DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Report to Congress:

Pediatric Research in Fiscal Years 2021 and 2022

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PEDIATRIC RESEARCH AT THE NATIONAL INSTITUTES OF HEALTH

Research advances supported by the National Institutes of Health (NIH) have transformed the diagnosis, treatment, and prevention of disease. Children comprise more than 22% of the population in the United States, with more than 73 million children between the ages of 0 and 17. Children have benefited greatly from revolutionary progress in biomedical research. Taking folic acid before and during pregnancy prevents most neural tube defects. Survival rates for preterm infants have increased substantially. The genetic causes of several disorders have been identified, such as Fragile X syndrome (FXS) and Rett syndrome. Several conditions that once caused intellectual disability, like congenital hypothyroidism or phenylketonuria (PKU), are no longer major threats. Scientists' understanding of how children grow and develop has grown immensely and informed early intervention efforts that have dramatically improved the lives of millions of children worldwide.

Pediatric research continues to be an NIH priority. NIH's strong basic and clinical research portfolio provides the foundation for pediatric research in a variety of scientific areas, including neurodevelopment, cardiology, cancer, pharmacology, and behavioral and social sciences. In fiscal year 2022 (FY22), NIH funded research grants and projects directed specifically at pediatric research for a total of $5,706,585,183, as detailed in Table 1 in the appendix. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) funds the largest portion of pediatric research among the NIH institutes, centers, and offices (ICOs), taking a leadership role in many pediatric research efforts that involve NIH-wide collaborations. For example, NICHD leads the Pediatric Research Consortium (N-PeRC), which was established to coordinate pediatric research programs, best practices, and training opportunities across all NIH ICOs. All the ICOs support pediatric research; NICHD alone accounts for only 16% of the total NIH support for pediatric research. This reflects the breadth of the research portfolio at NIH dedicated to improving the health of children everywhere.

NEW IN FISCAL YEAR 2021 (FY21) AND FY22

Despite the challenges posed by a global pandemic, pediatric researchers supported by NIH continued to develop new technologies to improve clinical care for children, including screening and diagnostic tools and therapeutics for illnesses and disorders in pediatric populations. For example, researchers supported by the National Center for Advancing Translational Sciences (NCATS), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Fogarty International Center (Fogarty), and the National Heart, Lung, and Blood Institute (NHLBI) developed a point-of-care diagnostic device that can quickly detect the presence of sickle cell disease in newborns using a droplet of blood. The National Institute of Allergy and Infectious Diseases (NIAID) is supporting the development of a solid-state nanopore biosensor assay that can rapidly diagnose pediatric tuberculosis by measuring *Mycobacterium tuberculosis*–secreted antigens in patient serum samples. In a study supported by NICHD and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), a team of scientists used technology similar to that used in newborn screening to identify a collection of proteins which, when measured in combination, accurately identified differences between individuals with and without Duchenne muscular dystrophy (DMD), a rare genetic disorder—even before they began to show symptoms. Using machine learning, researchers supported by the National Institute of Environmental Health Sciences (NIEHS), NICHD, and the National Institute of General Medical Sciences (NIGMS) identified several patterns of maternal autoantibodies highly associated with the diagnosis and severity of maternal autoantibody-related autism spectrum disorder (ASD), a condition that accounts for around 20% of all autism cases. Scientists funded by NICHD developed a same-day test to identify abnormal fetal chromosomes using samples collected from prenatal tests, as well as tissue obtained from miscarriages and biopsies from pre-implantation embryos produced using *in vitro* fertilization. Investigators supported

by the National Cancer Institute (NCI) have uncovered new molecular underpinnings of certain types of rhabdomyosarcoma, the most common soft-tissue cancer in children, setting out a potential path forward for novel therapeutic strategies. The National Eye Institute (NEI) supported researchers that developed a wearable sensor that allows assessment of eyeglass compliance by infants and toddlers. The National Center for Complementary and Integrative Health (NCCIH) supported scientists that are examining implementation of a novel biofeedback-based virtual reality therapy for postoperative pain management in children. A trial supported by NIDDK showed that both children and adults using a novel bionic pancreas had improvements in average blood glucose levels compared to participants in the control group, indicating that this device could help individuals achieve recommended blood glucose levels with less burden.

From the beginning of the pandemic, pediatric scientists worked to rapidly pivot existing research efforts to mitigate the impact of coronavirus disease 2019 (COVID-19). NIH has worked diligently to understand the effects of SARS-CoV-2—the virus that causes COVID-19— and multisystem inflammatory syndrome in children (MIS-C) among children and adolescents. The NICHD–led project Predicting Viral-Associated Inflammatory Disease Severity in Children with Laboratory Diagnostics and Artificial Intelligence (PreVAIL kIds) is part of NIH's Rapid Acceleration of Diagnostics (RADx) initiative to speed innovation in the development, commercialization, and implementation of technologies for COVID-19 testing. Several investigators are looking for biomarkers to help differentiate MIS-C—a severe complication associated with SARS-CoV-2 infection that is characterized by significant inflammation of organs and tissues—from Kawasaki disease, severe COVID-19, and other childhood illnesses. One group found that higher levels of the cytokine CXCL10, when measured in saliva, were associated with more severe forms of COVID-19 in children. They also identified several microRNAs, also from saliva samples, that correlated with severe infection in children.

Further testing and validation of such biomarkers can help predict a child's risk for complications and enable early monitoring and preventive treatment. The Safe Return to School Diagnostic Testing Initiative, part of the NIH Rapid Acceleration of Diagnostics Underserved Populations (RADx-UP) initiative, addressed the needs of children with unequal access to COVID-19 testing, as well as those facing barriers to attending school remotely. Several publications resulted from this initiative—including a suite of research on COVID-19 and the return to in-person learning in underserved K–12 schools—and a collection of current evidence and best practices to safely return children with disabilities to in-person school during the pandemic. NIH's Researching COVID to Enhance Recovery (RECOVER) initiative seeks to understand, prevent, and treat the potential consequences of a SARS-CoV-2 infection, including Long COVID. This study will follow up on pregnant patients with COVID-19 and their offspring for four years to establish incidence, prevalence, and long-term sequelae of SARS-CoV-2 infection; characterize the clinical course and recovery; determine risk factors; and define the pathophysiology and biologic mechanisms.

NIH has also supported research to understand and improve treatments for COVID-19 and MIS-C. Researchers supported by NICHD offered key information about a common MIS-C treatment called intravenous immune globulin (IVIG), finding that IVIG likely works by depleting immune cells called neutrophils. This important research promises to aid health care providers as they continue to identify and improve treatments for MIS-C.

NIH also launched several initiatives that will provide insight into child development and childhood disorders. NICHD launched a technology and digital media (TDM) exposure/usage initiative to support multi-project research programs that examine the pathways by which TDM exposure and usage impact

developmental trajectories and health outcomes in early childhood and adolescence. NIAID, NIEHS, and NICHD participated in an initiative for research to define the mechanisms regulating the establishment, development, and maintenance of immunity throughout childhood (from birth to less than 18 years of age). NICHD, the National Institute of Dental and Craniofacial Research (NIDCR), and the NIH Office of Research Infrastructure Programs (ORIP) supported an initiative to promote the screening, functional validation, and characterization of birth defect–associated genetic variants identified through public-facing databases and individual efforts using *in silico* tools, appropriate animal models, *in vitro* systems, or multipronged approaches.

THE PEDIATRIC RESEARCH INITIATIVE

In the Public Health Service Act (the Act), Congress directed the Secretary of Health and Human Services (HHS) to establish a Pediatric Research Initiative (PRI) in the NIH Office of the Director (OD). The Act also directed the OD to:

> " … annually report to Congress and the public on the extent of the total funds obligated to conduct or support pediatric research across the National Institutes of Health, including the specific support and research awards allocated through the Initiative."
>
> – Pediatric Research Initiative, 42 U.S.C. § 284h(c)(3)

In response to this directive, NIH has prepared the following report for FY21 and FY22. The overall purpose of the PRI is to "conduct and support research that is directly related to diseases, disorders, and other conditions in children" (42 U.S.C. § 284h(a)). More specifically, the purpose of the PRI is:

> (1) "to increase support for pediatric biomedical research within the National Institutes of Health to realize the expanding opportunities for advancement in scientific investigations and care for children;
> (2) to enhance collaborative efforts among the Institutes to conduct and support multidisciplinary research in the areas that the Director deems most promising; and
> (3) in coordination with the Food and Drug Administration (FDA), to increase the development of adequate pediatric clinical trials and pediatric use information to promote the safer and more effective use of prescription drugs in the pediatric population."
>
> – Pediatric Research Initiative, 42 U.S.C. § 284h(b)

NIH has funded the initiative through (1) a one-time, $5 million distribution from the NIH Director's Discretionary Fund (FY 2001) and (2) individual and collaboratively funded ICO grants and contracts (FY 2002 and thereafter). Therefore, rather than restricting the report to research associated with the PRI, this Pediatric Research Report highlights research advances and ongoing programs in pediatric research at NIH. Table 1 in the appendix of this report shows the funding amounts for NIH's total investment in pediatric research by ICO in FY21 and FY22.

A core component of NICHD's mission is to improve and promote children's health and development. Therefore, the NIH Director requested that the NICHD Director oversee and coordinate the preparation of the Pediatric Research Report.

Additionally, the Childhood Cancer Survivorship, Treatment, Access, and Research (STAR) Act of 2018 (Public Law 115–180) directs NIH to ensure that the childhood cancer research projects it conducts and supports are included in appropriate reports to Congress, noting that this may include the Pediatric Research Report. Accordingly, this report includes selected NIH–supported pediatric cancer research

efforts throughout its main sections: research advances, new and expanded efforts, major ongoing programs, and additional collaborations.

SELECTED SCIENTIFIC RESEARCH ADVANCES IN PEDIATRICS

Selected recent advances in pediatric research are described below. Each of these advances has resulted from NIH–supported studies. Although these advances are by no means a comprehensive compilation, they represent the wide range of NIH's scientific portfolio in pediatrics, including advances in child and adolescent development, rare diseases, prevention and treatment of pediatric illnesses, innovative technologies, and global health research. Many of these advances resulted from programs that are supported by multiple NIH components. A list of ICOs, organizations, abbreviations, and acronyms can be found in Table 3 in the appendix.

Bone and Muscle Health

Finding the Optimum Corticosteroid Regimen for Duchenne Muscular Dystrophy
Duchenne muscular dystrophy (DMD) is a progressive genetic disorder that primarily affects boys and is one of the most common childhood neuromuscular diseases. DMD leads to progressive weakness and wasting of both skeletal and heart muscle, causing loss of walking ability and subsequent breathing and/or heart failure. Some patients also experience deficits in communication and memory. Treatment with corticosteroids, including prednisone and deflazacort, improves muscle function and maintains walking for several years. However, it has been difficult to develop a corticosteroid treatment regimen that helps maintain muscle and yet minimizes adverse side effects. Researchers conducted a double-blind, parallel-group randomized clinical trial comparing daily prednisone, daily deflazacort, and intermittent prednisone (alternating 10 days on and 10 days off) in 196 boys with DMD ages 4 to 7 years and following them over 3 years. The trial found daily prednisone or daily deflazacort to be superior to intermittent prednisone on a combined outcome, including measures of motor and lung function and satisfaction with treatment. These findings support the use of a daily corticosteroid regimen over an intermittent prednisone regimen.
Supported by: NINDS
Grants: U01NS061799, U01NS061795
Publications: https://pubmed.ncbi.nlm.nih.gov/35381069/
Clinical Trials Study: NCT01603407

New Method for Identifying Proteins Could Aid in Studies of Duchenne Muscular Dystrophy
Duchenne muscular dystrophy (DMD) is a rare genetic disease that affects boys almost exclusively. About 1 in 5,000 boys are born with DMD. The disease has no cure, and it ultimately leads to severe disability and death. Even with intensive research efforts, only two new drugs for treating DMD have been approved in the last 15 years. This is partly because the disease is rare; therefore, it is often difficult to recruit enough patients to conduct a high-quality clinical trial. Moreover, the tests most commonly used to determine if a drug works in muscular dystrophy, like tests of walking ability, cannot be used in younger children who are not yet walking well. These tests are often inconsistent and unreliable in older children. The ideal solution to this testing issue would be to find a simple blood test that can indicate whether a drug is working in children with DMD, but no such blood marker has yet been found. In this study, a team of scientists used technology similar to that used in newborn screening to identify a collection of proteins which, when measured in combination, accurately identified differences between individuals with and without DMD— even before they began to show symptoms. This technology may therefore help researchers conduct clinical trials in younger children with DMD, who may receive the greatest potential benefit from future interventions.

Supported by: NICHD, NIAMS
Grants: P50HD090254, R01AR061875
Publications: https://pubmed.ncbi.nlm.nih.gov/33110978/

Evaluating the Immunoinflammatory Profiles of Localized Aggressive Periodontitis and its Treatment

Localized aggressive periodontitis (LAP) is a rare and severe form of periodontitis (gum disease) with rapid onset and progression that is more common in African Americans. Early diagnosis and intervention are critical to prevent premature tooth loss. Gingival crevicular fluid (GCF), the fluid residing in close proximity to the gums, can be used to monitor and understand gum health and disease. Individuals with LAP have overactive immune responses; prior studies have shown that levels of certain substances that regulate immuneresponses and bone-resorption (breakdown) are increased in the GCF of individuals with LAP. In this study, researchers analyzed the levels of 16 inflammatory and bone-resorption markers in GCF from diseased and healthy sites in the mouths of 66 African American patients aged 7-21 with LAP, before and after nonsurgical treatment consisting of mechanical plaque removal and systemic amoxicillin/metronidazole. The researchers found that most clinical measures of LAP, and several GCF biomarker levels, improved following the treatment, and differences between the immune profiles of GCF from LAP-diseased sites and healthy sites decreased. These findings suggest that this nonsurgical method is effective in controlling LAP progression.
Supported by: NIDCR
Grants: R01DE019456, R90DE022530,
Publications: https://pubmed.ncbi.nlm.nih.gov/33205510/

Using Stem Cells to Restore Skull Shape and Brain Function in Mice

Craniosynostosis is a disorder in which the fibrous joints that separate an infant's skull bones, called sutures, fuse into bone before the brain is fully formed. As a result, the skull grows abnormally. Craniosynostosis is also associated with developmental delays and learning deficits. Scientists wanted to know if restoring normal skull development could improve neurocognitive function in mice. They showed that mice with craniosynostosis, like humans, have increased pressure inside their skulls and perform poorly on tests of social and spatial memory. The researchers prepared a biodegradable gel infused with a type of stem cells called Gli1+ cells and surgically implanted the mixture into the skulls of young mice with craniosynostosis. The surgery restored sutures, partially corrected skull shape, and reduced internal skull pressure. Spatial memory and motor learning also improved. Next steps include determining the optimal timing of the surgery and the ideal type and number of stem cells to implant. This study provides a foundation for developing a stem cell–based therapy for craniosynostosis.
Supported by: NIDCR, NINDS
Grants: R01DE026339, R01DE012711, R01NS097231, R01NS110687, R01DE022503, U24DE026914, U24DE029463
Publications: https://pubmed.ncbi.nlm.nih.gov/33417861/

New Treatment for Rare Bone Disease Shows Promise

Fibrous dysplasia/McCune Albright syndrome (FD/MAS) is a rare disease that affects the development of bones during childhood, making them break easily and grow irregularly. Many patients with FD/MAS have low blood levels of phosphate due to overexpression of a protein called FGF23. The FDA has approved a monoclonal antibody that targets FGF23 overexpression, called burosumab, to treat other conditions marked by high levels of phosphate, but it has not been studied in FD/MAS. Scientists used burosumab to treat a 7-year-old patient with severe FD/MAS—the first reported use of the drug for this condition. The treatment improved the patient's phosphate levels, decreased bone pain, and improved muscle strength and stamina. Also, no fractures occurred in the 17 months following treatment. The patient's encouraging response warrants continued study of burosumab in the FD/MAS pediatric population.

Supported by: NIDCR
Grants: ZIADE000758
Publications: https://pubmed.ncbi.nlm.nih.gov/33984553/

Predictors of Treatment Responses Identified in Juvenile Dermatomyositis
Researchers examined the treatment responses for 307 patients with juvenile dermatomyositis, a rare systemic muscle autoimmune disease, to determine factors affecting timelines to favorable clinical outcomes. The scientists determined the probability of treatment responses among the patients, including corticosteroid discontinuation (56%), complete clinical response (38%), and remission by 60 months after initial treatment (30%). Several clinical features and unique serologies were identified as predictors of good treatment responses. Photosensitivity, contractures (rigid joints), and a longer time to complete clinical response were predictive of the time to final corticosteroid discontinuation. The presence of antiMJ (NXP2) autoantibodies and living in a Northwest geoclimatic zone were predictive of shorter time to complete clinical response. Difficulty speaking, contractures, an increase in medications within 24 months, and a longer time to corticosteroid discontinuation were associated with longer time to complete clinical response (remission on medication). Anti-p155/140 (TIF1) autoantibodies, an increase in medications within 124 months, and longer times to corticosteroid discontinuation and complete clinical response were associated with longer time to remission.
Supported by: NIEHS, NIAMS
Grants: ZIAES101074, ZIAES101081, ZIAAR041170
Publications: https://pubmed.ncbi.nlm.nih.gov/33067611/

Child Development

Promoting Caregiver–Child Relationships for a Native Community
Researchers tested a strengths-based intervention to promote positive caregiver-child relationships on a rural Native reservation. The preventive intervention program has been found effective in other communities, but previous implementations of the program have included only a few Native families. In this study, which also builds on values of Native families and communities, the researchers found that caregivers in the program showed greater knowledge about children's social–emotional needs and less severe depressive symptoms immediately after the intervention and three months later.
Supported by: NINR
Grants: R01NR014153
Publications: https://pubmed.ncbi.nlm.nih.gov/35997845/

Mapping in Brain Anatomy Across the Lifespan
Humans brains continue to develop in size, shape, and structure throughout childhood and adolescence. Researchers developed a new technique to compare the relative size of an individual's brain regions with those typically seen in a broader population. The researchers applied this technique—called anatomical imbalance mapping, or AIM—to data from 20,000 brain scans. Early in life, relative sizes of brain regions varied greatly compared with the population norm. By adolescence, brain size, shape, and structure varied less, showing convergence toward population norms by the time people reached their mid-20s. In future studies, researchers plan to examine whether individual differences in sizes of brain structures are associated with observable differences in cognition, behavior, or other aspects of brain function.
Supported by: NIMH, NIGMS
Grants: ZIAMH002949, T32GM007753
Publications: https://pubmed.ncbi.nlm.nih.gov/33811142/
News Link: Mapping 'Imbalance' in Brain Anatomy Across the Lifespan

Neurodevelopmental Outcomes in Children Born Extremely Preterm

Babies born before 28 weeks of pregnancy are considered extremely preterm, and those that survive often have serious and sometimes long-term health problems and disabilities. Neurodevelopmental impairment is found frequently among children born extremely preterm, but developmental assessments during infancy do not always accurately predict long-term neurodevelopmental outcomes. Researchers used data from a large multicenter U.S. study of extremely preterm infants who had neurodevelopmental assessments at 2 and 10 years of age. Of the children having moderate to severe neurodevelopmental impairment at 2 years of age, more than half—63%—had none to mild neurodevelopmental impairment at 10 years. Of the children who had profound neurodevelopmental impairment at 2 years of age, more than a third—36%—had none to mild neurodevelopmental impairment at 10 years. These findings provide a hopeful message for parents at risk of delivering an extremely preterm infant.
Supported by: NICHD, NIEHS, NCATS, OD, NINR
Grants: T32ES007018, UL1TR002489, R01HD092374, UG3OD023348, K23NR017898
Publications: https://pubmed.ncbi.nlm.nih.gov/33824183/

Comparing Two Generations: Adolescent Technology Use, Sleep, and Physical Activity
How adolescents use technology has been rapidly transformed by Internet-enabled mobile digital devices. These advanced tools have largely displaced desktop computers, handheld gaming devices, and cell phones that were previously used for learning, video games, and communication. In 2012, slightly less than half of adolescents owned or had access to a smartphone; by 2018, that proportion had increased to 9%. Researchers analyzed time-based data from a long-standing household survey, comparing data collected from children 11–17-years of age in 2002–2003 with data from those 11–17 years of age in 2014–2016. The more recent group spent about 40 minutes more per week in technology-focused activities, though the types of technology used were more varied than in the previous generation. In 2002–2003 and 2014–2016, the share of adolescents engaged in video game play and audio entertainment increased substantially. Adolescents who engaged in frequent video game play spent less time in physical activity compared with peers who used other technology. Adolescents also shifted away from television as a primary activity and increased technology use as a secondary activity. The study has some limitations; for example, the data collection may have missed quick, frequent usage, such as checking a phone at the dinner table. That said, across sociodemographic groups, three consistent patterns emerged: (1) time engaged in technology use increased, (2) time spent sleeping remained roughly constant, and (3) time in physical activity declined between groups.
Supported by: NICHD
Grants: P2CHD041028, P2CHD066613
Publications: https://pubmed.ncbi.nlm.nih.gov/33911316/

Young Children's Mobile Device Use
Children's use of mobile devices has increased rapidly over the past decade, raising concerns about how mobile device use may affect cognitive, emotional, and social development. Researchers implemented a new tracking technique to accurately measure young children's mobile device use, using a passive-sensing application (Chronicle) in Android data devices and screenshots of the battery feature in iOS devices. In addition, the parents completed questionnaires in which they estimated the amount of time their preschoolers spent with mobile devices. The researchers compared the data from the parents' estimates with the children's actual use. Children who had their own device spent an average of 115.3 minutes on their devices each day, which was similar between iOS and Android device users. More than half (59.5%) of children used their device at least 1 hour a day, and 14.9% of children averaged at least 4 hours a day. When the researchers compared the data from the parent's estimates with the children's actual use, they found that 35.7% of parents underestimated the children's usage and 34.8% overestimated use. These findings show that parental reports on their children's device usage had low accuracy.
Supported by: NICHD
Grants: K23HD092626, R21HD094051, R41HD100230, UL1TR002240

