deliveries a year, and their racial, ethnic, and geographic diversity allows researchers to generalize their study findings to the general U.S. population. Further, MFMU investigators will seek to establish the risk of pregnant women with SARS-CoV-2 infection transmitting the virus to their fetus, and newborns will be monitored and assessed until they are discharged from the hospital. This portion of the GRAVID study will track more than 3,000 pregnant women confirmed with COVID-19, monitoring their health for six weeks after childbirth. The investigators also plan to contribute data collected from the current study to a larger registry to help inform future studies of how SARS-CoV-2 affects maternal health and pregnancy.

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<sup>200</sup> Wright L & McNellis D; *Semin Perinatol*. 1995;19(2):112-23.



Looking forward, NICHD is taking an in-depth look at what will be the most effective way to support clinical trials involving pregnant women. A wide range of public input on this topic was solicited from the scientific community and public through a variety of means, e.g., a well-attended live, interactive public webinar, publication of a Request for Information, and an open discussion at NICHD's National Advisory Council in January 2020. NICHD has also led the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC), which submitted an Implementation Plan to the U.S. Department of Health and Human Services Secretary in September 2020 that included steps aimed at increasing participation of pregnant and lactating women in clinical trials. NICHD will consider what clinical trials infrastructure will best address its goals for improving the health of pregnant and lactating women, through carrying out the PRGLAC recommendations, supporting clinical trials conducted by a wider range of qualified investigators, taking advantage of advances in technology, and by providing the ability to respond nimbly to emerging public health crises.

## Melanoma

The Committee encourages NCI to continue its support of research on melanoma, including the development of experimental models to identify mechanisms and associated biomarkers, new technologies such as artificial intelligence systems for detection and classification, and clinical trials that provide population-based evidence for public health guidelines for screening and sun protection practices. In addition, the Committee encourages research on therapies for metastatic melanoma, including CNS, LMD, uveal, mucosal and pediatric melanomas; neoadjuvant therapies in trials designed to test for clinical benefit; and risk factors for recurrence. The Committee also urges NCI to continue to evaluate clinical trial eligibility criteria so that patients with brain metastases can also be included in trials whenever clinically appropriate and urges inclusion of melanoma in enhancements to the SEER registry. Finally, in the U.S., there are now more than 1.3 million survivors of melanoma. The Committee encourages further research into survivorship care for melanoma patients. The Committee requests an update on these requests in the fiscal year 2022 Congressional Justification (House Report, p. 95).

### **Action Taken or To Be Taken**

The National Cancer Institute (NCI) continues to support a wide variety of research to improve the prevention, early detection, and treatment of melanoma. Much of this research hinges on a better understanding of melanoma biology in preclinical models being developed by NCI-supported researchers. For example, a recent report described the development of a rapid way to generate custom, complex genetically engineered melanoma mouse models that has the potential to transform the study of melanoma biology and its molecular mechanisms.<sup>201</sup> In another example, intramural NCI researchers developed a panel of mouse models, representing a variety of melanoma subtypes, and found a molecular signature predictive of patient outcome in response to immune checkpoint inhibitor immunotherapies.<sup>202</sup>

Agents that have benefited patients with cutaneous melanoma have largely been ineffective against rare melanoma subtypes which, in fact, may represent biologically distinct diseases. Thus, NCI-funded basic and translational research is improving the understanding of the pathways driving these cancers and identifying new targets for therapy. For example, a recent paper reported that a combination of two U.S. Food and Drug Administration (FDA) approved drugs showed effectiveness in mouse models of uveal melanoma.<sup>203</sup> In addition, intramural NCI researchers showed that drugs targeting two pathways (Ras/MAPK and PI3K/Akt/mTOR) using one FDA-approved and one investigational drug, appear promising therapies for mucosal melanoma in preclinical models, including mucosal melanoma cells from dogs (which is spontaneously occurring in canines).<sup>204</sup>

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<sup>201</sup> [pubmed.ncbi.nlm.nih.gov/31744817/](https://pubmed.ncbi.nlm.nih.gov/31744817/)

<sup>202</sup> [pubmed.ncbi.nlm.nih.gov/32284588/](https://pubmed.ncbi.nlm.nih.gov/32284588/)

<sup>203</sup> [pubmed.ncbi.nlm.nih.gov/32933997/](https://pubmed.ncbi.nlm.nih.gov/32933997/)

<sup>204</sup> [pubmed.ncbi.nlm.nih.gov/32943547/](https://pubmed.ncbi.nlm.nih.gov/32943547/)

Additional recent high-impact NCI-funded research includes research showing that melanoma metastasis may be determined in part by the cancer cell's metabolism, pointing to a potential new target for therapy.<sup>205</sup>

Melanoma is one cancer type that is most likely to spread to the brain. While NCI has supported multiple clinical trials testing therapies for patients,<sup>206,207</sup> more research is needed to understand the biology of melanoma brain metastases. NCI-funded researchers recently reported that samples of melanoma brain metastases had different T-cell content and other characteristics compared with metastases from other sites in the body and that these markers correlated with 1-year survival from diagnosis of brain disease.<sup>208</sup> Additional research will be needed to further study these markers and determine if they should be incorporated into prospective therapeutic clinical trials.

NCI has also promoted the use of thoughtful, less restrictive eligibility criteria in NCI-sponsored clinical trials. In 2018, NCI engaged in discussions about expansion of eligibility criteria for clinical trials with colleagues at the FDA, and the Association of Clinical Oncology, and the Friends of Cancer Research, and subsequently issued guidance broadening eligibility for NCI-supported clinical trials, which would allow inclusion of patients with brain metastasis under certain conditions.<sup>209</sup>

New technologies have the potential to aid early detection. Recently, NCI-funded researchers reported on the development of a new platform for detecting circulating melanoma cells in blood, which has potential for early melanoma screening, assessment of disease recurrence, and monitoring of treatment response.<sup>210</sup> Advances in artificial intelligence (AI) are applicable to many cancer types, including melanoma. To advance AI in cancer, NCI is supporting research, developing infrastructure, and training the workforce. Data sharing is being enhanced by NCI's Cancer Research Data Commons,<sup>211</sup> which includes an Imaging Data Commons that will connect to The Cancer Imaging Archive, a unique resource of publicly available, archival cancer images with supporting data to enable research and discovery.

AI is also being used to enrich the collection of population data on melanomas and other cancers captured through NCI's Surveillance, Epidemiology, and End Results (SEER) registries, including information on recurrence and metastatic disease. *See the SEER Significant Item response for additional details.*

With more than 16.9 million cancer survivors in the U.S. in 2019, research to understand and meet the needs of survivors of all cancer types is an NCI priority.<sup>212</sup> One example of NCI-

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<sup>205</sup> [pubmed.ncbi.nlm.nih.gov/31853067/](https://pubmed.ncbi.nlm.nih.gov/31853067/)

<sup>206</sup> [www.ncbi.nlm.nih.gov/pubmed/30134131](https://www.ncbi.nlm.nih.gov/pubmed/30134131)

<sup>207</sup> [www.ncbi.nlm.nih.gov/pubmed/30407895](https://www.ncbi.nlm.nih.gov/pubmed/30407895)

<sup>208</sup> [pubmed.ncbi.nlm.nih.gov/32974852/](https://pubmed.ncbi.nlm.nih.gov/32974852/)

<sup>209</sup> [ctep.cancer.gov/protocolDevelopment/docs/NCI\\_ASCO\\_Friends\\_Eligibility\\_Criteria.pdf](https://ctep.cancer.gov/protocolDevelopment/docs/NCI_ASCO_Friends_Eligibility_Criteria.pdf);  
[www.cancer.gov/news-events/cancer-currents-blog/2019/expanding-clinical-trial-eligibility-criteria](https://www.cancer.gov/news-events/cancer-currents-blog/2019/expanding-clinical-trial-eligibility-criteria)

<sup>210</sup> [pubmed.ncbi.nlm.nih.gov/31189720/](https://pubmed.ncbi.nlm.nih.gov/31189720/)

<sup>211</sup> [datascience.cancer.gov/data-commons](https://datascience.cancer.gov/data-commons)

<sup>212</sup> [www.cancer.gov/research/annual-plan/scientific-topics/survivorship](https://www.cancer.gov/research/annual-plan/scientific-topics/survivorship)

funded research includes understanding the effects of individuals with melanoma and other cancers treated with immune checkpoint inhibitors.<sup>213</sup>

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<sup>213</sup> [pubmed.ncbi.nlm.nih.gov/32599411/](https://pubmed.ncbi.nlm.nih.gov/32599411/)

## **Mitochondrial Disease Research Coordination**

The Committee is aware that NIH has spearheaded a number of initiatives to identify new mitochondrial disorders, discover the linkages between mitochondrial disorders, and translate advances in mitochondrial research to treatments, cures, and other medical interventions for mitochondrial disorders and their secondary diseases, such as Alzheimer's disease, Parkinson's disease, and cancer. The Committee is supportive of NIH's efforts through the formation of the North American Mitochondrial Disease Consortium and its associated registry, as well as coordination among NIH Institutes, to support the Mitochondrial Disease Sequence Data Resource Consortium, which serves as a robust central repository for genomic sequencing data for mitochondrial disorders. Given the advancements seen through peer-reviewed research into mitochondrial disorders, the Committee urges NIH to expand its research through available mechanisms. In addition, the Committee is aware that multiple Federal agencies and outside stakeholders are invested in mitochondrial disorder research, including CDC, FDA, DOD, and the patient advocacy and medical research communities, among others, many of which participated in scientific workshops held in 2018 and 2019. The Committee requests that NIH provide an update in the fiscal year 2022 CJ on areas of cooperation and collaboration regarding mitochondrial disorder research (Senate Report, p. 118).

### **Action Taken or to be Taken**

Given the important and essential roles mitochondria play in energy metabolism and other cellular functions and the range of mitochondrial diseases affecting multiple organ systems, many NIH Institutes, Centers, and Offices (ICOs) support and conduct research on mitochondria and mitochondrial disorders. A trans-NIH Mitochondrial Disorders Working Group (WG), co-chaired by staff from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute on Aging (NIA), and the National Institute of General Medical Sciences (NIGMS), aims to increase trans-NIH communication and collaboration. This group coordinates mitochondrial research across NIH, including trans-NIH proposals for funding opportunities and scientific workshops, which have included participants from the Centers for Disease Control and Prevention (CDC), U.S. Food and Drug Administration (FDA), U.S. Department of Defense (DOD), and the patient advocacy and medical research communities. With the WG's support and to facilitate high-quality clinical research studies and data harmonization, NINDS initiated the development of standard data types and definitions for mitochondrial disease as part of the NINDS Common Data Elements project. These common data elements aid mitochondrial disease research coordination by helping investigators to share and synthesize data across clinical studies. The WG also has initiated a series of webinars on mitochondrial research topics. The webinars are open to the public and provide an opportunity for researchers and NIH to discuss research progress and challenges, share information, and receive input from the community. The WG will continue to engage with the CDC, FDA, DOD, and the patient advocacy and research communities and discuss additional opportunities for coordination and information sharing.

As an example of jointly funded research, NINDS, National Center for Advancing Translational Sciences (NCATS), NICHD, and the NIH Office of Dietary Supplements support the North American Mitochondrial Disease Consortium (NAMDC), a member of the NCATS Rare Disease

Clinical Research Network. This multi-center collaboration conducts research on primary mitochondrial diseases, trains clinician scientists in mitochondrial disease research, and works closely with the United Mitochondrial Disease Foundation (UMDF), a patient advocacy organization. NAMDC has established a network of clinical centers connecting investigators and clinicians who see patients with mitochondrial diseases, a patient registry with over 1,600 enrolled, a biorepository, and consensus criteria for diagnosis for mitochondrial diseases that will aid research toward improved care and treatment. In addition, the Mitochondrial Disease Sequence Data Resource Consortium (MSeqDR) was established by NAMDC, NICHD, other NIH partners, mitochondrial disease researchers from around the world, and the UMDF. MSeqDR works to organize and curate mitochondrial disease genomic knowledge, genomic analysis and data sharing tools, and disease phenotypes.

NIH ICOs and partners support a wide range of additional studies on mitochondrial function and primary and secondary mitochondrial diseases. Finding new ways to evaluate compounds that could damage mitochondria is a primary focus of the Toxicology in the 21st Century (Tox21) program, a collaborative program through which NCATS, the National Toxicology Program, the Environmental Protection Agency, and the FDA aim to improve laboratory testing methods to identify toxic chemicals and predict their toxicity in humans. Researchers supported by NIGMS developed a novel version of DNA editing that for the first time opens mitochondrial DNA (mtDNA) to precision genome editing. The ability to precisely install or correct mtDNA mutations could facilitate disease modelling, preclinical drug testing, and therapeutic approaches that correct mtDNA mutations. A NINDS intramural investigator received the 2021 Breakthrough Prize in Life Sciences for showing how mutations in the genes PINK1 and Parkin disrupt the disposal of damaged mitochondria inside cells and informing new treatment ideas for Parkinson's disease and other disorders linked to damaged mitochondria. Lastly among other examples, NICHD supports an initiative to encourage research on Oocyte Mitochondrial Function in Relation to Fertility, Aging, and Mitochondrial Diseases and has supported projects on mitochondrial diseases through its Genomic Clinical Variant Expert Curation Panels program.

## **Multiple Sulfatase Deficiency (MSD)**

MSD is an ultra-rare genetic disorder in which all of the known sulfatase enzymes are unable to be fully activated causing neurologic impairment and other symptoms including bone abnormalities, deafness, and hepatosplenomegaly. There are currently no targeted therapies for MSD, and treatment is limited based on specific symptoms. However, multiple lines of therapeutic development including gene therapy, small molecule (drugs), and bone marrow transplant are being pursued by preclinical researchers. The agreement directs NINDS, in concert with the Office of Rare Diseases Research, to provide an update on research progress towards a treatment in the fiscal year 2022 Congressional Justification on MSD and related rare disorders (Joint Explanatory Statement, p.49).

### **Action taken or to be taken**

Multiple Sulfatase Deficiency (MSD) is an ultra-rare disease with an estimated prevalence of one in 1.4 million people. MSD results from mutations in the *SUMF1* gene, which encodes a protein required for activating enzymes called sulfatases that degrade complex carbohydrate and lipid molecules inside cells. Insufficient sulfatase activity in MSD leads to a wide range of clinical symptoms affecting multiple organ systems. With support from the National Institutes of Health (NIH), international funding agencies, and disease foundations, researchers are making progress toward treatments for MSD.

German and Italian investigators identified the genetic basis for MSD in 2003, developed a mouse model of the disease in 2007, and showed in 2011 that gene therapy in the mouse model activated sulfatases, decreased inflammation in the nervous system and other organs, and improved behavioral abilities. In the largest cohort reported to date for MSD, researchers supported by the National Institute of Neurological Disorders and Stroke (NINDS) and the National Center for Advancing Translational Sciences (NCATS) have analyzed molecular, biochemical, and longitudinal clinical data in 32 MSD patients. The analyses, reported in 2020, add to knowledge about the natural history of MSD, an important prerequisite for future clinical trials to test the effectiveness of gene therapy or other potential therapies.

Although NIH does not currently support studies specifically focused on treatment for MSD, there is considerable NIH-funded research on lysosomal storage disorders, the broader family of disorders to which MSD belongs. This research may inform further progress in MSD, given that this family of disorders shares overlapping clinical symptoms and similar treatment approaches. For example, NINDS, NCATS, and the National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK) support the Lysosomal Disease Network (LDN), part of the NIH Rare Diseases Clinical Research Network led by the Office of Rare Diseases Research within NCATS. The LDN conducts multiple clinical studies, works closely with patient advocacy organizations, and supports scientific conferences and research training to grow the pool of investigators focused on lysosomal storage disorders including MSD.

In addition, NINDS and NCATS both support research programs and resources applicable to the development of gene and other targeted therapies for a broad range of rare and ultra-rare disorders, including MSD. For example, NINDS supports a suite of translational research

initiatives designed to move therapies toward clinical trials, including programs for developing model systems for testing and biomarkers for measuring disease progression or response to treatment. In late 2021, NINDS expects to launch the Ultra-rare Gene Therapy (URGenT) program to support the development of gene-based therapies for ultra-rare neurological diseases. Successful gene-based therapies for diseases such as spinal muscular atrophy have fueled promise for the rarest of diseases, and reports of custom-designed treatments for individual patients have gained public attention. However, these efforts present complex challenges for research and commercialization processes built around larger patient populations. URGenT is a late-stage preclinical therapy development program that aims to address challenges of gene-targeting technologies, de-risk these approaches for industry adoption, and coordinate their entry into clinical trials. The program will facilitate ways to standardize and share resources, data, and best practices across diseases to make therapy development for ultra-rare diseases like MSD more efficient and accessible. NINDS staff have recently discussed these and other programs and resources with the United MSD Foundation and a family affected by the disease.



## **Myotonic Dystrophy**

The Committee recognizes there are significant opportunities to advance the science regarding the causes of myotonic dystrophy, a serious degenerative genetic condition, and support current efforts to develop the first ever FDA-approved treatment for this inherited genetic disorder. The Committee directs NIH to prioritize the recruitment of young researchers to this field to grow the number of high-quality research proposals submitted for peer review as these efforts hold significant promise for major advances across many neurodegenerative diseases, particularly other triplet repeat expansion diseases. The Committee requests an update on these activities in the fiscal year 2022 Congressional Justification (House Report, p. 105).

### **Action taken or to be taken**

The National Institute of Neurological Disorders and Stroke (NINDS) remains committed to supporting a broad array of research aimed at understanding the cellular, biochemical, and genetic factors that contribute to myotonic dystrophy type 1 and type 2 (DM1 and DM2), and congenital myotonic dystrophy (CDM); and toward developing treatments for these diseases along with necessary training and support for young researchers within this field.

Scientists are identifying the factors that influence trinucleotide repeat instability in DM and investigating potential strategies for mitigating that instability, investigating how RNAs are localized and translated in neurons and how this is disrupted in DM, and determining which RNA processing defects contribute to brain dysfunction in DM. Researchers are exploring the relationship between the biological changes that cause CDM and the symptoms that develop with the goal of developing biomarkers and determining how to extend the targeted, disease modifying, therapies developed for adults with myotonic dystrophy to children. NINDS is also supporting a comprehensive, prospective longitudinal study of brain and muscle structure and function in DM1 with the goal of identifying biomarkers that can track disease progression both within the central nervous system and limb muscles.

NINDS-funded researchers are exploring multiple novel therapeutic strategies for treating DM. Researchers are developing a form of gene therapy that utilizes an RNA-targeting CRISPR/Cas (RCas9), which, if successful, might also be useful for other triplet repeat expansion diseases. Researchers are also developing an RNA-targeting approach that focuses on the RNA interference (RNAi) pathway normally present in cells so that it reduces the toxic ‘gain-of-function’ RNA in DM1 patients. Other researchers are pursuing lessons from an unsuccessful DM1 clinical trial of an antisense oligonucleotide drug to improve the chances of success in ensuing trials. NINDS is also supporting a small business in its effort to develop orally available small molecule therapeutics for DM1.

NINDS supports a Wellstone Muscular Dystrophy Specialized Research Center (MDSRC) that brings together clinical and translational researchers at the University of Rochester with RNA scientists and geneticists at the University of Florida and University of Albany to conduct research to clarify disease mechanisms, strengthen the pipeline of preclinical therapeutic agents, and generate the tools and knowledge for conducting highly informative clinical trials (including biomarkers, natural history studies, and a patient registry). Training the next generation of

muscular dystrophy researchers, particularly focusing on clinician scientists, therapeutic trialists, computational biologists, and RNA researchers, is also an important component of this Wellstone Center.

NINDS has a number of individual training fellowships, career development awards, institutional training grants, and other training programs aimed at preparing graduate, postdoctoral, and physician- scientists for careers in neuroscience and neuromuscular disease research.

Recognizing that the transition to independence is a pivotal time in a researcher's career, NINDS funds grant applications from early-stage investigators with scores beyond the percentile payline used to determine funding for more experienced researchers. In recent years, NINDS has funded new myotonic dystrophy researchers and trainees through these programs, and NINDS continues to encourage myotonic dystrophy research trainees and new investigators to take advantage of these programs to help launch and establish their research careers.

## **National Commission on Lymphatic Diseases**

The agreement encourages NIH to work with relevant stakeholders to advance the establishment of a National Commission on Lymphatic Diseases that will make critical recommendations on coordinating NIH-wide lymphatic disease research. The Director is requested to provide an update to the Committees no later than 90 days after the enactment of this Act about specific next steps to establish the Commission. In addition, there are concerns that not enough research is focused on lymphedema and the Director is requested to provide a report to the Committees within 120 days of enactment of this Act regarding the annual support level for lymphatic research funding over the past five years, including the types of grants supported in the last five fiscal years (Joint Explanatory Statement, p. 66-67).

### **Action Taken or to be Taken**

The National Institutes of Health (NIH) is committed to advancing research on the lymphatic system and lymphatic diseases. As many NIH Institutes and Centers (ICs) support research relevant to lymphatic disease, the Trans-NIH Lymphatic Coordinating Committee (TNLCC) provides a framework for these ICs to collaborate and set a lymphatic research agenda by engaging the research community and stakeholder organizations. This Committee is led by the National Heart, Lung, and Blood Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, and the National Institute of Allergy and Infectious Diseases. The Committee has expanded over the years and now also includes representatives from the National Cancer Institute, the National Eye Institute, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the National Center for Advancing Translational Sciences. The TNLCC works closely with the Lymphatic Education and Research Network (LE&RN) as well as other stakeholders including the North American Vascular Biology Organization and the American Venous Forum to create awareness of lymphatic diseases, to assist researchers in navigating the NIH funding process, and to address the most pressing research challenges in the field. NIH also participates in and supports many of the meetings, educational offerings, video sessions, trainings, and workshops led by these and other lymphatic stakeholder groups.