Publications: https://pubmed.ncbi.nlm.nih.gov/32482771/

The Maturation and Cognitive Relevance of Structural Brain Networks During Development
Brain network organization develops in a predictable fashion: first, through strengthening of local connections within networks; and next, by strengthening of long-range connections that span discrete brain networks. Researchers examined the maturation of brain networks by measuring the thickness of brain cortex tissue in neuroimaging data collected longitudinally from infancy to 6 years of age. At the group level, over the course of development, local brain network connections strengthened, and long-range brain network connections weakened. Scientists also related an individual's brain network connections to their performance on a motor learning task. Individuals with weaker long-range brain connections in infancy had better motor learning in childhood compared to their peers, demonstrating the impact of early long-range brain networks on later learning behavior.
Supported by: NIMH, NICHD
Grants: R01MH116225, R21HD096232
Publications: https://pubmed.ncbi.nlm.nih.gov/34091033/

The Roles of Two Parts of the Human Brain in Early Reading Ability and Development
The cerebellum, a part of the brain, plays an important role in learning through the processes of, for example, seeing, paying attention, building knowledge, remembering, learning language, and problem-solving. Past research has shown the importance of the right side (hemisphere) of the cerebellum in reading. Scientists aimed to better understand how the cerebellum works in very young children learning to read and whether the right and left hemispheres play different roles that could predict the ease of learning to read. They used brain imaging to see which sides of the cerebellum were active and contributing to reading success in kindergarten students. They found that the two hemispheres play different roles, with activation of the right hemisphere being a predictor of good reading ability and reading development. These findings can inform improved approaches to addressing reading disorders in children.
Supported by: NICHD, NCCIH
Grants: R01HD092498, R01HD086168, R01HD096261, R01HD094834, U24AT011281
Publications: https://pubmed.ncbi.nlm.nih.gov/34102410/

Imaging Differences in the Circle of Willis Between Healthy Children and Adults
The Circle of Willis (CoW) is a ring of arteries at the base of the brain that plays an important role in maintaining adequate circulation to the brain's front and back hemispheres. Certain variations, or asymmetries, in the CoW may be associated with stroke risk and migraine. Asymmetries in the CoW appear to be more common with advancing age; however, few imaging studies have been conducted to establish normal parameters for the CoW in healthy children. Recently, scientists used magnetic resonance angiography to visualize the CoW in healthy children and adults, ages 4–74; to measure the diameter of the arteries in the CoW; and to measure cerebral perfusion, or blood flow, within the brain tissue. They found that the CoW is larger and more symmetrical in healthy children than in adults, and that changes to the CoW are associated with developmental and aging changes in perfusion. In addition to providing important insight into normal brain physiology in children, these findings open new avenues of research around the role of the CoW in brain development in children, as well as the reasons why asymmetries develop with normal aging or disease.
Supported by: NIA, NINDS
Grants: R01AG057536, K23NS099472
Publications: https://pubmed.ncbi.nlm.nih.gov/34556478/

Brain Receptor Links Childhood Nutrition to the Timing of Puberty and Growth
Children have been growing taller and reaching puberty earlier over the past century. It was thought that better nutrition was the likely cause, but exactly how a child's nutritional state affects the brain and

impacts the onset of puberty was not understood. Researchers explored the role of melanocortin receptor MC3R in the brain. Melanocortins are a group of hormones involved in appetite and food intake. Identifying thousands of individuals in a genomic database with mutations to the *MC3R* gene, researchers found that these individuals had a later onset of puberty. Researchers also identified records for six children carrying mutations that cause dysfunction in *MC3R*. All were shorter than average. Lastly, additional experiments showed that mice lacking *Mc3r* reached sexual maturity later. Taken together, the results suggest that *MC3R* plays an important role in influencing puberty and growth.
Supported by: NICHD, NIDDK
Grants: F32HD095620, F32DK123879, R01DK070332, R01DK126715, K99DK127065, R01DK106476
Publications: https://pubmed.ncbi.nlm.nih.gov/34732894/
News Link: Brain Receptor Linked to Puberty and Growth

Racial Residential Segregation, Early Childhood Lead Exposure, and Fourth-grade Standardized Test Scores
According to the Centers for Disease Control (CDC), the primary sources of lead exposure among children in the United States are found within their own homes. Homes built prior to 1978 are more likely to have lead-based paint, lead-contaminated dust, and pipes and plumbing fixtures containing lead. Neighborhoods that are racially segregated and/or in low socioeconomic areas tend to have higher proportions of homes built before 1978. After controlling for a number of variables, the research team linked 25,699 North Carolina birth records to blood lead surveillance data and educational test scores. The research team assigned geographic locations based on census tract–level data to create a unique population-based dataset that links the information across time and geography. The study showed that lead exposure is associated with lower test scores among all children. Further, non-Hispanic Black children are more likely to be exposed to lead and more likely to live in racially segregated neighborhoods, which amplifies the negative effects of lead exposure. Importantly, there is no safe level of lead exposure, and childhood lead poisoning is preventable.
Supported by: NIEHS, NIMHD
Grants: R00MD011304, R01ES028819
Publications: https://pubmed.ncbi.nlm.nih.gov/35969764/

Childhood Diseases, Allergies, and Immunity

Efficacy and Safety of Immunosuppression Withdrawal in Pediatric Liver-Transplant Recipients
A transplanted organ remaining stable without the need for immunosuppression is considered the ideal outcome of an organ transplantation surgery, as it avoids toxicities and other detrimental health impacts caused by long-term immunosuppression. In a clinical trial involving 88 selected pediatric liver transplant recipients, slightly more than one-third of the transplant patients were able to have immunosuppression completely withdrawn. None of the 88 had any evidence of permanent liver injury as a result of immunosuppression withdrawal. Histological and immunohistochemical characteristics of the liver graft prior to drug withdrawal correlated with ability to tolerate immunosuppressant withdrawal, but clinical and biochemical characteristics did not. These recipients would be able to markedly decrease the risk of infections, a major cause of morbidity and mortality in transplant recipients. These findings suggest that periodic histological evaluation after transplantation is critical to predict potential impacts of future immunosuppressant withdrawal.
Supported by: NIAID, NCATS
Grants: U01AI100807, UM1AI109565, UL1TR000004, UL1TR001872, UL1TR001425, UL1TR000003, UL1TR001878, UL1TR000454, UL1TR002378
Publications: https://pubmed.ncbi.nlm.nih.gov/32786149/

Biomarker Identified for Diagnosis of Peanut Allergy in Infancy

Peanut allergy is prominent in children, but recently a large-scale clinical trial showed that peanut allergy may be prevented in most children with early introduction of dietary peanut. The results of this study led to guidelines for the prevention of peanut allergy that call for testing of high-risk infants to ensure they are not already allergic prior to peanut introduction. Researchers studied 321 infants with atopic dermatitis or other risk factors for developing allergy to peanut. The scientists found that the presence of an antibody specific to the peanut protein Ara h 2, known as Ara h 2-specific IgE, is the best predictor of peanut allergy at that age. This study supports Ara h 2-specific IgE as the most important marker that should be used for screening of high-risk infants before early peanut introduction.
Supported by: NIAID, NCATS
Grants: U01AI125290, UL1TR002541, UL1TR003098
Publications: https://pubmed.ncbi.nlm.nih.gov/33483152/

Efficacy and Safety of Oral Immunotherapy in Children Aged 1–3 Years with Peanut Allergy
Because rates of peanut allergies in preschool-aged children are not improving, there is a need for safe and effective therapies. Researchers assessed whether peanut oral immunotherapy, a method of slow introduction of peanut, could induce desensitization (an increase in allergic threshold while on therapy) or remission (a state of nonresponsiveness after discontinuation of therapy) compared with treatment with placebo. In children with an existing peanut allergy, peanut oral immunotherapy given before 4 years of age was associated with both increased desensitization and remission compared with children treated with placebo. The outcomes suggest a sensitive window for young children for intervention to induce desensitization and remission of peanut allergy.
Supported by: NIAID, NCATS
Grants: UM1AI109565, UM2AI117870, UL1TR001111, UL1TR003107, UL1TR003142, UL1TR000424, UL1TR000067
Publications: https://pubmed.ncbi.nlm.nih.gov/35065784/
News Link: Oral Immunotherapy Induces Remission of Peanut Allergy in Some Young Children

Infant Antibiotic Exposure Can Affect Future Immune Responses
Right after birth, infants begin to create their own microbiome, as communities of microbes assemble throughout the body. The composition of this microbiome affects the development of the infant's immune system, but exactly how this works has not been well understood. Scientists used a rodent model to examine how antibiotic exposure early in life can affect immune system development in newborns. They found that exposure to antibiotics through breastfeeding and skin exposure can compromise the development of infant microbome and specific immune cells, and this could lead to poor immune system development. Unfortunately, once an unbalanced microbiome was developed, its effects were long-lasting and were not reversed by decreasing antibiotic exposure even in adulthood.
Supported by: NCATS, NIAID
Grants: TL1TR001447, U01AI122285, UL1TR001445, TL1TR002386
Publications: https://pubmed.ncbi.nlm.nih.gov/33531385/

Unraveling the Genetic Basis of Vesicoureteral Reflux
Vesicoureteral reflux (VUR) is a condition in which urine flows backward from the bladder to one or both ureters and sometimes to the kidneys. VUR is most common in infants and young children and can cause urinary tract infections and, less commonly, kidney damage. However, relatively little has been known about the genetic factors that contribute to VUR. Scientists performed a genome-wide association study and rare copy number variant analysis with the largest VUR cohort to date. Their analyses identified three significant and five suggestive genetic regions associated with VUR. The study also showed that about 6% of study participants harbored high-risk genotypes. These findings may provide the foundation for improved VUR screening methodologies.
Supported by: NIDDK, NHGRI, NCATS

Grants: U54DK104309, R01DK080099, U01HG008680, U01DK094530, R01DK105124, RC2DK116690, UH3DK114926, U01HG008680, R01DK103184, R21DK098531, UL1TR000040, R21DK119802
Publications: https://pubmed.ncbi.nlm.nih.gov/33597122/

Biomarkers of Tuberculosis in Children
Most current diagnostic protocols for tuberculosis (TB) call for sputum-based samples, which are difficult to obtain from young children. Moreover, children often have low amounts of *Mycobacterium tuberculosis*, the bacterium that causes TB, in their sputum. There is an urgent need for a non-sputum-based diagnostic tool that could give an early and precise diagnosis of TB disease in children. To characterize biomarkers of TB in children, scientists analyzed the blood plasma from children with and without TB and found that levels of specific immune response-associated proteins called cytokines were significantly higher during active TB in children compared with those unlikely to have TB. The same cytokine levels were reduced following anti-TB treatment. These results suggest that a baseline cytokine signature could serve as an accurate biomarker for the diagnosis of pediatric TB.
Supported by: NIAID
Grants: Intramural research (NIAID) ZIAAI001065
Publications: https://pubmed.ncbi.nlm.nih.gov/33936077/

New, Easier Method Shows Promise for Detecting Tuberculosis Infection in Young Children
Tuberculosis (TB) is the leading cause of deaths from infection worldwide. It is caused by *Mycobacterium tuberculosis* (*Mtb*) bacteria. In 2017, 1.6 million people died from TB, including 230,000 children. Effective TB treatment exists, but almost all children who die from TB are not treated, mostly because it is difficult to detect the infection in children before it is too late. An important reason for delayed diagnosis is the challenge of collecting mucus samples from infants and young children. Scientists tested a new method of diagnosis that uses tiny samples of blood instead of mucus to detect a bacterial protein called CFP-10, which is produced by *Mtb*. Using samples from 500 young children, the scientists found that the CFP-10 test detected *Mtb* infections with high accuracy. In addition, the test identified five cases of TB that mucus testing missed. Having a new diagnostic test that works well for young children could help ensure they get early treatment to prevent death.
Supported by: NICHD, NIAID
Grants: UM1AI068632, UM1AI106716, R01AI113725, R21AI143341, K23AI120793, UM1AI068616, R21AI126361, R01AI122932, R01HD090927
Publications: https://pubmed.ncbi.nlm.nih.gov/34001096/

Variation in the *IFNL4* Gene Associated with Increased Infection Risk in African Children
Genetic code variations within the interferon lambda *(IFNL) 3* and *4* genes that code for type III interferons have been strongly associated with clearance of hepatitis C virus. Scientists investigated if these interferons are also key in the immune response to pathogens other than hepatitis C. In a cohort of 914 Malian children, researchers found variants in the *IFNL4* gene were correlated with episodes of malaria, gastrointestinal, and respiratory infections recorded at 30,626 clinic visits. One specific *IFNL4* gene variant, or allele, the *rs368234815-dG* allele, was associated with an earlier first episode of gastrointestinal infection as well as increased risk for gastrointestinal infection and malaria during follow up. This supports a role for type III interferons, and specifically for *IFN-λ4* (coded by the *IFNL4* gene), in the immune response to several infections in young children in Africa.
Supported by: NIAID, NCI
Grants: Intramural Research (NCI) ZIACP010201, Intramural Research (NIAID) ZIAAI001063, ZIAAI000723
Publications: https://pubmed.ncbi.nlm.nih.gov/33850301/

Gene Therapy Restores Immune Function in Children with Adenosine Deaminase Deficiency, a Rare Severe Combined Immunodeficiency
Adenosine Deaminase (ADA)–Deficient Severe Combined Immunodeficiency (SCID), which is estimated to occur in approximately 1 in 200,000 to 1,000,000 newborns worldwide, is caused by mutations in the *ADA* gene. This impairment leaves children highly susceptible to severe infections. If untreated, the disease is fatal, usually within the first two years of life. An investigational gene therapy was shown to safely restore the immune systems of infants and children with ADA-SCID. In clinical trials, 48 of the 50 children who received the gene therapy retained their replenished immune system function two to three years later and did not require additional treatments for their condition. These findings suggest that this novel experimental gene therapy may be a viable treatment option for young children with ADA-SCID.
Supported by: NIAID, NHLBI, NHGRI
Grants: U01AI100801, P01HL073104, Contract (NHLBI) 75N92019D00018
Publications: https://pubmed.ncbi.nlm.nih.gov/33974366/
News Link: Gene Therapy Restores Immune Function Children Rare Immunodeficiency

Genetics of Inflammatory Bowel Disease in Children
To understand the underlying causes of inflammatory bowel disease (IBD) in children, scientists examined the expression of a protein called MDA5 in 42 children with inflammatory bowel disease. MDA5, a protein encoded by the *IFIH1* gene in humans, has a central role in virus detection. Rare variants of MDA5 were identified in eight patients and additional analyses showed complete and partial MDA5 deficiency was associated with very early onset IBD, suggesting that impaired intestinal viral detection could be a mechanism for IBD in children.
Supported by: NIAID, NHGRI
Grants: Intramural research (NIAID) ZIAAI001059, UM1HG006542
Publications: https://pubmed.ncbi.nlm.nih.gov/34185153/

Severe Delayed Hypersensitivity Reactions to Immunosuppressants Linked to a Common Genetic Profile
Over the past decade, a potentially lethal form of lung disease has emerged among a subset of children with systemic juvenile idiopathic arthritis (sJIA) receiving treatment with interleukin-1 (IL-1) and interleukin-6 (IL-6) inhibitors. In a recent clinical study, scientists discovered that all sJIA and adult-onset Still's disease participants with lung disease, and some without, experienced delayed hypersensitivity reactions to the treatment they had received. Further, a specific genetic marker was strongly linked to the development of delayed hypersensitivity reactions. Therefore, pre-treatment screening for this gene may prevent delayed hypersensitivity reactions and improve treatment safety. Additionally—as this marker is quite common, and several of these immunosuppressants have recently been used in patients experiencing cytokine storms due to severe COVID-19—these results suggest caution when using the drugs to treat people who have COVID-19.
Supported by: NIAMS, NHGRI
Grants: Intramural Research (NIAMS) ZIAAR041198, Intramural Research (NHGRI) ZIAHG200370
Publications: https://pubmed.ncbi.nlm.nih.gov/34789453/

Clinical Care, Outreach, and Services

Legacy-Making Activities Improve Emotional Symptoms for Children in Pediatric Palliative Care and Their Families
Legacy-making interventions are opportunities for seriously ill individuals to document their lives, providing reassurance that they will be remembered after death. To help children with advanced illness record their legacies, researchers adapted a face-to-face legacy-making intervention to a more portable

web-based model that allowed children with advanced cancer and their parents to participate. The intervention improved emotional symptoms for participating children, parents, and families.
Supported by: NINR, NCATS
Grants: U24NR014637, U2CNR014637, UL1TR000445
Publications: https://pubmed.ncbi.nlm.nih.gov/31804281/

Patients' Informed Access to Noninvasive Prenatal Genetic Testing
Noninvasive prenatal genetic testing is expanding rapidly. Researchers studied the interaction between the patient and provider to understand factors critical to informed and shared decision-making. Their findings suggested that primary drivers in patient decision-making about use of these technologies were outdated or inaccurate perceptions of advanced maternal age and procedure-related risks to the fetus, and financial considerations. Researchers also found many patients felt a mismatch between their priorities at the first prenatal visit and those of their providers.
Supported by: NHGRI
Grants: R01HG010092
Publications: https://pubmed.ncbi.nlm.nih.gov/32441820/

Peer Support and Disparities in Outpatient Mental Health Service Use among Minority Youth with Serious Mental Illness
Racial and ethnic minority youth face disparities in both mental health treatment and outcomes. Researchers examined whether the availability of peer support reduces disparities in service use among racial and ethnic minority youth with serious mental illness 16–24 years of age in Los Angeles and San Diego Counties. Using administrative data from 2015–2018, scientists summarized service use among 13,363 transition-age youth who received services from 183 outpatient public mental health programs. Nearly half (46%) of youth received services from programs that employed peer specialists. The availability of peer support was associated with an increase in annual outpatient visits; in Los Angeles County only, peer support was also associated with reductions in service use disparities among African American or Black and Hispanic or Latino youth.
Supported by: NIMHD
Grants: R01MD011528
Publications: https://pubmed.ncbi.nlm.nih.gov/32728991/

Dental Caries Disparities Among Medicaid-Enrolled Young Children
Low-income and racial/ethnic minority children are more likely to experience dental caries (tooth decay) than non-Hispanic White children. Because low-income families are more likely to bring their children to well-child visits than preventive dental visits, the U. S. Preventive Services Task Force (USPSTF) has recommended that pediatricians help address the gaps in access to preventive dental care. Researchers assessed oral health among Medicaid-enrolled young children (3 to 6 years of age) seen in primary care settings and reported on the predictors of caries in this population. Overall, nearly half (49%) of the children had dental caries, with African American or Black children having significantly higher frequency of untreated and overall caries compared to non-African American or Black children. Race, increased age, and lower oral health-related quality of life among caregivers were associated with greater likelihood of the child having caries. This study shows that racial disparities affect the rates of untreated and overall caries in Medicaid-enrolled children.

Supported by: NIDCR
Grants: UH3DE025487, U01DE025507
Publications: https://pubmed.ncbi.nlm.nih.gov/33135213/

Adolescent and Young Adult Cancer Survivors Should be Encouraged to Follow Screening Guidelines to Mitigate Late Effects of Cancer Treatment

Pediatric, adolescent, and young adult cancer survivors are all at risk of late adverse effects of treatment for their cancers. Cardiovascular complications are a particularly serious group of complications, and early detection of cardiovascular abnormalities is essential. Although screening guidelines for early detection have been established, in a recent study researchers found that adolescent and young adult cancer survivors had low adherence to the screening guidelines.
Supported by: NCI
Grants: R21CA198042
Publications: https://pubmed.ncbi.nlm.nih.gov/33170480/

Telemedicine for the Physical Examination of Children with Fetal Alcohol Spectrum Disorders
Early diagnosis (before 6 years of age) offers the best chance for improved outcomes for children with fetal alcohol spectrum disorders (FASDs). However, access to specialists can be a barrier to care, particularly in underserved or rural areas. Researchers compared the diagnostic accuracy of face-to-face physical examinations and two different telemedicine systems (a specialized mobile assessment station and a secure video conferencing platform). Scientists demonstrated that telemedicine can be used to accurately distinguish between the physical features of fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (pFAS), and no fetal alcohol syndrome. This approach holds promise for populations in underserved areas.
Supported by: NIAAA
Grants: U24AA014815, R00AA022661
Publications: https://pubmed.ncbi.nlm.nih.gov/33316074/

Early Identification and Service Linkage for Children with Autism Spectrum Disorder
Early identification of autism spectrum disorder (ASD) is associated with improved cognitive and behavioral outcomes. Unfortunately, low-income and racial/ethnic minority families often have limited access to diagnostic and treatment services. Researchers tested a comprehensive service systems intervention aimed at addressing these disparities. In the study, researchers provided an intervention coordinator (called a "family navigator") for families of children who were detected in primary care settings as having increased likelihood, but still undiagnosed, for ASD. The researchers found that utilizing "family navigators" to engage caregivers in recommended services improved the likelihood of receiving diagnoses among children from families with increased likelihood for ASD.
Supported by: NIMH
Grants: R01MH104355, K23MH109673, R01MH104355-02S1
Publications: https://pubmed.ncbi.nlm.nih.gov/33427861/

Racial and Ethnic Disparities in Acute Care Use for Pediatric Asthma
Research has shown that African American or Black and Hispanic or Latino populations have the highest asthma-related emergency department (ED) use. Scientists measured disparities by race, ethnicity, and language in pediatric acute asthma care using data from U.S. primary care community health centers. The researchers compared clinic visits for asthma flare-ups among African American or Black children, English-preferring Hispanic or Latino children, Spanish-preferring Hispanic or Latino children, and White children 3 to 17 years of age. African American or Black children had lower use of clinics, whereas Spanish-preferring Hispanic or Latino children had higher use, including for acute asthma attacks.
Supported by: NIMHD
Grants: R01MD011404
Publications: https://pubmed.ncbi.nlm.nih.gov/35346926/

Antimicrobial Peptide Variant is Associated with Pediatric Urinary Tract Infections
Pediatric urinary tract infections (UTIs) are more prevalent in girls than in boys. UTIs can lead to kidney damage, high blood pressure, and chronic kidney disease. RNASE7, an antimicrobial peptide produced in the body, protects the urinary tract from infection with certain types of bacteria. Researchers found a

higher prevalence of a specific genetic variant of RNASE7 in girls with UTIs, compared with those without UTIs. They also showed that cells with this variant are less able to kill or be protected from infection with certain bacteria. Hence, this is a new potential risk factor for pediatric UTI and may help to improve treatments and health of children who develop UTI in the future.
Supported by: NIDDK
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Publications: https://pubmed.ncbi.nlm.nih.gov/34779412/

Coronavirus Disease 2019 (COVID-19)