NIH is also working to improve the robustness and visibility of its lymphatic disease portfolio through the NIH Research Portfolio Online Tool (RePORT).<sup>214</sup> Working with NIH IC subject matter experts, the Office of Extramural Research is developing a new category within RePORT that will enable NIH to better quantify and analyze its annual investments in lymphatic research. This also will allow the public to see NIH's total funding of lymphatic research projects for each fiscal year and to quickly access the details of each project, including published results and patents, at the Research, Condition, and Disease Categories (RCDC) webpage.<sup>215</sup> This new RePORT category is expected to be operational in 2021. Even now, members of the public can find many studies of interest by searching for "lymphatics" or specific conditions such as "lymphedema" at the NIH RePORT website. Additionally, at the request of Congress, NIH is currently developing a report on lymphedema, in which dysfunction or damage to the lymphatic system leads to inflammation, swelling, and pain in one or more parts of the body. Information from this report will be used to develop new online content about lymphedema for the public and

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<sup>214</sup> [report.nih.gov](https://report.nih.gov)

<sup>215</sup> [report.nih.gov/categorical\\_spending.aspx](https://report.nih.gov/categorical_spending.aspx)

patients as part of our efforts to increase visibility of NIH's research efforts and investments related to lymphatic diseases.

## **Office of Cancer Survivorship**

The agreement directs NIH to include updates on the following research, projects, and programs in the fiscal year 2022 Congressional Justification: gastric cancer; psycho-social distress in cancer research; the Office of Cancer Survivorship; progress in treating rare cancers; the Surveillance, Epidemiology, and End Results [SEER] Registry; Temporomandibular Disorders; diabetes, Rapid Acceleration of Diagnostics; 7q1 1.23 Duplication Syndrome; and Hereditary Spastic Paraparesis 49 (TECPR2). (Joint Explanatory Statement, p. 45)

### **Action Taken or to be Taken**

Please see responses for Childhood Cancer Survival Metrics and the STAR Act.

## **Pediatric Cancer**

The Committee continues \$30,000,000 for the implementation of the STAR Act (Public Law 115–180) to expand existing biorepositories for childhood cancer patients enrolled in NCI-sponsored clinical trials to collect and maintain relevant clinical, biological, and demographic information on all children, adolescents, and young adults with cancer. As part of this funding, the Committee expects NCI to carry out childhood cancer survivorship research and programs as authorized, such as developing best practices for the treatment of late effects of childhood cancers. In addition, the Committee recognizes NCI's efforts to develop a new Childhood Cancer Data Initiative and continues to support and expand new and innovative research efforts to advance progress for children with cancer. These include the Pediatric MATCH precision medicine trial and a pediatric immunotherapy translational science network established through the Cancer Moonshot, in addition to NCI's long-standing support for the Children's Oncology Group, the Childhood Cancer Survivor Study, the Pediatric Preclinical Testing Consortium, and several other critical programs. The Committee also commends NIH for its efforts to coordinate pediatric research across its Institutes and Centers through the recently established Trans-NIH Pediatric Research Consortium. The Committee understands NCI participates in the Consortium, and that childhood cancer research is an important part of the pediatric research portfolio across NIH. The Committee requests an update in the fiscal year 2022 CJ on opportunities to enhance childhood cancer research efforts, including coordination efforts already underway through the Trans-NIH Pediatric Research Consortium (Senate Report, p. 87-88).

### **Action Taken or to be Taken**

The National Cancer Institute (NCI) continues to implement sections of the Childhood Cancer STAR Act directed toward the Institute, most notably Sections 101 and 202, the biobanking and childhood cancer survivorship research provisions of the Act. NCI-supported cancer registry efforts, including ongoing improvements to the Surveillance, Epidemiology and End Results (SEER) Registry, continue to be complementary to the enhancements the Centers for Disease Control and Prevention (CDC) is leading through its implementation of Section 102 of the Act. Additionally, in FY 2020, NCI entered into an Inter-Agency Agreement with the Agency for Healthcare Research and Quality (AHRQ) to support AHRQ's work to implement Section 203 of the Act, focused on identifying best practices in survivorship care through AHRQ Evidence Reviews on Childhood Cancer Survivorship.

NCI plans to continue efforts to implement the biobanking provisions of the STAR Act by building upon prior investments to support immediate enhancements to the Children's Oncology Group (COG) Biorepository, including new projects to advance scientific opportunities and expand specimen collection for the most difficult to treat childhood and adolescent and young adult (AYA) cancers and subtypes. NCI is supporting new biobanking projects through COG to focus attention to rare cancer subtypes that are currently underrepresented in NCI-supported biorepositories and tumor types with a high risk of treatment failure. NCI anticipates that these efforts will also continue in partnership with the Childhood Cancer Data Initiative (CCDI). STAR Act efforts will support collection of specimens, and CCDI efforts will support sequencing of samples and the related data storage and data sharing to qualified researchers.

NCI continues to conduct and support childhood and AYA cancer survivorship research that advances additional goals of the STAR Act. For example, across FY 2019 and FY 2020, NCI supported seven projects in response to the funding opportunity “*Improving Outcomes for Pediatric, Adolescent and Young Adult Cancer Survivors*,”<sup>216</sup> which is directly aligned with research areas emphasized in the STAR Act. To build upon these research efforts, NCI developed a new funding opportunity accepting applications as of June 2020, “*Research to Reduce Morbidity and Improve Care for Pediatric, and Adolescent and Young Adult (AYA) Cancer Survivors*,”<sup>217,218</sup> which also aligns with survivorship research priorities emphasized in the STAR Act. Following peer review, NCI anticipates funding a first round of awards in the summer of 2021, and a second round in the spring of 2022.

As both CCDI and STAR Act implementation efforts move forward, NCI also maintains a strong commitment to advancing childhood and AYA cancer research across its portfolio, including in collaboration with other National Institutes of Health (NIH) Institutes and Centers. NCI’s Board of Scientific Advisors recently approved a new five-year funding commitment for both the Childhood Cancer Survivor Study and the COG Biorepository, providing support that is in addition to NCI’s STAR Act implementation efforts, subject to available appropriations. NCI is supporting an expansion of the Pediatric Brain Tumor Consortium (PBTC), also recently approved for an additional five-year funding period, subject to available appropriations. This expansion will allow the PBTC to add up to six additional sites and to increase its organizational capabilities so that it can support more clinical trials. An important part of this expansion includes several efforts focused specifically on the pediatric brain tumor Diffuse Intrinsic Pontine Glioma (DIPG). The expansion of the PBTC will enable the growth of the clinical research program for DIPG and other pediatric brain tumors, ultimately allowing for greater access to clinical trials for children and families throughout the country.

NCI is also partnering with the Foundation for the NIH, along with the U.S. Food and Drug Administration and partners in academia and industry, to build upon NCI’s existing Pediatric Preclinical Testing Consortium and launch the Pediatric Preclinical Testing Public-Private Partnership (PPTP3). This collaborative research effort will serve as an important contribution to the ongoing implementation of the Research to Accelerate Cures and Equity (RACE) for Children Act, which adds a new requirement for testing molecularly targeted drugs in pediatric cancers for certain oncology medicine applications. The PPTP3 will provide the key preclinical data that is required for an expansion of preclinical testing, which in turn will inform evidence-driven prioritization decisions.

In addition, NCI is maintaining important investments in the Pediatric MATCH precision medicine trial and the broader NCI-supported National Clinical Trials Network infrastructure (including the COG); the NCI Pediatric Oncology Branch and key cohort and natural history studies supported through the NCI intramural research program; and several pediatric and AYA research efforts supported through the Cancer Moonshot. All of the efforts described above contribute to a diverse pediatric oncology research portfolio at NCI and across NIH. NCI is pleased to continue to serve as a partner with the NIH Common Fund in scientific leadership of

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<sup>216</sup> [grants.nih.gov/grants/guide/rfa-files/RFA-ca-19-033.html](https://grants.nih.gov/grants/guide/rfa-files/RFA-ca-19-033.html)

<sup>217</sup> [grants.nih.gov/grants/guide/rfa-files/RFA-CA-20-027.html](https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-20-027.html)

<sup>218</sup> [grants.nih.gov/grants/guide/rfa-files/rfa-ca-20-028.html](https://grants.nih.gov/grants/guide/rfa-files/rfa-ca-20-028.html)

the Gabriella Miller Kids First Research Program, and with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) as a member of the Trans-NIH Pediatric Research Consortium (N-PeRC).

Established by NICHD in 2018, N-PeRC aims to harmonize NIH's pediatric research efforts. Nearly all of NIH's Institutes, Centers, and Offices (ICOs) appointed senior level representatives to N-PeRC, including both extramural and intramural scientists. In its short history, N-PeRC has already made progress toward identifying and facilitating collaborations among ICOs at NIH. Emerging issues of clear importance to multiple ICOs, including NCI, are research on issues faced by adolescents in transitioning to adult health care, drug and device development appropriate for pediatric use, consolidated pediatric data resources, and pediatric research workforce training. In late September 2020, N-PeRC held a scientific conference to help identify common issues that arise when adolescents with various chronic conditions transition to adult health care. These transitions can raise many issues, such as consent and shared medical decision-making, and the use of technologies and telehealth. NIH is committed to conducting further research to ensure that the transition to adult care is successfully coordinated, particularly for those adolescents with relatively rare conditions, including pediatric cancers. NCI will continue to support basic, translational, and clinical research to increase our understanding of all pediatric cancers; develop safe, effective treatments for children with cancer; and address the late effects of cancer and its treatment in childhood and AYA cancer survivors.



## **Pediatric Nephrology**

The Committee recognizes the importance of research funded by NIDDK to develop the infrastructure required to enhance biomedical research focused on advancing innovations in kidney care, including research on pediatric kidney injury and disease. The Committee has raised concerns about the lack of clinical trials in pediatric nephrology. One way to address this problem is to ensure there is a robust training pipeline for the pediatric nephrology biomedical research workforce. The Committee encourages NIDDK to prioritize mechanisms to incentivize researchers to enter this field. The Committee requests that NIDDK report back in the fiscal year 2022 Congressional Justification on the progress made to bolster this biomedical workforce, including opportunities so that young investigators may be further encouraged to explore research in this space (House Report, p. 103).

### **Action Taken or To Be Taken**

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports a multi-faceted program of research to identify the causes, understand and halt disease progression, develop and improve treatments, and ultimately prevent kidney diseases and kidney failure in children. Maintaining a robust training pipeline and supporting early-stage investigators continue to be essential components of NIDDK's efforts in pediatric nephrology. NIDDK currently supports eight junior investigators in the field of pediatric nephrology through its career development ("K") research grants. The NIH Loan Repayment Program for Pediatric Research is recruiting and retaining highly qualified health professionals into biomedical or biobehavioral research careers as pediatric investigators.

Many NIDDK-supported research activities, including clinical studies and clinical networks, also include components that foster research training. Focal and Segmental Glomerulosclerosis, Minimal Change Disease, and Membranous Nephropathy, presenting as Nephrotic Syndrome, are rare diseases that prominently affect children, causing catastrophic complications and end stage kidney disease. Applying a novel investigative approach, the Nephrotic Syndrome Network (NEPTUNE) established a rich translational and clinical research infrastructure—including detailed clinical, histological, genetic, transcriptomic and proteomic data—from more than 750 study participants.<sup>219</sup> NEPTUNE has also established robust training and ancillary study programs that will benefit patients now and in the future. NIDDK has funded and overseen the launch of a prospective, randomized, multi-center clinical trial in childhood chronic kidney disease (FIT4KIDS) and have included a specific role for junior faculty to learn about clinical trial design and implementation through participation in this consortium.

The Pediatric Centers of Excellence in Nephrology (PCEN) program aims to attract a partnership of interdisciplinary research among investigators with scientific expertise who will use complementary and integrated approaches to study kidney diseases endemic to the pediatric population.<sup>220</sup> One primary objective of PCEN is to design pilot and feasibility studies that should lead to new and innovative approaches to study kidney disease in the pediatric

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<sup>219</sup> [repository.niddk.nih.gov/studies/neptune/](https://repository.niddk.nih.gov/studies/neptune/)

<sup>220</sup> [www.niddk.nih.gov/about-niddk/advisory-coordinating-committees/national-diabetes-digestive-kidney-diseases-advisory-council/concept-clearances/pediatric-centers-excellence-nephrology](https://www.niddk.nih.gov/about-niddk/advisory-coordinating-committees/national-diabetes-digestive-kidney-diseases-advisory-council/concept-clearances/pediatric-centers-excellence-nephrology)

population. For example, the Pediatric Center at Children's Hospital of Philadelphia was established to build an interdisciplinary partnership between researchers in childhood kidney disease with expertise in measurement, design, and analysis of observational studies and clinical trials.

NIDDK supports programs to explore new, innovative research pathways for diseases within NIDDK's mission, including pediatric kidney diseases. For example, the Innovative Science Accelerator (ISAC) Program<sup>221</sup> was recently launched to foster collaborations and “seed” high-impact science. Another initiative<sup>222</sup> will support grants to promote development of innovative, enabling tools and technologies for NIDDK diseases. The first step in developing a clinical trial is often exploratory, short-term work to investigate new ideas and approaches. A new NIDDK-supported program<sup>223</sup> will support small, short-term clinical trials in humans to acquire preliminary data regarding the effects of the intervention, as well as feasibility data related to recruitment and retention, and study conduct.

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<sup>221</sup> [grants.nih.gov/grants/guide/rfa-files/RFA-DK-20-010.html](https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-20-010.html)

<sup>222</sup> [grants.nih.gov/grants/guide/pa-files/PA-20-140.html](https://grants.nih.gov/grants/guide/pa-files/PA-20-140.html)

<sup>223</sup> [grants.nih.gov/grants/guide/pa-files/PAS-20-160.html](https://grants.nih.gov/grants/guide/pa-files/PAS-20-160.html)

## Pediatric Research

The Committee requests an update from the Director within 120 days of enactment of this Act on how NIH will focus on the unique needs of children in its NIH-wide initiatives that span multiple Institutes and Centers, as well as its highest priority initiatives, including but not limited to the All of Us Research Program and the Cancer Moonshot. The Committee asks that with respect to these major NIH initiatives, this update describe the inclusion of pediatric subjects, research relevant to pediatrics, specific funding allocations, support for pediatric physician scientists, and a strategy to more proportionally target funds within these initiatives to pediatric research. The Committee commends NIH for the establishment of the Trans-NIH Pediatric Research Consortium to help coordinate pediatric research at NIH. The Committee also requests an update in the fiscal year 2022 Congressional Justification on the activities of the Consortium and its plans to better coordinate pediatric research across the institutes, including identifying gaps and opportunities for collaboration (House Report, p. 141).

### **Action Taken or To Be Taken**

NIH remains committed to understanding the healthy development of children, as well as the causes of and treatment for diseases, illnesses, and conditions affecting children. Funding for pediatric research has increased steadily over the past few years; in FY 2019, NIH spent over \$4.9 billion in this area.<sup>224</sup> The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) provides approximately 18 percent of the total amount, joined by 24 other NIH Institutes and Centers (ICs). In 2018, a new group to harmonize pediatric research efforts, the NIH Pediatric Research Consortium (N-PeRC), was established, led by NICHD.<sup>225</sup> Nearly all of the ICs and offices appointed senior level representatives to N-PeRC, including both extramural and intramural scientists. In its short history, N-PeRC has already made progress toward identifying and facilitating collaborations among ICs. Emerging issues of clear importance to multiple ICs include research on issues faced by adolescents in transitioning to adult health care, drug and device development appropriate for pediatric use, consolidated pediatric data resources, and pediatric research workforce training.

In late September 2020, N-PeRC leaders held a scientific workshop to identify common issues arising when adolescents with chronic conditions transition to adult health care. Although young people with some of these serious conditions are living longer than in the past, research is still needed to ensure that the transition to adult care is successfully coordinated, particularly for those adolescents with relatively rare conditions. These transitions can raise many issues, such as consent and shared medical decision-making, the use of technologies and telehealth, and for those young people with chronic pain, identifying alternative interventions to opioid use. Defining outcome measures to help determine the parameters of a successful transition was identified as a critical need to move the research in this under-studied area ahead.

N-PeRC member ICs are also closely tracking and supporting pediatric training and career development programs. Since 1989, NICHD has been funding the Pediatric Scientist Development Program aimed at increasing the number of pediatrician-scientists who are

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<sup>224</sup> [report.nih.gov/rcdc/](https://report.nih.gov/rcdc/)

<sup>225</sup> [www.nichd.nih.gov/research/supported/nperc](https://www.nichd.nih.gov/research/supported/nperc)

competitive in peer review.<sup>226</sup> Over half of the graduates of this program subsequently received NIH funding. The Child Health Career Development Award program provides a mechanism for mentoring and intense scientific training by providing protected time for research training with pediatric scientific leaders, with the goal of becoming successful physician-scientists.<sup>227</sup> Over 800 scholars have participated in this program, helping to maintain the scientific workforce needed to address pediatric conditions relevant across NIH.

The value of a standing pediatric group within NIH that can respond quickly to emerging public health crises became starkly apparent as the number of COVID-19 cases surged within the U.S. As early as March 2020, N-PeRC rapidly formed a working group with representation from 18 ICs, which was led by NICHD and the National Institute on Drug Abuse, to address pediatric issues related to COVID-19. Its immediate goal was to create a funding strategy based on an analysis of current and potential studies of COVID-19 in pregnant women and children. Of the 700 COVID-19 awards made to date, 80 include pregnant women and children, with 51 of these focused on children alone. For example, one study will examine both the vulnerability and resistance toward COVID-19 infections among youth with varying physical and demographic characteristics to find out who may be more susceptible to infection or its serious consequences, and another newly funded project will examine the impact of COVID-19-related school closures on children's weight status.

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<sup>226</sup> [www.nichd.nih.gov/research/supported/PSDP](http://www.nichd.nih.gov/research/supported/PSDP)

<sup>227</sup> [www.nichd.nih.gov/research/supported/chrcda](http://www.nichd.nih.gov/research/supported/chrcda)

## Pelvic Floor Disorder

The Committee recognizes that pelvic floor disorders, including such conditions as urinary incontinence, accidental bowel leakage, and pelvic organ prolapse, have a large financial impact on individuals and society, and significant negative quality of life impact for more than 25 million women annually, in the U.S. alone. The Committee urges NICHD, NIDDK, and NIA to collaborate on the development of universally accepted disorder specific data sets for the purpose of research studies on patient outcomes of current and future therapies used to treat pelvic floor disorders and the pathogenesis of these conditions. The Committee requests that NICHD, NIDDK and NIA provide a report on current research and future initiatives to address pelvic floor disorders in the fiscal year 2022 Congressional Justification and provide timely updates to the Committee on advances being made with respect to prevention, treatment and understanding the mechanisms of these conditions (House Report, p. 141).

### **Action Taken or to be Taken**

According to National Health and Nutrition Examination Survey estimates, pelvic floor disorders (PFDs) affect almost one-quarter of women between the ages of 20 and 80, projecting that up to 58 million women will have at least one pelvic floor disorder in 2050. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) funds the Pelvic Floor Disorders Network (PFDN),<sup>228</sup> a consortium of seven academic centers with the research expertise needed to perform studies under rigorous common protocols. The network has been able to provide evidence-based clinical answers more efficaciously than would otherwise be possible for an individual research center. An NICHD-conducted impact analysis found that over 25 percent of PFDN publications have been cited in clinical practice guidelines, thus ensuring that women with PFDs are receiving the most up-to-date evidence-based care. The network has begun to conduct translational research using collected data and biospecimens from prior clinical studies with patients suffering from incontinence and correlating them with surgical failure for pelvic organ prolapse. The network has also initiated a study<sup>229</sup> to address the feasibility of regenerating novel vaginal supports via fabrication of uterosacral ligaments for the treatment of pelvic floor prolapse. These are novel areas of exploration for PFDs, as few studies have examined these types of treatments.

In addition to the PFDN, the NICHD supports a wide range of investigator-initiated grants in genetics, stem cells, epidemiology, and other treatments related to PFDs. A recent funding opportunity announcement was published to stimulate applications investigating the use of stem and/or progenitor cells in the treatment of pelvic organ prolapse. NICHD has collaborated with the National Institute on Diabetes and Digestive and Kidney Diseases (NIDDK) on three meetings regarding benign urologic disorders, including PFDs, over the past two years to encourage further collaboration among researchers working in this field.

The National Institute on Aging (NIA) supports studies on a range of issues related to the causes, prevention, and treatment of PFDs. For example, NIA is currently soliciting research to elucidate how age-related changes in the detrusor – the smooth muscle in the bladder wall that

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<sup>228</sup> [www.nichd.nih.gov/research/supported/pelvicfloor](http://www.nichd.nih.gov/research/supported/pelvicfloor)

<sup>229</sup> [grants.nih.gov/grants/guide/rfa-files/RFA-HD-20-007.html](http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-20-007.html)

facilitates urination – can cause underactive bladder, anticipating that preventive interventions and treatments for prolonged or incomplete voiding resulting from detrusor dysfunction will be supported under this initiative. Elsewhere, NIA-supported investigators are working to identify the brain mechanisms involved in urinary incontinence; determine how age-related changes in the immune system may increase risk of urinary tract infection; and examining whether lower body muscle dysfunction in older women may contribute to the development of both urinary incontinence and mobility limitations. Finally, NIA supports clinical trials of potential interventions for PFDs. For example, investigators recently found that a two-hour group class at which women learned about bladder anatomy and function and behavioral strategies for bladder control was modestly effective in reducing frequency and severity of symptoms of urinary incontinence and improving quality of life. Other investigators found that a breathing intervention practiced over 12 weeks was associated with a modest improvement in perceived stress in women with overactive bladder symptoms, but it was no more effective than a control intervention for reducing those symptoms.

The NIDDK supports a robust research portfolio devoted to study of urologic and bowel conditions related to pelvic floor dysfunction in women, such as urinary and fecal incontinence. A key facet of this portfolio, the Prevention of Lower Urinary tract Symptoms (PLUS) Research Consortium, is focused on the goal of preventing lower urinary tract problems in girls and women by understanding what constitutes a healthy bladder in this population—and will yield information on pathogenesis of urologic PFDs as well. The NIDDK will continue to coordinate with NICHD and NIA within the broad area of PFDs so as to identify areas for research collaboration and/or leveraging of research resources that can ultimately improve women’s health and quality of life.

## **Polycystic Ovary Syndrome (PCOS, NICHD)**

The Committee recognizes the significant health burden of PCOS, the most common cause of female infertility. About 10 million women have PCOS, which has affected their reproductive, mental, and metabolic health and wellness. The Committee commends NICHD for its continued leadership in PCOS research. Over 70 percent of NIH's investment in PCOS research has focused on symptoms and comorbidities that impact women's reproductive health. Pregnant women with PCOS are more likely to develop preeclampsia (pregnancy-related hypertension) and have emergency C-sections. Given that the majority of NIH research on PCOS has focused on reproductive implications of the syndrome, critical gaps still exist in understanding the connections between these severe comorbidities and PCOS. The Committee encourages NIH to expand its PCOS research activities and programs to include research on comorbidities associated with PCOS, including liver disease, uterine cancer, heart disease, stroke, diabetes, anxiety, depression, sleep disorders, and suicide. Therefore, the Committee requests an update in the fiscal year 2022 Congressional Justification on current PCOS research activities on related comorbidities and existing research gaps, as well as opportunities for trans-NIH research efforts to address PCOS and related diseases. The Committee urges NIH to prioritize PCOS research funding for New and Early Stage Investigator Awards, and to encourage experienced biomedical and public health researchers to study PCOS and collaborate with patients to identify more effective treatments and a possible cure for PCOS (House Report, p. 142).

### **Action Taken or to be Taken**

In its recent *Strategic Plan 2020*, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) made "Promoting Gynecologic, Andrologic, and Reproductive Health" one of its five major research themes. Among the scientific priorities listed under this theme is to expand the genomic understanding, phenotypic characterization, and use of advanced technologies to inform new prevention and treatment strategies to uncover factors leading to gynecologic conditions such as polycystic ovary syndrome (PCOS). NICHD funds a range of research on PCOS, including trainee grants, career development awards, and large multi-investigator projects. Recently, NICHD published a Notice of Special Interest<sup>230</sup> entitled, "Optimizing Precision Treatment of Gynecologic, Reproductive and Obstetrical Outcomes in Adolescents and Adults with PCOS and Associated Comorbid Conditions." The goals of this initiative are to stimulate interdisciplinary scientific collaborations between gynecologists, reproductive endocrinologists, obstetricians, and other specialists in diverse medical fields to advance individualized treatments consistent with women's health care needs; promote translational and clinical research to increase understanding of the effects of various therapies on gynecologic, reproductive, and obstetric outcomes; and discover and develop novel safe and more effective therapies for adolescents and women with PCOS along with underlying co-occurring conditions. Ultimately, this research could advance precision therapeutics for adolescents and adults with PCOS who have concomitant medical conditions.

In addition, other research projects are investigating the genetic and pathophysiologic underpinnings of PCOS, including studies on specific genetic determinants and the biologic mechanisms that may cause PCOS and co-occurring clinical conditions. More specifically, these

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<sup>230</sup> [grants.nih.gov/grants/guide/notice-files/NOT-HD-20-026.html](https://grants.nih.gov/grants/guide/notice-files/NOT-HD-20-026.html)

include additional studies on the microbiome in both women with PCOS and in an animal model, the role of testosterone exposure on the fetuses of female sheep with PCOS, studies using innovative non-invasive imaging techniques to understand the role of ovarian structure for diagnosis as well as the effects of weight change on ovarian structure, studies of the role that hormones and genetics may play on the reproduction and metabolism of women with PCOS, and studies to develop diagnostic tests to personalize treatment in women with PCOS. NICHD is funding postdoctoral trainees, new and early stage investigators, as well as seasoned investigators to carry out these studies.



## Polycystic Ovary Syndrome (PCOS, NHLBI)

PCOS affects up to 15 percent of women and has metabolic, reproductive, mental, and maternal/child health manifestations. PCOS is the most common endocrine disorder in women and is a significant risk factor for high blood pressure, sleep disorders, heart disease, pregnancy-induced hypertension, preeclampsia, cholesterol disorders, and other disorders that impact cardiovascular and metabolic health. The Committee encourages NICHD to partner with NHLBI to promote research in PCOS, particularly with a focus on comorbidities associated with PCOS that impact heart, blood, lung, sleep, and maternal/fetal health as they contribute to negative health outcomes. The Committee also encourages NHLBI to report on research that has been conducted on PCOS and its impact on cardiovascular health to date in the fiscal year 2022 Congressional Justification (House Report, p. 113).

### **Action Taken or To Be Taken**

Polycystic ovary syndrome (PCOS) is an infertility disorder in women that can cause excessive circulating male sex hormones (androgen), obesity and insulin resistance, and increases in blood pressure and risk of cardiovascular disease. The National Heart, Lung, and Blood Institute (NHLBI) is committed to understanding and reducing the impact of PCOS on cardiovascular health. Recent studies suggest that elevated androgen levels have a negative impact on cardiovascular function in women, independent from other comorbidities of cardiovascular disease.<sup>231</sup> For example, in NHLBI's Coronary Artery Risk Development in Young Adults (CARDIA) study, low levels of sex hormone-binding globulin, a protein that helps regulate free androgens circulating in the body, were associated with higher risk of subclinical cardiovascular disease in young to middle-aged women.<sup>232</sup>

Current NHLBI-funded research focuses on understanding how excess androgens impair the cardiovascular system and increase the long-term risk of cardiovascular disease. One NHLBI-funded group has developed a rodent model of PCOS, in which female rats are given a testosterone pump, implanted four weeks after birth, and maintained throughout life. These rats develop higher body weight, insulin resistance, and high blood pressure, suggesting that they will be a useful model for investigating mechanisms of PCOS, as well as potential therapeutic interventions.<sup>233</sup> By studying women with PCOS, as well as this animal model, the researchers are investigating a theory that excess androgen in the female body activates the sympathetic ("fight or flight") nervous system, leading to high blood pressure.<sup>234</sup>

Other research suggests that excess androgens during prenatal life—for example, caused by exposure to endocrine-disrupting chemicals—can increase a child's risk of developing cardiovascular disease<sup>235</sup>—and for girls, the risk of PCOS<sup>236</sup>—during their lifetime. The NIH-funded New England Family Study is helping researchers investigate how prenatal androgen

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<sup>231</sup> [pubmed.ncbi.nlm.nih.gov/32727622/](https://pubmed.ncbi.nlm.nih.gov/32727622/)

<sup>232</sup> [pubmed.ncbi.nlm.nih.gov/20554712/](https://pubmed.ncbi.nlm.nih.gov/20554712/)

<sup>233</sup> [academic.oup.com/endo/article/157/7/2920/2423013](https://academic.oup.com/endo/article/157/7/2920/2423013)

<sup>234</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9619086](https://projectreporter.nih.gov/project_info_description.cfm?aid=9619086)

<sup>235</sup> [pubmed.ncbi.nlm.nih.gov/32776198/](https://pubmed.ncbi.nlm.nih.gov/32776198/)

<sup>236</sup> [pubmed.ncbi.nlm.nih.gov/31792459/](https://pubmed.ncbi.nlm.nih.gov/31792459/)

exposure affects the first of cardiovascular disease in middle age. That study collected data, including maternal androgen levels, from more than 17,000 childbirths in New England from 1959-1966. NHLBI-funded researchers have re-contacted more than 500 mother-child pairs from the study to examine the cardiovascular health of the children, now in their 50s.<sup>237</sup> Another NHLBI-funded team is using an animal model to determine whether prenatal excess testosterone has adverse effects on heart development in females, with consequences for cardiovascular disease risk in later life.<sup>238</sup>

To inform the development of future PCOS research initiatives, the NHLBI is planning to hold a workshop in the spring of 2021 in collaboration with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and other Institutes, Centers, and NIH Offices called “Cardiovascular Risk Across the Lifespan for Polycystic Ovarian Syndrome.” The goal is to bring together PCOS experts to review current knowledge of cardiovascular risk factors associated with PCOS and identify research gaps needed to improve prevention, intervention and implementation strategies.

In addition, NICHD recently released a Notice of Special Interest entitled: “Optimizing Precision Treatment of Gynecologic, Reproductive and Obstetrical Outcomes in Adolescents and Adults with PCOS and Associated Comorbid Conditions.” The goals of this initiative are to stimulate interdisciplinary scientific collaboration between gynecologists/reproductive endocrinologists/obstetricians and subspecialists in diverse medical fields to advance individualized treatments consistent with gynecologic, reproductive, and obstetrical needs and desires; promote translational and clinical research to increase knowledge and understanding of interaction of various therapies on gynecologic, reproductive, and obstetric outcomes; and discover and develop novel safe and more effective therapies for adolescents and women with PCOS with underlying comorbid conditions. Ultimately, this research would advance precision therapeutics for adolescents and adults with PCOS who have concomitant medical conditions.

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<sup>237</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9898427](https://projectreporter.nih.gov/project_info_description.cfm?aid=9898427)

<sup>238</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9971301](https://projectreporter.nih.gov/project_info_description.cfm?aid=9971301)

## Premature Births

Infants who are born preterm can face a range of health challenges throughout their lives, and yet the mechanisms that lead to preterm birth remain poorly understood. The agreement includes an increase to NICHD of \$10,000,000 for research aimed at enhancing the survival and healthy development of preterm infants. These studies may include research efforts to identify and understand the causes of preterm birth and the development of evidenced-based strategies to address the short- and long-term complications in children born preterm, including children with intellectual, developmental, and physical disabilities. The agreement especially urges NICHD to support studies that address health disparities in preterm birth and its consequences and requests an update on these efforts in the fiscal year 2022 Congressional Justification (Joint Explanatory Statement, p. 53-54).

### **Action Taken or to be Taken**

The National Institutes of Health (NIH) is committed to obtaining a better understanding of how pregnancy-related conditions contribute to maternal mortality, severe morbidity, and preterm birth. Twelve percent of infant mortality worldwide is due to being born too early. In FY 2019, NIH funded \$374 million in research on preterm birth, low birthweight, and the health of the newborn<sup>239</sup>. As stated in its Strategic Plan 2020, the prevention and management of preterm birth is a top priority for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD).<sup>240</sup> Among the specific objectives included in the plan are several related to preterm birth and its consequences, such as understanding the composition and function of human milk and the mode of nutrient delivery to the infant, especially preterm infants.

NICHD supports a wide range of research on the prevention of preterm birth and treatment for premature infants through investigator-initiated grants and through its major research networks, the Maternal-Fetal Medicine Units Network (MFMU) and the Neonatal Research Network (NRN). NICHD also supports an intramural program, the NICHD Perinatology Research Branch (PRB), at Wayne State University and Hutzel Hospital in Detroit. In one recent study from the PRB, researchers found that premature rupture of membranes (PROM) – when a woman’s “water breaks” early – may account for about a third of preterm births. The researchers tested a new device, which can collect fluid when membrane rupture occurs, finding that their noninvasive technique was better able to correctly identify those patients with inflammation and those without it.<sup>241</sup> Early identification and intervention may help treat infants following PROM.

Necrotizing Enterocolitis (NEC) is the most common gastrointestinal disease affecting newborns. Considered a medical emergency, NEC is most often seen in premature infants. NICHD and the NIH Office of the Director recently funded several projects to address NEC in newborns and other conditions affecting premature infants, including research to test the idea

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<sup>239</sup> [report.nih.gov/funding/categorical-spending#](https://report.nih.gov/funding/categorical-spending/)

<sup>240</sup> [www.nichd.nih.gov/sites/default/files/2019-09/NICHD\\_Strategic\\_Plan.pdf#search=strategic-plan-2020](https://www.nichd.nih.gov/sites/default/files/2019-09/NICHD_Strategic_Plan.pdf#search=strategic-plan-2020)

<sup>241</sup> Oh KJ, Lee JH, Romero R, Park HS, Hong J-S, Yoon BH. “A New Rapid Bedside Test to Diagnose and Monitor Intra-Amniotic Inflammation in Preterm Birth Using Trans-Cervically Collected Fluid.” *Am J Obstet Gynecol* 2020 Feb 27

that bacteria in a baby's gut may cause inflammation and NEC,<sup>242</sup> and a small business grant that is seeking to develop a compound aimed at preventing NEC.<sup>243</sup> A recent investigator-initiated study explored the immune systems of preterm infants who have a high risk of infections. Women who have preterm deliveries often do not make enough milk to feed their babies and may rely on donated breast milk. They found that cells treated with donor milk made more proteins linked to inflammation and infection than cells treated with milk from mothers who delivered preterm. These results may help researchers develop new ways to prevent infections and other health problems in preterm babies.<sup>244</sup>

In addition to supporting investigator-initiated grants, NICHD funds major research networks that provide the infrastructure to conduct widespread testing in larger groups of pregnant women and infants. The MFMU studies ways to reduce maternal, fetal, and infant morbidity and mortality, with a focus on preventing preterm birth, growth abnormalities, and maternal complications. This network includes 12 centers with 37 hospitals across the United States, with about 160,000 births to a diverse group of women annually. Ongoing studies include approaches to preventing preterm birth in women with a short cervix and therapies taken during pregnancy to prevent preeclampsia. The NRN, comprising 15 centers and 40 hospitals, studies new and innovative treatments to help newborns, particularly premature infants, survive without impairment. Current studies include testing of treatments for congenital diaphragmatic hernia and hypothermia in preterm infants. NICHD's Global Network for Women's and Children's Health Research supports clinical studies on cost-effective and sustainable interventions to improve maternal and infant health outcomes in resource-limited countries. For example, to assess whether low-dose aspirin may reduce the risk of preterm birth in low-resource settings, researchers found fewer preterm births occurred in women who took aspirin than women who took the placebo. Women in the aspirin group also had a lower rate of perinatal mortality (stillbirth or newborn death in the first seven days of life), leading to a potentially low-cost preventive measure for preterm birth and its consequences.<sup>245</sup>

In addition, NICHD works closely with other NIH Institutes and Centers (ICs), such as the National Institute on Minority Health and Health Disparities (NIMHD) to address disparities in preterm birth. Disparities in preterm birth is a major concern among African American women who have more than a 50 percent higher rate of preterm birth deliveries than White women.<sup>246</sup> Through the implementation of the <sup>247</sup>*NIH Minority Health and Health Disparities Strategic Plan (2020-2024)*, NIH ICs have an opportunity to partner with NIMHD to increase research and outreach on disparities in preterm birth and birth outcomes. One example of current research in this area is the Vaginal Microbiome and Racial Disparity in Preterm Delivery study<sup>248</sup> that is

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<sup>242</sup>[projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9893335&icde=52429987](https://projectreporter.nih.gov/project_info_description.cfm?aid=9893335&icde=52429987)

<sup>243</sup>[projectreporter.nih.gov/project\\_info\\_description.cfm?aid=10010634&icde=52430328](https://projectreporter.nih.gov/project_info_description.cfm?aid=10010634&icde=52430328)

<sup>244</sup> Demers-Mathieu V, Huston RK, Dallas DC. "Cytokine Expression by Human Macrophage-Like Cells Derived from the Monocytic Cell Line THP-1 Differs Between Treatment with Milk from Preterm- and Term-Delivering Mothers and Pasteurized Donor Milk." *Molecules*, 2020, 25(10), 2376.

<sup>245</sup> Hoffman, MK, et al. Low dose aspirin for the prevention of preterm delivery in nulliparous women with a singleton pregnancy (ASPIRIN): a randomized multi-country placebo-controlled trial. *The Lancet*, 2020 Jan 25

<sup>246</sup> [www.cdc.gov/minorityhealth/chdir/2011/factsheets/PretermBirth.pdf](https://www.cdc.gov/minorityhealth/chdir/2011/factsheets/PretermBirth.pdf)

<sup>247</sup> [nimhd.nih.gov/about/overview/strategic-plan.html](https://nimhd.nih.gov/about/overview/strategic-plan.html)

<sup>248</sup>[projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9855072&icde=52329843](https://projectreporter.nih.gov/project_info_description.cfm?aid=9855072&icde=52329843)

investigating factors that may lead to an unfavorable vaginal microbiome in a diverse cohort of women.

## Primate Research

The agreement recognizes the use of nonhuman primates in biomedical research for developing vaccines and treatments for public health threats. It also acknowledges the obligation in Federal law to minimize animal research and consider the use of alternatives wherever possible. The agreement directs NIH to commission an independent study by the National Academies of Sciences, Engineering, and Medicine (NASEM) to explore the current and future use of nonhuman primates in intramural NIH research. This study should include, but not be limited to: an assessment of the extent to which primates will continue to be necessary for intramural NIH biomedical research and, if so, in what areas; an analysis of primate availability and transportation options to fulfill current and future research needs; and a review of existing and anticipated future alternatives to the use of primates and how these could reduce NIH's reliance on nonhuman primates to fulfill the agency's mission currently and in the future (Joint Explanatory Statement, p. 69).

### **Action taken or to be taken**

As requested in the Joint Explanatory Statement, the NIH is working with the National Academies of Sciences, Engineering, and Medicine to commission an independent study of the current and future use of nonhuman primates (NHPs) in intramural NIH research. The commissioned study will add to our existing understanding of the current use and future needs for NHPs as a model system for biomedical research, briefly outlined below.

Because of our shared anatomy, physiology, behavior, and development, NHPs are critical to improving our understanding of human biology and developing treatments for diseases. NHPs and humans share up to 98.77 percent<sup>249</sup> of the human genetic sequence. Although NHPs have been estimated to account for just one-half of one percent of animals used in current biomedical research studies, their use has produced benefits to human health, some of which would likely not have occurred without them. Our biological similarities make NHP models critical for studying neurobiology, transplant tolerance and rejection, infectious diseases, reproductive biology, and regenerative medicine.

Given their unique similarities to human neuroanatomy, cognitive development and function, and some complex higher-order behaviors, NHPs are the best animal models for studies of the human brain. For example, advances in basic neuroscience research in NHPs have resulted in the Nobel prize for understanding the visual cortex and the mechanisms underlying motor dysfunction. Moreover, NHPs often provide a critical steppingstone to validate new therapies for complex human brain disorders, such as Alzheimer's disease, multiple sclerosis, and Parkinson's disease.<sup>250</sup>

In addition to their highly similar neuroanatomy and higher order cognitive functions, NHPs also share close similarities in immune systems and functions to that of humans. These animal models have been pivotal in our efforts to develop medical countermeasures for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease

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<sup>249</sup> [science.sciencemag.org/content/295/5552/131.long](https://science.sciencemag.org/content/295/5552/131.long)

<sup>250</sup> [www.nationalacademies.org/our-work/transgenic-and-chimeric-neuroscience-research-exploring-the-scientific-opportunities-afforded-by-new-nonhuman-primate-models-a-workshop](https://www.nationalacademies.org/our-work/transgenic-and-chimeric-neuroscience-research-exploring-the-scientific-opportunities-afforded-by-new-nonhuman-primate-models-a-workshop)

2019 (COVID-19). They serve as essential experimental models for understanding viruses and their effects on human physiology. NHPs are also critical for understanding how other pathogens are transmitted and spread in the body, which provides an essential tool for developing novel vaccines and other prevention approaches, as well as treatments. Studies attempting to determine the efficacy of prevention therapies, including vaccines, often require the use of NHPs per U.S. Food and Drug Administration regulations (21CFR314.600-650 for drugs and 21CFR601.90-95 for biologics). The NHP immune system's ability to express broadly and mimic the essential mechanisms of the human patient's immune system and its interactions with cancer cells and infectious disease agents cannot at this time be replicated in other animals, cell cultures, or computer-based applications.