Children Exhibit Distinct Antibody Responses Compared with Adults with COVID-19
Severe respiratory symptoms are seldom seen in children with COVID-19, while adults exhibit symptoms of varying severity. Occasionally, different organs (e.g., heart, lungs, kidney, brain, skin, gastrointestinal) become inflamed in children with COVID-19, resulting in a condition called multisystem inflammatory syndrome in children (MIS-C), leading to a variety of symptoms that can potentially become life threatening. Researchers investigated the antibody response after SARS-CoV-2 infection in adult and pediatric patients. The results suggest that children have different patterns of antibody responses to the virus and a distinct infection course compared with adults, indicating the importance of developing strategies specifically focused on children in order to prevent development of MIS-C.
Supported by: NIAID, NINDS, NIDDK
Grants: U01AI100119, R01AI121349, U19AI128949, K23AI141686, R01AI146980, R0AI1114736, R01NS105699, R01NS091263, K08DK122130, P01AI106697
Publications: https://pubmed.ncbi.nlm.nih.gov/33154590/

Dysfunction in Gastrointestinal Barrier and Multisystem Inflammatory Syndrome in Children
Weeks after SARS-CoV-2 exposure or infection, some children develop a severe, life-threatening illness called multisystem inflammatory syndrome in children (MIS-C). Many patients with MIS-C have gastrointestinal symptoms—including abdominal pain, vomiting, and diarrhea—with a severe inflammation that can potentially cause heart problems. Researchers analyzed blood samples and fecal samples from 100 children, including 19 with MIS-C and 26 with acute COVID-19. They found that higher levels of the SARS-CoV-2 virus in the gastrointestinal tract led to cells releasing more zonulin, a protein that regulates the permeability of the intestinal barrier. The viral spike proteins has been thought to have a similar structure to the antigen that causes toxic shock syndrome (TSS), which has similar symptoms to MIS-C. The researchers also treated one patient with a molecule that counteracts zonulin, which resulted in less viral spike protein in the bloodstream, along with clinical improvement. The results from this study identify potential targets for diagnosing, preventing, and treating MIS-C in children.
Supported by: NICHD, NIDDK, NHLBI, NIAID
Grants: R01HD100022, P30DK040561, P30DK043351, R01DK104344, T32HL007627, K08HL143183, R01AI072726
Publications: https://pubmed.ncbi.nlm.nih.gov/34032635/

No Serious Adverse Events from COVID-19 Vaccine in Breastfeeding Women or Their Children
In 2020, the FDA granted emergency use authorization for the Pfizer-BioNTech and Moderna messenger RNA (mRNA) COVID-19 vaccines after evaluating clinical trial data and determining their safety and effectiveness for prevention of COVID-19, in individuals 12 years of age and older (Pfizer-BioNTech) and 18 years of age and older (Moderna). Although the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) recommended these vaccines be made available to breastfeeding women, this population was excluded from the initial trials. Researchers sought to evaluate potential adverse effects from the vaccine in a group of 180 breastfeeding women and their infants. They collected information from women on symptoms and their children's

outcomes for seven days after each dose of vaccine. No serious adverse events were reported by women receiving either the Pfizer-BioNTech or Moderna COVID-19 vaccine, either among themselves or in their infants. Women were more likely to report a reduction in milk supply after the second dose of the Moderna vaccine than after the second dose of the Pfizer vaccine. However, all women reported a return to normal milk volume within 72 hours.
Supported by: NICHD, NCATS
Grants: R21HD104412, UL1TR001442
Publications: https://pubmed.ncbi.nlm.nih.gov/34492204/
News Link: No Serious Adverse Events from COVID-19 Vaccine in Breastfeeding Women or Their Children

Diabetes

Increases in Youth Living with Diabetes in the United States

Diagnosed cases of type 1 and type 2 diabetes are surging among youth in the United States. From 2001–2017, the number of people under 20 years of age living with type 1 diabetes increased by 45%, and the number living with type 2 diabetes grew by 95%. Type 1 diabetes remains more common among White youth than among youth from racial or ethnic minority groups, while type 2 diabetes remains more common among youth in racial or ethnic minority groups than among White youth. The greatest increases in type 2 diabetes prevalence were seen in youth who are Black or Hispanic, and the highest number of youth per 1,000 living with type 2 diabetes were seen in youth who are Black or American Indian. These findings—– from a study funded by both the CDC and the NIH—– highlight highlight the continued need for research to prevent and treat type 1 and type 2 diabetes.
Supported by: NIDDK, NCATS
Grants: R01DK127208, UC4DK108173, P30DK057516, UL1TR000062, UL1TR001450, UL1TR000423, UL1TR000154, UL1TR000077, UL1TR001425
Publications: https://pubmed.ncbi.nlm.nih.gov/34427600/
News Link: New Research Uncovers Concerning Increases in Youth Living with Diabetes in the U.S.

Long-Term Complications in Youth-Onset Type 2 Diabetes

The prevalence of type 2 diabetes in youth is increasing, and more information is needed about how diabetes-related complications occur as these youths transition to adulthood. In a longitudinal study of youth with type 2 diabetes, researchers found that the risk of complications, including microvascular complications, increased steadily over time and affected most participants by the time of young adulthood. Complications were more common among participants of minority race and ethnic groups and among those with hyperglycemia, hypertension, and dyslipidemia.
Supported by: NCATS, NIDDK
Grants: U01DK061212, U01DK061230, U01DK061239, U01DK061242, U01DK061254, M01RR000036, M01RR000043, M01RR000069, M01RR000084, M01RR001066, M01RR000125, M01RR014467, UL1RR024134, UL1RR024139, UL1RR024153, UL1RR024989, UL1RR024992, UL1RR025758, UL1RR025780
Publications: https://pubmed.ncbi.nlm.nih.gov/34320286/

Global Pediatric Health

Confirming Safety of Low-Dose Aspirin to Reduce Preterm Birth Risk in Low- and Middle-Income Countries

According to the World Health Organization (WHO), each year 15 million infants are born preterm—meaning before the 37th week of pregnancy. Worldwide, preterm birth is the leading cause of death among children under 5 years of age, accounting for roughly 1 million deaths each year. Advances in

newborn care have improved survival for preterm infants, but this care is limited or unavailable in many low- and middle-income countries. Researchers analyzed data from a prior study to determine if daily low-dose aspirin might increase the risk for emergency medical visits or for nausea, vomiting, rash or hives, diarrhea, gastritis, vaginal bleeding, allergic reaction, and any other potential side effects. The original study enrolled 11,976 women who were pregnant for the first time with a single fetus from seven sites in India, Pakistan, Zambia, Democratic Republic of the Congo, Guatemala, and Kenya. Researchers found no statistically significant increased risk for an emergency medical visit between the two groups. For seven of the eight potential side effects the researchers assessed, there was no statistical difference between groups. However, 4.2% of women in the group given aspirin developed a rash or hives, compared with 3.5% in the placebo group. None of the rashes or hives were serious or required emergency medical care or hospitalization. This suggests that daily low-dose aspirin from 6–36 weeks of pregnancy appears to be a well-tolerated, safe intervention for reducing the risk of preterm birth in low- and middle-income countries.
Supported by: NICHD
Grants: UG1HD076457
Publications: https://pubmed.ncbi.nlm.nih.gov/34085052/
News Link: NIH-funded Study Confirms Safety of Aspirin to Reduce Preterm Birth Risk in Low- and Middle-Income Countries

Injuries, Maltreatment, and Violence

Brain Response to Mindfulness Interventions Among Young Adults Who Were Maltreated as Children

Studies have shown that childhood abuse is a significant risk factor for various mental health issues, including depression, anxiety, and post-traumatic stress disorder (PTSD). The amygdala is a part of the brain with a left and right side that regulates responses to fear and stress. Researchers used brain imaging to assess changes in the right and left amygdala following a mindfulness-based intervention in young adults who experienced maltreatment as children. The scientists found differences in the right and left amygdala, depending on when the abuse occurred (early childhood versus adolescence). They also found differences based on measures such as self-compassion, stress, and interpersonal distress.
Supported by: NCCIH
Grants: K01AT009085
Publications: https://pubmed.ncbi.nlm.nih.gov/33249071/

Bruising Clinical Decision Rule Can Correctly Identify Abuse Cases

Bruising is the most common injury from physical child abuse, but it is easily overlooked or misdiagnosed because accidents can also cause bruising. A team of scientists developed a “bruising clinical decision rule” to help detect whether bruising to several specific areas of the body was due to child abuse. Clinical decision rules can be especially important for detecting maltreatment in infants and young children who are at the highest risk of serious, potentially fatal abuse, and who are too young or afraid to state what happened. The scientists studied more than 2,000 children in pediatric emergency departments at five urban children’s hospitals. After the researchers carefully evaluated each child and photographed all bruises, an expert panel reviewed the anonymized data and categorized each case as abuse (410), nonabuse (1,713), or indeterminate (38). The scientists found that bruising on the torso, ear, and neck correctly identified 81% of abuse patients. However, the researchers cautioned that the rule was valid only in children under 4 years of age who had bruises at the time of examination. Moreover, the validated decision rule was not intended to diagnose abuse definitively, but to function as a screening tool to improve the recognition of potentially abused children with bruising, who may require further evaluation.
Supported by: NICHD, NCATS

Grants: UL1TR001863, R01HD102428, R01HD060997
Publications: https://pubmed.ncbi.nlm.nih.gov/33852003/

Childhood Gun Access, Adult Suicidality, and Crime
Childhood gun access is a risk factor for firearm-related suicides, homicides, and unintentional injuries. Researchers used a 20-plus-year community-representative longitudinal sample from a mixed urban-rural population of the Southeast United States to examine whether access to guns in childhood is associated with increased risk for criminality and suicidality after the transition to adulthood. Researchers analyzed data on 1,420 children (9–16 years of age) at multiple times during childhood about access to guns in their home. They followed up the children four additional times in adulthood (at 19, 21, 25, and 30 years of age) about criminality and suicidality. Of the children in homes with guns, about 63% had access to a gun, and 25% owned a gun themselves. Having gun access as a child was associated with higher levels of carrying and owning guns as adults, exposure to gun violence, criminality, and suicidality, even after adjusting for other factors. The risk of adult criminality and suicidality among those with childhood in-home gun access was greatest in White, male individuals; those living in urban areas; and children with a history of behavior problems. Even in these groups, however, most children did not display adult criminality or suicidality.
Supported by: NICHD, NIMH, NIDA, NCATS
Grants: R01HD093651, R01MH117559, R01DA040726, P30DA023026, UL1TR000142, R01MH104576, R01DA011301
Publications: https://pubmed.ncbi.nlm.nih.gov/34210740/

Home Visit Program After Birth May Reduce Incidence of Child Maltreatment
Children in their first year of life have the highest rate of child abuse victimization. Family Connects is a program that arranges for one to three home visits for new parents from trained nurses when the baby is about 3 weeks of age. During visits, nurses educate parents on infant care and assess infant and maternal health needs, parenting and childcare plans, and such aspects of parent well-being as mental health, substance use, and availability of social and emotional support. The visiting nurses also refer families to appropriate community resources, such as childcare agencies, mental health counseling, social services, and long-term programs such as Early Head Start. Researchers studied the effects of this program in a group of families of 4,777 infants. The families were assigned at random to receive the nurse visits or usual hospital services for newborns. Researchers reviewed subsequent hospital and child protective services records for five years after the children's births. The researchers found that children whose families participated in Family Connects experienced fewer average investigations for suspected child abuse and fewer emergency department visits in the first five years of life, compared with children in the usual services group.
Supported by: NICHD
Grants: R01HD069981
Publications: https://pubmed.ncbi.nlm.nih.gov/34232300/
News Link: Home Visit Program After Birth May Reduce Incidence of Child Maltreatment

Intellectual and Developmental Disabilities, Neurological Disorders, and Mental Health

Potential Gene Therapy for Angelman Syndrome
Angelman syndrome (AS) is a severe neurodevelopmental disorder caused by a mutation or deletion of the maternally inherited copy of the *UBE3A* gene. In a new study, researchers devised a gene editing strategy to unsilence the paternal *UBE3A* copy in neurons and thereby compensate for mutation or deletion of the maternal copy. In a mouse model of AS, administering this gene targeting therapy during the embryonic and early postnatal stages reduced structural and behavioral impairments.

Supported by: NINDS, NIMH, NICHD, NCI
Grants: R01MH120125, R01NS109304, P50HD103573, P30CA016086, P30NS045892
Publications: https://pubmed.ncbi.nlm.nih.gov/33087932/
News Link: Scientists Take Major Step Toward Angelman Syndrome Gene Therapy

Presymptomatic Training Could Delay and Reduce Symptoms in Rett Syndrome
Mutations in the gene *MECP2* cause Rett syndrome, a severe and progressive neurological disorder with no effective treatments. Children with Rett syndrome develop normally for their first one or two years of life, then develop profound motor and cognitive decline. Researchers hypothesized that intensive motor and cognitive training during the early period of normal development could reduce the severity of eventual disease. In a mouse model of Rett syndrome, they showed that beginning intensive training in the presymptomatic period, but not after symptom onset, improved performance on motor and memory tasks and significantly delayed the onset of disease symptoms. The researchers also showed that the improvements were associated with structural and functional changes in neurons that were repeatedly activated during training. These results suggest a rationale for genetic screening that would identify children affected by Rett syndrome early and allow for presymptomatic intervention.
Supported by: NINDS, NICHD
Grants: F30HD097871, P50HD103555, R01NS057819, U54HD083092
Publications: https://pubmed.ncbi.nlm.nih.gov/33762729/
News Link: Behavioral Training Could Help Babies with Rett Syndrome, Mouse Study Suggests

Early Signs of Fragile X Syndrome
People with Fragile X syndrome (FXS) usually have delays in learning to walk and talk, as well as anxiety and behavior problems. Most children with FXS are not diagnosed until preschool or school age, so researchers know little about when symptoms of FXS first occur in infants and toddlers, and what those symptoms look like. This makes diagnosis at an early age—when therapies would be most effective—difficult. Another type of mutation in the *FMR1* gene involves having a medium number of DNA repeat. This type of mutation—called the *FMR1* premutation—can cause health problems in adults. Researchers are still trying to understand whether the premutation also causes health or developmental problems in children. To learn more, scientists combined data from eight studies that together included nearly 1,200 evaluations of the developmental progress of 508 children who carried either the full mutation or a premutation of the *FMR1* gene. The researchers found that boys with a full mutation of *FMR1* showed developmental delays in learning, motor skills, and language development as early as 6 months of age. Most girls with a full mutation showed language and motor delays before their first birthday. Children with a premutation were mostly typical in their development, but they had mild delays in fine motor skills by 18 months of age. The researchers hope their findings will allow earlier detection and treatment of FXS and Fragile X–associated conditions.
Supported by: NICHD, NINDS, NIMH
Grants: R01MH091131, R01MH090194, R01HD038819, P30HD003110, R01HD056031, U01NS096767, R01MH107573
Publications: https://pubmed.ncbi.nlm.nih.gov/33911031/

Scientists Discover a New Genetic Form of Amyotrophic Lateral Sclerosis in Children
In a study of 11 medical-mystery patients, an international team of researchers discovered a new and unique form of amyotrophic lateral sclerosis (ALS). Unlike most cases of ALS, the disease began attacking these patients during childhood, worsened more slowly than usual, and was linked to a gene called *SPTLC1* that is part of the body's fat-production system. Preliminary results in experiments using cells from patients suggested that genetically silencing *SPTLC1* activity may be an effective strategy for combating this type of ALS.
Supported by: NINDS
Grants: Intramural research (NINDS), K08NS107621, R01NS072446

Publications: https://pubmed.ncbi.nlm.nih.gov/34059824/
News Link: Scientists Discover New Genetic form of ALS in children

Epileptic Seizures in Children Detected by Cardiac Activity
Detecting seizures immediately is important so that caregivers of people with seizure disorders can quickly provide potentially life-saving interventions. Measuring brain activity via an electroencephalogram (EEG) is the gold standard method for detecting seizures in clinical settings. But this is generally impractical on a day-to-day basis because EEGs require electrodes to be connected to a patient's head. Changes in cardiac activity during seizures have been studied for some time and this method is now being used to predict seizures. A study in 62 children with limited physical activity showed that cardiac measures can detect seizures with high sensitivity.
Supported by: NIBIB
Grants: R01EB014742
Publications: https://pubmed.ncbi.nlm.nih.gov/34147021/

Oxytocin Does Not Improve Social Functioning in Children with Autism Spectrum Disorder
Autism spectrum disorder (ASD) is a complex neurological and developmental disorder that begins early in life and affects how a person interacts with others, communicates, and learns. Many individuals with ASD have been prescribed oxytocin by their physicians. Several small studies have tested the potential of oxytocin to improve social functioning in ASD, but have produced inconsistent results. Researchers gave oxytocin daily for 24 weeks by nasal spray to children with ASD who are minimally or fluently verbal. Of those completing the study, 139 received oxytocin and 138 received a placebo. During the study, participants' caregivers rated them on a questionnaire measuring irritability, social withdrawal, and other behaviors associated with ASD. When the participants completed the trial, the differences between the two groups' initial score and last score did not differ significantly. The researchers concluded that the 24-week course of oxytocin did not improve social interaction or other measures of social function related to ASD.
Supported by: NICHD, NCATS
Grants: U01HD073984, UL1TR002489
Publications: https://pubmed.ncbi.nlm.nih.gov/34644471/
News Link: Oxytocin Does Not Improve Social Functioning in Children with Autism Spectrum Disorder

Multistage Autism Screening in Early Intervention Settings May Reduce Disparities
Early identification can help children with autism spectrum disorder (ASD) receive services and supports as early as possible, improving their daily functioning and well-being. However, many families may not receive early screening and diagnosis due to disparities in access. For example, families with low household income, families that are non–English speaking, and families that belong to certain racial or ethnic minority groups are much less likely than other families to receive timely ASD diagnosis. Researchers found that a multistage screening method, compared with standard screening methods, was associated with a substantial increase in ASD diagnoses compared with standard care; the most significant increases among Spanish-speaking families compared with English-speaking families. This study suggests that multistage screening for ASD may improve early ASD detection and reduce health disparities.
Supported by: NIMH
Grants: R01MH104400
Publications: https://pubmed.ncbi.nlm.nih.gov/34982099/
News Link: Multistage Autism Screening in Early Intervention Settings May Reduce Disparities

Changes in Brain's Visual Areas in Infancy May Precede Autism Diagnosis
Researchers theorized that disruption in visual processing could interfere with how infants see the world around them, changing how they interact with and learn from caregivers and their environment. These

early changes could affect further brain development and play a role in autism spectrum disorder (ASD) symptoms. The study enrolled 384 pairs of siblings, the oldest of which had been diagnosed with ASD. Previous research by the team found that younger siblings were more likely to develop ASD if their older siblings had higher levels of ASD traits. Researchers performed magnetic resonance imaging (MRI) scans on the brains of the younger siblings at 6, 12, and 24 months of age. Infants who were diagnosed with ASD at 24 months of age had differences in the visual processing areas of the brain that were apparent at 6 months of age. Among the 89 younger siblings who developed ASD, those whose older siblings had severe ASD traits had greater volume and surface area of the cerebrum, which controls speech, thought, emotions, reading, writing, and learning; larger surface area in the part of the visual cortex important for recognizing objects; and less mature connections in the splenium, which connects the brain's left and right visual cortices and plays a role in visual attention.
Supported by: NICHD, NIMH, NINDS
Grants: K01MH122779, R01HD055741, T32HD040127, P30HD003110, R01MH118362, R01MH118362, P30NS098577
Publications: https://pubmed.ncbi.nlm.nih.gov/35615814/
News Link: Changes in Brain's Visual Areas in Infancy May Precede Autism Diagnosis

Amygdala Overgrowth That Occurs in Autism Spectrum Disorder May Begin During Infancy
Autism spectrum disorder (ASD) is a complex developmental disorder that affects how a person behaves, interacts with others, communicates, and learns. To assess brain differences in children with ASD, researchers studied 408 infants, 270 of whom were at higher likelihood of ASD because they had an older sibling with ASD; 109 typically developing infants; and 29 infants with Fragile X syndrome (FXS), an inherited form of developmental and intellectual disability that is also associated with ASD. The researchers conducted magnetic resonance imaging (MRI) scans of the children at 6, 12 and 24 months of age. The scientists discovered that the amygdala—a brain structure enlarged in children 2 years of age who are diagnosed with ASD—begins its accelerated growth between 6 and 12 months of age. The amygdala is involved in processing emotions, such as interpreting facial expressions or feeling afraid when exposed to a threat. The findings indicate that therapies to reduce the symptoms of ASD might have the greatest chance of success if they begin in the first year of life, before the amygdala begins its accelerated growth.
Supported by: NICHD, NIMH, NIBIB
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Publications: https://pubmed.ncbi.nlm.nih.gov/35331012/
News Link: Amygdala Overgrowth That Occurs in Autism Spectrum Disorder May Begin During Infancy

Micronutrients and Attention-Deficit/Hyperactivity Disorder in Youths
Researchers conducted a randomized clinical trial to evaluate whether micronutrients could reduce Attention-Deficit/Hyperactivity Disorder (ADHD) irritability symptoms in 135 children 6 to 12 years of age who were not taking medication for ADHD. Children at three sites were randomized to take multiple capsules daily of either a placebo or micronutrient formula for eight weeks. The micronutrient formula consisted of all known essential minerals and vitamins plus amino acids and antioxidants. After eight weeks, the micronutrient formula showed benefit over placebo when symptoms were measured by clinicians, but not when symptoms were assessed by parents. No serious adverse events or clinically significant changes were seen in either group, and there were no differences between the two groups in treatment-related side effects.
Supported by: NCCIH, NCATS
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Publications: https://pubmed.ncbi.nlm.nih.gov/34303786/

Nutrition and Obesity

Genetic Risk Factors and Disease Severity in Children with Nonalcoholic Fatty Liver Disease
Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in children. To identify key genetic factors related to NAFLD, researchers analyzed single nucleotide polymorphisms in children with confirmed NAFLD. The scientists found several factors associated with the severity of disease, identifying possible targets for new treatment approaches.
Supported by: NIDDK, NCATS
Grants: U01DK061731, UL1TR000006, P30DK120515, U01DK061728, UL1TR000454
Publications: https://pubmed.ncbi.nlm.nih.gov/35560106/
Website: Nonalcoholic Steatohepatitis Clinical Research Network