Due to the need for NHPs in biomedical research, in 2018 the National Institutes of Health (NIH) Office of Research Infrastructure Programs (ORIP) undertook an evaluation and analysis of NIH-supported NHP resources to aid in determining the best strategy to facilitate execution of NIH's research programs.<sup>251</sup> This analysis indicated an increased demand for both rhesus macaques and marmosets over the following five years<sup>252</sup> which was primarily driven by infectious disease and neuroscience research. Since completion of the report, the COVID-19 pandemic has resulted in further NHP shortages, since NHPs are a critical model in the development of vaccines and therapeutics as detailed above. In September 2020, ORIP released a notice to inform biomedical and behavioral scientists who are currently conducting or planning to conduct COVID-19 research studies involving NHP species housed at facilities supported by ORIP that access to and availability would be limited due to higher demand than available resources (NOT-OD-20-173).<sup>253</sup>

To address the availability of NHPs, NIH is focusing efforts on increasing production in existing domestic colonies located across the United States. The initial focus is on improving and increasing appropriate infrastructure for breeding animals. With animals located geographically across the United States, transportation by approved carriers in climate-controlled trailers is possible within one day. Importation of NHPs from other countries will require coordination with appropriate airline carriers, which will likely be through chartered flights. NHP vendors have established procedures for this process. Collaborative projects with other countries are being considered to improve genetic diversity of domestic colonies and establish ongoing resources in the country of origin.

At the core of its mission, NIH funds research to define the biology and behavior of living systems with the ultimate goal of extending human life and diminishing the challenges of illness and disability. Research using animal models, including NHP models, has led to tremendous advances critical for saving countless lives and extending life expectancy around the world. NIH decisions to conduct or support research that uses animals are made with careful consideration of a variety of factors—including the scientific merits of the research—and not solely based on statements of the utility of any specific research. NIH treats animal welfare concerns as a top

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<sup>251</sup> [orip.nih.gov/sites/default/files/508%20NHP%20Evaluation%20and%20Analysis%20Final%20Report%20-%20Part%201%20Update%2017Oct2018.pdf](https://orip.nih.gov/sites/default/files/508%20NHP%20Evaluation%20and%20Analysis%20Final%20Report%20-%20Part%201%20Update%2017Oct2018.pdf)

<sup>252</sup> [orip.nih.gov/sites/default/files/NHP%20Evaluation%20and%20Analysis%20Final%20%20Report%20-%20Part%202%20Final%20508%2021Dec2018\\_002.pdf](https://orip.nih.gov/sites/default/files/NHP%20Evaluation%20and%20Analysis%20Final%20%20Report%20-%20Part%202%20Final%20508%2021Dec2018_002.pdf)

<sup>253</sup> [grants.nih.gov/grants/guide/notice-files/NOT-OD-20-173.html](https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-173.html)

priority through comprehensive policies and protocols that require the ethical treatment and use of these resources.



## Psychosocial Distress Complications

The agreement directs NIH to include updates on the following research, projects, and programs in the fiscal year 2022 Congressional Justification: gastric cancer; psycho-social distress in cancer research; the Office of Cancer Survivorship; progress in treating rare cancers; the Surveillance, Epidemiology, and End Results [SEER] Registry; Temporomandibular Disorders; diabetes, Rapid Acceleration of Diagnostics; 7q1 1.23 Duplication Syndrome; and Hereditary Spastic Paraparesis 49 (TECPR2). (Joint Explanatory Statement, p. 45)

### **Action Taken or to be Taken**

The diagnosis of and treatment for cancer can cause psychosocial distress for both patients and their families and caregivers. The National Cancer Institute (NCI) is committed to supporting research to understand the psychosocial impact of cancer, develop screening and assessment tools, and provide evidence-based screening and care to both patients and their caregivers. NCI also supports training programs to prepare early career scientists for independent careers focused on psychosocial and behavioral issues across the cancer control continuum, including one program that is in its 37<sup>th</sup> year of funding. This program alone has trained over 150 researchers in psycho-oncology.<sup>254</sup>

NCI supports a broad portfolio of research in this area focusing on patient populations from pediatric and young adult cancer patients to older adults and caregivers and family.<sup>255,256,257,258</sup> The research being supported is investigating various methods including eHealth and telehealth interventions. One group of researchers, developing a psychosocial eHealth intervention program for parents of children with cancer, first developed strategies to recruit and retain parents in such studies. The researchers identified a number of barriers to participation and showed it is important to engage parents in all phases of intervention programs.<sup>259</sup>

The National Institute of Mental Health (NIMH) is supporting a clinical trial to develop and validate an electronic screening tool for pediatric psychosocial distress screening.<sup>260</sup> The Checking Out Checking In trial enrolls patients 8-21 years of age who are enrolled in a research protocol at the NIH Clinical Center or receiving cancer treatment or follow up care at one of the three participating institutions. Trial participants will be asked questions related to mood, pain, fatigue, peer relationships, and sleep to help researchers develop an effective electronic screening tool.

The Cancer Moonshot program, authorized by the 21st Century Cures Act, also supports research to improve the quality of life of cancer patients. This includes research projects to test interventions to address medical and psychosocial effects of cancer diagnosis and treatment.<sup>261</sup>

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<sup>254</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9902338&icde](https://projectreporter.nih.gov/project_info_description.cfm?aid=9902338&icde)

<sup>255</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9750647&icde=47202797](https://projectreporter.nih.gov/project_info_description.cfm?aid=9750647&icde=47202797)

<sup>256</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9733171&icde=47202797](https://projectreporter.nih.gov/project_info_description.cfm?aid=9733171&icde=47202797)

<sup>257</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9741129&icde=47202742](https://projectreporter.nih.gov/project_info_description.cfm?aid=9741129&icde=47202742)

<sup>258</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9655009&icde=47202742](https://projectreporter.nih.gov/project_info_description.cfm?aid=9655009&icde=47202742)

<sup>259</sup> [pubmed.ncbi.nlm.nih.gov/32196090/](https://pubmed.ncbi.nlm.nih.gov/32196090/)

<sup>260</sup> [clinicaltrials.gov/ct2/show/NCT02423031](https://clinicaltrials.gov/ct2/show/NCT02423031)

<sup>261</sup> [www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/implementation/symptom-management](https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/implementation/symptom-management)

In particular, the Improving the Management of symptoms during And following Cancer Treatment (IMPACT) initiative is working to integrate evidence-based symptom management (including management of anxiety, depression, etc.) into routine clinical care throughout the course of cancer treatment and survivorship.<sup>262</sup>

In addition, NCI's Coordinating Center for Clinical Trials coordinates the Symptom Management and Health-Related Quality of Life Steering Committee.<sup>263</sup> This steering committee informs research on psychosocial care and addresses the design, prioritization, and evaluation of clinical trials on symptom management and quality of life. One provision of the NCI Community Oncology Research Program (NCORP) is that institutions must demonstrate that they are able to provide distress screening to patients to be eligible to become an NCORP site.

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<sup>262</sup> [impactconsortium.org/](http://impactconsortium.org/)

<sup>263</sup> [www.cancer.gov/about-nci/organization/ccct/steering-committees/ncorp/symptom-management](http://www.cancer.gov/about-nci/organization/ccct/steering-committees/ncorp/symptom-management)

## RADx

The agreement directs NIH to include updates on the following research, projects, and programs in the fiscal year 2022 Congressional Justification: gastric cancer; psycho-social distress in cancer research; the Office of Cancer Survivorship; progress in treating rare cancers; the Surveillance, Epidemiology, and End Results [SEER] Registry; Temporomandibular Disorders; diabetes, Rapid Acceleration of Diagnostics; 7q1 1.23 Duplication Syndrome; and Hereditary Spastic Paraparesis 49 (TECPR2). (Joint Explanatory Statement, p. 45)

### **Action Taken or to be Taken**

The National Institute of Biomedical Imaging and Bioengineering (NIBIB) and the Office of the Director, National Institutes of Health (NIH) invested a total of \$730 million from the Paycheck Protection Program and Health Care Enhancement Act to develop new diagnostic tests for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. NIBIB quickly stood up the Rapid Acceleration of Diagnostics (RADx<sup>SM</sup>) Tech and Advanced Technology Platforms (ATP) programs.<sup>264</sup> These multi-phase technology accelerator programs are based on an “innovation funnel” design and have successfully developed and deployed new laboratory-based and point-of-care (POC) tests to help contain the coronavirus disease 2019 (COVID-19) global pandemic. This innovative funding and support structure have succeeded in accelerating the typical 5- to 6-year technology development and commercialization timeline to under six months. Complementing RADx Tech/ATP, NIH also launched the RADx Underserved Populations (RADx-UP) program to assess and expand COVID-19 testing for underserved and/or vulnerable populations and the RADx Radical (RADx-rad) program to support new, non-traditional approaches to COVID-19 testing that require a longer development timeline.<sup>265</sup>

The highly specialized RADx Tech/ATP program mechanisms were built on a process framework that has been evolving since 2007 through the NIBIB Point of Care Technology Research Network (POCTRN).<sup>266</sup> This framework, expanded in scope through RADx, has proved to be ideally suited to draw innovation from the nation’s bioengineering and biomedical research communities and to quickly transform prototypes into marketable products. As of March 23, 2021, RADx Tech/ATP has reviewed 716 proposals submitted into the innovation funnel and vetted 137 of the most promising solutions through a nationally competitive “Shark Tank”-style review process designed to identify projects with the greatest chance of success. RADx Tech/ATP has administered 47 “Phase 1” awards for technology validation and de-risking and is supporting 29 “Phase 2” contracts for scale-up and manufacturing expansion totaling more than \$507 million, with additional projects in the pipeline. These Phase 2 projects represent technologies that were evaluated using rigorous criteria for speed, accuracy, cost, and accessibility. Tests are optimized within the NIH RADx Tech/ATP development pipeline with guidance from scientific, technical, clinical, regulatory, commercialization, and other healthcare experts engaged through POCTRN, NIH, and other federal agencies. RADx supported companies produced 94 million tests per day in 2020. Capacity is expected to increase throughout the first quarter of 2021, including innovative tests for at-home use. Fifteen

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<sup>264</sup> [www.nibib.nih.gov/covid-19/radx-tech-program](http://www.nibib.nih.gov/covid-19/radx-tech-program)

<sup>265</sup> [www.nih.gov/research-training/medical-research-initiatives/radx/radx-programs](http://www.nih.gov/research-training/medical-research-initiatives/radx/radx-programs)

<sup>266</sup> [www.poctrn.org/covid19](http://www.poctrn.org/covid19)

companies have already leveraged RADx Tech/ATP support to obtain required Emergency Use Authorization from the U.S. Food and Drug Administration (FDA). RADx technologies are adding new dimensions to the marketplace, including tests that return immediate results with the accuracy of lab-based diagnostics such as the Visby Medical COVID-19<sup>267</sup> and the Mesa Accula,<sup>268</sup> and the nation's first at-home COVID-19 test available over the counter developed by Ellume USA.<sup>269</sup>

The RADx Tech/ATP program design successfully shortened the technology development timeline by providing coordinated infrastructures for rapidly identifying the most promising technologies, funding prototype development and proof-of-concept studies, rigorously and independently validating their performance, and contributing wrap-around support to enable market entry. NIH-funded technology accelerator programs and networks like RADx complement NIH's strengths in basic, clinical, and translational research with expertise and training in healthcare product design and usability, regulatory requirements, business development, manufacturing, logistics, and distribution. These programs and networks offer nimble proposal solicitation and review infrastructures that can be rapidly expanded and are effective in broadening the base of innovators supported by NIH, especially among startup companies and small businesses. The urgency of addressing the COVID-19 pandemic also propelled unprecedented levels of communication, coordination, and collaboration with agencies across the federal government, including the U.S. Department of Health and Human Services Assistant Secretary for Health, Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority, FDA, Centers for Disease Control and Prevention, Centers for Medicaid and Medicare Services, and Department of Defense. NIH anticipates that the new connections and partnerships made in this all-of-government response will carry forward to tackling future national health concerns.

The above factors critical to RADx Tech/ATP's demonstrated success are likely to be translatable to delivering innovative technologies for other diseases or conditions. The breakthrough innovations in infectious disease diagnostics catalyzed by RADx can be repurposed in the marketplace to underpin technologies for early detection of cancer, chronic diseases, and degenerative disorders like Alzheimer's disease. NIH can apply the RADx approach to more effectively feed innovation into the commercial ecosystem where market forces will build upon the validated technologies, drive expansion to other uses, and dramatically increase the speed with which NIH-supported innovations reach the public.

NIH is already planning to apply this approach to the development of medical devices to treat neurological disorders through the NIH Blueprint for Neuroscience Research<sup>270</sup>, a collaborative consortium of 14 NIH Institutes and the Office of the Director. The Blueprint MedTech program is adopting successful elements of RADx: first, the "Shark Tank" multi-faceted review process examining technical, regulatory, clinical, and commercial components; second, a cadre of expert consultants to spur development on a critical path to commercialization; and, third, resource

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<sup>267</sup> [www.visbymedical.com/covid-19-test](http://www.visbymedical.com/covid-19-test)

<sup>268</sup> [www.mesabiotech.com/](http://www.mesabiotech.com/)

<sup>269</sup> [www.nih.gov/news-events/news-releases/nih-funded-covid-19-home-test-first-receive-over-counter-authorization-fda](http://www.nih.gov/news-events/news-releases/nih-funded-covid-19-home-test-first-receive-over-counter-authorization-fda)

<sup>270</sup> [neuroscienceblueprint.nih.gov/](http://neuroscienceblueprint.nih.gov/)

infrastructures tightly managed to support projects from academia, startups, and small businesses as they advance through performance milestones. Resource management and allocation throughout the development pipeline will be critical, as new technologies typically spend years waiting to secure public or private funding for each stage.

NIH looks forward to implementing the best practices learned from the RADx experience to accelerate the development and availability of new technologies for additional areas of biomedical research.

## **Rare Cancers Therapeutics Research and Development – DART Study**

Rare cancers, defined as those cancers that have fewer than six new cases per 100,000 Americans per year, represent over 30 percent of all cancers. Rare cancers present a unique research challenge for many reasons, including the difficulty in accruing enough patients to participate in clinical trials, the lack of industry focus on these cancers due to the relatively small number of patients diagnosed with each cancer, the lack of rare cancer tumor models and cell lines, and the difficulty of patients receiving accurate and precise diagnoses due in part to the lack of clinician familiarity with rare cancers. The Committee commends NCI's investment in the Rare Tumor Patient Engagement Networks, including NCI CONNECT and MyPART, and in particular the NCI Experimental Therapeutics Program, with a focus on supporting the most promising new drug discovery and development projects. The Committee encourages NCI to expand these initiatives to include additional rare cancers not covered in prior and existing efforts and to issue a report on this progress and an update on the DART study in the fiscal year 2022 Congressional Justification (House Report, p. 96-97).

### **Action Taken or To Be Taken**

The National Cancer Institute (NCI) supports many clinical trials of novel and targeted therapies, including immunotherapies, and trials for cancer control in patients with rare cancers through several of its clinical trial networks and intramural research program. NCI-supported research and clinical trials are responsible for a number of the U.S. Food and Drug Administration (FDA) approvals for immunotherapy for rare cancers. For example, a clinical trial conducted by the Cancer Immunotherapy Trials Network led to the December 2018 FDA approval of the immunotherapy agent pembrolizumab for Merkel cell carcinoma, a rare form of skin cancer.<sup>271</sup> Prior to this, the only other FDA-approved therapy for Merkel cell carcinoma was another immunotherapy agent, avelumab. The first in human trial of avelumab for Merkel cell carcinoma was conducted at the NIH Clinical Center by NCI intramural researchers.

A trial led by NCI's Developmental Therapeutics Clinic, part of the Experimental Therapeutics Clinical Trials Network (ETCTN),<sup>272</sup> showed the immunotherapy agent, atezolizumab, was effective for the treatment of alveolar soft part sarcoma. This is a rare form of sarcoma for which few tested treatments had shown any effect in the past. NCI worked with the drug maker to obtain orphan drug status for atezolizumab in sarcomas based on this trial. ETCTN was created by NCI to speed up clinical trials of investigational drugs in rare cancer types. The network has investigators at more than 50 hospitals and treatment centers across the U.S. and Canada. This infrastructure aids in more rapid patient accrual for rare cancer trials and reduces travel for this patient population.

In partnership with the SWOG Cancer Research Network (SWOG), one of the five NCI National Clinical Trials Network (NCTN) groups, the Dual Anti-CTLA-4 & anti-PD1 blockade in Rare Tumors (DART) study focuses on extending the promise of innovative immunotherapy treatments to patients whose cancers are often so rare that a clinical trial is considered unfeasible due to small patient populations. In addition, genomes from patients with extremely rare

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<sup>271</sup>[cancer.gov/news-events/cancer-currents-blog/2019/pembrolizumab-merkel-cell-carcinoma-fda-approval](https://cancer.gov/news-events/cancer-currents-blog/2019/pembrolizumab-merkel-cell-carcinoma-fda-approval)

<sup>272</sup>[ctep.cancer.gov/initiatives/Programs/etctn.htm](https://ctep.cancer.gov/initiatives/Programs/etctn.htm)

malignancies will be sequenced and analyzed to determine if there are any hereditary or immune system factors associated with response to therapy, which can help doctors in developing future clinical trials for patients with these rare malignancies.

Launched in 2017, the DART study<sup>273</sup> is an immunotherapy basket trial open at 942 hospitals across 49 states and the District of Columbia, bringing innovative immunotherapy options to patients with rare cancers to every corner of the U.S., including many underserved urban and rural communities. A basket trial tests a drug or a combination of drugs in multiple tumor types in the same trial as opposed to a more traditional clinical trial design that focuses on a single tumor type. DART is a phase 2 study made up of 53 separate baskets (or cohorts) of rare tumors evaluating the promising immunotherapy combination of ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1). Adult patients with certain types of rare tumors that no longer respond to standard treatment or experience recurrence are eligible to have a sample of their tumor sequenced and stored prior to enrollment. Currently, 750 participants have enrolled on the trial. Out of the 53 cohorts being studied, 34 have completed accrual, 5 are temporarily closed and expect to be permanently closed after data submission is complete, and 14 are currently open to accrual.

In 2020, DART investigators published results for the neuroendocrine tumor cohort, a cancer of the neuroendocrine cells (cells that signal for the release of hormones into the blood) that often form tumors in the lungs and along the digestive tract of patients.<sup>274</sup> For this cohort, 32 eligible patients received the ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1) combination. Of the 32, 18 had high-grade cancer, with tumors most commonly appearing in the lungs or rectum. Regardless of where their tumors appeared, 8 out of 18 high-grade patients—or 44 percent—saw them shrink partially or completely. By contrast, patients with intermediate or low-grade tumors saw no response. Preliminary results have also been presented at professional society meetings for the metastatic breast cancer, salivary gland, and small bowel cohorts.<sup>275</sup> Results from two more cohorts (metastatic or unresectable angiosarcoma and thyroid tumors) are expected to be presented at the Society for Immunotherapy of Cancer Annual Meeting in November 2020.

The Cancer Moonshot-funded Cancer Immune Monitoring and Analysis Centers (CIMACs), led by researchers at the University of Texas M.D. Anderson Cancer Center are spearheading the in-depth immune profiling necessary to advance the science of rare cancers. Together with laboratory and clinical scientists, SWOG and NCI investigators are seeking to determine why some patients respond to immunotherapies and some do not. This can help empower research going forward by generating new avenues for discovery for rare cancers.

NCI is also evaluating targeted therapies for patients with rare cancer subtypes through the NCI-MATCH (Molecular Analysis for Therapy Choice) trial. This basket trial includes nearly 40 treatment arms evaluating therapies that target unique molecular abnormalities in tumors, which often occur in rare cancers. The trial is particularly important for patients with rare cancers for which there is no standard treatment and those who have exhausted standard treatment options.

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<sup>273</sup>[clinicaltrials.gov/ct2/show/NCT02834013](https://clinicaltrials.gov/ct2/show/NCT02834013)

<sup>274</sup>[pubmed.ncbi.nlm.nih.gov/31969335/](https://pubmed.ncbi.nlm.nih.gov/31969335/)

<sup>275</sup>[meetinglibrary.asco.org/record/185172/abstract](https://meetinglibrary.asco.org/record/185172/abstract); [www.abstractsonline.com/pp8/#!/9045/presentation/6909](https://www.abstractsonline.com/pp8/#!/9045/presentation/6909);  
[www.abstractsonline.com/pp8/#!/9045/presentation/6908](https://www.abstractsonline.com/pp8/#!/9045/presentation/6908)

Genomic sequencing of tumors is conducted to reveal rare genetic alterations, and eligible patients are matched to a therapeutic arm with a targeted drug that has shown success in other cancer types driven by the same molecular aberration. Recent NCI-MATCH results show that around 12 percent of patients received targeted treatment based on a molecular abnormality found in their cancer via this disease-agnostic approach.<sup>276</sup>

In addition, NCI is supporting ongoing efforts focused on drug repurposing, investigating natural products as anti-cancer drugs, and developing better animal models of rare and common cancers. The NCI Patient-Derived Model Repository (PDMR) is a national repository that serves as a resource for models for academic drug discovery efforts.<sup>277</sup> The repository currently has available models for approximately 20 rare cancers<sup>278</sup> and this number will continue to grow as model development continues.

NCI's Rare Tumor Patient Engagement Network, including NCI CONNECT (Comprehensive Oncology Network Evaluating Rare CNS Tumors) and MyPART (My Pediatric and Adult Rare Tumor network), also continues to expand its activities, in alignment with the goals outlined as part of the Cancer Moonshot. As of September 2020, more than 200 individuals have been enrolled in MyPART's Natural History Study of Rare Solid Tumors, with the goal of collecting information and biospecimens from people with rare tumors and their relatives and tracking their health history over time. The Network's rare cancer clinics build upon the success of NCI's wild-type gastrointestinal stromal tumor (GIST), which launched in 2008 and now also includes pediatric GIST. MyPART, now leads annual clinics for medullary thyroid cancer, since 2018, and pediatric chordoma (a rare tumor of the spine), launched in 2019. The network has plans for the development of several rare tumor clinical trials and currently has over a dozen advocacy partners.

NCI-CONNECT is studying 12 rare central nervous system cancers in adults. Some of these 12 tumor types are diagnosed in a few thousand people each year. Others are so rare that only a few dozen have ever been reported. NCI CONNECT conducts weekly tumor clinics for rare CNS cancer patients and also leads the Natural History of and Specimen Banking for People with Tumors of the Central Nervous System, with 830 patients enrolled as of September 2020.<sup>279</sup> The network currently has 32 participating sites across the U.S. and 9 advocacy partners. NCI CONNECT currently has seven clinical studies and trials open.<sup>280</sup>

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<sup>276</sup> [ascopubs.org/doi/full/10.1200/JCO.19.03010](https://ascopubs.org/doi/full/10.1200/JCO.19.03010)

<sup>277</sup> [pdmr.cancer.gov/](https://pdmr.cancer.gov/)

<sup>278</sup> Rare cancer models in the NCI PDMR include: Merkel Cell Carcinoma, Mesothelioma, Hurthle Cell Neoplasm of the Thyroid, Malignant Peripheral Nerve Sheath Tumor, Salivary Gland Squamous Cell Carcinoma (SCC), Pharyngeal SCC, Nasopharyngeal SCC, Laryngeal SCC, Carcinosarcoma of the Uterus, Vaginal Cancer, Cervical SCC, Synovial Sarcoma, Liposarcoma, Uterine and non-uterine Leiomyosarcoma, Rhabdomyosarcoma, Osteosarcoma, Chondrosarcoma, Malignant fibrous histiocytoma, Fibrosarcoma (not infantile), Ewing Sarcoma/Peripheral Primitive Neuroectodermal Tumors.

<sup>279</sup> [www.cancer.gov/rare-brain-spine-tumor/blog/2020/natural-history](https://www.cancer.gov/rare-brain-spine-tumor/blog/2020/natural-history)

<sup>280</sup> [www.cancer.gov/rare-brain-spine-tumor/refer-participate/clinical-studies](https://www.cancer.gov/rare-brain-spine-tumor/refer-participate/clinical-studies)



## Rare Cancer Therapeutic Research and Development

The Committee recognizes that nearly 500,000 Americans are diagnosed with a rare form of cancer every year. The Committee requests an update in the fiscal year 2022 CJ on progress in treatment for rare cancers and how the Federal Government can accelerate the development of rare cancer therapies, including expanding the availability of biorepository resources for rare cancers, and improving clinical trial participation for rare cancer patients (Senate Report, p. 88).

### Action Taken or to be Taken

The National Cancer Institute (NCI) continues to support and expand its extensive portfolio of research that is relevant to advancing progress against rare cancers, including many preclinical and clinical research efforts to accelerate the development of rare cancer therapies. Examples of programs and initiatives are provided below but are not a comprehensive list; also see the Rare Cancers Therapeutics Research and Development—DART Study response for additional information.

NCI's support of rare cancer research is realized not only through funding investigator-initiated awards, such as uncovering mechanisms of pancreatic cancer initiation,<sup>281</sup> understanding molecular drivers of ependymomas (a type of tumor of the brain or spinal cord),<sup>282</sup> and optimizing a candidate drug for Ewing sarcoma,<sup>283</sup> but through targeted programs, initiatives, networks, and infrastructure support. The NCI National Clinical Trials Network (NCTN) and the NCI Community Oncology Research Program (NCORP) are two key infrastructure investments that are particularly relevant to rare cancers due to the nature of their focus on early phase trials. Trials include the NCI-Molecular Therapy for Choice (MATCH) and Pediatric MATCH trials, which identify treatments for patients based on genomic characteristics of their tumor, rather than the organ in the body where the tumor originated. These types of trials, referred to as basket trials, represent greater opportunities for patients with rare types of cancer to both participate in clinical trials and receive precision therapies. The targeted therapy larotrectinib, for example, received U.S. Food and Drug Administration (FDA) approval for adult and pediatric patients with solid tumors that have a rare genetic alteration in the neurotrophic receptor tyrosine kinase gene (TRK fusions) based on data from a basket trial. To date, TRK fusions have been identified in more than 20 different cancers.

Other recent FDA drug approvals for rare cancers include selumetinib to treat children with Neurofibromatosis type 1 with plexiform neurofibromas,<sup>284</sup> pembrolizumab for patients with Merkel cell cancer,<sup>285</sup> and moxetumomab pasudotox for hairy cell leukemia.<sup>286</sup> NCI support was critical to all three of these approvals, and moxetumomab pasudotox was developed and evaluated in clinical trials by researchers in NCI's intramural program. The FDA also recently approved an Orphan Drug Status designation for atezolizumab in the treatment of Alveolar Soft

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<sup>281</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?icde=0&aid=9886096](https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=9886096)

<sup>282</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?icde=0&aid=10049851](https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=10049851)

<sup>283</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?icde=0&aid=10049627](https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=10049627)

<sup>284</sup> [www.cancer.gov/research/progress/discovery/selumetinib-plexiform-neurofibromas](https://www.cancer.gov/research/progress/discovery/selumetinib-plexiform-neurofibromas)

<sup>285</sup> [www.cancer.gov/news-events/cancer-currents-blog/2019/pembrolizumab-merkel-cell-carcinoma-fda-approval](https://www.cancer.gov/news-events/cancer-currents-blog/2019/pembrolizumab-merkel-cell-carcinoma-fda-approval)

<sup>286</sup> [www.cancer.gov/news-events/cancer-currents-blog/2018/moxetumomab-fda-hairy-cell-leukemia](https://www.cancer.gov/news-events/cancer-currents-blog/2018/moxetumomab-fda-hairy-cell-leukemia)

Part Sarcoma. The NCI-supported clinical trial that showed efficacy of atezolizumab was conducted by the Experiential Therapeutics Clinical Trials Network (ETCTN), another component of the NCI-supported clinical trials infrastructure.<sup>287</sup> ETCTN evaluates innovative cancer therapies in a coordinated, collaborative, and team-based manner and seeks to speed clinical trials of investigational drugs in rare cancer types. In 2020, NCI expanded the geographic reach of this network through supplemental funding to eight NCI-designated cancer centers, with a total of more than 30 accrual sites added to the network.

In addition, the Dual Anti-CTLA-4 & anti-PD1 blockade in Rare Tumors (DART) study, launched in 2017, is an NCTN basket trial that extends the promise of innovative immunotherapy treatments to patients whose cancers are often so rare that a clinical trial is considered unfeasible due to small patient populations. Currently, the trial is open at 942 hospitals across 49 states and the District of Columbia, bringing immunotherapy options to rare cancer patients in every corner of the United States. A detailed update on the DART trial is provided in the Rare Cancers Therapeutics Research and Development—DART Study response. Briefly, out of the 53 cohorts of rare cancers being studied, 34 have completed accrual, five are temporarily closed and expect to be permanently closed after data submission is complete, and 14 are currently open to accrual. Results have been published for the neuroendocrine tumor cohort, and results on additional cohorts are expected soon.

As part of the Cancer Moonshot, NCI launched the Rare Tumor Patient Engagement Network, with the goal of connecting researchers, healthcare providers, advocacy groups, and patients to accelerate progress against rare cancers. This national network to study adult and pediatric rare tumors is comprised of the Moonshot Pediatric, Adolescent, and Adult Rare Tumors Network<sup>288</sup> (MyPART) and the Comprehensive Oncology Network Evaluating Rare CNS Tumors<sup>289</sup> (CONNECT). The Natural History Study of Rare Solid Tumors, a cornerstone of MyPART, is collecting information, tissue and tumor samples (biobanking), and data from patients to better understand how rare cancers develop and grow. The network has over a dozen advocacy partners including the Chordoma Foundation, which is working with MyPART to enroll patients in the natural history study.<sup>290</sup> As of September 2020, more than 200 individuals have been enrolled in the natural history study. In addition, MyPART conducts a series of clinics focused on rare cancers. NCI-CONNECT is studying 12 rare central nervous system cancers in adults. NCI-CONNECT conducts weekly tumor clinics for rare CNS cancer patients and also leads a natural history and biobanking study, with 830 patients enrolled as of September 2020.<sup>291</sup> NCI-CONNECT currently has seven clinical studies and trials open.<sup>292</sup>

In 2020, NCI also began supporting a new Moonshot network to directly engage cancer patients and post-treatment cancer survivors as partners in generating a shared database of clinical, genomic, molecular, and patient-reported data that should accelerate treatments and help develop

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<sup>287</sup> [cancer.gov/news-events/cancer-currents-blog/2019/atezolizumab-alveolar-soft-part-sarcoma-trial](https://cancer.gov/news-events/cancer-currents-blog/2019/atezolizumab-alveolar-soft-part-sarcoma-trial)

<sup>288</sup> [www.cancer.gov/pediatric-adult-rare-tumor/](https://www.cancer.gov/pediatric-adult-rare-tumor/)

<sup>289</sup> [ccr.cancer.gov/neuro-oncology-branch/connect](https://ccr.cancer.gov/neuro-oncology-branch/connect)

<sup>290</sup> [chordomafoundation.org/latest-updates/chordoma-community-invited-to-participate-in-natural-history-study-of-rare-solid-tumors/](https://chordomafoundation.org/latest-updates/chordoma-community-invited-to-participate-in-natural-history-study-of-rare-solid-tumors/)

<sup>291</sup> [www.cancer.gov/rare-brain-spine-tumor/blog/2020/natural-history](https://www.cancer.gov/rare-brain-spine-tumor/blog/2020/natural-history)

<sup>292</sup> [www.cancer.gov/rare-brain-spine-tumor/refer-participate/clinical-studies](https://www.cancer.gov/rare-brain-spine-tumor/refer-participate/clinical-studies)

new standards of care. This network includes the Count Me In initiative which will engage adult and pediatric participants with osteosarcoma and leiomyosarcoma.<sup>293</sup>

Additionally, all pediatric cancers are rare diseases, and NCI supports a robust and always expanding portfolio of pediatric cancer research. See the Pediatric Cancer response for additional details on page XX. As part of NCI's implementation of the Childhood Cancer STAR Act, the Institute began supporting several new biobanking projects in FY 2020 through the Children's Oncology Group (COG) to focus attention to rare cancer subtypes that are currently underrepresented in NCI-supported biorepositories, as well as tumor types with a high risk of treatment failure. This includes projects with an emphasis on specimens taken at the time of relapse (particularly for children with rhabdomyosarcoma), as well as collecting diagnostic samples for children, adolescents, and young adults who have already submitted samples at relapse through the Pediatric MATCH Trial. These efforts also support the Childhood Cancer Data Initiative. The COG Rare Tumor Populations Biobanking project supports tumor tissue and blood collection for specific groups of patients for which current tumor tissue collection is lacking or inadequate, with priority for tumor types with high risk of treatment failure. NCI has also recently expanded the Pediatric Brain Tumor Consortium and formed a new public-private partnership to accelerate therapeutic development for pediatric cancers, working with the Pediatric Preclinical Testing Consortium to expand preclinical drug testing.

NCI also supports a number of ongoing, longitudinal studies of rare cancer syndromes including the Li-Fraumeni Syndrome Study,<sup>294</sup> the Inherited Bone Marrow Failure Syndromes Study,<sup>295</sup> the Pleuropulmonary Blastoma (rare lung tumor) DICER1 Syndrome Study,<sup>296</sup> and the RASopathies Longitudinal Cohort Study.<sup>297</sup> All of these studies seek to learn more about these rare syndromes to develop effective treatments for the individuals afflicted with them. Long-term commitment to studies like these lead to discoveries to develop new treatments and make progress against all types of cancer.

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<sup>293</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=10048560](https://projectreporter.nih.gov/project_info_description.cfm?aid=10048560)

<sup>294</sup> [lfs.cancer.gov/](https://lfs.cancer.gov/)

<sup>295</sup> [marrowfailure.cancer.gov/index.html](https://marrowfailure.cancer.gov/index.html)

<sup>296</sup> [ppb.cancer.gov/](https://ppb.cancer.gov/)

<sup>297</sup> [rasopathies.cancer.gov/](https://rasopathies.cancer.gov/)

## Research in Pregnant and Lactating Women

The Committee is pleased with the progress being made by the Task Force on Research Specific to Pregnant Women and Lactating Women in identifying and developing strategies to address gaps in knowledge and research on safe and effective therapies for pregnant and lactating women to carry out the recommendations in its 2018 report. The Committee directs NICHD to provide the Task Force's recommendations to the Committee within 60 days of enactment of this Act. The Committee also directs NICHD, along with other relevant NIH Institutes and Centers, CDC, FDA, and other relevant agencies, to prepare to implement these recommendations to the extent appropriate and feasible under the legal authorities available to the Secretary. Finally, the Committee directs NICHD, in conjunction with the Secretary, to report back to the Committee on the feasibility of implementing these policies and any additional authorizations or appropriations required in the fiscal year 2022 Congressional Justification (House Report, p.113-114).

### **Action Taken or To Be Taken**

Most prescription medications have not been tested in, nor are labeled for use by, pregnant and lactating women. Yet, on average, over 90 percent of pregnant women in the U.S. take at least one medication during their pregnancies and 70 percent use at least one prescription medication. The 21st Century Cures Act established The Task Force on Research in Pregnant Women and Lactating Women (PRGLAC or Task Force) to advise the Secretary of Health and Human Services (HHS) about gaps in current knowledge and research on safe and effective therapies for pregnant women and lactating women. As required, in September 2018, the Task Force submitted a report on its findings to the Secretary and to Congress, along with 15 recommendations for addressing these gaps in knowledge. On March 13, 2019, the federal charter for the Task Force was renewed for an additional two years. The HHS Secretary requested that the Task Force provide advice and guidance related to the implementation of recommendations that were set forth in the 2018 report. PRGLAC submitted its Implementation Plan to the Secretary in September 2020.<sup>298</sup>

Led by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the Task Force included a wide range of federal health agencies, including representatives from the Centers for Disease Control and Prevention, the Food and Drug Administration, professional societies, patient organizations, and representatives from industry. Four working groups – Research, Regulatory, Communications, and Discovery – were established to provide expert guidance on the development and use of therapeutics by pregnant women and lactating women, including the appropriate inclusion of pregnant and lactating women in clinical research. A number of core themes emerged from the working group deliberations, including recommendations to leverage or expand existing federal programs or networks; consider use of alternative trial designs (such as observational or adaptive designs); establish a prioritization process for studying therapeutics used during pregnancy and lactation; address ethical considerations, liability concerns, and potential research incentives to pursue research; and foster education and awareness among health care providers and pregnant and lactating women about participation in research. In describing potential steps, the

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<sup>298</sup> [www.nichd.nih.gov/sites/default/files/inline-files/PRGLAC\\_Implement\\_Plan\\_083120.pdf](http://www.nichd.nih.gov/sites/default/files/inline-files/PRGLAC_Implement_Plan_083120.pdf)

Implementation Plan also refers to which agency or entity might be appropriately involved in carrying them out, and whether creation of partnerships might help facilitate these activities. NIH has already begun its efforts to support research on therapeutics used by pregnant and lactating women. To assist in tracking the research that NIH funds, three new public reporting categories were developed: Pregnancy; Maternal Health; and Breastfeeding, Lactation, and Breast Milk.<sup>299</sup> To gain a more thorough understanding of what medications and dosages women take during their pregnancies and postpartum, NICHD added a new feature – a medications tracker – to PregSource®, its online pregnancy research registry.<sup>300</sup> This new tool allows women enrolled in PregSource® to report on the name, frequency, and dosage of their medications. NICHD remains committed to advancing research on therapeutics used during pregnancy and lactation. The Institute’s strategic plan, which guides its research activities, addresses five broad research themes, one of which is Advancing Safe and Effective Therapeutics and Devices for Pregnant and Lactating Women, Children, and People with Disabilities. For example, NICHD’s Pediatric Trials Network (PTN) supports the Pharmacokinetics and Safety of Commonly Used Drugs in Lactating Women and Breastfed Infants (CUDDLE) study, which is designed to assess the safety of commonly used off-patent medications when they are given to breastfeeding mothers.<sup>301</sup> It is common for new mothers to have symptoms or medical conditions that must be treated with drugs, yet these mothers often struggle with their decision to take their medications because of the fear that the drugs will harm their children. With this study, PTN aims to find doses of commonly used drugs that are safe for both mothers and their breastfed infants.

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<sup>299</sup> [report.nih.gov/categorical\\_spending.aspx](https://report.nih.gov/categorical_spending.aspx)

<sup>300</sup> [pregsource.nih.gov/](https://pregsource.nih.gov/)

<sup>301</sup> [pediatrictrials.org/pharmacokinetics-and-safety-of-commonly-used-drugs-in-lactating-women-and-breastfed-infants-cuddle/](https://pediatrictrials.org/pharmacokinetics-and-safety-of-commonly-used-drugs-in-lactating-women-and-breastfed-infants-cuddle/)

## Sickle Cell Disease (SCD)

The Committee commends NIH for its ongoing support of clinical research for SCD, which imposes major morbidity on an estimated 90,000 to 100,000 individuals in the U.S., with three million Americans carrying the sickle cell trait. The Committee encourages NIH to support clinical trials for prenatal and postnatal treatment of SCD, which includes multiple promising approaches to eradicate this disease, save lives, and dramatically reduce the substantial health care costs associated with SCD for children and adults. The Committee encourages NIH to consider programs both domestically and globally to evaluate the effectiveness of screening technologies for infants and children with the sickle cell trait and disease. Further, while the Committee is aware that NHLBI is funding very promising areas of innovation related to curative gene therapies, the Committee strongly encourages NHLBI to increase its focus as well on disease-modifying therapies that could improve day-to-day care for the vast majority of patients and address issues such as organ damage and pain management. Lastly, the Committee encourages NHLBI to fund the training of more sickle cell disease clinicians and researchers in order to maintain this essential workforce pipeline and to make advances on the transition from childhood medical care to adult (House Report, p. 100-101).

### **Action Taken or To Be Taken**

The National Heart, Lung, and Blood Institute (NHLBI) is committed to extending and improving life for people with sickle cell disease (SCD) through new treatments and cures. In the U.S., SCD was considered an almost uniformly fatal pediatric disease in the 1970s, but today most people with the disease live into their 50s and beyond, thanks in part to NHLBI-funded research.<sup>302</sup> However, more progress is needed to address mortality and morbidity from SCD, especially to reduce pain, improve quality of life, and reduce health care costs.

NHLBI supports basic, translational, and clinical research that contributes to a range of potential new therapies, including behavioral interventions (e.g., for pain), blood transfusion and bone marrow transplantation (BMT), and new disease-modifying drugs. Such research is yielding improvements in day-to-day care of individuals with SCD. For example, NHLBI investments helped lead to the development of the two newest drugs for SCD, approved in 2019—crizanlizumab-tmca (Adakveo) to reduce episodes of severe pain (crisis),<sup>303</sup> and voxelotor (Oxbryta) to reduce red blood cell sickling.<sup>304</sup>

Additionally, NHLBI-funded clinical trials have helped establish that SCD can be cured by BMT from an immune-matched, unaffected relative. However, because fewer than one in four patients have an appropriate donor, and others face a high risk of complications, researchers are working to develop new BMT regimens. NHLBI funds efforts to improve bone marrow transplantation through the BMT Clinical Trials Network, which is co-funded by the National Cancer Institute. For example, one current trial is investigating treatment of severe SCD with a BMT procedure that involves either a related or unrelated immune-matched donor.<sup>305</sup>

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<sup>302</sup> [pubmed.ncbi.nlm.nih.gov/26547630/](https://pubmed.ncbi.nlm.nih.gov/26547630/)

<sup>303</sup> [pubmed.ncbi.nlm.nih.gov/27959701/](https://pubmed.ncbi.nlm.nih.gov/27959701/)

<sup>304</sup> [pubmed.ncbi.nlm.nih.gov/15341482/](https://pubmed.ncbi.nlm.nih.gov/15341482/)

<sup>305</sup> [clinicaltrials.gov/ct2/show/NCT02766465](https://clinicaltrials.gov/ct2/show/NCT02766465)

While newborn screening for SCD has been the nationwide standard in the U.S. since 2006, it has not been widely implemented across countries in sub-Saharan Africa, the region with the highest proportion of SCD-affected births annually. The NHLBI-funded Sickle In Africa consortium provides research infrastructure and training in sub-Saharan Africa and is supporting studies to enhance newborn screening, lower the high risk of infection associated with SCD, and increase use of the drug hydroxyurea, which can help control pain and reduce the need for transfusions.<sup>306</sup> NHLBI also supports research toward new screening technology, including an affordable, easy-to-use microchip for point-of-care SCD diagnosis from a drop of blood.<sup>307</sup> NHLBI also supports the development of gene-based cures with the potential to work for all patients in all settings through its Cure Sickle Cell Initiative and an NIH collaboration with the Bill & Melinda Gates Foundation. Researchers continue to unravel the mechanisms of SCD to inform emerging gene and cell-based approaches. Using a mouse model, one team recently found that SCD disorganizes the blood vessels that supply bone marrow. The researchers also found that six weeks of blood transfusion improved blood vessel organization in the mice, suggesting a similar protocol could be used in conjunction with new gene- and cell-based therapies.<sup>308</sup>

The NHLBI Sickle Cell Disease Implementation Consortium (SCDIC), initiated in 2016, continues to identify barriers to evidence-based care and to improve healthcare delivery for adolescents and adults with SCD. The Consortium consists of eight geographically diverse U.S. centers that have conducted community assessments of patients and providers, developed a patient registry of over 2400 participants, and initiated several new studies to address identified barriers to care. Examples of studies underway include improving emergency department visits by making individualized pain plans available in electronic health records and developing mobile phone applications to improve medication adherence. Finally, NHLBI continues to nurture the next generation of investigators in hematology and SCD research. For example, the Stimulating Hematology Investigation: New Endeavors (SHINE) program, which is co-funded by NHLBI and two other Institutes and Centers, is focused on basic and early translational hematology research and encourages applications from investigators at all career stages.<sup>309</sup> NHLBI also supports dozens of graduate and postdoctoral trainees around the world who are conducting basic, translational, and clinical research on sickle cell disease. To reach young emerging investigators, the NHLBI's Hope for Sickle Cell Challenge, announced in September 2020, has invited college and graduate students to work with experienced mentors to develop evidence-based tools and programs to raise awareness about SCD.<sup>310</sup>

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<sup>306</sup> [pubmed.ncbi.nlm.nih.gov/32004491/](https://pubmed.ncbi.nlm.nih.gov/32004491/)

<sup>307</sup> [pubmed.ncbi.nlm.nih.gov/32123889/](https://pubmed.ncbi.nlm.nih.gov/32123889/)

<sup>308</sup> [www.ncbi.nlm.nih.gov/pmc/articles/PMC7273832/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7273832/)

<sup>309</sup> [grants.nih.gov/grants/guide/pa-files/PAS-19-105.html](https://grants.nih.gov/grants/guide/pa-files/PAS-19-105.html)

<sup>310</sup> [www.nhlbi.nih.gov/grants-and-training/sickle-cell-challenge](https://www.nhlbi.nih.gov/grants-and-training/sickle-cell-challenge)

## Spina Bifida

The Committee encourages NIA, NIDDK, NICHD, and NINDS to study the causes and care of neurogenic bladder and kidney disease to improve the quality of life of children and adults with spina bifida; to support research to address issues related to the treatment and management of spina bifida and associated secondary conditions, such as hydrocephalus and sudden death in the adult spina bifida population; and to invest in understanding the myriad co-morbid conditions experienced by individuals with spina bifida, including those associated with both paralysis and developmental delay; and to provide an update on research findings related to spina bifida in the fiscal year 2022 Congressional Justification. The Committee supports the specific efforts of NICHD to understand early human development; set the foundation for healthy pregnancy, and lifelong wellness of women and children; and promote the gynecological, andrological and reproductive health for people with spina bifida. In addition, the Committee encourages NICHD to identify sensitive time periods to optimize health interventions; improve health during transition from adolescence to adulthood; and ensure safe and effective therapeutics and devices for adults as well as children (House Report, p. 143-144).