Assessing Genetic and Dietary Risk Factors for Nonalcoholic Fatty Liver Disease
Nonalcoholic fatty liver disease (NAFLD) can progress to a buildup of scar tissue called liver fibrosis. If diagnosed early, liver fibrosis may be reversible, so it is necessary to understand risk factors. Researchers sought to identify potential biological and dietary components that influence liver fibrosis. The scientists also assessed whether the association between dietary components and liver fibrosis differs by a specific genotype found more frequently in Hispanic or Latino adolescents. Researchers found that arachidonic acid, an essential fatty acid, was associated with liver fibrosis after accounting for sex, genotype, and liver fat. Results from this study suggest that reduction of arachidonic acid and polyunsaturated fatty acid intake might be important for the prevention of NAFLD progression.
Supported by: NIMHD, NICHD
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Publications: https://pubmed.ncbi.nlm.nih.gov/34065978/

Seasonal Variability in Weight Gain among American Indian, Black, White, and Hispanic Children
Research has shown that children gain more weight during the summer, but most of these studies have not included American Indian or Alaska Native children. Researchers studied seasonal weight variation among racial and ethnic minority children—including 2,184 American Indian and Alaska Native children—over three and a half years. Children of American Indian and Alaska Native, Hispanic or Latino, and African American or Black backgrounds had significantly higher baseline obesity rates than White children. During the summer, children accumulated more weight, and children with obesity experienced the greatest effects. American Indian and Alaska Native children had higher overall obesity rates and lower seasonal variability than White children. The findings suggest that while summer may be a vital time for obesity prevention among children with overweight/obesity in general, differing seasonal trends among American Indian and Alaska Native children may require ongoing prevention efforts in this population.
Supported by: NIMHD
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Publications: https://pubmed.ncbi.nlm.nih.gov/33632651/

Long-Term Effects of a Comprehensive Preschool Program on Obesity
Obesity is associated with increased risk of many serious diseases and health conditions. Researchers assessed the long-term effects of a preschool program that was designed to improve health and educational equity. The main elements of the program, which was targeted to low-income families, included small classes, individualized learning experiences, parenting classes on health and nutrition, support groups, and community engagement. Researchers measured the body mass index (BMI) and obesity at 37 years of age for children who particiapted in the program, comparing their results with those for a similar group of children who grew up in poverty. Furthermore, they examined and assessed the effects of covariables—including gender, neighborhood characteristics, and family sociodemographic risk factors—on this association. The results showed that female participatns had lower BMI and were less

likely to be obese compared with women who had not attended the program. No differences by program participation were found for male individuals, however.
Supported by: NICHD, NIMH
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Publications: https://pubmed.ncbi.nlm.nih.gov/33749715/

Microbiome-Directed Foods for Childhood Malnutrition
Researchers developed a "microbiota-directed complementary food" containing ingredients from locally available, nutrient-dense foods. When given to malnourished children living in Bangladesh along with their regular diet, this gut microbiome–directed food improved growth and neural development. This therapeutic food intervention holds promise as a more effective treatment for childhood malnutrition.
Supported by: NIDDK
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Publications: https://pubmed.ncbi.nlm.nih.gov/33826814/

Guided Imagery Might Increase the Effect of Other Approaches to Improve Diet and Exercise in Latinx Youth
Latinx adolescents suffer from a high rate of obesity and obesity-related problems, such as type 2 diabetes. Scientists studied whether a lifestyle behavioral approach combined with guided imagery (Imagine HEALTH) could reduce stress and change negative behaviors, including unhealthy diet, in Latinx youth. Guided imagery is a program where an instructor (live or taped) helps direct one's thoughts and guides the imagination toward a more relaxed, focused state. The researchers found that Imagine HEALTH improved eating habits, reduced sedentary activity, and increased physical activity, suggesting that guided imagery combined with lifestyle education could help improve health in Latinx youth.
Supported by: NCCIH
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Publications: https://pubmed.ncbi.nlm.nih.gov/34037459/

Development and Application of a Total Diet Quality Index for Toddlers
The 2020–2025 Dietary Guidelines for Americans include recommendations for infants and toddlers under 2 years of age. Researchers created and evaluated a diet quality index based on a scoring system for 12–23.9 months of age, called the Toddler Diet Quality Index (DQI). Children with a higher Toddler DQI score had better diet quality. Toddlers under-consumed seafood, greens, beans, and plant proteins, and over-consumed refined grains and added sugars. Toddler DQI scores were higher among children who were breastfed for any amount of time, lived in households with higher incomes, and who were Hispanic or Latino. The Toddler DQI performed as expected and offers a measurement tool to assess the dietary quality of young children in accordance with federal nutrition guidelines.
Supported by: NIMHD
Grants: U54MD012530
Publications: https://pubmed.ncbi.nlm.nih.gov/34198828/

Characterizing Dietary Supplement Usage Among U.S. Children and Young Adults
NIH scientists characterized dietary supplement usage among U.S. children and young adults, helping to better understand whether specific pediatric age groups and populations are achieving adequate intakes of certain nutrients. A study of vitamin D intake in infants (1–13 months of age) from a national sample participating in the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) from 2013–2015 found that a small percentage of children received supplemental vitamin D, and breastfed infants who did not receive supplementation were less likely to meet the recommendation than those who were formula fed across 3–13 months of age. Researchers characterized trends in micronutrient-containing dietary supplement intake, based on data from National Health and Nutrition

Examination Survey. They found that supplement usage among food-insecure children (1–18 years of age) increased from 24% to 31% over the years 2007–2018.
Supported by: OD/DPCPSI/ODS
Publications: https://pubmed.ncbi.nlm.nih.gov/35288058, https://pubmed.ncbi.nlm.nih.gov/35918260/

Pain and Pain Management

Use of Medications for Neonatal Opioid Withdrawal Syndrome

Due to the ongoing opioid epidemic, more than 32,000 infants a year are exposed to opioids before birth. Many of these infants go through opioid withdrawal shortly after birth—a process that can cause tremors, seizures, vomiting, and fever, among other symptoms. When swaddling or keeping the infant in a quiet, dark room aren't enough to manage an infant's symptoms, doctors will consider adding medication to the infant's treatment. In addition to morphine-based tapered medication, doctors may prescribe either phenobarbital or clonidine. Researchers looked at medical records of infants who underwent opioid withdrawal after birth. Phenobarbital had been given to 108 infants; 72 infants had received clonidine as part of their treatment. The researchers found that infants treated with phenobarbital had shorter hospital stays than infants who received clonidine. This was likely due to differences in how each medication can be administered. Clonidine is administered only in the hospital, so infants must remain there until they are well enough to stop treatment. In contrast, phenobarbital can be administered by caregivers, meaning that children can leave the hospital sooner and continue treatment at home.
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Grants: UG1OD024944, U10HD027904, UG1OD024951, UG1OD024945, UG1HD021364, UG1HD027853, UG1OD024946, U2COD023375, UG1OD024955, UG1OD024959, UG1HD068278, UG1OD024958, U10HD036790, U24OD024957, UG1OD024948, UG1OD024943, UG1OD024954, UG1OD024942, UG1OD024952, UG1OD024953, U10HD053089, UG1OD024947, UL1TR000041, UG1OD024950, UG1OD024956, UG1OD024949
Publications: https://pubmed.ncbi.nlm.nih.gov/33632932/

Cognitive Behavioral Therapy for Children with Abdominal Pain Disorders Can Reduce Caregiver Anxiety

Functional abdominal pain disorders (FAPD) in children can give rise to anxiety in both the children and their caregivers. The emotional distress experienced by parents of children with FAPD may bring about "pain-promoting caregiver behaviors" (e.g., reinforcement of the child's pain through attention and specific privileges) in an effort to improve the symptoms. The parent's behaviors, though well-intended, may contribute to increased pain perception and child maladjustment. Researchers evaluated whether a brief, child-focused cognitive behavioral therapy (CBT) program could affect caregiver anxiety and pain-related symptoms in the child. The results showed that caregivers of children who received the CBT intervention had lower anxiety than those of children who received only usual care. Also, regardless of child treatment group, caregivers with greater anxiety had children who reported more pain and anxiety, but not more functional disability. Therefore, the researchers concluded that a child-focused CBT program may improve caregiver mental health, and this in turn may help improve pediatric outcomes.
Supported by: NCCIH
Grants: K23AT009458
Publications: https://pubmed.ncbi.nlm.nih.gov/34902549/

Alteration of Grey Matter Volume is Associated with Pain and Quality of Life in Children with Sickle Cell Disease

Pain is the most common symptom in people with sickle cell disease (SCD). Although there have been recent advances in SCD management, pain control remains inadequate, and many patients continue to rely on opioids. Because a wide range of grey matter structural changes in the brain have been reported in pain

syndromes, researchers investigated the structural changes in grey matter volume and their association with the number of pain crises in SCD patients. Using brain scans, the researchers found that lower grey matter volume of the anterior cingulate cortex of the brain was associated with higher frequency of pain crises.
Supported by: NCCIH
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Publications: https://pubmed.ncbi.nlm.nih.gov/34418575/

Opioid Prescribing for Dental Pain in Adolescents
While the overall rate of dentist-prescribed opioids decreased in 2010–2015, the number of dentist-prescribed opioids for those 11–18 years of age increased during this same time. Understanding how adolescent patients make decisions about pain management after complex dental procedures could help reduce the use of opioid medications and the potential for future opioid misuse. Researchers interviewed parents or guardians and their adolescent children (15–17 years of age) after the child had their wisdom tooth extracted. All 15 participants reported that the adolescents received an opioid prescription for pain management after tooth extraction. However, the researchers found that most adolescents undergoing tooth extractions reported little to no use of the opioids prescribed to them. Morover, the patients typically did not receive provider guidance on how to safely dispose of unused opioids. This highlights the importance of involving adolescent patients in the pain management decision-making process. It also suggests an opportunity for providers to reduce the number of opioids prescribed following tooth extractions and educate patients and their parents about safe disposal of opioids to reduce the risk of misuse.
Supported by: NIDCR
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Publications: https://pubmed.ncbi.nlm.nih.gov/35392856/

Pediatric Cancer

Addition to Standard-of-Care Therapy Improved Disease-Free Survival for T-cell Acute Lymphoblastic Leukemia Patients
T-cell acute lymphoblastic leukemia (T-ALL) represents approximately 15% of all newly diagnosed acute lymphoblastic leukeumia (ALL) cases in pediatric patients. Historically, treatment successes for this form of the disease have lagged behind successes for B-cell lymphoblastic leukemia (B-ALL). A previously FDA–approved drug for refractory or relapsed T-ALL was tested in a Phase III clinical trial for newly diagnosed T-ALL. The drug, nelarabine, was shown to be safe and effective for the treatment of newly diagnosed T-ALL in both children and young adults. The trial showed that addition of the drug to standard-of-care therapy improved disease-free survival without increased toxicity. Furthermore, the results showed a decrease in central nervous system relapse in patients treated with nelarabine.
Supported by: NCI
Grants: U24CA196173, U10CA098413, U10CA098543, U10CA180899, U10CA180886
Publications: https://pubmed.ncbi.nlm.nih.gov/32813610/

First-In-Class Inhibition of NSD1 Histone Methyltransferase
NSD1 is a protein that regulates chromatin integrity and gene expression. Altered amounts of NSD1 are associated with various cancers. Translocation of *NSD1* with another gene produces a potent oncogene, which occurs predominantly in pediatric patients with acute leukemia. Hence, NSD1 is an attractive therapeutic target for inhibition. However, developing inhibitors to NSD1 has posed significant challenges to date, because this protein exists in a self-inhibited state that makes it difficult for drug-like molecules to bind. Researchers used a fragment-based screening strategy to identify and optimize an initial lead compound that binds NSD1 irreversibly and inhibits it. Additionally, this compound showed

promising activity in a preliminary experiment using cells from a pediatric acute myeloid leukemia (AML) patient with a specific *NSD1* chromosomal translocation.
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Grants: R01CA226759, R01CA207272, R01CA160467, R01CA229250, T32GM008597, R35CA210065, P30CA013696
Publications: https://pubmed.ncbi.nlm.nih.gov/32868895/

Analysis Reveals Age-Associated Driver Alterations in Neuroblastoma
Neuroblastoma is a common childhood solid tumor, which accounts for half of all cancers in infants. Neuroblastoma arises during development from the sympathetic nervous system. Although past research has identified some genomic driver alterations, neuroblastoma pathogenesis is still not well understood. In this study, researchers analyzed a large cohort of neuroblastoma tumors and found that specific driver gene mutations were more likely to occur at different patient ages, suggesting that the sympathetic nervous system becomes susceptible to different "oncogenic insults" (genomic alterations) during development. They also found that a known mutation signature, associated with reactive oxygen species, is the most common cause of driver point mutations in neuroblastoma. These findings reveal possible approaches for developing precision medicines to improve outcomes in pediatric patients with neuroblastoma.
Supported by: NCI
Grants: P30CA021765, R35CA220500, U10CA180899, R01CA216391
Publications: https://pubmed.ncbi.nlm.nih.gov/33056981/
News Link: Researchers Mine Data and Connect the Dots About Processes Driving Neuroblastoma

Novel Strategy to Produce Highly Specific Chimeric Antigen Receptor T-Cell Therapy for Neuroblastoma
Neuroblastoma most commonly affects children 5 years of age and younger. Despite intense multimodal therapy, outcomes for patients with high-risk neuroblastoma remain poor, with a long-term survival rate of less than 50%. Previously, intramural researchers demonstrated that a protein, called glypican 2, is abundant on the surface of neuroblastoma, but largely absent from normal tissues, making it an attractive candidate for chimeric antigen receptor (CAR) T-cell therapy. CAR-T therapy relies on making an antibody that specially binds to its target, which in this case is glypican 2. Researchers developed a clever strategy to screen antibodies produced against different parts of the same glypican 2 protein, selecting the antibody that binds the least to normal tissues. Researchers used this antibody to develop CAR-T cells that regressed tumors in preclinical mouse models of neuroblastoma. These CAR-T cells are ready to be tested in the clinic. Moreover, the strategy developed in this work may be used to create novel targeted therapies for other cancers.
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Publications: https://pubmed.ncbi.nlm.nih.gov/34195677/

Rigosertib Induces Cell Death in Rhabdomyosarcoma
Relapsed pediatric rhabdomyosarcomas (RMS) and neuroblastomas (NB) have a poor prognosis despite multimodality therapy. In addition, the current standard of care for these cancers includes a class of drugs (vinca alkaloids) that induce debilitating adverse effects, further underscoring the need for novel therapies for these cancers. Rigosertib is a novel compound that induces cell death in many human cancer cell lines, including RMS and NB cell lines. Researchers sought to better understand the mechanism of action of rigosertib, including helping to mitigate a controversy surrounding this drug as a RAS-targeting agent. RAS is a protein that is a common driver of pediatric cancers. This research took a unique approach of evaluating the mechanism of action in both RAS-mutant and non-mutant pediatric cancer cells to identify RAS-dependent and independent mechanisms and showed that rigosertib induces cell death in a RAS-independent manner.

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Publications: https://pubmed.ncbi.nlm.nih.gov/33158997/

New Knowledge Changes Risk Stratification for Children and Adolescents with Rhabdomyosarcoma

Rhabdomyosarcoma is the most common soft-tissue sarcoma affecting children and adolescents. While the classification of pediatric-type rhabdomyosarcoma RMS) has historically relied on histologic features, recent developments in molecular testing have revealed that the alveolar subtype of RMS is correlated with chromosomal translocations that result in fusion oncoproteins (PAX3-FOXO1 or PAX7-FOXO1). Analyzing data from a large cohort of patients treated in Children's Oncology Group studies between 1997 and 2013, researchers concluded that patients 10 years of age or older with fusion oncoprotein-positive tumors greater than 5 centimeters are being under-treated and should be classified and treated as "high-risk" in future studies. This will allow these patients access to more intensive treatments—and potentially better outcomes.
Supported by: NCI
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Publications: https://pubmed.ncbi.nlm.nih.gov/33216382/

International Study on Rhabdomyosarcoma Provides New Cues on the Genetics of this Rare Disease

Rhabdomyosarcoma is the most common soft-tissue sarcoma—cancers that arise in connective tissues such as muscle, tendons, and the lining of joints—of childhood. Despite aggressive therapy, the five-year survival rate for patients with metastatic or recurrent disease remains poor. An international consortium conducted the largest genomic characterization to date of rhabdomyosarcoma patient samples and identified genetic features of the disease to aid in risk stratification and development of targeted treatments. The data from the study is provided in a searchable database containing all the genomic variants identified and annotated clinical data.
Supported by: NCI
Grants: Intramural Research (NCI), U10CA098413, U10CA098543, U10CA180886, U10CA180899
Publications: https://pubmed.ncbi.nlm.nih.gov/34166060/

Frequency of Pathogenic Germline Variation in Cancer Susceptibility Genes in Children and Young Adults with Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is the most common soft-tissue pediatric cancer and accounts for 3% of all pediatric cancer. A recent study that included intramural researchers examined germline genetic sequences and the resulting structural variation in two clinical RMS cohorts across a wide number of cancer susceptibility genes. Researchers identified disease-causing germline variants, including one never reported in RMS patients, and found a correlation between pathogenic/likely pathogenic cancer susceptibility genes and earlier age of RMS tumor development. These results highlight specific genetic variants that could be treated with gene therapies or allow patients to enter a clinical trial, monitored to improve outcomes and quality of life for pediatric patients, or lead to genetic counseling and/or genetic testing of other family members, as well as providing insight into RMS etiology.
Supported by: NCI
Grants: Intramural Research (NCI), U10CA180886, U24CA114766, U24CA196173, U10CA180899, U10CA098413, U10CA098543
Publications: https://pubmed.ncbi.nlm.nih.gov/34095712/

New Molecular Underpinnings of Fusion-Negative Rhabdomyosarcoma

Rhabdomyosarcoma is the most common soft-tissue sarcoma in childhood. There are two types of rhabdomyosarcoma: One type arises from a fusion of two abnormal proteins; the other type is fusion-negative rhabdomyosarcoma (FN-RMS). FN-RMS tumors are genetically heterogenous and usually lack driver mutations, which complicates our understanding of tumor initiation in this cancer type. Most FN-RMS tumors have low levels of a protein called PTEN, a known tumor suppressor. Researchers discovered new PTEN-interacting partners. They showed the interaction occurs in the cell nucleus and is required to keep the tumor cells alive. When the quantity of the interaction partners was lowered by the researchers, the tumors shrunk, suggesting a possible future therapeutic strategy for fusion-negative rhabdomyosarcoma.
Supported by: NCI
Grants: R01CA216344, R01CA251436, F31CA250398, P30CA021765
Publications: https://pubmed.ncbi.nlm.nih.gov/34535684/
News Links: Possible New Treatment Approach for Pediatric Rhabdomyosarcoma, Control of Rhabdomyosarcoma Cell Identity Provides Clues to Possible Treatments

Study Reveals New Information About the Development of High-Grade Gliomas and Points to Novel Treatment Options
High-grade gliomas are deadly primary brain tumors and a leading cause of mortality in children and young adults. These tumors frequently harbor mutations in genes encoding histone 3 (H3). Histones are proteins that bind and organize DNA in the cell nucleus. Researchers found that a specific mutation in H3 occurs in an early developmental stage, namely in interneuron progenitor cells. The mutation activates a certain receptor, known for oncogenic signaling, which can be inhibited by approved drugs. This finding raises hope that high-grade gliomas with a specific H3 mutation may be inhibited in a targeted way.
Supported by: NCI
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Publications: https://pubmed.ncbi.nlm.nih.gov/33259802/

Preventing Severe Cytokine Release Syndrome Associated with Chimeric Antigen Receptor T-cell Therapy in Pediatric and Young Adult Leukemia Patients
Cell therapy with CD19-directed chimeric antigen receptor (CAR) T-cells is an FDA–approved treatment for children and young adults (up to 25 years of age) with relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL). While this treatment has been transformative, it is associated with severe side effects including cytokine release syndrome (CRS). This syndrome is the result of the body releasing too many cytokines—molecules that play a role in the body's immune system—into the blood too quickly, causing life-threatening consequences. A clinical trial showed preemptive use of a drug (tocilizumab) that can block the release of a major cytokine involved in CRS reduced the most severe effects of the syndrome by one third and did not affect the efficacy of the CAR T-cell therapy. This approach may improve the safety of, and broaden the use of CAR T-cell therapy for, relapsed or refractory B-ALL.
Supported by: NCI, NIDDK
Grants: P01CA214278, P30CA016520, K23DK119463
Publications: https://pubmed.ncbi.nlm.nih.gov/33417474/

Stem Cell Transplant After Chimeric Antigen Receptor T-Cell Therapy Is Effective for Pediatric, Adolescent, and Young Adult Leukemia Patients
A clinical trial found that long-term survival for children, adolescents, and young adults with relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL) was significantly better for patients who received CD19-chimeric antigen receptor (CAR) T-cell therapy followed by a stem cell transplant, compared with CAR T-cell therapy alone. The patients were followed for an average of close to five years, and the median overall survival rate was 70.2 months for the transplant group compared with 10.5

months for the non-transplant group. As a result of this research, stem cell transplants are now recommended following CAR T-cell therapy for these patients.
Supported by: NCI
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Publications: https://pubmed.ncbi.nlm.nih.gov/33764809/

Phase III Clinical Trial Finds Targeting CD33 in Addition to Standard Chemotherapy Improved Survival for Acute Myeloid Leukemia Patients
Novel treatment approaches are needed for acute myeloid leukemia (AML) patients with the most common genomic abnormality associated with the disease: chromosomal rearrangement of the *KMT2A* gene. Pediatric *KMT2A*–rearranged AML is characterized by high expression of the CD33 protein; therefore, researchers tested whether the addition of a CD33-targeted drug (gemtuzumab ozogamicin) to standard chemotherapy would confer a survival benefit for these patients. The Phase III clinical trial showed the CD33-targeted drug significantly improved event-free survival and reduced relapse risk in *KMT2A*–rearranged AML. Future studies will determine if targeting CD33 in combination with hematopoietic stem cell transplant may provide an additional clinical benefit.
Supported by: NCI
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Publications: https://pubmed.ncbi.nlm.nih.gov/34048275/

Phase II Clinical Trial Shows Promise of New Treatment for Neurofibromatosis Type 1 Associated Plexiform Neurofibromas
Neurofibromatosis type 1 (NF1) is a cancer predisposition syndrome diagnosed in childhood and characterized by the development of non-cancerous peripheral nerve tumors called plexiform neurofibromas. These tumors arise within nerves, grow rapidly during childhood, and can lead to motor and sensory dysfunction, pain, and disfigurement in as many as 40% of patients with NF1. The targeted drug, cabozantinib, showed efficacy first in preclinical animal models and then in a Phase II clinical trial of patients with inoperable plexiform neurofibromas. The drug reduced the volume of the tumors in patients who responded to treatment and improved pain. Ongoing preclinical studies are being conducted to optimize drug dosing and minimize toxicity.
Supported by: NCI, NICHD
Grants: U54CA196519, K12HD000850
Publications: https://pubmed.ncbi.nlm.nih.gov/33442015/

New Blood Test Useful in Diagnosing Cancer in Patients with Neurofibromatosis Type 1 Cancer Predisposition Syndrome
Neurofibromatosis type 1 (NF1), the most common cancer predisposition syndrome, is almost always diagnosed in childhood. NF1 patients frequently develop non-cancerous tumors that grow along nerves. These tumors can turn into aggressive cancers known as malignant peripheral nerve sheath tumors, and doctors lack a good way to determine whether this transformation to cancer has occurred. Furthermore, patients who develop these tumors have a poor prognosis. Researchers recently developed a blood test to detect cancer early in NF1 patients. Although the initial study was conducted in a small number of patients, the promising results are being expanded. In addition to detecting cancer, the blood test was also useful in monitoring response to treatment in the initial study.
Supported by: NCI, NIGMS
Grants: T32GM007200, K08CA238711, Intramural Research (NCI), ZIABC011722, ZIABC010801
Publications: https://pubmed.ncbi.nlm.nih.gov/34464388/

Subsequent Cancer Risk in Retinoblastoma Survivors
Retinoblastoma (RB) is a rare eye cancer usually diagnosed in early childhood that can be inherited from parents (hereditary) or not inherited (nonhereditary). It is known that survivors of hereditary RB have a

high risk of developing certain subsequent cancers, including soft-tissue cancer, bone cancer, and melanoma. Using data from a long-term study of RB survivors, researchers, including intramural researchers, found that hereditary RB survivors have an increased risk of developing other cancers—including nervous system, naval cavity, oral cavity, and breast cancers—compared with the general population. Researchers estimated that 33% of RB survivors developed a subsequent cancer and 6% developed two or more subsequent cancers; there was no increased risk for subsequent cancers in nonhereditary RB survivors. These results advance the current understanding of subsequent cancer risks for hereditary RB survivors and illustrate the substantial long-term burden of certain cancers on these survivors, which should be considered for future surveillance strategies.
Supported by: NCI
Grants: P30CA008748, Intramural Research (NCI)
Publications: https://pubmed.ncbi.nlm.nih.gov/33473166/
News Link: Subsequent Cancer Risk in Retinoblastoma Survivors

Stem Cell–Derived Retinal Organoid Developed to Study Childhood Cancer
Retinoblastoma is a rare cancer of the retina that typically begins during development, in utero. Caused by a genetic mutation, retinoblastoma disease models in mice have elucidated molecular mechanism, but differ from human pathology in key aspects, such as the timeline of tumor development, how protein production is altered within the cells, and sensitivity to drug treatments. To study retinoblastoma in human cells, scientists created stem cells from retinoblastoma patients and coaxed them into retinal organoids, multilayered "organs in a dish." These organoids developed tumors that were indistinguishable from patient tumors in size and shape, genetics, and other key features. These patient cell lines and tumors have been made available for free to the research community and will be a valuable preclinical resource for developing therapies.
Supported by: NEI, NCI
Grants: R01EY030180, R01CA245508
Publications: https://pubmed.ncbi.nlm.nih.gov/34315877/,
News Link: Researchers Create More Accurate Research Model

Antibody-Drug Conjugate Is Effective Against Patient-Derived Models of Pediatric Solid Tumors
Whereas some adult solid cancers have responded to immune checkpoint inhibitors and cell-based immunotherapy, pediatric solid cancers largely have not. Another immunotherapy approach is to use an antibody-drug conjugate against a protein that is present on the surface of tumors and absent in healthy tissues. B7-H3 is a protein present in high amounts in many pediatric solid tumors and largely absent in healthy tissues. Previous research on a conjugate of a B7-H3 antibody and a tumor-killing drug showed antitumor activity. In new work, researchers further developed the antibody-drug conjugate to limit off-target killing and tested the resulting conjugate, called m276-SL-PDB, in patient-derived models of pediatric solid tumors. Researchers observed potent antitumor activity in most models—a result that warrants further clinical development of m276-SL-PBD for treatment of high-risk childhood solid malignancies.
Supported by: NCI
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Publications: https://pubmed.ncbi.nlm.nih.gov/33619171/

A Genome-First Approach to Characterize DICER1 Pathogenic Variants
The DICER1 genetic disorder is often defined through its physical disease presentation, and not through identification of disease-causing genetic variants. A recent study examined the efficacy of using a "genome-first" approach to characterize the clinical traits associated with DICER1 germline variants. Extracting data from more than 92,000 participants in a community DNA–sequencing program, researchers looked at DICER1 variation, presence, and severity of malignant tumors, and sequenced

DICER1 in available tumors. Researchers found double the expected prevalence of DICER1 loss-of-function variants; 16% of participants with these variations also had malignant tumors. These DICER1 variants were also significantly associated with thyroid cancer and thyroid removal compared with control participants. Overall, this study showed that this type of genome-first approach can be used to identify individuals with DICER1 variants instead of a phenotype-first approach and could be combined with current diagnostic methods or to evaluate risk.
Supported by: NCI, NCATS
Grants: R01CA143167, UL1TR001863
Publications: https://pubmed.ncbi.nlm.nih.gov/33630087/

Pediatric Testicular Stromal Tumors Are Associated with DICER1 Syndrome
DICER1 syndrome is a rare inherited disease that predisposes those with pathogenic germline variants in the *DICER1* gene to develop various benign and malignant tumors. Around 60% of rare ovarian stromal tumors contain inherited DICER1 variants, but no DICER1–related testicular stromal tumors have been documented. A recent intramural study reported the first two cases of DICER1 variant–related pediatric testicular stromal tumors. These results expand the clinical spectrum of DICER1–associated tumors and indicate that pediatric patients with certain types of testicular tumors should undergo genetic testing to benefit from established DICER1–variant surveillance protocols. Additionally, this study provides further insight into the etiology of certain testicular cancers through dysregulation of the DICER1 protein.
Supported by: NCI
Grants: Intramural Research (NCI)
Publications: https://pubmed.ncbi.nlm.nih.gov/33782093/

New Molecular Insights Explain How Fusion Oncoproteins Initiate Ewing Sarcoma
Ewing sarcoma is the second-most-common pediatric bone tumor. This aggressive bone and soft-tissue tumor arises due to fusion oncoproteins, which are abnormal proteins formed as a result of chromosomal rearrangements. Fusion oncoproteins are notoriously difficult to inhibit with drugs. The most common fusion oncoprotein in Ewing sarcoma, called EWS/FLI1, is known to reprogram cell metabolism and initiate tumor formation. Researchers discovered that EWS/FLI1 directly binds to a protein that is a master transcriptional regulator in other tumors. The binding event reprograms the cell and contributes to tumorigenesis. In addition, researchers discovered another protein that activates the same master regulator. These findings elucidate how the EWS/FLI1 fusion oncoprotein initiates tumor formation and provide new drug targets that may lead to new therapeutic strategies for Ewing sarcoma.
Supported by: NCI
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Publications: https://pubmed.ncbi.nlm.nih.gov/33741715/

Understanding Ancestral Influences on Ewing Sarcoma Risk
Ewing sarcoma is the second-most-common pediatric bone cancer, with little known about its international incidence rates and trends or genomic ancestry risk factors. Using data from five continents, researchers estimated incidence rates by geographic region and race/ethnicity over 25 years. They found that incidence rates varied across geographical region and subpopulations, although most were increasing over time. Those with Africa, East Asian, and Southeast Asian ancestry had the lowest rates, while Pacific Islanders and those with mainly European and North African/Middle Eastern ancestry had the highest rates. There was also a higher incidence rate in males for most regions. Within mainly European populations, there was a fivefold difference in rates, indicating that there is not a consistent incidence rate even across geographic regions. These results indicate that there could potentially be ancestral influence on Ewing sarcoma risk due to the observed variations across countries and populations—and that more in-depth future research could aid in prevention strategies and risk identification.
Supported by: NCI

Grants: P30CA077598, T32CA099936, Intramural Research (NCI)
Publications: https://pubmed.ncbi.nlm.nih.gov/33961701/

Mapping Pediatric Cancer Dependency Genes to Identify Novel Treatments
There is a dire need for novel therapeutic strategies to specifically target pediatric solid tumors and brain tumors. By using gene-editing technology to systematically delete genes in cell lines representing 13 types of childhood solid tumors, researchers created a Pediatric Cancer Dependency Map that identifies genes required for cell survival in each tumor type. These "pediatric dependency genes" are often different from adult-dependency genes, which means that repurposing of adult oncology drugs for childhood cancers may be insufficient to produce desired clinical outcomes. Importantly, these pediatric dependency genes are potential therapeutic targets that may be useful in preclinical support of ongoing precision medicine clinical trials. Drugs targeting some of these dependency genes already exist, and studies are now underway to test their effectiveness against pediatric cancers.
Supported by: NCI, NIGMS
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Publications: https://pubmed.ncbi.nlm.nih.gov/33753930/
News Link: Looking for Cancer's Achilles Heel: The Pediatric Cancer Dependency Map

Uncovering How Fusion Oncoproteins Drive Epithelioid Hemangioendothelioma
Epithelioid hemangioendothelioma (EHE) is a rare type of vascular tumor in adolescents, which metastasizes early and lacks effective therapy. EHE is known to be caused by two different fusion oncoproteins that facilitate uncontrollable growth. However, key molecular details of how these fusion oncoproteins work are missing. Researchers used genetic and proteomic screens to identify a protein complex that binds both fusion oncoproteins. This complex resides in the cell nucleus and ultimately results in increased protein production. This research identified a new protein complex that unifies signals from fusion oncoproteins to initiate tumor formation in EHE. This complex is an attractive target for drug development for EHE.
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Publications: https://pubmed.ncbi.nlm.nih.gov/33913810/

Development and Validation of a Breast Cancer Risk Prediction Model for Childhood Cancer Survivors Treated with Chest Radiation
Multiple pediatric cancers require radiation as a treatment, which causes an increased risk for breast cancer. One in three pediatric cancer survivors treated with radiation will develop breast cancer. While multiple models have been developed to predict breast cancer risk for the general population, no such model exists to estimate risk among women treated with radiation for childhood cancers. A recent study developed a breast cancer prediction model for this very high-risk population that takes treatment-related and reproductive factors and family history into account. The model was validated in an international cohort of more than 2,100 female childhood cancer survivors. The highest predicted risk was for premenopausal women over the 40 years of age who received radiation treatment within one year of their first period and who also had a parent, offspring, or sibling who had breast cancer. Overall, the model estimated a risk of 2%–23% for 30-year-old women and 5%–34% for 40-year-old women. By having a model for this specific high-risk population, surveillance, counseling, and preventative strategies can be better tailored and implemented for these childhood cancer survivors.
Supported by: NCI
Grants: K08CA234232, R01CA136783, U24CA055727, R01CA134722, K05CA160724, P30CA008748
Publications: https://pubmed.ncbi.nlm.nih.gov/34048292/
News Link: Breast Cancer Probability Calculator

Breast Cancer Screening Among Childhood Cancer Survivors Treated Without Chest Radiation May Have Clinical Benefits and Is Cost-Effective

Childhood cancer survivors treated with chest radiation are considered high-risk for breast cancer and are recommended to start breast cancer screening early. Women who have survived certain childhood cancers, including leukemia and sarcoma, that were not treated with chest radiation have also recently been found to have a high risk for early onset breast cancer, but the clinical benefits and cost effectiveness of early screening have not been examined for this group. A recent study used model simulations to look at elevated risks, mortality, and cost effectiveness for early screening and found that starting mammogram screenings at 40 years of age was the best option and could prevent half of breast cancer deaths in this population. These results can inform and lead to expansion of the breast cancer screening guidelines for childhood cancer survivors who did not receive chest radiation and can contribute to efforts preventing secondary breast cancer development in this survivor population.

Supported by: NCI

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Publications: https://pubmed.ncbi.nlm.nih.gov/34324686/

Physiologic Frailty and Neurocognitive Decline Among Young Adult Survivors of Childhood Cancer

Up to 35% of childhood cancer survivors have cancer-related neurocognitive impairment, but the exact cause has not been determined. Once such possibility is frailty, which is associated with poor health and neurocognitive decline in older adult populations. Some 8% of young adult childhood cancer survivors meet the clinical criteria for frailty, but the association with neurocognitive decline in this population has not been examined before. A recent study looked at frail and pre-frail young adult cancer survivors over 5 years of age and found that they had clinically relevant and greater cognitive decline than nonfrail survivors. This demonstrates a correlation between frailty and cognitive decline through accelerated aging in childhood cancer survivors. This indicates that global interventions for frailty could also aid in preventing neurocognitive decline in this population.

Supported by: NCI

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Publications: https://pubmed.ncbi.nlm.nih.gov/34283634/

Characterizing Cancer-Susceptibility Genes in Childhood Cancer Survivors to Increase Understanding of Pediatric Cancer Development

While survival rates for pediatric cancer have been improving for years, cancer is still the leading mortality-causing disease for children. The contribution of germline genetic susceptibility to pediatric cancer survivors has not been extensively characterized and is the focus of a recent study. Researchers sequenced the protein-coding DNA in more than 5,400 European pediatric cancer survivors from the Childhood Cancer Survivor Study who had survived at least five years from their initial diagnosis and compared those with almost 600 European cancer-free controls. New pathogenic variations were identified in these pediatric cancer survivors, including those in genes normally associated with adult cancers. A significantly high number of disease-causing variants were found in survivors with certain cancers, including non-Hodgkin lymphoma, and central nervous system and soft-tissue cancers. These new associations between cancer susceptibility genes and pediatric cancer offer opportunities for further research into pathogenicity of these variants, provide a better understanding of pediatric cancer development, and can aid with genetic counseling for patients and their families.

Supported by: NCI

Grants: Intramural Research (NCI), U24CA055727, P30CA021765

Publications: https://pubmed.ncbi.nlm.nih.gov/34308104/

Proteomic Analysis Offers New Insights on Pediatric Brain Tumor Biology

The leading cause of cancer-related deaths in children are brain tumors. Genomic-based analyses of tumors have shed light on how brain tumors form, but our knowledge remains incomplete, resulting in a paucity of treatment options beyond surgery and radiation. One major knowledge gap has been our lack of understanding of protein levels and protein signaling in forming tumors. Recent advances in proteomics have enabled scientists to look at thousands of different proteins from tumor samples. Researchers performed proteomic and genomic analyses on seven distinct types of pediatric brain tumors across a large cohort of tumor samples. This was the first large-scale integrative study aimed at discovering new targeted therapies for pediatric brain tumors. It revealed new insights, which include novel druggable targets. This study suggests that some of the current treatments for specific tumor types can be applied to other types that share the same proteomic features.
Supported by: NCI
Grants: U01CA214114, U24CA210993, U24CA210967, U24CA210954, U24CA210972, U24CA210955, U24CA210979, R50CA211499
Publications: https://pubmed.ncbi.nlm.nih.gov/33242424/

Pediatric Critical Care and Emergency Care

Biomarkers for Estimating Risk of Hospital Mortality and Long-Term Quality-of-Life Morbidity Following Pediatric Septic Shock
Pediatric sepsis is a life-threatening condition in which the body launches an exaggerated immune response to an infection. Researchers studied a group of children with sepsis to determine if a model that incorporated risk due to different biomarkers could predict the risk of dying in the hospital or suffering long-term effects on quality of life after survival. They found that their model had "modest" performance for estimating long-term risks. The researchers plan to further develop this approach to potentially target rehabilitation efforts among children surviving septic shock.
Supported by: NICHD, NIGMS
Grants: R01HD073362, R35GM126943
Publications: https://pubmed.ncbi.nlm.nih.gov/33003178/

Adaptive Screener May Help Identify Youth at Risk of Suicide
Many youths who die by suicide access health care systems, particularly emergency departments (EDs), in the year preceding their death. Therefore, universal screening for suicide risk in EDs is a key suicide-prevention strategy. Researchers used data from self-report questionnaires assessing suicide risk and subsequent suicide attempts to create a computerized adaptive screen for suicidal youth (CASSY) that can be implemented in EDs. When tested on a separate cohort of adolescents seen in EDs, the CASSY identified 82.4% of youth who went on to attempt suicide in the three months following screening. The results suggest the CASSY could be a feasible and sensitive tool for providers to use in EDs to detect youth suicide risk.
Supported by: NIMH
Grants: U01MH104311
Publications: https://pubmed.ncbi.nlm.nih.gov/33533908/

Personalized Timing of Treatment Used to Help Children Recover from Severe Blood Clots
While it is uncommon for children to experience severe blood clotting, it can occur after a surgery, severe infection, or an extreme response to COVID-19. When severe blood clots do occur in children, physicians often use adult studies to guide pediatric treatment practices, like implementing a three-month regimen for severe blood clotting. A new study suggests that a six-week treatment approach for blood clotting or extreme bleeding events is just as safe and effective as the conventional three-month treatment course. These research findings are broad, and additional studies are needed to understand the best treatment

approaches for different situations, such as when children receive care for cancer or a pulmonary embolism.
Supported by: NHLBI
Grants: 5U01HL130048, 5K23HL084055
Publications: https://pubmed.ncbi.nlm.nih.gov/35015038/

Pediatric Pharmacology

Udenafil Improves Exercise Capacity in Children with Congenital Heart Disease
The Pediatric Heart Network's research is leading to the development of improved treatment and care of children with congenital heart disease. For example, the Fontan Udenafil Exercise Longitudinal (FUEL) trial tested udenafil, a drug that increases blood flow to the lungs, in children who have only one working heart ventricle. Although surgery in early childhood can stabilize heart function in these children, they often face a decline in exercise capacity and an increased risk of heart failure over time. The FUEL trial found that udenafil improved exercise capacity in teenagers with single-ventricle defects.
Supported by: NHLBI, NCATS
Grants: UG1HL135665, UG1HL135666, U10HL109818, UG1HL135680, UG1HL135646, UG1HL135683, UG1HL135685, UG1HL135689, U10HL068270, U24HL135691, UG1HL135682, U10HL109673, UG1HL135678, KL2TR002367
Publications: https://pubmed.ncbi.nlm.nih.gov/31736357/

Risks of Short-Term Steroid Use in Children
Upper respiratory infections, including laryngitis and tonsillitis, are common illnesses of childhood. In addition, 7% of children in the United States live with asthma. When a child is struggling to breathe or has a painful case of tonsillitis, physicians commonly prescribe drugs called oral corticosteroids—but only for short courses of 14 days or less. Taking corticosteroids for an extended time increases risks for gastrointestinal bleeding, infections, and other health problems. However, the risks associated with short-term use of corticosteroids in children are unclear. Scientists analyzed data on more than 1 million children who received oral corticosteroids for less than 14 days. This treatment was most often prescribed for children with respiratory infections and allergic conditions. The researchers found that children who took oral corticosteroids for less than 14 days had an increased risk of gastrointestinal bleeding, pneumonia, and sepsis in the month following the start of treatment. The risk of pneumonia and sepsis—which can be fatal—increased twofold. The researchers believe that their findings call for caution when prescribing oral corticosteroids for children, even for short periods of time.
Supported by: NICHD
Grants: R01HD085993
Publications: https://pubmed.ncbi.nlm.nih.gov/32628532/

Effect of Antibiotic Use Within the First 48 Hours of Life on the Preterm Infant Microbiome
Preterm infants are often given antibiotics immediately after birth due to the assumed risk of early infections. However, antibiotics can lead to changes in the accumulation of natural bacteria within the gastrointestinal system. Researchers compared outcomes for low-risk preterm infants when half were randomized to receive the standard dose of antibiotics (ampicillin and gentamicin), and the other half received placebo in place of the antibiotics. At the same time, the scientists conducted a similar experiment in mice. The analysis did not find any significant statistical differences between the antibiotic group and the placebo group—in either the human infants or the mice—that would affect the microbiome or other early clinical outcomes.
Supported by: NICHD, NIDDK
Grants: P30DK042086, R01HD083481
Publications: https://pubmed.ncbi.nlm.nih.gov/33196773/

Racial and Ethnic Diversity in Studies Funded Under the Best Pharmaceuticals for Children Act
Testing the safety and efficacy of medications in children presents significant scientific, clinical, ethical, technical, and logistical challenges. Under the Best Pharmaceuticals for Children Act (BPCA), NIH works with FDA as well as industry and academic experts to identify off-patent drugs in need of further study, prioritizes needs in pediatric therapeutics, and sponsors clinical studies of on-patent drugs to establish safety and efficacy information for children. Researchers analyzed data obtained for 10,918 participants enrolled in 33 federally funded studies of drugs and devices conducted from 2008 through June 2020. Enrollment of individuals from racial and ethnic minority groups was comparable to or higher than expected for all groups except Asian Americans. American Indian and Alaska Native, and multiracial enrollment significantly increased over the time period.
Supported by: NICHD
Grants: BPCA (RePORTER)
Publications: https://pubmed.ncbi.nlm.nih.gov/33846237/

Pregnancy and Newborn Health

Preterm Birth More Likely with Exposure to Pthalates
Researchers found that women with higher concentrations of several phthalate metabolites in their urine were more likely to deliver their babies preterm, defined as delivering three or more weeks before a mother's due date and can be dangerous for both mom and baby. Phthalates are chemicals used in personal care products, such as cosmetics, as well as in solvents, detergents, and food packaging. In this study—the largest study to date on this topic—the research team pooled data from 16 studies conducted across the United States that included individual participant data on prenatal urinary phthalate metabolites (representing exposure to phthalates), as well as the timing of delivery. Researchers analyzed data from a total of 6,045 pregnant women who delivered between 1983–2018. Nine%, or 539, of the women in the study delivered preterm. Phthalate metabolites were detected in more than 96% of urine samples. The researchers also used statistical models to simulate interventions that reduce phthalate exposures. They found that reducing the mixture of phthalate metabolite levels by 50% could prevent preterm births by 12% on average. Interventions targeting behaviors—such as trying to select phthalate-free personal care products (if listed on label); eating fresh, home-cooked food; avoiding processed food that comes in plastic containers or wrapping; and selecting fragrance-free products or those labeled "phthalate-free"—are examples of things people can do that may reduce their exposures. Voluntary actions from companies to reduce phthalates in their products, or changes in standards and regulations, could contribute to exposure reduction and protect pregnancies.
Supported by: NIEHS, OD/ECHO
Grants: P30ES010126, T32ES007018, L40ES032257, P30ES017885, UH3OD023251
Publications: https://pubmed.ncbi.nlm.nih.gov/35816333/