### **Action taken or to be taken**

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) continues its longstanding research commitment on Spina Bifida (SB). SB is the most common neural tube defect in the U.S., the Centers for Disease Control and Prevention (CDC) estimates that about 1,500 babies in the U.S. are born with SB each year.

A core theme of NICHD's *Strategic Plan 2020* emphasizes the need for improving child and adolescent health and the transition to adulthood, an important consideration for individuals with SB. In late September 2020, the NICHD-led Pediatric Research Consortium held a scientific workshop to identify common issues arising when adolescents with chronic conditions transition to adult health care, specifically including young people with SB. Research is still needed to ensure that the transition to adult care is successfully coordinated, particularly for adolescents with relatively rare conditions. Defining outcome measures to help determine the parameters of a successful transition was identified as a critical need to move ahead the research in this understudied area.

NICHD-funded researchers continue to develop and analyze interventions to improve outcomes for children with SB. Following up on NICHD's landmark Management of Myelomeningocele (MOMS) study that showed the advantage of fetal surgery over postnatal surgery for this condition, the MOMS-2 study, co-funded by NICHD and the National Institute of Neurological Disorder and Stroke (NINDS), followed children in the original MOMS study cohort to school age to assess health and mental health outcomes as well as their capacity to live more independently.<sup>311</sup> By 30 months of age, the fetal surgery group was more likely to walk without crutches or other devices. More recently, when these children were followed up to 10 years of age, children in the prenatal surgery group walked independently more often than those in the postnatal surgery group. Those in the prenatal surgery group also had fewer shunt placements for hydrocephalus, fewer shunt replacements, and higher scores on a measure of motor skills.

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<sup>311</sup> [clinicaltrials.gov/ct2/show/NCT00060606](https://clinicaltrials.gov/ct2/show/NCT00060606)



Research funded by the NICHD continues to investigate co-occurring conditions for people affected by SB. One study showed that children with a severe form of SB had abnormal biochemical markers for cardiovascular disease, insulin resistance, and bone and mineral metabolism, suggesting potential interventions. In another study supported by the National Center for Medical Rehabilitation Research within NICHD, investigators retooled a toy car so that it could serve as a mobility device for children with SB.<sup>312</sup> In addition, NICHD plays a leadership role in the Gabriella Miller Kids First Pediatric Research Program, a NIH Common Fund program, whose mission is to better understand structural birth defects such as neural tube defects and a variety of childhood cancers. Researchers are also finding that certain drugs used during pregnancy may increase the risks of neural tube defects; a NICHD-funded study recently showed that children born to women on HIV therapy containing the drug dolutegravir since conception have a slightly higher risk of neural tube defects compared to children born to women on regimens of other antiretroviral drugs.

NINDS also funds research to understand the normal development of the neural tube, including studies to identify the mechanisms of action of folate and neurotransmitter activity during neural tube development. Other NINDS-funded projects target hydrocephalus, which often affects people with SB. In 2019, NINDS supported new projects through a funding opportunity to encourage research on the mechanisms involved in prenatal and pediatric hydrocephalus and to develop new research tools and therapies, including work to understand and prevent complications linked to the infection and failure of shunts, the most common treatment for hydrocephalus. In addition, NINDS supports research relevant to paralysis and neurogenic bladder in SB. Current NINDS-funded studies are pursuing multiple different strategies to restore bladder function, including a surgical approach to reestablish neural connectivity to the bladder and urethral sphincter, a method to promote regeneration of brainstem nerve fibers that control urination, electrical stimulation of spinal cord reflex pathways involved in bladder control, and a novel drug to induce “on-demand” bladder voiding.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports research investigators in contributing to better understanding of the urologic and kidney complications of SB and how to improve care for these complications, such as through retrospective studies leveraging the CDC-sponsored National Spina Bifida Patient Registry and research on strategies to improve adherence to treatment strategies in youth with SB. An NIDDK-supported research consortium, GenitoUrinary Development Molecular Anatomy Project (GUDMAP), also continues efforts to expand understanding of normal development of the human genitourinary system, which can inform future efforts to treat urologic problems in people with SB.

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<sup>312</sup> [programme.ias2019.org/Abstract/Abstract/4822](http://programme.ias2019.org/Abstract/Abstract/4822)

## STAR Act

The Committee includes no less than \$25,000,000, the same as the fiscal year 2020 enacted level, for continued implementation of sections of the Childhood Cancer Survivorship, Treatment, Access, and Research (STAR) Act to expand existing biorepositories for childhood cancer patients enrolled in NCI-sponsored clinical trials to collect and maintain relevant clinical, biological, and demographic information on children, adolescents, and young adults, with an emphasis on selected cancer subtypes (and their recurrences) for which current treatments are least effective. Funding provided this year will allow NCI to continue to conduct and support childhood cancer survivorship research as authorized in the STAR Act (House Report, p. 97).

### **Action Taken or To Be Taken**

The National Cancer Institute (NCI) received \$25 million in FY 2020 to support the Institute's STAR Act implementation efforts. As the STAR Act emphasizes, NCI continues to enhance and expand existing biorepositories, with a focus on cancer subtypes and their recurrences for which current treatments are least effective. NCI also continues to conduct and support childhood cancer survivorship research as encouraged by the STAR Act.

NCI's efforts to implement the biobanking provisions of the Act in FY 2020 aim to build upon investments the Institute made in FY 2019 to support immediate enhancements to the Children's Oncology Group (COG) Biorepository, including new projects to advance scientific opportunities and expand specimen collection for the most difficult to treat childhood and adolescent and young adult (AYA) cancers and subtypes.

NCI is supporting new biobanking projects through COG to focus attention to rare cancer subtypes that are currently underrepresented in NCI-supported biorepositories and tumor types with a high risk of treatment failure. To achieve these goals, NCI and COG plan to work with patient organizations to support rapid autopsy collection of tumor samples from children and AYAs who have died of their disease. Foundations and families within the pediatric brain tumor community have been leaders in such specimen collection programs, and NCI hopes to learn from their experiences to expand this model to other childhood cancers. NCI is incredibly grateful to these parents and caregivers, who amidst unimaginable grief and loss, contribute to future research to advance science and help other families.

NCI is supporting new projects to focus on specimens taken at the time of relapse, as well as collecting diagnostic samples for children and AYAs who have already submitted samples at relapse through NCI's Pediatric MATCH Trial.<sup>313</sup> This will enable more in-depth study of the molecular changes that occur between diagnosis and relapse. NCI is also funding a specimen collection and sequencing effort through NCI's Childhood Cancer Survivor Study for samples from study participants diagnosed with subsequent cancers, as well as participants experiencing severe or life-threatening chronic health conditions.

In addition to new biobanking projects, NCI continues to conduct and support childhood and AYA cancer survivorship research that advances additional goals of the STAR Act. This

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<sup>313</sup> [www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/pediatric-match](http://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/pediatric-match)

includes new projects to address topics such as reducing accelerated or premature aging and identifying barriers to follow-up care. NCI also made four new awards in FY 2020 to support applications submitted to the second receipt for NCI's funding opportunity "*Improving Outcomes for Pediatric, Adolescent and Young Adult Cancer Survivors*."<sup>314</sup> NCI aligned this funding opportunity with research areas emphasized in the STAR Act, and made three awards in FY 2019. In FY 2020 NCI is supporting the second-year costs of those three awards (outyear costs), as well as outyear costs for an additional nine survivorship research projects newly awarded in FY 2019 from the investigator-initiated grant pool.

Additionally, NCI entered into an Inter-Agency Agreement with the Agency for Healthcare Research and Quality (AHRQ) to support its work to implement Section 203 of the STAR Act, focused on identifying best practices in survivorship care, through AHRQ Evidence Reviews on Childhood Cancer Survivorship.

As these efforts aligned with the STAR Act move forward, NCI's Childhood Cancer Data Initiative (CCDI) is also underway. CCDI aims to optimize the important investments NCI has already made in pediatric cancer studies and the data those studies are generating. This includes survivorship research projects and biospecimen collection supported through the STAR Act. Connecting these and other data sets, such as cancer registry data, another priority area within the STAR Act, will allow NCI to maximize every opportunity to understand and treat childhood and AYA cancers better (*See the CCDI Significant Item response for additional details*).

NCI is also identifying research opportunities that span both the STAR Act and CCDI goals. For example, CCDI will support sequencing for specimens collected through the STAR Act projects described above, focused on subsequent cancers and on diagnostic specimens collected through the Pediatric MATCH trial. These sequencing efforts supported through CCDI are in addition to the STAR Act investments described above. NCI is also continuing our commitment to childhood cancer biobanking by initiating a new five-year funding grant to support the COG Biorepository, subject to available appropriations. This award is in addition to NCI's STAR Act investments.

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<sup>314</sup> [grants.nih.gov/grants/guide/rfa-files/RFA-ca-19-033.html](https://grants.nih.gov/grants/guide/rfa-files/RFA-ca-19-033.html)

## **Suicide Prevention**

The Committee continues to be alarmed with the growing rates of suicide across the country, with the CDC reporting a 30 percent increase since 1999. Suicide is currently the tenth leading cause of death for all ages and the second leading cause of death for young people aged 10 to 34. To address and combat this crisis, the Committee encourages NIMH to prioritize its suicide screening and prevention research efforts, with special emphasis on producing models that are interpretable, scalable, and practical for clinical implementation, including healthcare, education, and criminal justice systems that serve populations at risk. In addition, the Committee believes increased collaboration between NIMH and other Institutes holds immense value. The Committee strongly encourages NIMH to partner with NIDA and NIAAA to examine the multifaceted relationship between suicide and substance use disorder (SUD), including opioid abuse. Enhanced research into these relationships will provide critical knowledge regarding common risk factors, and preventive and intervention efforts that reduce morbidity associated with suicide risk. The Committee directs NIMH to provide an update on these efforts in the fiscal year 2022 Congressional Justification (House Report, p. 123).

### **Action Taken or To Be Taken**

Suicide prevention research is a top priority for the National Institute of Mental Health (NIMH). The national suicide rate in the United States has continued to rise over the past two decades; in 2018 alone, more than 48,000 Americans died by suicide.<sup>315</sup> NIMH is committed to reducing the national suicide rate and has focused on areas of research that could swiftly make an impact, such as improving and implementing risk detection and screening methods, while not losing sight of longer term prevention strategies. To advance its suicide prevention research agenda, NIMH partners with the National Action Alliance for Suicide Prevention (NAASP), whose goal is to reduce the suicide rate by 20 percent between 2015 and 2025.<sup>316</sup>

NIMH-funded research has shown that most suicide decedents in the U.S. have accessed healthcare services in the 12 months preceding their death, indicating that healthcare systems can play a vital role in identifying individuals at risk and preventing suicide attempts.<sup>317</sup> NIMH research has focused on emergency departments (EDs) as a critical entry point, demonstrating that brief screening tools can improve providers' ability to identify individuals at risk for suicide and refer them to treatment.<sup>318</sup> Further, NIMH-supported researchers have shown that the combination of universal screening for all ED patients and Safety Planning and follow-up contact with individuals identified as at risk for suicide reduced suicide attempts in the following year by 30 percent.<sup>319</sup> NIMH recently announced a funding opportunity that will enable transdisciplinary teams to establish Suicide Prevention Research Centers; these Centers will be dedicated to the rapid development of scalable approaches to identify high-risk individuals and improve continuity of care across healthcare settings.<sup>320</sup>

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<sup>315</sup> [www.cdc.gov/nchs/data/databriefs/db362-h.pdf](http://www.cdc.gov/nchs/data/databriefs/db362-h.pdf)

<sup>316</sup> [theactionalliance.org/news/national-action-alliance-suicide-prevention-announces-goal-reduce-suicide-20-percent-2025](http://theactionalliance.org/news/national-action-alliance-suicide-prevention-announces-goal-reduce-suicide-20-percent-2025)

<sup>317</sup> [pubmed.ncbi.nlm.nih.gov/24567199/](http://pubmed.ncbi.nlm.nih.gov/24567199/)

<sup>318</sup> [pubmed.ncbi.nlm.nih.gov/23027429/](http://pubmed.ncbi.nlm.nih.gov/23027429/)

<sup>319</sup> [jamanetwork.com/journals/jamapsychiatry/fullarticle/2623157](http://jamanetwork.com/journals/jamapsychiatry/fullarticle/2623157)

<sup>320</sup> [grants.nih.gov/grants/guide/pa-files/PAR-20-286.html](http://grants.nih.gov/grants/guide/pa-files/PAR-20-286.html)

Detecting suicide risk in educational settings is another critical opportunity for suicide prevention, as schools are often a primary source of mental health care for youth and young adults. NIMH is supporting a number of school-based studies in students ranging from adolescents to college-age.<sup>321,322,323,324</sup> In the Electronic Bridge to Mental Health study, researchers have developed, pilot tested, and refined a theoretically-driven intervention which identifies college students at elevated risk for suicide and connects them to mental health services.<sup>7</sup> If the intervention is shown to be effective in this large-scale trial, it could be disseminated broadly to address suicide risk and associated mental illnesses among young adults nationwide.

NIMH is also supporting efforts to reduce suicide among individuals, including youth, in the criminal justice system who are at increased risk for suicide.<sup>325,326,327,328</sup> For example, NIMH-funded researchers are developing and implementing e-Connect, a training program for probation officers that uses mobile technology to help them identify suicidal behaviors and make rapid, targeted referrals to behavioral health services with the hope of reducing suicide behaviors.<sup>13</sup>

In addition to collaborations with NAASP, NIMH continues to work with federal and other private partners to advance suicide prevention efforts. In 2019, NIMH and its partners, including the National Institute on Drug Abuse (NIDA) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA), gathered information on current clinical experience in the use of telehealth for suicide prevention and overdose risk reduction and prevention practices in EDs.<sup>329</sup> Using this information, NIMH developed a funding opportunity to support efforts in EDs to identify and implement telehealth-supplied suicide prevention practices.<sup>330</sup> As part of the NIH Helping End Addiction Long-term (HEAL) Initiative<sup>SM</sup>, NIMH is partnering with NIDA and NIAAA to support research on the treatment and management of common co-occurring conditions and suicide risk in people affected by the opioid crisis.<sup>331</sup> NIMH is also working with NIDA to address substance use and/or mental health among American Indian and Alaska Native communities, which have been significantly impacted by the opioid crisis and are also at high risk for suicide.<sup>332</sup> NIMH is also supporting four HEAL projects aimed at adapting the Collaborative Care model, a specific service delivery model for treating mental and behavioral health conditions in primary care settings, to meet the needs of individuals with opioid use disorders and co-occurring mental illnesses, including those who are at risk for suicide.<sup>333</sup>

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<sup>321</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9487307](https://projectreporter.nih.gov/project_info_description.cfm?aid=9487307)  
<sup>322</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=10005477](https://projectreporter.nih.gov/project_info_description.cfm?aid=10005477)  
<sup>323</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9996789](https://projectreporter.nih.gov/project_info_description.cfm?aid=9996789)  
<sup>324</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9874234](https://projectreporter.nih.gov/project_info_description.cfm?aid=9874234)  
<sup>325</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9817490](https://projectreporter.nih.gov/project_info_description.cfm?aid=9817490)  
<sup>326</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9923764](https://projectreporter.nih.gov/project_info_description.cfm?aid=9923764)  
<sup>327</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9747363](https://projectreporter.nih.gov/project_info_description.cfm?aid=9747363)  
<sup>328</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=10123624](https://projectreporter.nih.gov/project_info_description.cfm?aid=10123624)  
<sup>329</sup> [grants.nih.gov/grants/guide/notice-files/NOT-MH-19-030.html](https://grants.nih.gov/grants/guide/notice-files/NOT-MH-19-030.html)  
<sup>330</sup> [grants.nih.gov/grants/guide/rfa-files/RFA-MH-20-226.html](https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-20-226.html)  
<sup>331</sup> [grants.nih.gov/grants/guide/notice-files/NOT-MH-20-025.html](https://grants.nih.gov/grants/guide/notice-files/NOT-MH-20-025.html)  
<sup>332</sup> [grants.nih.gov/grants/guide/notice-files/NOT-DA-20-033.html](https://grants.nih.gov/grants/guide/notice-files/NOT-DA-20-033.html)  
<sup>333</sup> [grants.nih.gov/grants/guide/rfa-files/RFA-MH-19-525.html](https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-19-525.html)

## **Surveillance, Epidemiology, and End Results (SEER) Program Registry**

The SEER Program is an authoritative source of information on cancer incidence and survival in the U.S. SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 34.6 percent of the U.S. population. The Committee encourages NCI to continue to advance efforts to modernize the SEER Registry and better capture key data points, such as metastatic recurrence and cancer migration. The Committee requests an update on plans to cover more of the U.S. population in the fiscal year 2022 Congressional Justification (House Report, p. 97).

### **Action Taken or To Be Taken**

The National Cancer Institute Surveillance, Epidemiology and End Results (SEER) Program sets national benchmarks for incidence and survival rates and is the primary source of reports on trends in cancer death rates.<sup>334</sup> SEER is the only population-based source of long-term incidence and survival data in the U.S. The objective of this program is to continue the collection of high-quality cancer surveillance data while addressing the challenges of a rapidly evolving cancer care environment. Several key components of the SEER Program are being expanded, including increasing coverage of the U.S. population and collecting new data on patients' treatments, genomics, and cancer recurrence.

Among the enhancements to the SEER program is the expansion of the size and diversity of the population it covers. SEER currently covers 34.6 percent of the U.S. population, up from 28 percent in 2018 and moving closer to the goal of expanding coverage to 50 percent of the U.S. population in the future. This expansion was implemented by adding U.S. cancer registries that include more underserved and ethnic and racial minorities.<sup>335</sup> This broader coverage includes 30 percent of African Americans, 44 percent of Hispanics, 49.3 percent of American Indians and Alaska Natives, 57.5 percent of Asians, 68.5 percent of Hawaiian/Pacific Islanders, 66.9 percent of Chinese, 64.9 percent of Filipinos, and 74.4 percent of Japanese, across 17 states. With this expansion, SEER is capturing data on cancer that more fully represents the U.S. population. This will allow researchers to perform studies to more completely understand how cancer affects different patient subgroups and inform the development of interventions intended to address cancer disparities.

SEER continues to expand by capturing new types of data in the program. A series of pilot studies have been launched to better understand the barriers and challenges to collecting these new types of data on treatments, genomic composition of patients' tumors, and cancer recurrence, including metastatic disease (the spread of cancer from its site of origin to another part of the body).