Exposure to Antibacterial Chemical via Lactation Linked to Liver Damage
Researchers reported that lactating mice expose their feeding pups to triclosan, resulting in early signs of liver damage that can eventually lead to more serious impairment and illness. Triclosan is an antimicrobial commonly used in products from pesticides to cleaning products to clothing and toys. In 2017, fueled by rising evidence and public health concerns, the FDA ruled that triclosan could not be used in new products without premarket approval. Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver condition in the United States, affecting an estimated 100 million adults. It occurs when fat accumulates in liver cells due to causes other than excessive alcohol use, impairing organ function. The precise cause is not known, but diet and genetics play substantial roles. Approximately 20% of persons with NAFLD transition to nonalcoholic steatohepatitis (NASH), a more advanced form of the disease characterized by increasingly severe inflammation and organ damage that may result in scarring

of the liver, cirrhosis, and cancer. The latest research in mice shows that triclosan is efficiently passed from nursing mothers to pups, who develop early signs of fatty liver pathogenesis and perhaps a greater likelihood of fatty liver disease later in life. The authors also posit that recent increases in pediatric NAFLD could be a consequence of mother-to-child transmission of environmental toxicants like triclosan. The research further revealed that triclosan modified the expression of two metabolic mechanisms involved in NAFLD development. When the scientists blocked these mechanisms, it reduced triclosan-induced fat accumulation in the liver and prevented the expression of genes associated with a key feature of NAFLD, offering a potential intervention.
Supported by: NIEHS
Grants: R21ES031849, P42ES010337
Publications: https://pubmed.ncbi.nlm.nih.gov/35896521/
News Link: Exposure to Antibacterial Chemical via Lactation Linked to Liver Damage in Newborn Mice

Maternal Lifetime Exposure to Stress Is Associated with Increased Placental Mitochondrial DNA Mutations
The placenta plays a central role in optimal fetal maturation, and perturbations in the maternal environment can be transmitted across the placenta, affecting fetal development. A hallmark of the placenta is its capacity to adapt in response to variations in the maternal-fetal environment, making it an excellent target for the identification of biomarkers/mechanisms of adverse development. Maternal lifetime exposure to stress is associated with increased placental mitochondrial DNA (mtDNA) mutations—especially in genes encoding for parts of the mtDNA variants associated with metabolic, cardiac, and neurodevelopmental outcomes. In the study of a cohort of urban, ethnic women, White women and Black women who reported more lifetime stress had a greater degree of mtDNA mutations compared with Hispanic women. The association was strongest among Black women. These results suggest a possible link between oxidative stress—a key pathway between stress and cognitive, emotional, and physiological health; mitochondrial function; and consequences of mothers' stress on subsequent generations.
Supported by: NIEHS, NHLBI, NCATS
Grants: R00ES024116, P30ES006096, P30ES023515, UL1TR001433, R01HL095606, R01HL114396
Publications: https://pubmed.ncbi.nlm.nih.gov/3322903/, https://pubmed.ncbi.nlm.nih.gov/33229036/

Same-day STORK Test Detects Abnormal Fetal Chromosomes
Scientists have developed a same-day test to identify abnormal fetal chromosomes. The Short-read Transpore Rapid Karyotyping (STORK) test can detect extra or missing chromosomes (i.e., aneuploidy) using samples collected from prenatal tests—such as amniocentesis and chorionic villus sampling—as well as tissue obtained from miscarriage and biopsies from pre-implantation embryos produced using *in vitro* fertilization (IVF). The study team compared STORK with standard methods by testing 218 samples that included tissue from miscarriage, chorionic villi, amniotic fluid, and trophectoderm biopsies, which are used to evaluate embryos before IVF implantation. In this set of samples, STORK had an accuracy of 98% to 100%. In another set of 60 samples, technicians in a clinical laboratory certified for quality testing—called a Clinical Laboratory Improvement Amendments certification—performed STORK. In these samples, STORK was 100% in accordance with standard clinical testing. Overall, the study shows that STORK is comparable to standard clinical tests and has many advantages. STORK is faster, providing results within hours versus several days. It is also cheaper, with the study team estimating STORK to cost less than $50 per sample if 10 samples are run at the same time, or up to $200 if a sample is run on its own. STORK can also be done at the point-of-care for a patient, eliminating the need to ship a sample to a clinical laboratory. According to the study authors, STORK may be particularly useful in identifying genetic causes of miscarriage. Currently, professional societies only recommend genetic testing if a person has had multiple miscarriages, but an easy, cost-effective test like STORK can potentially be offered after the first miscarriage. STORK can also be used to streamline the IVF process. Currently, embryos must be frozen while genetic tests are run and analyzed before implantation.

STORK's ability to provide results within hours can presumably eliminate this freezing step, which would save time and cost. More work is needed to validate STORK, but if results continue to show promise, STORK could improve the quality of reproductive health care.
Supported by: NICHD, NCI
Grants: K08HD068546, R01HD100013, U19CA179564
Publications: https://pubmed.ncbi.nlm.nih.gov/36070716/,
News Link: NIH-Funded Researchers Develop Same-Day Test to Detect Abnormal Fetal Chromosomes

Evaluating Outcomes of Pediatric Patients with Perinatally Acquired HIV
The International epidemiology Databases to Evaluate AIDS (IeDEA) research consortium harmonizes globally diverse HIV/AIDS data from routine clinical care. Researchers analyzed mortality and clinical events rates among children, adolescents, and youth with perinatally acquired HIV (PHIV) 0–24 years of age in the pediatric IeDEA multiregional collaboration (East, West, Central, and Southern Africa; Asia-Pacific; and Central/South America and the Caribbean). The results demonstrate that mortality and incidence of clinical events were highest in both younger (<2 years of age) and older (>19 years of age) youth with PHIV. These data suggest that increasing services for <2 years of age by enhancing early access to HIV diagnosis and care, and >19 years of age by instituting adolescent- and youth-focused health services, could improve outcomes among youth with PHIV.
Supported by: NIAID, NHLBI, NICHD, NIMH, NIAAA, NLM, NCI, FIC, NIDDK
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Publications: https://pubmed.ncbi.nlm.nih.gov/33034417/

Evaluating the Pharmacokinetics, Feasibility, Acceptability, and Safety of Oral Pre-Exposure Prophylaxis for HIV Prevention During Pregnancy and Postpartum
Pregnancy and the postpartum period represent important windows of elevated HIV risk for women and this has important implications for both mothers and infants in generalized HIV epidemics. When taken as prescribed, daily oral pre-exposure prophylaxis (PrEP) with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) is highly effective for reducing HIV acquisition among men who have sex with men (MSM) and HIV-serodiscordant couples. PrEP use during pregnancy and breastfeeding appears feasible, safe, and acceptable and a growing number of national HIV programs now recommend PrEP for women at elevated HIV risk during these critical periods. This study evaluated the pharmacokinetics, feasibility, acceptability, and safety of FTC/TDF as oral daily PrEP to prevent HIV during pregnancy and postpartum in adolescents and young women and their infants. Intracellular tenofovir diphosphate (TFV-DP) concentration in dried blood spots was used to monitor cumulative PrEP adherence among pregnant and postpartum adolescent girls and young women in Sub-Saharan Africa. This study showed that TFV-DP concentrations were approximately one-third lower during pregnancy compared with postpartum. These Population-specific benchmarks can be used to guide PrEP adherence support in pregnant/postpartum African women.
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Grants: UM1AI068632, UM1AI068616, UM1AI106716 Contract (NICHD) HHSN275201800001I
Publications: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8492211/
Clinical Trials Study: NCT03386578

Evaluating the Efficacy and Safety of Dolutegravir-Containing Versus Efavirenz-Containing Antiretroviral Therapy Regimens in HIV-1-Infected Pregnant Women and Their Infants
Antiretroviral therapy (ART) during pregnancy is important for both maternal health and prevention of perinatal HIV-1 transmission; however adequate data on the safety and efficacy of different ART regimens that are likely to be used by pregnant women are scarce. This trial compared the safety and efficacy of three antiretroviral regimens started in pregnancy. This multicentre, open-label, randomised

controlled, phase 3 trial was done at 22 clinical research sites in nine countries (Botswana, Brazil, India, South Africa, Tanzania, Thailand, Uganda, the USA, and Zimbabwe). Pregnant women (aged ≥18 years) with confirmed HIV-1 infection and at 14–28 weeks' gestation were eligible. Participants were randomly assigned to receive either dolutegravir, emtricitabine, and tenofovir alafenamide fumarate; dolutegravir, emtricitabine, and tenofovir disoproxil fumarate; and efavirenz, emtricitabine, and tenofovir disoproxil fumarate. The study showed that, when started in pregnancy, dolutegravir-containing ART regimens had superior virological efficacy at delivery compared with the efavirenz, emtricitabine, and tenofovir disoproxil fumarate regimen. These findings affirm the WHO recommendation to use dolutegravir in all populations, including in pregnant women, and suggest that dolutegravir, emtricitabine, and tenofovir alafenamide fumarate might be preferred over dolutegravir, emtricitabine, and tenofovir disoproxil fumarate when started during pregnancy due to the lower risk of adverse pregnancy outcomes.
Supported by: NIAID, NICHD, NIMH
Grants: UM1AI068632, UM1AI068616, UM1AI106716 Contract (NICHD) HHSN275201800001I
Publications: https://pubmed.ncbi.nlm.nih.gov/33812487/
Clinical Trials Study: NCT03048422

Isoniazid Preventive Therapy to Prevent Tuberculosis in HIV-Infected Pregnant and Postpartum Women

Tuberculosis (TB) is a leading cause of death among HIV-infected persons in low-income settings and can be a serious complication for HIV-infected pregnant women and their infants. Isoniazid (INH) preventive therapy (IPT) is effective in preventing TB infection in HIV-infected adults, but the safety of IPT in pregnant women is unknown. This study evaluated the safety of IPT among HIV-infected pregnant women. In this multicenter, double-blind, placebo-controlled, noninferiority trial, pregnant women with HIV infection were randomly assigned to receive isoniazid preventive therapy for 28 weeks, initiated either during pregnancy (immediate group) or at week 12 after delivery (deferred group). Mothers and infants were followed through week 48 after delivery. The primary outcome was a composite of treatment-related maternal adverse events of grade 3 or higher or permanent discontinuation of the trial regimen because of toxic effects. In this study, there was a higher incidence in the immediate group than in the deferred group of an event included in the composite adverse pregnancy outcome. These findings indicate that the risks associated with initiation of isoniazid preventive therapy during pregnancy appeared to be greater than those associated with initiation of therapy during the postpartum period.
Supported by: NIAID, NICHD, NIMH
Grants: UM1AI068632, UM1AI068616, UM1AI106716, UM1AI069453, U01AI069521, UM1AI069436, U01AI068632, R21MH083308, UM1AI069521, UM1AI069465, UM1AI106716, U01AI069436, Contract (NICHD) HHSN275201800001I
Publications: https://pubmed.ncbi.nlm.nih.gov/31577875/, https://pubmed.ncbi.nlm.nih.gov/33217810/
Clinical Trials Study: NCT01494038

Maternal Depressive Symptoms, Lung Function, and Severe Asthma Exacerbations in Puerto Rican Children

Maternal depression has been linked to health care use for asthma in cross-sectional or short-term follow-up studies of school-aged children. This study examined whether increased or persistent maternal depressive symptoms over approximately five years were associated with severe asthma exacerbations or worse lung function in youth. Two visits were performed with 386 youth living in Puerto Rico. The first visit included children 6–14 years of age; the second visit cohort was 9–20 years of age. Researchers' exposure of interest was change in persistence of maternal depressive symptoms, assessed at both visits using the Center for Epidemiologic Studies Depression Scale (CES-D). In a multivariable analysis, the presence of maternal depressive symptoms at the second visit or at both visits was significantly associated with 3.17 to 3.52 times increased odds of more than one severe asthma exacerbation in the year before the second visit. Increasing or persistent maternal depressive symptoms were associated with worse lung

function measures and severe asthma exacerbations among Puerto Rican youth. The findings point to the need for physicians caring for children with asthma to be aware of potential maternal depression—and to appropriately address it when suspected.
Supported by: NIMHD, NHLBI
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Publications: https://pubmed.ncbi.nlm.nih.gov/33127521/

Identification of Maternal Risk Factors Associated with Development of Thyroid Cancer in Offspring
The number of thyroid cancer cases worldwide has increased substantially over the last few decades. Thyroid cancer is more prevalent in women than men and is usually diagnosed at a younger age than most other cancers, such as breast or lung cancer. The impact of environmental and in-utero exposure that contribute to thyroid cancer risk are mostly unknown, so intramural researchers used previously collected data from four Nordic countries to identify early risks. The researchers identified multiple factors that impact thyroid cancer risk, including maternal thyroid disorders (such as hypothyroidism) and diabetes before pregnancy, and a higher birth weight. These results should encourage future research into more early exposure risks for thyroid cancer and determine how these known factors can be incorporated into preventative treatment for this population.
Supported by: NCI
Grants: Intramural Research (NCI)
Publications: https://pubmed.ncbi.nlm.nih.gov/33347809/

Amniotic Fluid Cytokines Are Superior Predictors of Fetal Lung Injury Compared with Maternal or Placental Biomarkers
Intra-amniotic infection or inflammation is common in early preterm birth and associated with substantial neonatal lung morbidity, owing to fetal exposure to proinflammatory cytokines and infectious organisms. Researchers sought to determine whether fetal lung injury is best predicted by placental histopathology or the cytokine response in amniotic fluid or maternal plasma. Chronically catheterized pregnant monkeys (pigtail macaques) received an inoculation of saline (control), low virulence (weakly hemolytic) Streptococcus bacteria, or high virulence (hyper-hemolytic) Streptococcus bacteria into a fetal tissue layer surrounding the amnion between 116 and 125 days of gestation. The duration of a full-term pregnancy in this species of monkey is 172 days. The researchers found that the levels of two cytokines in amniotic fluid (interleukin 6 and 8) were superior predictors of fetal lung injury compared with placental histopathology or maternal plasma cytokines. This finding suggests that amniocentesis may enable prediction of fetuses at risk to develop neonatal lung morbidity due to intra-amniotic infection—an outcome that is not predicable via cytokine analysis of maternal plasma or placental histopathology
Supported by: OD/DPCPSI/ORIP, NIAID, NICHD
Grants: P51OD010425, R01AI133976, R01AI145890, R01AI043265, R01HD098713, R01AI152268
Publications: https://pubmed.ncbi.nlm.nih.gov/33412130/

Machine Learning Used to Identify Biomarkers in Mother's Plasma Associated with Diagnosis and Severity of Autism
Using machine learning, researchers identified several patterns of maternal autoantibodies highly associated with the diagnosis and severity of maternal autoantibody-related autism spectrum disorder (MAR ASD)—a condition that accounts for around 20% of all autism cases. Researchers have previously found that a pregnant mother's autoantibodies can react with her growing fetus's brain and alter its development. This study analyzed plasma samples from 450 mothers of children with autism and 342 mothers of typically developing children to detect reactivity to eight different proteins that are abundant in the fetal brain. A machine-learning algorithm was then applied to determine which autoantibody patterns were specifically associated with a diagnosis of ASD. The algorithm identified with 100%

accuracy MAR ASD–specific patterns as potential biomarkers of ASD risk. The findings present the possibility of very early detection of MAR autism.
Supported by: NIEHS, NICHD, NIGMS
Grants: R01ES015359, U54HD079125, R35GM138353
Publications: https://pubmed.ncbi.nlm.nih.gov/33483694/

General Anesthesia During Infancy Reduces White Matter Micro-Organization in Developing Monkeys
Nonhuman primates are commonly used in neuroimaging research with general anesthesia. Researchers investigated the cumulative effects of exposing 20 female and 23 male infant rhesus monkeys to general anesthesia/sedation by examining early brain development using diffusion weighted magnetic resononance imaging (MRI). Multiple exposures to commonly used anesthetics for periods of up to two hours each were associated with marked changes in white matter microstructure. These effects were dose-dependent, became worse with multiple long exposures, and were adversely affected by duration of anesthesia. This study is among the first to examine clinically relevant effects of anesthesia exposures on the developing primate brain. The degree to which the developing primate brain can recover from these drug effects remains to be investigated.
Supported by: OD/DPCPSI/ORIP, NIMH, NICHD, NIBIB
Grants: P51OD011132, R01MH086633, P50MH064065, R01MH070890, R01MH091645, P50MH078105, P50MH100031, U54HD079124, R01HD053000, P30HD003110, P30HD003352, R21HD055255, U54EB005149
Publications: https://pubmed.ncbi.nlm.nih.gov/33549320/

Erythropoietin Does Not Prevent Acute Kidney Injury in Extremely Low Gestational Age Infants
Acute kidney injury (AKI) is common among extremely low gestational age neonates (ELGANs, born at 22–26 months of corrected gestational age). Erythropoietin (Epo) has been considered a promising treatment for various conditions in ELGANs due to its potential tissue-protective effects across several organ systems. In a recent ancillary study of the randomized controlled Preterm Epo NeuroProtection Trial (PENUT), scientists compared health outcomes of ELGANs given Epo with those given a placebo. The trial confirmed the high rate of AKI (18.2% overall) in ELGANs. They found that Epo did not significantly reduce the rates of severe AKI in ELGANs, nor did it improve other indicators of kidney health or diastolic blood pressure. Epo did, however, appear to improve systolic blood pressure long-term (up to 2 years of age). This study provides evidence for the high risk of AKI and other kidney diseases in ELGANs, and reveals the critical need for novel intervention strategies.
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Publications: https://pubmed.ncbi.nlm.nih.gov/33484699/

Moderate Daily Caffeine Intake During Pregnancy May Lead to Smaller Birth Size
Previous studies have linked consumption of more than 200 milligrams (mg) of caffeine per day—about two cups of coffee—during pregnancy with lower infant birth weight. However, studies on moderate daily caffeine consumption (200 mg or less) during pregnancy have produced mixed results. Researchers analyzed data on more than 2,000 racially and ethnically diverse women at 12 clinical sites who were enrolled from 8–13 weeks of pregnancy. From weeks 10–13 of pregnancy, the women provided a blood sample that was later analyzed for caffeine and paraxanthine, a compound produced when caffeine is broken down in the body. The women also reported their daily consumption of caffeinated beverages (coffee, tea, soda, and energy drinks) over the past week—once when they enrolled and periodically throughout their pregnancies. Compared with infants born to women with no or minimal blood levels of caffeine, infants born to women who had the highest blood levels of caffeine at enrollment were an average of 84 grams lighter at birth (about 3 ounces), were .44 centimeters (cm) shorter (about .17 inches), and had head circumferences .28 cm smaller (about .11 inches). Based on the women's own

estimates of the beverages they drank, those who consumed about 50 mg of caffeine a day (equivalent to a half cup of coffee) had infants 66 grams (about 2.3 ounces) lighter than infants born to non-caffeine consumers. Similarly, infants born to the caffeine consumers also had thigh circumferences .32 cm smaller (about .13 inches). These findings suggest that even moderate caffeine consumption may be associated with decreased growth of the fetus.
Supported by: NICHD
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Publications: https://pubmed.ncbi.nlm.nih.gov/33764424/
News Link: Moderate Daily Caffeine Intake During Pregnancy May Lead to Smaller Birth Size

Prenatal Exposure to Glyphosate and Its Environmental Degradate, Aminomethylphosphonic Acid, and Preterm Birth
Glyphosate (GLY) is the most heavily used herbicide in the world. This study examined prenatal exposure to GLY and a highly persistent environmental degradate of GLY—aminomethylphosphonic acid (AMPA)—and odds of preterm birth in a nested case-control study within the ongoing Puerto Rico Testsite for Exploring Contamination Threats (PROTECT) pregnancy cohort in northern Puerto Rico. Urine GLY and AMPA levels in maternal samples collected near the 26th week of pregnancy were associated with increased odds of preterm birth of 35% and 67% for GLY and AMPA, respectively. These findings are significant given the widespread use of GLY, multiple potential sources of AMPA, and AMPA's persistence in the environment, as well as the potential for long-term adverse health effects in preterm infants.
Supported by: NIEHS, OD
Grants: P42ES017198, P50ES026049, P30ES017885
Publications: https://pubmed.ncbi.nlm.nih.gov/34009015/

Molecular Mechanisms of Environmental Toxin Cadmium at the Feto-Maternal Interface Investigated Using an Organ-on-Chip Model
Human labor is associated with feto-maternal-derived signals that coordinate to initiate delivery. Exposure to environmental chemicals can prematurely trigger labor-initiating signals at the feto-maternal interface (FMi: decidua, amniochorion), leading to spontaneous preterm birth (PTB). Testing the association between environmental chemical exposure and PTB is difficult due to many limitations *in vivo* or *in vitro*. Physiological organ-on-chips (OOCs) are potential alternatives for studying mechanisms leading to PTB. The study tested the effect of maternal exposure to cadmium (Cd), an environmental toxin, using the FMi-OOC that incorporates maternal decidua cells and three different fetal cells (chorion, amnion mesenchymal, and amnion epithelial cells). Cd transport through the FMi and its impact on cell cycle, cell death, and inflammation were analyzed. Cd treatment resulted in significant cell death and a pro-inflammatory environment in the maternal decidua, but had minimal effect on the fetal chorion cells and no effect on the fetal amnion cells compared to controls. The maternal response, but lack of fetal response, indicates that Cd-mediated adverse effects originate from maternal pathophysiology rather than fetal-derived triggers of preterm labor. This study demonstrates that the FMi-OOC can indeed predict the response of FMi upon exposure to chemicals, opening the possibility for using OOC models for environmental toxin screens.
Supported by: NCATS, NICHD, NIEHS
Grants: R01HD100729, T32ES026568, P42ES027704, P30ES029067, UG3TR003283
Publications: https://pubmed.ncbi.nlm.nih.gov/34391970/

Higher Dose of DHA Associated with Lower Early Preterm Birth Rate
Preterm birth—which is birth before 34 weeks of pregnancy—increases the risk of infant death and disability. Previous studies on docosahexaenoic acid (DHA) and other omega-3 fatty acids—which are nutrients found in fish and eggs and supplements like algal oil—and their possible effects on the rate of

early preterm birth have been inconclusive and have not identified a specific type or dose of omega-3 fatty acids. Researchers enrolled nearly 1,100 women and compared the early preterm birth rate of women given 1,000 mg of DHA to those given 200 milligrams (mg). Overall, 1.7% of women in the high-dose group delivered early preterm compared to 2.4% in the standard dose group. Women in the high-dose group with low DHA levels at study entry had the greatest reduction in early preterm birth (2% rate, compared to a 4.1% rate for those with low DHA levels on the standard dose). Among women who had high DHA levels at study entry, the rate of early preterm birth was low and did not differ by dose (1.4% vs. 1.1%). The authors called for screening DHA levels in pregnancy so that women with low levels could consider taking a higher daily dose.
Supported by: NICHD
Grants: R01HD083292
Publications: https://pubmed.ncbi.nlm.nih.gov/34308309/
News Link: DHA lower early preterm birth

Maternal Antibody Treatment Fails to Reduce Infant Cytomegalovirus Infection
Cytomegalovirus (CMV) is a common virus that causes few symptoms in healthy people but can cause death and serious health effects when transmitted to fetuses during pregnancy. Newborn CMV infection affects as many as 40,000 U.S. infants each year. The infection is linked to stillbirth, newborn death, deafness, and cognitive and motor delays. Among pregnant women with CMV infection, 30% to 45% of their fetuses can become infected, with 10% having symptoms at birth. For infants born to infected mothers, 20% have no signs of infection at birth but develop deafness and other neurologic effects later in life. CMV hyperimmune globulin contains antibodies against CMV derived from the plasma of people who have been infected with the virus. Previous studies of CMV hyperimmune globulin have suggested that it may be effective in treating CMV infection during pregnancy. In the current study, roughly 400 women who tested positive for the virus before the 23rd week of pregnancy were assigned at random to receive hyperimmune globulin or a placebo. The researchers evaluated the results in terms of a single primary outcome: whether the fetus had CMV infection, the newborn had a cytomegalovirus infection by three weeks of age, or the fetus or newborn died. The study was stopped early when interim results indicated it was unlikely to achieve statistically significant results. The primary outcome occurred in almost 23% of infants receiving hyperimmune globulin and slightly more than 19% receiving the placebo—a difference that was not statistically significant. Death occurred in nearly 5% of fetuses or newborns in the hyperimmune globulin group and in 2.6% of the placebo group. Preterm birth occurred in more than 12% of the hyperimmune globulin group and more than 8% of the women in the placebo group. Participants receiving hyperimmune globulin were more likely than those receiving the placebo to develop headaches and chills. The authors concluded that hyperimmune globulin treatment of CMV infection in pregnancy did not decrease the likelihood of fetal or newborn CMV infection or death.
Supported by: NICHD
Grants: UG1HD027869, UG1HD040500, UG1HD027915, UG1HD087192, UG1HD040544, UG1HD034208, UG1HD040512, U10HD027869, U10HD036801, U24HD036801
Publications: https://pubmed.ncbi.nlm.nih.gov/34320288/
News Link: Maternal Antibody Treatment Fails to Reduce Infant Cytomegalovirus Infection

Effects of Alcohol on Placental Function and Fetal Growth in Rhesus Monkeys
Prenatal alcohol exposure is the most common cause of birth defects and intellectual disabilities. Prenatal alcohol exposure also increases the risk of stillbirth and reduces fetal growth. Using a rhesus monkey model, researchers investigated the effects of early prenatal alcohol exposure on placental function and fetal growth. They found that early chronic prenatal alcohol exposure significantly diminished placental perfusion at mid- to late-gestation and significantly decreased the oxygen supply to the fetal vasculature throughout pregnancy. These findings were associated with the presence of microscopic placental infarctions in the rhesus monkeys. Although placental adaptations may compensate for early

environmental perturbations to fetal growth, placental blood flow and oxygenation were reduced, consistent with the evidence of placental ischemic injury.
Supported by: OD/DPCPSI/ORIP, NICHD, NIAAA
Grants: P51OD011092, K12HD000849, R01HD086331, R01AA021981
Publications: https://pubmed.ncbi.nlm.nih.gov/34364844/

Alteration of the Maternal-Fetal Interface Following Zika Virus Infection of Rhesus Monkeys
Congenital infections resulting from vertical transmission of infectious organisms from mother to fetus during pregnancy are a common cause of severe birth defects in newborns. The maternal decidua is an immunologically complex tissue barrier that protects the fetus from infections during pregnancy. To better understand immune determinants of protection against congenital infection at the maternal-fetal tissue interface, researchers performed a comprehensive analysis of immune cell subsets in the decidua of healthy rhesus monkey pregnancies across all trimesters of gestation and determined changes after Zika virus (ZIKV) infection. Decidual leukocytes in a normal, healthy, pregnant animal showed a striking enrichment of activated effector memory and tissue-resident memory T-lymphocytes. They also revealed unique populations of natural killer, T-lymphocyte, dendritic cell, and monocyte/macrophage subsets compared with peripheral blood. Decidua from ZIKV–infected mothers showed a significant reduction in the frequency of activated and cytotoxic conventional and gamma-delta T-lymphocytes compared with normal decidua, suggesting that ZIKV induces local immunosuppression and suppression of inflammation. This research adds to the immune characterization of the maternal-fetal interface in a translational nonhuman primate model of congenital infection and provides novel insight into putative mechanisms of vertical transmission.
Supported by: OD/DPCPSI/ORIP, NIAID
Grants: P51OD011092, P51OD011104, U42OD023038, S10OD026800, U24AI126683, P01AI129859
Publications: https://pubmed.ncbi.nlm.nih.gov/34394129/

Maternal HIV Drug Resistance Is Associated with Vertical Transmission and Is Prevalent in Infected Infants
Resistance to first-line antiretroviral therapy (ART) drugs is a threat to HIV prevention, particularly among women of child-bearing age, who have shown greater rates of resistance compared with men. In this study, researchers examined whether maternal HIV drug resistance is associated with an increased risk of vertical transmission (i.e., transmission from mother to child during pregnancy). The study demonstrated that maternal resistance to a specific antiretroviral (ARV) drug class known as non-nucleoside reverse transcriptase inhibitors (NNRTIs)—which include nevirapine, an ARV drug often given to infants as part of HIV postnatal prophylaxis—and maternal viral load were independent risk factors for vertical transmission during breastfeeding. These findings suggest that nevirapine alone may be insufficient to protect infants against drug-resistant variants in maternal breast milk. These findings also support efforts to achieve suppression of HIV replication during pregnancy and suggest that breastfeeding infants may benefit from prophylaxis with ART drugs that present a greater barrier to drug resistance than nevirapine alone.
Supported by: NIAID
Grants: T32AI007509, UM1AI068632, UM1AI069518, UM1AI068616, P30AI027757
Publications: https://pubmed.ncbi.nlm.nih.gov/34467974/

Maternal Cardiovascular Health in Pregnancy Associated with Offspring's Heart Health in Early Adolescence
Researchers used data from an observational study of pregnant women and their offspring to examine the associations between maternal cardiovascular health (CVH) during pregnancy (with data gathered from 2000–2006) with CVH of their offspring examined at the 10–14 years of age (with data gathered from 2013–2016). This Hyperglyecemia and Adverse Pregnancy Outcomes (HAPO) Study and HAPO Follow-Up Study included 2,302 mother-child pairs from six different countries. The results showed that better

cardiovascular health among pregnant women was significantly associated with better cardiovascular health among their children at 10–14 years of age. Children born to mothers in the poorest category of cardiovascular health had almost 8 times higher risk of being in the poorest cardiovascular health category at 10–14 years of age, compared with children born to mothers who were in the ideal cardiovascular category in pregnancy. In this multinational cohort, better maternal CVH at 28 weeks of gestation was significantly associated with better offspring CVH at 10–14 years of age.
Supported by: NICHD, NIDDK, NHLBI
Grants: R01DK117491, R01HD034243, K23HL145101, R01DK095963
Publications: https://pubmed.ncbi.nlm.nih.gov/33591345/

Rare Pediatric Diseases

Genetic Disorder Alters Blood Vessel Formation in the Eyes, Brain, Neck, and Spine
EPAS1 gain-of-function syndrome is a rare disease, first reported in 2012, that affects the HIF-2a protein, which is involved in normal development, blood vessel formation, immune responses and inflammation, and tumor development. To better understand the disease, researchers examined the blood vessels of nine patients with the disease and mice bred to have the disease. The study team found excessive blood vessels in the eyes, brain, neck, and spines of both patients and mice. Importantly, while other symptoms such as hormone-secreting tumors are known to emerge in adulthood, these blood-vessel malformations would have been present since birth. That means that providers should be aware that patients with *EPAS1* gain-of-function syndrome may present with symptoms, such as impaired vision, that are caused by stable, congenital problems present since birth. Next steps involve understanding how these malformations form in the body, potentially leading to new or better treatments.
Supported by: NICHD
Grants: Intramural Research (NICHD)
Publications: https://pubmed.ncbi.nlm.nih.gov/33497361/
News Link: NIH Researchers Shed Light on Symptoms of Rare Disease

Antisense Therapy for a Rare Premature Aging Syndrome in Children
Hutchinson-Gilford Progeria Syndrome (HGPS) is a disorder of premature aging, which results in multiple organ defects, cardiac disease, and premature death. HGPS is caused by aberrant splicing of ribonucleic acid (RNA). Correction of the disease-causing splicing event has long been proposed as a therapeutic approach to HGPS. Researchers identified therapeutically active antisense oligonucleotides that extended lifespan of a mouse model of HGPS. This antisense oligonucleotide is currently being considered for Phase I clinical trials.
Supported by: NCI
Grants: Intramural (NCI), ZIABC010309
Publications: https://pubmed.ncbi.nlm.nih.gov/33707772/

Novel Treatment Strategy for Congenital Myasthenia
Congenital myasthenia (CM) is a rare, early onset neuromuscular disease that leads to severe muscle weakness. Existing therapies for CM only partially improve symptoms. An important cause of CM are mutations in a protein called DOK7, which is involved in the formation and maintenance of connections between nerve and muscle cells. Using new experimental mouse models, researchers found that CM-causing mutations in DOK7 led to deficient activation of another protein called Muscle-Specific Kinase (MuSK). They used these findings and their prior knowledge about MuSK to design synthetic antibodies that boosted MuSK activation, and they showed that the antibody treatment rescued CM mice from early death and also reversed disease relapse in adult mice. The researchers suggest that therapeutic antibodies targeting the downstream protein MuSK may be more practical than gene therapy to compensate for

disease-causing mutations in DOK7. Similar strategies may be applicable to therapy development for other genetic diseases as well.
Supported by: NINDS
Grants: R01NS075124, R37NS036193
Publications: https://pubmed.ncbi.nlm.nih.gov/34163073/,
News Link: Antibody Therapy Rescues Mice Lethal Nerve Muscle Disease

Gene Therapy May Restore Missing Enzyme in Rare Disease
A new study suggests that gene therapy delivered into the brain may be safe and effective in treating aromatic L-amino acid decarboxylase (AADC) deficiency, a rare neurological disorder that develops in infancy. Children with AADC lack an enzyme necessary for producing the brain chemicals serotonin and dopamine, which are critical for movement, behavior, and sleep. In the study, seven children received infusions of the gene for the missing enzyme, packaged in an adenovirus for delivery into brain cells. Positron emission tomography (PET) scans performed 3 and 24 months after the surgery revealed that the gene therapy led to the production of dopamine in deep brain structures involved in motor control, and all of the children showed improvements in movement and motor function. Sleep, mood, feeding behavior, the ability to sit independently, and speaking also improved. The gene therapy was well tolerated by all participants, and no adverse side effects were reported.
Supported by: NINDS
Grants: R01NS094292
Publications: https://pubmed.ncbi.nlm.nih.gov/34253733/,
News Link: Gene Therapy May Restore Missing Enzyme in Rare Disease
Clinical Trials Study: NCT02852213

Development of Therapeutics for Two Rare Conditions
Patients with a specific type of propionic acidemia (PA) cannot break down dietary protein, and this can lead to chronic, sometimes life-threatening metabolic, kidney, and cardiac conditions. Researchers have developed an investigational gene therapy for this disorder, and recently this potential treatment received a designation that could allow the expedited development of this product. Additionally, in May 2022, the first FDA–approved treatment for eosinophilic esophagitis (EoE), a chronic immune disorder, received approval for both adult and pediatric patients. The clinical trials required for this approval was made possible by a collaborative team of patients, advocates, researchers, and clinicians. Collaborating with EoE patients and caregivers—as well as researchers and clinicians around the world—researchers were able to develop meaningful outcome measures for both children and adults, allowing for treatment comparisons and improving the quality of data synthesis.
Supported by: NCATS, NIAID, NIDDK, NINDS, NHGRI, NICHD
Grants: Intramural research (NCATS), ZIATR000281, U54AI117804
Publications: https://pubmed.ncbi.nlm.nih.gov/36694456, https://pubmed.ncbi.nlm.nih.gov/29852258, https://pubmed.ncbi.nlm.nih.gov/27330494, https://pubmed.ncbi.nlm.nih.gov/34242635,
News Links: NCATS Receives FDA Rare Pediatric Disease Designation to Treat Propionic Acidemia, About the AAV9-hPCCA Rare Pediatric Disease Designation Request Documents

Social and Environmental Influences

Influence of Childhood Adversity on Later-Life Health
Biological aging—the gradual physiological decline in multiple organ systems across time—is a distinct construct from health. However, people who age quickly are more likely to experience poor health. Investigators have identified a number of modifiable risk factors for accelerated biological aging that, if appropriately managed, may slow such processes and extend optimal health into older age. For example, in a recent study of 127,495 adults 40–69 years of age in the UK Biobank, childhood adversity was

significantly associated with acceleration of phenotypic aging as measured via a suite of biomarkers. These investigators further found that an unhealthy lifestyle—as measured via body mass index, smoking status, alcohol consumption, physical activity, and diet—significantly mediated these associations, suggesting that avoidance of unhealthy behaviors could delay physiological aging and extend years of healthy life. In a separate study, investigators analyzed data from 910 participants in the Dunedin Study, a longitudinal investigation of health and behavior among a birth cohort born between April 1, 1972, and March 31, 1973, in Dunedin, New Zealand. Study participants were assessed at 45 years of age using a midlife aging factor composite score comprising four measures of biological aging: (1) pace of aging, (2) gait speed, (3) brain age (specifically, BrainAGE score), and (4) facial age. The investigators found that adolescent smoking, obesity, and psychological disorder diagnoses were associated with older biological age at midlife, while asthma was not. These results suggest that successful treatment of smoking, obesity, and psychological disorders during adolescence could reduce the risk of accelerated biological aging later in life.
Supported by: NIA
Grants: K01AG053408, R01AG077529, P30AG021342, UL1TR001863, R01AG069939, R01AG049789, R01AG032282, T32AG000029
Publications: https://pubmed.ncbi.nlm.nih.gov/36066889, https://pubmed.ncbi.nlm.nih.gov/35188538

Systems Science Model Predicts Potential Health Impacts of Green Energy Retrofits to Housing on Pediatric Asthma
Pediatric asthma is currently the most prevalent chronic disease in the United States, with children in lower-income families disproportionately affected. Researchers combined indoor air-quality modeling with information from an actual energy retrofit at an affordable housing site in Boston to simulate the effects of different types of energy retrofits. This approach allowed them to estimate changes in infrequent but costly health outcomes (asthma hospitalizations) due to building changes, which would not be possible in an intervention field study due to the availability of subjects and the prohibitive costs of recruiting a large enough sample size. The results suggest that energy-efficiency retrofits that followed ASHRAE 62.2 standards provided a reduction in average serious asthma-related events and associated health care costs. However, similar retrofits meeting state mandated minimum ventilation rates led to an increase of asthma related events and related health care costs. Especially in buildings where occupants smoke tobacco and/or use gas stoves intensively, retrofits in the absence of exhaust fans increased levels of indoor pollutants and thus induced higher number of asthma events. Simulation results show that retrofits lead to overall better health outcomes and health care cost savings if reduced air exchange due to energy-saving air tightening is compensated by mechanical ventilation. Especially when exposed to indoor tobacco smoke and intensive gas-stove cooking, such retrofit would lead to an average annual cost savings of more than $200, while without mechanical ventilation, the same children would have experienced an increase of almost $200 a year in health care utilization cost.
Supported by: NIEHS
Grants: T32ES01456, R01ES027816
Publications: https://pubmed.ncbi.nlm.nih.gov/33583411/

Exposure to Bisphenols and Asthma Morbidity among Low-Income Urban Children with Asthma
Bisphenol A (BPA) has been linked with pediatric asthma development and allergic airway inflammation in animal models. It is unclear whether exposure to BPA and other bisphenols (BPS or BPF) is associated with asthma morbidity. This research examined associations between bisphenols and morbidity due to pediatric asthma. Researchers studied concentrations of BPA, BPS, and BPF in 660 urine samples from 148 predominantly low-income, African American or Black children (5–17 years of age) with established asthma. Over the course of one year, every three months, investigators collected data on symptoms, health care utilization, and pulmonary function and inflammation. There were consistent positive associations between BPA exposure and measures of asthma morbidity. BPA concentrations were associated with increased odds of having a day with symptoms, and health care utilization among boys only. The findings

showed BPA exposure is associated with asthma morbidity, and that associations may differ by sex. The results highlight the importance of further research given the high pediatric asthma burden and widespread exposure to BPA in the United States.
Supported by: NIMHD, NIAID, NIEHS, NHLBI
Grants: K01HL138124, P50ES018176, R01ES022607, R01ES023500, R21ES025840, R01ES023447, R01ES026170, P50MD010431, K24AI114769
Publications: https://pubmed.ncbi.nlm.nih.gov/32736870/

A Viable Alternative to Whole Blood Samples for Retrospective Public Health Surveillance of Environmental Exposure to Lead
Exposure to lead (Pb) is linked to a host of adverse health effects, and there is a need to evaluate biological samples other than regularly prepared whole blood for biomonitoring of lead exposure. Researchers developed a method that utilizes clotted erythrocyte fraction samples—which are commonly archived along with serum (or plasma) in biorepositories—to predict whole blood lead levels. Modeled blood lead predicted from clotted erythrocyte fraction was evaluated at a test threshold of 3 µg/dL and found to have diagnostic sensitivity of 88% and specificity of 100%.
Supported by: NIEHS
Grants: P42ES013661, P30ES005605
Publications: https://pubmed.ncbi.nlm.nih.gov/32920407/

Male Adolescents in Disadvantaged Neighborhoods
Male youths living in concentrated disadvantaged neighborhoods disproportionately witness and experience violence. Exposure to high levels of violence can increase the risk for both committing and being a victim of violence, and can shape behaviors that increase the risk of substance abuse, injury, and incarceration. Researchers studied these issues among Black male youths, 14–19 years of age, that were part of a sexual violence prevention program trial. The participants expressed visions of manhood that included many traditionally masculine attributes. The participants also expressed the importance of nontraditional attributes of masculinity, such as the role of emotional expression, moral agency, and emotional vulnerability. The most common definition of manhood focused on the theme of responsibility and the role of provider. Three influences emerged as shaping their experiences of manhood: (1) family and community connections, (2) interpersonal and structural racism, and (3) racial pride. The role of family—particularly fathers and community father figures—was reported as invaluable in aiding youths to understand manhood and a potential path to get to manhood, as well as navigating racial identities.
Supported by: NICHD
Grants: K23HD098277
Publications: https://pubmed.ncbi.nlm.nih.gov/32943288/

Association Increases Between Childhood Socioeconomic Disadvantage and Adult Health Outcomes
Understanding the associations between childhood socioeconomic disadvantage and adult health outcomes is important to the development of health policy. However, little is known about how these associations have changed over time. Using data from two national samples (1995 and 2012) collected from the Midlife in the United States (MIDUS) study, investigators combined three self-reported measures of childhood disadvantage—(1) poverty exposure, (2) parents' occupational prestige, and (3) parents' education—into an aggregate index. They then analyzed the association between this aggregate index and a variety of health outcomes (body mass index, waist circumference, chronic conditions, functional limitations, and self-rated health). The association between adverse health outcomes and both the aggregate index of childhood disadvantage and each individual measure of disadvantage was significantly stronger in the 2012 sample than in the 1995 sample. These results persisted after adjusting for age, race, sex, marital status, and number of children. These findings suggest that childhood socioeconomic status is becoming increasingly important predictor of health later in life, and suggests potential policy solutions for future exploration.