Capturing disease recurrence is a challenging aspect of cancer surveillance. Cancer is a chronic disease that requires capturing longitudinal information, such as recurrence and metastasis, subsequent courses of therapy, and other health conditions that can impact the therapy a patient receives or can result from therapy. With nearly 17 million cancer survivors in the U.S., the lack

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<sup>334</sup> [seer.cancer.gov/](https://seer.cancer.gov/)

<sup>335</sup> [seer.cancer.gov/registries/](https://seer.cancer.gov/registries/)

of recurrence information across the registry system is limiting. NCI is taking deliberate steps to better capture these critical data. Ongoing efforts to enhance SEER's capabilities include several pilot initiatives that aim to expand the types and quality of data SEER is able to collect and make these data available more quickly. These efforts include addressing the challenges of documenting cancer recurrence and/or metastatic disease. NCI is supporting a variety of programs and grants with a specific focus in this area.

For example, the SEER Program now collects pharmacy claims data for oral chemotherapy for all registries from 2003-present and has successfully created linkages with Genomic Health, Inc. In addition, a collaboration with the Department of Energy focuses on computational tool development that will allow SEER to collect new data elements (e.g., biomarkers, recurrences), as well as those it has traditionally captured (e.g., cancer type and grade) from patient medical records. NCI is also supporting several projects to investigate approaches to identifying recurrence using available data such as treatment claims. For example, a project at the Fred Hutchinson Cancer Research Center entitled "RECAPSE: **R**ecurrence from **C**laims **A**nd **P**ros (patient reported outcomes) for SEER Enhancement" aims to develop a scalable approach for population-based ascertainment of cancer recurrence with a specific focus on breast cancer.<sup>336</sup> In addition to the RECAPSE project, NCI is supporting other projects focused on developing tools identifying cancer related treatment patterns using claims data.

Another enhancement to SEER is the development of a "virtual biorepository." The aim of this repository is to provide information on tumor samples stored at institutions across the country. This will allow investigators to search for samples from patients with certain demographic or clinical characteristics or certain outcomes, and then request those samples, including related clinical data, for use in their research studies. Some SEER registries are participating in a pilot study of the virtual biorepository, focusing on specific survivor groups for breast and pancreatic cancer.

With respect to the current pandemic, NCI is also exploring opportunities to collect data (e.g. telemedicine, treatment details) that can increase understanding of the impact of the COVID-19 pandemic on cancer patients and their long-term care.

The enhancement of the SEER program is continuing, with a goal to expand coverage to 50 percent of the U.S. population in the coming years. NCI plans to award new registries in early 2021 and continue to add new types of data, such as COVID-19 data to inform cancer patient care. The pilot studies described above will not only identify where the barriers and challenges might be, but also inform the necessary steps to make new resources and tools an integral part of SEER. This will open up new avenues of research opportunities and greatly expand the value of this unique program.

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<sup>336</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=10137355&icde](https://projectreporter.nih.gov/project_info_description.cfm?aid=10137355&icde)

## Swine Research

The agreement is aware of the value of some large animal models for use in expediting the translation of basic research to find cures and new therapeutics for many human diseases. Pigs are an appropriate animal model for human health and disease research in some areas given the similarities of their anatomy and physiology to humans. Additionally, their genomic structure is three times closer to that of humans than is the mouse genome. However, pigs have complex psychological needs and, when used in biomedical research, should be housed and cared for in accordance with those needs. Therefore, the agreement strongly encourages NIH to study elevating the pig to model organism status. In addition, NIH should identify how Institutes can evaluate the appropriateness of swine as a model for disease or system specific investigation. The agreement directs OD to include an update on the progress of potentially elevating the pig to model organism status in the fiscal year 2022 Congressional Justification (Joint Explanatory Statement, p. 69).

### **Action Taken or to be Taken**

The National Institutes of Health (NIH) has long acknowledged and invested in the value of the pig as a model organism. The NIH Office of Research Infrastructure Programs within the Office of the NIH Director (ORIP/OD), in partnership with the National Institute of Allergy and Infectious Diseases (NIAID) and the National Heart, Lung, and Blood Institute (NHLBI), has supported the National Swine Resource and Research Center (NSRRC<sup>337</sup>) at the University of Missouri since its creation in 2003. The NSRRC serves researchers across the Nation by assisting swine-based research across multiple disciplines, providing valuable services to the research community, and creating new genetically engineered swine models in collaboration with investigators. The NSRRC has facilities and laboratories with advanced biosecurity to ensure animals remain pathogen-free for 14 specific pathogens. In addition, the NSRRC serves as a central repository by importing, maintaining, preserving, and distributing swine models and wildtype animals, cells, tissues, and organs to investigators throughout the country while ensuring the highest possible level of animal care and model quality.

The availability of the pig genome, which NIH supported efforts to sequence, and the identification of many putative disease-causing variants have extended the potential applications of the pig as a model for biomedical studies. Recent technological advances in genetic engineering linked to the swine genome enhance the utility of swine as models of human genetic diseases. The ability to generate transgenics and knockouts in combination with somatic nuclear transfer procedures has led to the creation of several pig models for specific human diseases. The NSRRC was the first to use genome editing technologies to knock out a gene in a pig and to manipulate cultured embryos and pig zygotes (fertilized eggs; i.e., fused egg plus sperm) to produce genetically engineered pigs. Scientists working at the NSRRC were also the first to offer gene targeting, transgenesis, and gene editing services to NIH supported researchers who conduct studies with pig models. Examples of models created include immunocompromised/humanized pigs;  $\alpha$ Gal knockout pigs for xenotransplantation of pig kidneys into nonhuman primates; models of mammary tumors, congenital muscular dystrophy,

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<sup>337</sup> nsrrc.missouri.edu/



adenomatous polyposis coli, phenylketonuria, and Fanconi anemia group A; and the oncopig for cancer research.

In addition to the resources and services provided by the NSRRC, several NIH Institutes, Centers, and Offices support the development of pig models for use in basic and translational research to improve human health and develop preventatives and therapies for human diseases. ORIP/OD maintains research resources that develop humanized severe combined immunodeficient pigs as a valuable model for the study of interactions between human tumor cells and human immune cells and for use in preclinical testing of stem cell-based therapies. Scientific meetings such as the Swine in Biomedical Research Conferences are supported by ORIP/OD to raise awareness within the biomedical community of advances made in pig models and to increase the interactions between clinical and non-clinical scientists for the promotion of pig models in translational research. ORIP/OD also utilizes its Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs to support the participation of the small business community in creating pig models that can be commercialized. For example, ORIP/OD has provided support for feasibility studies (SBIR-Phase I) for the creation of a swine model of chronic obstructive pulmonary disease and of human nonalcoholic steatohepatitis, an advanced form of nonalcoholic fatty liver disease.

NIAID supports research using pig models to study infection, xenotransplantation, and radiation-induced injuries. NIAID-funded researchers use swine models to study multiple pathogens, including *Pseudomonas aeruginosa* and *Candida auris*. The NIAID Centers of Excellence for Influenza Research and Surveillance<sup>338</sup> also use pig models for research on influenza pathogenesis, immunity, and transmission to inform the development of improved vaccine strategies and to enhance pandemic preparedness. NIAID also supports xenotransplantation research to explore the possibility that pig organs may help alleviate the severe shortage of human organs for transplantation. In fiscal year 2020, NIAID renewed the Immunobiology of Xenotransplantation Cooperative Research Program, which aims to achieve long-term survival in pig-to-nonhuman primate xenotransplantation. Additionally, NIAID has supported the development of swine models of radiation-induced injuries to examine efficacy of radiation nuclear medical countermeasures.

NHLBI supports the development and study of pig models for heart and lung diseases through several programs. For example, the NHLBI Progenitor Cell Translational Consortium, which was formed to advance research on cell-based therapies, is supporting projects to test human adult-derived stem cells in pig models of heart failure and fibrotic lung disease. Through the NIH Regenerative Medicine Innovation Project, established by the 21<sup>st</sup> Century Cures Act, NHLBI also supports a study investigating adult stem cells combined with extracellular factors to stimulate heart regeneration in a pig model simulating a heart attack. Additionally, NHLBI supports several programs to develop and study transgenic pigs carrying the gene mutations that cause cystic fibrosis (CF) in humans. Through the Common Fund Somatic Cell Genome Editing Program, NHLBI also supports projects that are using pig models to test novel approaches to repair the CF gene.

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<sup>338</sup> [www.niaid.nih.gov/research/influenza-research-surveillance](http://www.niaid.nih.gov/research/influenza-research-surveillance)

## Temporomandibular Disorders (TMD)

The agreement directs NIH to include updates on the following research, projects, and programs in the fiscal year 2022 Congressional Justification: gastric cancer; psycho-social distress in cancer research; the Office of Cancer Survivorship; progress in treating rare cancers; the Surveillance, Epidemiology, and End Results [SEER] Registry; Temporomandibular Disorders; diabetes, Rapid Acceleration of Diagnostics; 7q1 1.23 Duplication Syndrome; and Hereditary Spastic Paraparesis 49 (TECPR2). (Joint Explanatory Statement, p. 45)

### **Action Taken or to be Taken**

The National Institute of Dental and Craniofacial Research (NIDCR) continues to collaborate with several National Institutes of Health (NIH) Institutes, Centers, and Offices (ICOs) and other federal agencies on research into temporomandibular disorders (TMDs). NIDCR works with the NIH Pain Consortium,<sup>339</sup> the NIH Interagency Pain Research Coordinating Committee,<sup>340</sup> the NIH Common Fund's Acute to Chronic Pain Signatures program,<sup>341</sup> the U.S. Food and Drug Administration Temporomandibular Joint (TMJ) Coordinated Registry Network (CRN)<sup>342</sup> (formerly the TMJ Patient-Led RoundTable), and the NIH Blueprint for Neuroscience Research.<sup>343</sup> Notably, the Blueprint collaboration has resulted in several funding opportunity announcements (FOAs) to better understand pain, including orofacial pain,<sup>344</sup> and a soon-to-be published NIH perspective paper in *Trends in Neuroscience*. In addition, in May 2020, NIDCR announced an initiative to study gene and protein expression in thousands of individual cells simultaneously to better understand the molecular mechanisms underpinning TMD pain.<sup>345</sup>

NIDCR is actively participating in the NIH Helping to End Addiction Long-term<sup>SM</sup> (HEAL) Initiative. Several HEAL-funded projects to enhance pain management are focused on TMD – one is investigating the role of neuronal proteins called ion channels in TMD pain, with the hope that these proteins could be targeted as a non-opioid pain treatment.<sup>346</sup> In another, researchers are validating a predictive biomarker to identify individuals at risk of developing severe and persistent pain, in order to promote early intervention that could halt the transition to chronic pain.<sup>347</sup> Further, in September 2020, NIDCR helped plan the trans-NIH HEAL workshop titled “Quantitative Evaluation of Myofascial Tissues: Potential Impact for Musculoskeletal Pain Research,” which brought together a multidisciplinary group of researchers and clinicians to develop strategies to improve diagnostic imaging of soft tissues involved in musculoskeletal pain, including TMDs.<sup>348</sup> Lastly, NIDCR is participating in trans-NIH FOAs soliciting research

<sup>339</sup> [www.painconsortium.nih.gov/](http://www.painconsortium.nih.gov/)

<sup>340</sup> [www.iprec.nih.gov/](http://www.iprec.nih.gov/)

<sup>341</sup> [www.commonfund.nih.gov/pain](http://www.commonfund.nih.gov/pain)

<sup>342</sup> [www.mdepinet.net/tmj](http://www.mdepinet.net/tmj)

<sup>343</sup> [www.neuroscienceblueprint.nih.gov/](http://www.neuroscienceblueprint.nih.gov/)

<sup>344</sup> [www.grants.nih.gov/grants/guide/rfa-files/RFA-AT-21-003.html](http://www.grants.nih.gov/grants/guide/rfa-files/RFA-AT-21-003.html)

<sup>345</sup> [www.nidcr.nih.gov/grants-funding/funding-priorities/future-research-initiatives/deconstructing-tmjd-classifiers-single-cell-level](http://www.nidcr.nih.gov/grants-funding/funding-priorities/future-research-initiatives/deconstructing-tmjd-classifiers-single-cell-level)

<sup>346</sup> [www.projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9998160&icde=46779633&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=](http://www.projectreporter.nih.gov/project_info_description.cfm?aid=9998160&icde=46779633&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=)

<sup>347</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9828948&icde=50220962&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=](http://projectreporter.nih.gov/project_info_description.cfm?aid=9828948&icde=50220962&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=)

<sup>348</sup> [www.nccih.nih.gov/news/events/nih-heal-initiative-workshop-on-myofascial-pain](http://www.nccih.nih.gov/news/events/nih-heal-initiative-workshop-on-myofascial-pain)

relevant to TMD, including two on chronic overlapping pain conditions<sup>349</sup> and two on a broad array of pain research, including the transition from acute to chronic pain.<sup>350</sup>

As the Committee is aware, the NAM report *Temporomandibular Disorders: Priorities for Research and Care*<sup>351</sup> was released in March 2020 and included 11 recommendations to improve TMD research and care, four of which are research-focused and align with NIH's mission. NIDCR is using the report to identify a roadmap of research and training priorities within NIH's TMD portfolio and recommend plans to implement them. To develop this roadmap, in July 2020, NIDCR launched a TMD Multi-Council Working Group made up of members of the advisory councils of NIDCR and seven NIH ICOs that support TMD-related research. Experts from those seven ICOs are participating to ensure that the roadmap will be developed with trans-NIH engagement and input so that the future of TMD research and training will be a collaborative effort across ICOs. The working group will report their recommendations to NIDCR's advisory council and the advisory councils of other select ICOs in 2021.

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<sup>349</sup> [www.grants.nih.gov/grants/guide/pa-files/PA-18-937.html](http://www.grants.nih.gov/grants/guide/pa-files/PA-18-937.html); [www.grants.nih.gov/grants/guide/pa-files/PA-18-939.html](http://www.grants.nih.gov/grants/guide/pa-files/PA-18-939.html)

<sup>350</sup> [www.grants.nih.gov/grants/guide/pa-files/PA-18-141.html](http://www.grants.nih.gov/grants/guide/pa-files/PA-18-141.html); [www.grants.nih.gov/grants/guide/pa-files/PA-18-159.html](http://www.grants.nih.gov/grants/guide/pa-files/PA-18-159.html)

<sup>351</sup> [www.nap.edu/catalog/25652/temporomandibular-disorders-priorities-for-research-and-care](http://www.nap.edu/catalog/25652/temporomandibular-disorders-priorities-for-research-and-care)

## **Thalassemia (NIA)**

Thanks to significant advances in medical science, thalassemia patients and others dealing with chronic diseases are now living well into adulthood, some even into their 60s. While this is a tremendous victory for research, it has opened new questions. Among these are female and male reproductive issues, the impact of non-disease related medicines, the relationship to diseases of aging such as Alzheimer's disease and other dementias, Parkinson's, arthritis, osteoporosis, and more. The Committee requests that NIA review these issues and report back on the steps that will be taken to address them in the fiscal year 2022 Congressional Justification (House Report, p. 117).

### **Action Taken or To Be Taken**

Thalassemia is an inherited disease in which the body produces an inadequate amount or abnormal form of hemoglobin, the protein within red blood cells that carries oxygen. Several types of thalassemia exist, with symptoms—including weakness, fatigue, facial deformities, jaundice, and pain—ranging from mild to debilitating. Without effective medical care or treatment, moderate to severe thalassemia can cause death at an early age. Advances in medicine have made it possible for people with even severe disease to live nearly normal lifespans. However, as people with thalassemia syndromes live longer, complications of the disease and its treatment, combined with aging-related physical changes, may result in significant adverse health outcomes.

Research on understanding the long-term effects of thalassemia and its comorbidities, as well as development of improved treatments, is supported across the NIH. For example, for many people with thalassemia, bone marrow transplantation (BMT) is curative. However, BMT can be associated with serious long-term health issues, including significant acceleration of the appearance of the signs and symptoms of biological aging in recipients. The National Institute on Aging (NIA) currently supports identification and characterization of factors that increase resilience to physical stressors, including BMT. In addition, the National Heart, Lung, and Blood Institute (NHLBI) supports research in understanding the mechanisms underlying both harmful and beneficial effects of transfusion in patients with blood disease. Finally, NHLBI supports the development of improved treatments for thalassemia and other blood diseases, including cutting-edge gene based therapies, which may have fewer short and long-term side effects than BMT.

Among individuals with thalassemia who do not undergo BMT, repeated blood transfusions—often a mainstay of treatment—can cause excessive iron to build up in the body, damaging multiple organs and potentially accelerating the appearance of age-related diseases. NIA supports research exploring the effects of iron overload on the brain, including potential links with Alzheimer's disease and other dementias. Also, the National Institute of General Medical Sciences (NIGMS) supports an ongoing project on the role of iron and copper in Parkinson's disease pathogenesis. Meanwhile, both NHLBI and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) support research to develop improved iron chelation, or removal, that includes therapies as well as interventions to limit iron absorption.

NIDDK and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) support research on fertility preservation in the context of sickle cell disease, which may also inform similar research being conducted in thalassemia. NICHD recently issued a research solicitation on fertility and fertility preservation for patients with conditions that once precluded reproduction, specifically including thalassemia.

Basic and translational research for thalassemia will be guided by a recent trans-NIH workshop to discuss new and improved tools for identification of disease pathways in a range of blood disorders. Both NHLBI and NIA participate in the NIDDK-led Stimulating Hematology Investigation: New Endeavors (SHINE) initiative to encourage research in the area of nonmalignant blood disorders. Finally, understanding the complexity of thalassemia and its contribution to other comorbidities is a focus of the Trans-NIH Collaborative Network on Multimorbidities, with a current emphasis on improved measures and development of interventions for thalassemia.

## Thalassemia (NHLBI)

Recent studies have shown that the length of time between when blood is donated and transfused does not impact outcomes for patients in need of an emergency blood transfusion. However, these studies do not determine the impact on chronically transfused patients, such as those with thalassemia, in which an administration of older red cells may exacerbate iron loading and contribute to worse outcomes. The Committee urges NHLBI to review the scientific literature on this issue and provide an update in the fiscal year 2022 Congressional Justification on the best way to address this public health issue (House Report, p. 101).

### **Action Taken or To Be Taken**

Individuals with inherited blood disorders such as thalassemia may need chronic red blood cell (RBC) transfusions throughout life. However, because RBCs contain iron bound to the hemoglobin protein, which carries oxygen, chronic transfusions can also lead to toxic levels of iron or iron overload. Iron accumulation can lead to heart problems, liver disease, diabetes, joint damage and pain, and other adverse health conditions. Healthy RBCs contain substances—including antioxidants—that help limit iron toxicity; likewise, blood plasma (the liquid part of blood) contains molecules that can capture and regulate free circulating iron. However, refrigerated storage of RBCs leads to a series of biochemical changes, referred to as the storage lesion, that eventually causes damage to the red blood cells and a breakdown of their antioxidant systems. Moreover, in patients who receive chronic RBC transfusions, the molecules in blood plasma that regulate iron can become overwhelmed.

Current guidelines for using RBC transfusion to treat thalassemia include using drugs that trap iron and help the body excrete it, called iron chelation therapy. Also recommended are monthly laboratory tests to measure iron in blood, as well as annual magnetic resonance imaging (MRI) scans to check for potential iron overload in organs, and an annual electrocardiogram to monitor heart function. The Thalassemia Longitudinal Cohort, which was funded in part by the National Heart, Lung, and Blood Institute (NHLBI), followed more than 325 patients with thalassemia for 10 years, and in 2012 reported that these practices have helped reduce iron overload.<sup>352</sup>

Other ongoing NHLBI-funded studies aim to better understand the aging of stored red blood cells to evaluate how to reduce the storage lesion. Current guidelines from the American Association of Blood Banks advise that RBCs may be stored under refrigeration for a maximum of 42 days. Yet recent studies suggest the metabolic age of red blood cells—in other words, how healthy they are—is not necessarily the same as their chronological age. The RBC-Omics study, which was developed under the NHLBI Recipient Epidemiology and Donor Evaluation Study (REDS), is studying blood samples from 13,400 healthy individuals to examine donor characteristics (e.g., genetics, diet) associated with metabolic aging and breakdown of stored RBCs. The study is also examining aspects of blood processing that could affect RBC metabolic changes during storage. For example, recent findings show that additives used in the RBC storage bag can affect RBC metabolism.<sup>353</sup> RBC-Omics continues to investigate how genetic or

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<sup>352</sup> [pubmed.ncbi.nlm.nih.gov/22279056/](https://pubmed.ncbi.nlm.nih.gov/22279056/)

<sup>353</sup> [pubmed.ncbi.nlm.nih.gov/30353560/](https://pubmed.ncbi.nlm.nih.gov/30353560/)

biological variations in donors, including iron levels, affect the metabolic age of stored RBCs, as well as transfusion outcomes in recipients.<sup>354</sup>

Other research focuses on mitigating the effects of storage lesion. For example, one NHLBI-funded team has developed a cocktail of four chemicals—phosphate/inosine/pyruvate/adenine (PIPA)—to “rejuvenate” stored RBCs by providing them with a boost of antioxidants. After showing that PIPA can improve the function of RBCs in a lab dish, the researchers compared blood transfusion using RBCs treated with PIPA versus use of standard RBC products in patients with sickle cell anemia (SCA). After transfusion, blood from patients with SCA who received the rejuvenated RBCs had markers for higher antioxidant and energy metabolism than blood from patients who received standard exchange transfusions.<sup>355</sup>

In other NHLBI-supported studies, researchers are investigating methods to improve chelation therapy, especially to reduce adverse side effects. For example, deferoxamine (DFO) can cause hearing loss, impaired growth and bone development, and kidney toxicity. To speed the clearance of DFO and iron from the liver, one research team attached DFO to nanoparticles made in part from a commonly used food preservative. In rodent models, this DFO-nanoparticle combination was a highly effective iron chelator and also significantly reduced DFO’s kidney toxicity.<sup>356</sup> These studies illustrate NHLBI’s ongoing commitment to address challenges associated with blood transfusion and chelation therapy in thalassemia in order to improve patients’ lives.

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<sup>354</sup> [pubmed.ncbi.nlm.nih.gov/31184580/](https://pubmed.ncbi.nlm.nih.gov/31184580/)

<sup>355</sup> [pubmed.ncbi.nlm.nih.gov/31385330/](https://pubmed.ncbi.nlm.nih.gov/31385330/)

<sup>356</sup> [pubmed.ncbi.nlm.nih.gov/31723130/](https://pubmed.ncbi.nlm.nih.gov/31723130/)

## Traumatic Brain Injury

The Committee understands that research on regenerative medicine and neuroplasticity, including the use of adult stem cells and neuroplasticity, may play an important role in developing treatments and identifying therapeutic targets for neuroprotection pre/post TBI. The Committee urges NINDS to work with all relevant Institutes and Centers, including NIA, to support a robust and coordinated portfolio of TBI research that explores all promising avenues to facilitate functional repair of damaged circuitry in TBI. Such analysis should include research on regenerative medicine and neuroplasticity, inclusive to preventative approaches in reducing risk or to eliminate vulnerabilities from a TBI. A potential mitigation approach is to develop interventions that protect from the delayed effects of TBI and associated pathology before they occur. The Committee directs NINDS to provide an update regarding these specific areas of TBI research in the fiscal year 2022 Congressional Justification (House Report, p. 106).

### **Action taken or to be taken**

Traumatic brain injury (TBI) is a multi-faceted problem that affects people of all ages. TBI may be life threatening, severely disabling, “mild” but with long term effects, or produce transient symptoms with full recovery, and the consequences may be immediately apparent, or not evident until many years after the event. The National Institute of Neurological Disorders and Stroke (NINDS) leads a broad spectrum of NIH research on TBI, which currently includes more than 300 active projects. As appropriate to the complexity of challenges that TBI presents, more than a dozen NIH Institutes and Centers bring their expertise to bear on TBI as appropriate to their missions. The National Institute of Aging, for example, attends to the special problems of TBI in the elderly and also works with NINDS on the intersection of TBI and dementia. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) focuses on TBI in infants and children. NICHD’s National Center for Medical Rehabilitation Research coordinates NIH rehabilitation research to improve recovery after TBI. NIH also collaborates extensively with the Department of Defense and other federal agencies on TBI research.

TBI sets in motion a cascade of biological processes involving energy metabolism, the brain’s blood vessels, the immune system, and supporting cells in the brain, as well as nerve cells. These processes contribute, variously, to progressive damage following the injury and to recovery, which occurs to a highly variable extent. Research on neuroplasticity has demonstrated generation of new nerve cells from resident stem cells in the brain and their movement to the region of injury, as well as rewiring of brain circuits and formation of new synapses. All aspects of plasticity and recovery are the focus of active research in TBI. NIH research is developing interventions based on neuroplasticity, either by encouraging the brain’s own adaptive reactions or building on advances in stem cell biology and regenerative medicine more generally. These changes can contribute to recovery of function, but also to problems, including the development of post-traumatic epilepsy. Ongoing research is developing strategies, mostly in laboratory animals, using small molecule drugs, gene transfer, or biologics to stimulate neurogenesis, encourage glial cells (the supporting cells of the brain) to repair damage, transplantation strategies employing various types of stem cells, and engineered biomaterials to enhance regeneration. Rehabilitation interventions, including exercise protocols, are also designed to encourage adaptive plasticity.



NIH is also exploring many other avenues of research to better understand, mitigate, or prevent the consequences of TBI. Research ranges from the laboratory to clinical trials and employs a broad array of approaches, including molecular biology, genetics guided precision medicine, electrical stimulation, brain imaging, hyperbaric oxygen therapy, artificial intelligence and machine learning, among many others. In addition to exploring the underlying biology and pathophysiology of damage and recovery and developing interventions, NIH is also developing better imaging diagnostics and fluid-based biomarkers and is advancing our understanding of how trauma may contribute to problems in later life, including chronic traumatic encephalopathy (CTE) and dementia. All of these topics of research are essential to advancing prevention of the consequences of TBI.

## Women and Lung Cancer

The Committee notes that lung cancer has a disparate impact on women, particularly younger women who have never smoked. Additional research strategies are needed to explore the differences in women with respect to lung cancer risk factors, incidence, and histology. The Committee urges NCI to accelerate research into treatments and implementation of lung cancer preventive services for women. The Committee requests an update on these activities in fiscal year 2022 Congressional Justification (House Report, p. 97-98).

### **Action Taken or To Be Taken**

Women's health research is an important part of the National Cancer Institute's (NCI) portfolio, including gender-related differences in lung cancer risk factors, incidence, and mortality. In July 2020, the U.S. Preventive Services Task Force (USPSTF), an independent body that offers clinical guidance about preventive health care, published a draft recommendation that would double the number of people eligible for annual CT scans to screen for lung cancer. The task force reviewed several randomized clinical trials and cohort studies, including results from the NCI-supported National Lung Screening Trial (NLST) and Cancer Intervention and Surveillance Modeling Network (CISNET), modeling studies as well as a large European trial. The recommendation lowers the age of starting annual exams from 55 to 50 years, and is expected to lead to higher screening rates among women, who tend to smoke fewer cigarettes than men, as well as Black patients, who are at higher risk of lung cancer.<sup>357</sup>

Research has shown that approximately 20 percent of women who have never smoked develop lung cancer compared with about 9 percent of nonsmoking men. In 2019, NCI began the Sherlock-lung study.<sup>358</sup> This study is a comprehensive genomic epidemiologic study of lung cancer in never smokers. It aims to identify processes involved in lung tumorigenesis to develop a more refined classification of lung cancer in never smokers and provide insights into prognosis and treatment strategies. Preliminary data is beginning to emerge highlighting the large differences in the molecular landscape of lung cancer in never-smokers from that of smokers. The study will collect data from 2,500 never smokers. We also recognize that 80% of lung cancers among women can be attributed to smoking. Therefore, NCI's ongoing efforts to reduce the uptake and use of tobacco, also remain paramount in female lung cancer prevention. NCI continues its efforts related to *Smokefree Women*, part of the larger Smokefree.gov website,<sup>359</sup> and remains committed to supporting research and resources to prevent lung cancer and advance progress for all cancer patients, whether their diagnosis is tobacco-related or not.

Currently, NCI is funding nearly a dozen individual investigator-initiated grants focused on women and lung cancer or lung cancer gender differences. Two investigator-initiated grants are examining the digital environment related to tobacco and younger people, specifically the projects are studying increased resistance to tobacco marketing among young adult sexual minority women, and electronic pediatric office systems to support treatment for parental

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<sup>357</sup> [www.uspreventiveservicestaskforce.org/uspstf/draft-update-summary/lung-cancer-screening-2020](http://www.uspreventiveservicestaskforce.org/uspstf/draft-update-summary/lung-cancer-screening-2020)

<sup>358</sup> [dceg.cancer.gov/research/cancer-types/lung/sherlock-lung-study](http://dceg.cancer.gov/research/cancer-types/lung/sherlock-lung-study)

<sup>359</sup> [smokefree.gov](http://smokefree.gov)

tobacco use.<sup>360</sup> Multiple projects investigating cancer risk and the biological mechanisms of lung cancer are underway, including an investigation of adipose (fat) and lean soft tissue depots associated cancer risk and mortality in postmenopausal women.<sup>361</sup> In addition, an R37 MERIT (Method to Extend Research in Time) award<sup>362</sup>, to an Early Stage Investigator is focused on examining disparities in access to and outcomes of cancer surgery for rural Medicare patients with lung and other cancers.<sup>363</sup>

There is also ongoing lung cancer research in NCI-supported programs such as the Specialized Programs of Research Excellence (SPOREs) and the Cancer Intervention and Surveillance Modeling Network (CISNET). Lung cancer was an early focus of the SPORE Program and presently there are five lung cancer SPORE programs.<sup>364</sup> CISNET conducts research on the impact of tobacco control policies and screening in lung cancer with a focus on disparities.<sup>365</sup>

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<sup>360</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=10170999](http://projectreporter.nih.gov/project_info_description.cfm?aid=10170999);

[projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9865418](http://projectreporter.nih.gov/project_info_description.cfm?aid=9865418)

<sup>361</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=10050524](http://projectreporter.nih.gov/project_info_description.cfm?aid=10050524)

<sup>362</sup> [www.cancer.gov/grants-training/grants-funding/funding-opportunities/merit](http://www.cancer.gov/grants-training/grants-funding/funding-opportunities/merit)

<sup>363</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9948356](http://projectreporter.nih.gov/project_info_description.cfm?aid=9948356)

<sup>364</sup> [trp.cancer.gov/spores/lung.htm](http://trp.cancer.gov/spores/lung.htm)

<sup>365</sup> [cisnet.cancer.gov/lung/](http://cisnet.cancer.gov/lung/)

## Women's Health Research Priorities

The Committee is concerned that funding for women's health research specifically related to gynecology and obstetrics remains disproportionately lower than other areas of research at NIH. The Committee believes that more focus on this research would help to address the rising maternal morbidity and mortality rates; rising rates of chronic debilitating conditions in women; and stagnant cervical cancer survival rates. The Committee encourages NIH to convene a consensus conference within six months of enactment of this Act to include representatives from the Office of Research on Women's Health, NICHD, NCI, NHLBI, and NIDDK, as well as any other relevant NIH Institutes and Centers, and researchers, clinicians, women's health advocates and other relevant public stakeholders, to evaluate research currently underway related to women's health. As part of the consensus conference, the Committee directs NIH to provide an update in the fiscal year 2022 Congressional Justification that identifies priority areas for additional study to advance women's health research, including reproductive sciences (House Report, p. 145).

### **Action Taken or To Be Taken**

The Office of Research on Women's Health's (ORWH) mission is to enhance research related to diseases, disorders, and conditions affecting women; to help ensure that women are appropriately represented in biomedical research supported by the National Institutes of Health (NIH); and to improve the advancement of women in biomedical careers. ORWH works with all NIH Institutes, Centers, and Offices (ICOs) to meet the goals laid out in the 2019–2023 Trans-NIH Strategic Plan for Women's Health Research<sup>366</sup> to: (1) Advance rigorous research that is relevant to the health of women; (2) Develop methods and leverage data sources to consider sex and gender influences; (3) Enhance dissemination and implementation of evidence to improve the health of women; (4) Promote training and careers to develop a well-trained, diverse, and robust workforce to advance science; and (5) Improve evaluation of research that is relevant to the health of women. At the NIH, advancing the science for the health of women is guided by three principles: (1) The consideration of the complex intersection among multiple factors affecting the health of women, foremost sex and gender; (2) Inclusion of diverse populations of women in clinical research, especially populations known to experience a disproportionate burden of illness; and (3) Active engagement to integrate perspectives from a diverse workforce of scientists with differing skills, knowledge, and experience.

The health and wellness of individuals are influenced by many internal factors (such as sex, genetics, reproductive stage, and hormones) and external factors (such as gender, other social determinants of health, and health policies) acting across the life course. Importantly, women's health encompasses reproductive health and female-specific conditions and disorders, including pregnancy, and their lifelong ramifications. Internal factors interact with external contextual factors—including environmental, economic, and societal influences—and together, they play a significant role in the health status, disease presentation, treatment response, and overall quality of women's and girls' lives. Interdisciplinary approaches are needed to address the risk factors of acute and chronic disease particular to women. For example, the NIH Maternal Mortality Task Force is coordinating the **Implementing a Maternal health and PR**egnancy **O**utcomes

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<sup>366</sup> [orwh.od.nih.gov/sites/orwh/files/docs/ORWH\\_Strategic\\_Plan\\_2019\\_02\\_21\\_19\\_V2\\_508C.pdf](https://orwh.od.nih.gov/sites/orwh/files/docs/ORWH_Strategic_Plan_2019_02_21_19_V2_508C.pdf)

Vision for Everyone (IMPROVE) Initiative that is utilizing a multi-pronged interdisciplinary approach to address maternal morbidity and mortality (MMM) through an integrated understanding of biological, behavioral, sociocultural and structural factors that engage the community in the development of solutions to improve outcomes in populations with a disproportional burden of MMM.<sup>367</sup> The Task Force is also planning for workshops that focus on strategies to prevent MMM.

Partnerships and engagement of multiple perspectives are key elements for advancing science for the health of women. In May 2021, ORWH plans to host the 5<sup>th</sup> NIH Vivian W. Pinn Symposium, to serve as a consensus forum for evaluating ongoing women's health research and advancing integration of sex and gender considerations across the biomedical research enterprise to lay the foundation for strengthening the science of women's health research through contemporary priority setting. Members of the NIH Coordinating Committee of Research on Women's Health with representation from all ICOs, along with professional organizations, will be included in planning efforts. This platform will engage partnerships across biomedical sectors that have a stake in research focused on the health of women—e.g., other Federal agencies, philanthropic organizations and foundations, private-sector businesses, journal editors and publishers, professional societies, academic researchers and institutions, and the public. A key goal will be to develop tangible strategies to act on priorities and move beyond inclusion to maximize the return on investment of biomedical research focused on prioritized areas to improve the health of women.

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<sup>367</sup> [www.nih.gov/research-training/medical-research-initiatives/improve-initiative](https://www.nih.gov/research-training/medical-research-initiatives/improve-initiative)

## Women's Health

The agreement supports more focus on this research, including research related to gynecology and obstetrics, to address rising maternal morbidity and mortality rates; rising rates of chronic debilitating conditions in women; and stagnant cervical cancer survival rates. The agreement encourages NIH to convene a consensus conference within 180 days of enactment of this Act to include representatives from relevant stakeholders to evaluate research currently underway related to such topics. The agreement requests an update on this effort in the fiscal year 2022 Congressional Justification (Joint Explanatory Statement, p. 70).

### **Action Taken or To Be Taken**

The mission of the NIH Office of Research on Women's Health (ORWH) is to enhance research related to diseases, disorders, and conditions affecting women; to help ensure that women are appropriately represented in biomedical research; and to improve the advancement of women in biomedical careers. ORWH works with all NIH Institutes, Centers, and Offices (ICOs) to meet the goals laid out in the 2019-2023 Trans-NIH Strategic Plan for Women's Health Research<sup>368</sup> with the ultimate goal to: advance rigorous research that is relevant to the health of women. Objective 1.5 in the strategic plan, *expand research on female-specific conditions and diseases, including reproductive stages, and maternal and gynecologic health*, demonstrates NIH's commitment to addressing the maternal mortality and morbidity crisis, the continued lethality of cervical cancers, as well as the rising rates of debilitating conditions in women.

In response to the maternal mortality and morbidity (MMM) crisis in America, the NIH formed the Maternal Morbidity and Mortality Task Force, co-chaired by the Directors of ORWH, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the NIH Associate Deputy Director, which is coordinating the Implementing a Maternal health and PRegnancy Outcomes Vision for Everyone (IMPROVE) Initiative<sup>369</sup> that is using a multi-pronged interdisciplinary approach to address MMM through an integrated understanding of biological, behavioral, sociocultural, and structural factors. Currently, members of the Task Force and other ICOs are working together using existing budgets in planning workshops and developing funding strategies to address MMM. In May 2020, NIH held a virtual workshop on "Pregnancy and Maternal Conditions that Increase Risk of Morbidity and Mortality" on research and strategies for improving maternal health. Past and present MMM-related activities can be found on the NIH ORWH MMM web portal<sup>370</sup>; in addition, NIH-wide efforts are ongoing that focus on research to address the health of women, maternal health, and pregnancy outcomes related to COVID-19.

NIH supports a diverse portfolio of research on breast and gynecologic cancers (ovarian, uterine/endometrial, vulvar, and cervical cancers). These efforts span basic science, translational research, and clinical trials, including those conducted through the National Clinical Trials

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<sup>368</sup> [orwh.od.nih.gov/sites/orwh/files/docs/ORWH\\_Strategic\\_Plan\\_2019\\_02\\_21\\_19\\_V2\\_508C.pdf](https://orwh.od.nih.gov/sites/orwh/files/docs/ORWH_Strategic_Plan_2019_02_21_19_V2_508C.pdf)

<sup>369</sup> [www.nih.gov/research-training/medical-research-initiatives/improve-initiative](https://www.nih.gov/research-training/medical-research-initiatives/improve-initiative)

<sup>370</sup> [orwh.od.nih.gov/research/maternal-morbidity-and-mortality/maternal-health-across-nih](https://orwh.od.nih.gov/research/maternal-morbidity-and-mortality/maternal-health-across-nih)

Network,<sup>371</sup> Experimental Therapeutics Clinical Trials Network,<sup>372</sup> and trials underway at the NIH Clinical Center led by the National Cancer Institute (NCI) Women’s Malignancies Branch.<sup>373</sup> NCI scientists contributed significantly to the development of human papillomavirus (HPV) vaccines,<sup>374</sup> and NCI is currently supporting extensive research to optimize the HPV vaccine dosing schedule,<sup>375</sup> encourage broader uptake of the HPV vaccine,<sup>376</sup> and continue to improve cervical cancer screening.<sup>377</sup> These complementary efforts aim to not only improve cervical cancer survival but to ultimately make cervical cancer a preventable disease.

There are numerous NIH efforts to reduce medical conditions that are rapidly escalating in women. For example, severe pain and prescription opioid addiction are more frequently seen in women than men, and rapidly escalating. In addition, across NIH research is supported to treat and prevent Polycystic Ovarian Syndrome (PCOS) an infertility disorder in women that is a debilitating chronic condition which can cause hormone imbalance, obesity and insulin resistance, elevated blood pressure, and risk of cardiovascular disease.<sup>378</sup> To inform future PCOS research, NHLBI, NICHD, and ORWH are planning a workshop in 2021 on “Cardiovascular Risk Across the Lifespan for Polycystic Ovarian Syndrome.” The goal is to bring together PCOS experts to review current knowledge of cardiovascular risk factors associated with PCOS and to identify steps needed to improve prevention and treatment.

At the NIH, advancing the science for the health of women is guided by three principles, one being, *active engagement to integrate perspectives from a diverse workforce of scientists with differing skills, knowledge, and experience*. The NIH plans to leverage many existing partnerships and engage multiple perspectives from across the NIH and beyond to inform and hold a consensus forum in the Fall of 2021. May 2021, ORWH will host the 5<sup>th</sup> NIH Vivian W. Pinn Symposium, to serve as a forum for advancing the integration of sex and gender considerations across the biomedical research enterprise, lay a foundation for strengthening the science of women’s health research, and inform a consensus conference to address women’s health priorities. This platform will engage partnerships across biomedical sectors that have a stake in research focused on the health of women—e.g., other Federal agencies, philanthropic organizations and foundations, private-sector businesses, journal editors and publishers, professional societies, academic researchers and institutions, and the public. A key goal will be to develop tangible strategies to move beyond inclusion with the goal of maximizing the return on investment of biomedical research focused on prioritized areas to improve the health of women. These and other efforts will inform an ORWH convening of the NIH Advisory Committee for Research on Women’s Health (ACRWH) to serve as the consensus forum focused on assessing research on the health of women currently underway, delineating research gaps, and in turn, opportunities, and contemporary priority setting during the Fall of 2021. The

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<sup>371</sup> [ctep.cancer.gov/initiativesPrograms/docs/nctn\\_trials/NCTN\\_GYNE\\_Trials.pdf](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_GYNE_Trials.pdf)

<sup>372</sup> [ctep.cancer.gov/initiativesprograms/docs/etctn\\_trials/Gynecologic.pdf](https://ctep.cancer.gov/initiativesprograms/docs/etctn_trials/Gynecologic.pdf)

<sup>373</sup> [ccr.cancer.gov/womens-malignancies-branch](https://ccr.cancer.gov/womens-malignancies-branch)

<sup>374</sup> [www.ncbi.nlm.nih.gov/pmc/articles/PMC6310227/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6310227/)

<sup>375</sup> [www.cancer.gov/news-events/cancer-currents-blog/2020/hpv-vaccine-single-dose-long-term-protection](https://www.cancer.gov/news-events/cancer-currents-blog/2020/hpv-vaccine-single-dose-long-term-protection)

<sup>376</sup> [cancercontrol.cancer.gov/research-emphasis/supplement/hpv-vaccine-uptake](https://cancercontrol.cancer.gov/research-emphasis/supplement/hpv-vaccine-uptake)

<sup>377</sup> [www.cancer.gov/news-events/press-releases/2020/automated-dual-stain-cervical](https://www.cancer.gov/news-events/press-releases/2020/automated-dual-stain-cervical)

<sup>378</sup> [orwh.od.nih.gov/in-the-spotlight/all-articles/orwh-publishes-informational-booklet-polycystic-ovaryovarian-syndrome](https://orwh.od.nih.gov/in-the-spotlight/all-articles/orwh-publishes-informational-booklet-polycystic-ovaryovarian-syndrome)

ACRWH<sup>379</sup> is a legislatively mandated committee that provides advice and makes recommendations on priority topics affecting women's health and sex differences research.

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<sup>379</sup> [orwh.od.nih.gov/about/advisory-committees/advisory-committee-research-womens-health](http://orwh.od.nih.gov/about/advisory-committees/advisory-committee-research-womens-health)