Supported by: NIA
Grants: P01AG020166, U19AG051426
Publications: https://pubmed.ncbi.nlm.nih.gov/33710274/

Food Insecurity in Families with Critically Ill Children
Food insecurity impacts millions of people across the United States. Pre-pandemic, food insecurity affected 15.1% of children in Pennsylvania, which was higher than the reported national average of 10.5%. Researchers conducted a study analyzing the prevalence and contributing factors of food insecurity among Pediatric Intensive Care Unit (PICU) families at a major urban medical center. Of the 137 families in the study, 20% were food insecure and 21% participated in Supplemental Nutrition Assistance Program (SNAP). Black families reported a higher prevalence of food insecurity compared with White families (56% vs. 30%). Prevalence of food insecurity among PICU families was double the general U.S. population. As a result of these findings, expanded universal social determinants of health (SDOH) screening and support in the PICU have been implemented.
Supported by: NICHD
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Publications: https://pubmed.ncbi.nlm.nih.gov/33790215/

The Influence of Parental Ethnic Identity on Children's Oral Health in American Indian Families
American Indian/Alaskan Native (AI/AN) children have the highest levels of severe early childhood caries (tooth decay) in the United States—nearly three times higher than White children. Ethnic identity, the feeling of belonging to a particular ethnic group, may be associated with health-related outcomes among AI/AN individuals. To help address longstanding oral health disparities specific to AI/AN populations, this study examined the association of ethnic identity with parental oral health knowledge, beliefs, behavior, and parents' and children's oral health status using secondary data from a clinical trial of almost 580 AI/AN parents and children. Tribal identity was significantly associated with higher levels of oral health knowledge and behavioral engagement, while tribal language proficiency demonstrated a significant association with parental oral health status over the three years of the study. These findings support an association between ethnic identity and oral health in AI/AN populations and indicate a need for further studies on the effect of bilingualism and biculturalism on parental oral health knowledge, beliefs, and behavior, and the relationship with oral health outcomes.
Supported by: NIDCR
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Publications: https://pubmed.ncbi.nlm.nih.gov/33919721/

Open, Expressive Family Life May Reduce Effects of Social Deprivation Among Adopted Children
A small study by researchers at NICHD suggets thsat an environment in which family members support one another and express their feelings can reduce the effects of social deprivation on cognitive ability and development among adopted children. In contrast, rule-driven households where family members are in conflict may increase an adopted child's chances for cognitive, behavioral and emotional difficulties. Researchers enrolled children who had spent at least eight months in Eastern European orphanages before their adoption by American families. The children ranged from 14–40 months of age and were evaluated with physical, psychological, and developmental tests twice during the following two years. Families also responded to questionnaires on the children's development and on various aspects of their home lives. The study included 10 adopted children and 19 similar children born to American families. Overall, the adopted children had significant deficits in growth, cognitive ability, and development in comparison to the American-born children. However, differences were smaller among children from families scoring higher in cohesion, where family members provided help and support for each other, and expressiveness—families whose members are encouraged to express their feelings. Children had greater deficits if their families scored higher in conflict (open expression of anger and aggression) and in control (a family life run according to set rules and procedures).The authors concluded that family cohesion and

expressiveness could moderate the effects of pre-adoption adversity, while family conflict and adherence to rules could increase the risk for behavioral problems. The authors added that larger studies are needed to verify their findings.
Supported by: NICHD
Grants: Intramural Research (NICHD), ZIAHD008920
Publications: https://pubmed.ncbi.nlm.nih.gov/34040161/
News Link: Open, Expressive Family Life May Reduce Effects of Social Deprivation Among Adopted Children

Racial Bias Drives Discipline Disparities in Preschool Children
There are large race- and socioeconomic status (SES)–based disparities in school suspension and expulsion rates in the United States, yet it is unknown how race/SES impacts classroom disciplinary practices. Researchers assessed children's earliest disciplinary experiences in educational settings by observing disruptive behavior in a diverse sample of preschool children and measuring the number of teachers' complaints about the children's behavior, as well as these teachers' recommended disciplinary actions. Overall, observed disruptive behavior did not differ based on race or SES. However, Black, Hispanic, or multiracial children from families with low SES, and Black children from families without low SES, received significantly more teacher complaints compared with White or Hispanic children from families without low SES. Regardless of race/SES profiles, teacher complaints in preschool were associated with lower cognitive performance in elementary school. These findings suggest that racial bias in early education disciplinary practices can negatively impact future school performance.
Supported by: NIMH
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Publications: https://pubmed.ncbi.nlm.nih.gov/34554578/

Early Life Social Stress in Rat Pups Leads to Social Behavior Deficits
Aberrant social behavior, which is often associated with mental disorders, emerges in early life and is closely linked to altered neural circuit function. However, little is known about how alterations in neural circuits develop. Researchers measured the impact of early-life stress in rat pups (8–12 days of age) on later (14–22 days of age) social interactions with mothers or peers and related brain circuitry. Early life stress was induced by poor maternal care or repeated shock (either in isolation or in the presence of the anesthetized mother). Whether the mother delivered poor maternal care, or was merely present during the repeated shock treatment, the pups spent less time socializing and had more activity in the neural circuitry underlying emotional arousal. When rat pups experienced the repeated shock without the mother present, these behavioral and brain changes did not occur. These data highlight that experiencing early life stress in the presence of others may cause alterations in neural circuitry and produce deficits in social interactions.
Supported by: NIMH, NICHD
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Publications: https://pubmed.ncbi.nlm.nih.gov/34706218/

Childhood Exposure to New Deal Policies
Investigators have provided some of the first evidence of consequences of New Deal policies on children's long-term life course outcomes. The investigators used individual-level data from the Wisconsin Longitudinal Study (WLS) to examine the enduring consequences of childhood exposure to local-area New Deal emergency employment work-relief activity. They found that children (0–3 years of age) living in neighborhoods with moderate work-relief activity in 1940 had higher adolescent IQ scores and higher high school class rank in 1957 than their counterparts in neighborhoods with lower work-relief activity. In addition, children who grew up in the most disadvantaged districts—i.e., those with the highest levels of work-relief activity—had similar adolescent IQ scores and class rank to children who grew up in the most advantaged districts. Investigators found no gender differences in adolescent IQ

scores or class rank, but male participants who lived in areas with moderate or high emergency employment were more likely to complete a bachelor's degree than their counterparts in neighborhoods with less. In addition, male participants who lived in neighborhoods with moderate emergency employment activity consistently exhibited higher cognitive scores later in life than males who lived in areas with low emergency employment activity—a pattern not seen among female participants.
Supported by: NIA
Grants: R01AG059791, R01AG050300, R01AG009775, R01AG033285, P2CHD041023
Publications: https://pubmed.ncbi.nlm.nih.gov/35852411/, https://pubmed.ncbi.nlm.nih.gov/36600558/

Structural Congenital Anomalies and Newborn Screening

Rapid Sequencing-Based Diagnosis of Thiamine Metabolism Dysfunction Syndrome
Approximately 30 years after the start of the Human Genome Project (HGP), rapid genome sequencing (RGS)—as part of a multidisciplinary, integrated, precision medicine delivery system—is being implemented in Australia, England, Germany, and Wales and in Medicaid pilot programs in California, Florida, and Michigan. This system includes identification of infants with suspected genetic diseases on the day of admission, RGS as a first-tier test, communication of results in a manner that facilitates prompt transition from empirical to etiologically informed treatment, and implementation within a learning health care system. To illustrate the potential for decreased suffering and improved outcomes through the implementation of RGS, the authors sequenced the genome of an infant with encephalopathy in just over 11 hours. The results led to a clinical diagnosis of thiamine metabolism dysfunction syndrome 2 (THMD2) 16.5 hours after a blood sample was obtained and 13 hours after they initiated sequencing, which informed treatment of the infant, thereby illustrating the fulfillment of the promise of the HGP to transform health care.
Supported by: NCATS
Grants: UL1TR002550
Publications: https://pubmed.ncbi.nlm.nih.gov/34077649/

Genetic Testing of the Siblings of Newborns with Cancer Genes Could Reduce Rare Pediatric Cancer Deaths by Half
Genetic testing of the siblings of newborns found to have mutations in any one of 11 genes most commonly associated with childhood-onset cancers could reduce deaths from these rare cancers by about 50%. Moreover, such routine testing could save nearly $17,000 per year for each year of life gained among the siblings, compared with not testing for the mutations. Based on current rates for childhood cancers associated with these 11 mutations, the researchers assumed that of an estimated 3.7 million U.S. newborns, 1,584 would have the mutations, 792 of their siblings would also carry these mutations, and 116 of the siblings would develop cancer before 20 years of age. If siblings carrying these mutations were diagnosed at birth and subsequently underwent regular screening, 15 out of 29 deaths before 20 years of age (52%) would be prevented, saving an estimated $16,910 per year of survival, compared with not routinely testing siblings. According to the authors, these benefits are comparable to those found in studies testing the relatives of adult cancer patients with known cancer-causing mutations.
Supported by: NICHD
Grants: K01HG009173, R01HD090019
Publications: https://pubmed.ncbi.nlm.nih.gov/34661666/,
News Link: Newborn screening

Multispectral Imaging for Microchip Electrophoresis Enables Point-of-Care Newborn Hemoglobin Variant Screening

HemeChip is a portable, low-cost, point-of-care (POC) diagnostic device that can quickly detect the presence of sickle cell disease (SCD) in newborns using a droplet of blood. The device is a miniaturized hemoglobin electrophoresis in a microchip format combining lab-on-a-chip technology with artificial intelligence. It can be used in populations in remote, underserved areas worldwide, and has the potential to save lives. The HemeChip has been commercialized under the product name Gazelle Hb Variant by Hemex Health (based in Portland, Oregon). To date, there is no other POC diagnostic technology that can provide quantitative, accurate, affordable screening of hemoglobin variants.
Supported by: NCATS, NIDDK, FIC, NHLBI
Grants: UL1TR002548, U54HL119810, R21TW010610, R44HL140739, R41HL151015, R41DK119048, R01HL133574
Publications: https://pubmed.ncbi.nlm.nih.gov/36478812/

Topical Therapy for Regression and Melanoma Prevention of Congenital Giant Nevi
Large congenital nevi, which are highly pigmented skin lesions, present major cosmetic and psychosocial concerns for patients and may develop into malignant melanoma. Unfortunately, current methods of treatment lead to considerable scarring while only providing partial removal and relief. For this study, researchers developed several genetically engineered nevus mouse models that include mice with melanocytes engineered to express a gene called *Nras* that contains the mutation *Nras(Q61R)*, known to cause most large congenital nevi in humans. The goal was to identify topical therapies that were highly effective at clearing nevi and protecting against melanoma development. Using these new models, investigators found that local delivery of MEK, PI3K, and c-KIT inhibitors led to nevi regression. Moreover, a pro-inflammatory compound called squaric acid dibutyl ester (SADBE) appeared particularly effective, as it regressed the nevi in mice and human congenital melanocytic nevi xenografts and prevented melanoma development in mice. The study revealed mechanistic vulnerabilities of nevi that may provide new topical therapeutic options for children with large congenital nevi.
Supported by: NIAMS
Grants: R01AR072304, R01AR043369
Publications: https://pubmed.ncbi.nlm.nih.gov/35561684/

Whole-Exome Sequencing in Individuals with Idiopathic Clubfoot Reveals a Recurrent Filamin B Deletion
Clubfoot is a congenital musculoskeletal birth defect in which one or both feet are rotated inward and downward. The condition affects approximately 1 in 1,000 infants; the genetic etiology, though, remains unclear for most patients. The first phase of this study applied genome-wide, whole-exome sequencing to 183 patients and 2,492 healthy controls. The analysis revealed a three-base pair deletion in the Filamin B (*FLNB*) gene in three of the patients but none of the healthy controls. The second phase applied a candidate gene-sequencing approach to an additional 974 patients and detected the same three-base pair FLNB deletion in 2 of the 974 patients. This study has led to the discovery of a novel gene for idiopathic clubfoot. The findings may help to improve understanding of FLNB's function in various biological processes and help illustrate how alterations in different FLNB domains contribute to disease development. Further research could ultimately determine how to prevent and treat various human diseases associated with clubfoot or FNLB mutations.
Supported by: NIAMS
Grants: R01AR067715
Publications: https://pubmed.ncbi.nlm.nih.gov/34491919/

Substance Use and Misuse

Use of E-Cigarettes and Other Tobacco Products on Progression to Daily Cigarette Smoking Among Adolescents and Young Adults

Over the past decade, adolescents and young adults (AYAs) have shifted toward experimentation with multiple tobacco products, including a rise in e-cigarette use. It is unknown how this trend will impact future daily cigarette use—which is the most harmful form of tobacco use and a health concern—as AYAs develop tobacco dependency over time. Researchers analyzed the national longitudinal Population Assessment of Tobacco and Health (PATH) Study to look at the progression of multiple tobacco product use by AYAs to daily cigarette use. Reported results found that each additional use of a tobacco product, as well as experimenting with tobacco before the age of 18, increased the odds of becoming a daily cigarette smoker. Additionally, e-cigarette users were three times as likely to become daily cigarette smokers compared to nonusers, suggesting that the rising use of e-cigarettes among AYAs could increase the future number of daily cigarette smokers in this group—a development that could have significant national health implications.
Supported by: NCI
Grants: R01CA234539
Publications: https://pubmed.ncbi.nlm.nih.gov/33431589/

Childhood Brain Correlates of Later Adult Alcohol Intake Differ Between Males and Females
Males and females exhibit marked differences in alcohol use and development of associated disorders. Researchers examined whether differences in childhood brain structure correlated with sex differences in alcohol use patterns in the same individuals in adulthood. The researchers found that the size and shape of specific brain structures, the amygdala and hippocampus, during childhood predicted adult alcohol use in females, but not in males. Specifically, females with a smaller amygdala and/or hippocampus in childhood showed higher alcohol use in adulthood compared with those with a larger amygdala and/or hippocampus. These findings suggest that a small amygdala and/or hippocampus may represent a sex-based developmental risk factor for later alcohol use.
Supported by: NIMH
Grants: Intramural Research (NIMH), ZIAMH002949
Publications: https://pubmed.ncbi.nlm.nih.gov/34359014/

Adaptive Treatment for Youth with Substance Use and Depression: Early Depression Response and Short-Term Outcomes
Researchers evaluated the effectiveness of motivation-enhancement therapy and cognitive-behavioral therapy (MET/CBT) in reducing alcohol or cannabis use and co-occurring depression among adolescents. Frequency of drinking, heavy drinking, and cannabis use declined significantly over the 14-week intervention period with MET/CBT for substance use. Approximately one-third of adolescents showed early improvement of depression with substance use treatment alone. After four weeks, participants whose depression did not respond well to the initial treatment received either supplemental CBT for depression or depression treatment delivered by a community health provider. Both depression treatment modes significantly decreased depression symptoms over time. This study indicates behavioral treatment for substance use among adolescents with depression not only improves substance use outcomes but can also improve depression outcomes in a subset of youth.
Supported by: NIAAA
Grants: R01AA021719, R01AA021735
Publications: https://pubmed.ncbi.nlm.nih.gov/34371102/

Galantamine Prevents and Reverses Neuroimmune Induction and Loss of Adult Hippocampal Neurogenesis Following Adolescent Alcohol Exposure
Previous preclinical research has demonstrated that adolescent alcohol consumption may result in reduced neurogenesis—the development of new neurons—in the hippocampus as well as an inflammatory response. Using a rodent model of adolescent alcohol exposure, researchers found that reduced hippocampal neurogenesis is caused by inflammatory mechanisms associated with cell death in immature hippocampal neurons. The researchers also demonstrated that galantamine—a cholinesterase inhibitor

with anti-inflammatory properties—may be able to prevent and reverse disruptions in hippocampal neurogenesis.
Supported by: NIAAA, NIA
Grants: U01AA020023, U24AA020024, P60AA011605, R01AG072894, U54AA019767, T32AA007573
Publications: https://pubmed.ncbi.nlm.nih.gov/34530858/

Community-Based and Culturally Informed Interventions Can Play an Important Role in reducing Co-Occurring Alcohol Misuse and Suicide Risk in Alaska Native youth
Researchers demonstrated the effectiveness of the Qungasvik (Tools for Life) intervention as a universal suicide- and alcohol-prevention strategy for young people 12–18 years of age living in rural Alaska Native communities. This study builds on a decades-long collaboration between these researchers and the *Yup'ik* Alaskan Native community to examine how tapping into a community's culture can provide a cornerstone for youth alcohol and other substance misuse and suicide-prevention efforts. Together, they developed the Qungasvik intervention, which uses community, cultural, and historical connectedness to build protective factors against suicide and alcohol misuse. The intervention was associated with an increase in protective factors (e.g., an individual's belief that they can overcome life's challenges, cultural and spiritual beliefs, and reflection of negative consequences of alcohol misuse). The principles of using community and culture to enhance protective factors against suicide and substance misuse could be extended to interventions for youth in other underserved populations.
Supported by: NIAAA, NIMH, NIMHD, NIGMS
Grants: R01AA023754, R21AA016098, U19MH113138, R24MD001626, P20RR061430, R01AA023754
Publications: https://pubmed.ncbi.nlm.nih.gov/36214726/

Technology and Tools

Kids First Data Used to Investigate Wide Variety of Pediatric Conditions
Researchers are using data generated by the Gabriella Miller Kids First Pediatric Research Program (Kids First) to better understand the role of compound heterozygous variants in pediatric conditions. Compound heterozygous (CH) variants occur when each copy of a gene inherited from one's parents contains one or more different mutations. If both copies of the gene lack function, it will often lead to development of specific diseases. CH variants have been understudied in pediatric diseases, because it can be difficult to tease out when mutations occur in different copies of a gene. The Kids First data can make identifying this kind of mutation easier because it often contains genetic information from a pediatric research participant as well as the participant's parents. Researchers used whole-genome-sequence data from the Kids First Data Resource Center to examine CH variants in a total of 1,629 participants across seven pediatric diseases—including adolescent idiopathic scoliosis, congenital heart defects, disorders of sex development, ewing sarcoma, neuroblastoma, orofacial cleft, and syndromic cranial dysinnervation—to understand their role in the development of these diseases. They observed across all pediatric diseases that 2.6% of the DNA samples from patients had a potentially damaging CH variant, and five genes per disease had a CH variant. This study provides novel insights about how often CH variants occur in diverse pediatric diseases. It shows that researchers could miss important genetic variants in many different kinds of pediatric diseases if they are not looking for this type of mutation. This study also exemplifies the goals of Kids First, aimed to help researchers uncover new insights into the biology of childhood cancer and structural birth defects, including the discovery of shared genetic pathways between these disorders.
Supported by: OD/DPCPSI/OSC
Grants: X01HL136997, X01HL136976, X01HL132370, X01HL132363, X0HL140547, X01HL132377, X01HL132375, X01HL132384
Publications: https://pubmed.ncbi.nlm.nih.gov/33828584/

New Technology for Antibody Delivery Suppresses Simian-Human Immunodeficiency Virus in the Central Nervous System of Infant Monkeys
In patients where HIV-1 is fully suppressed by antiretroviral drugs, HIV-1 still persists in reservoirs. If antiretroviral drugs are stopped, the virus will emerge from these reservoirs and reseed the body systemically. The central nervous system (CNS) is proposed to be a tissue compartment that harbors HIV-1. A key obstacle that constrains the treatment of CNS infection is the blood-brain barrier (BBB)—a highly restrictive barrier separating the circulating blood from the brain and extracellular fluid in the CNS. The BBB blocks almost all macromolecules, including broadly neutralizing antibodies (bNAbs) directed to HIV-1. To overcome this limitation, researchers developed a "nanocapsule" strategy for delivering the HIV-1 bNAb known as PGT121 across the BBB in infants. The researchers tested this novel technology in infant rhesus monkeys that were infected with a strain of simian-human immunodeficiency virus (SHIV strain SF162P3) that is known to infect the CNS. A single dose of PGT121 encased in nanocapsules, when delivered at 48 hours post-infection, delayed early acute infection with SHIV SF162P3 in these infants and reduced viremia, with one of four animals demonstrating viral clearance. The nanocapsule delivery of PGT121 improves suppression of SHIV in the CNS reservoir of infected infants relative to uninfected control monkeys, suggesting that this technology may contribute to HIV cure strategies for pediatric populations as well as adults.
Supported by: OD/DPCPSI/ORIP, NICHD, NIAID, NCI
Grants: P51OD011092, R01HD080459, P30AI028697, R01AI145038, R21AI114433, R01CA253215
Publications: https://pubmed.ncbi.nlm.nih.gov/34283885/

Three-Dimensional Organoid Culture Unveils Resistance to Clinical Therapies in Adult and Pediatric Glioblastoma
Glioblastoma (GBM) is the most common primary brain tumor with a dismal prognosis. The inherent cellular diversity and interactions within tumor microenvironments represent significant challenges to effective treatment. Traditional culture methods such as adherent or sphere cultures may mask such complexities, whereas three-dimensional (3D) organoid culture systems derived from patient cancer stem cells (CSCs) can preserve cellular complexity and microenvironments. The objective of this study was to determine if GBM organoids may offer a platform—complementary to traditional sphere culture methods—to recapitulate patterns of clinical drug resistance arising from 3D growth. Therapeutic resistance in organoids appears to be driven by altered biological mechanisms rather than physical limitations of therapeutic access. GBM organoids may therefore offer a key technological approach to discover and understand resistance mechanisms of human cancer cells.
Supported by: NCATS, NCI
Grants: KL2TR002547, R21CA256573
Publications: https://pubmed.ncbi.nlm.nih.gov/34700192/

Vision, Hearing, and Speech

Cochlear Implants for Deaf Children With Early Developmental Impairment
Approximately 2 to 3 out of every 1,000 children in the United States are born with a detectable level of hearing loss in one or both ears. Since 2020, cochlear implants have been approved for use by the FDA in eligible children beginning at 9 months of age. For young children who are deaf or severely hard-of-hearing, using a cochlear implant while they are young exposes them to sounds during an optimal period to develop speech and language skills. Studies have also shown that eligible children who receive a cochlear implant before 18 months of age can develop language skills at a rate comparable to children with normal hearing, and many succeed in mainstream classrooms. However, infants with both profound hearing loss and developmental impairments face inconsistent insurance coverage for cochlear implants. One study compared children with early developmental impairment and hearing aids to children with early developmental impairment who used cochlear implants. Researchers found that children with

cochlear implants had improved results in adaptive functioning, as well as cognitive, language and hearing skills. The study also found that cochlear implants were associated with less stress in the parent-child relationship. The results show that cochlear implant coverage of all children with severe to profound hearing loss—regardless of developmental impairment during a critical period of development—can lead to improved quality of life.
Supported by: NIDCD
Grants: R01DC010075
Publications: https://pubmed.ncbi.nlm.nih.gov/35607935/

Emergence of Prevocalic Stop Consonants in Children with Repaired Cleft Palate
Children born with cleft palate are at a significant risk of delays in development of early speech sounds, especially stop consonants (in English: T, D, B, P, G, and K). This delay may be driven by a combination of language deficits that children with cleft palate are at higher risk for and delayed motor practice following palate repair. In order to determine the age when prevocalic (immediately before a vowel) stop consonants emerge in children with repaired palatal clefts (with and without cleft lip) compared with noncleft peers, 120 children in cohorts corresponding to various stages of cleft lip and palate status and repair were seen in two-month intervals between the 12 and 24 months of age. During visits, the participants underwent oral/palatal examinations and a communication assessment to determine when prevocalic stops and symbolic language ability emerged. Four out of five children with repaired cleft palate will be able to produce prevocalic stop consonants by 19-22 months of age, corresponding to 9-12 months following palate repair. Researchers also confirmed that children with cleft palate lag behind their noncleft peers in their ability to pronounce oral stop consonants following palate repair.
Supported by: NIDCR
Grants: R01DE022566
Publications: https://pubmed.ncbi.nlm.nih.gov/33444099/

Wearable Sensor Allows Assessment of Eyeglass Compliance for Infants and Toddlers
Amblyopia, known as lazy eye, is a leading cause of pediatric vision loss, affecting 2% to 3% of children 6 months to 6 years of age in the United States. Amblyopia occurs in one eye when there's a breakdown between how the eye and the brain communicate. This causes the brain to favor the other, stronger eye and leads to visual input from the weaker eye being ignored. When caught early, amblyopia is manageable; permanent visual disability has traditionally been prevented by patching or applying eye drops to the dominant eye, which forces the brain to rely on input from the weaker eye and strengthening that connection in return. Though these treatments are reliable, compliance among children is particularly difficult, as these treatments severely limit their ability to see. Specialized eyeglasses—called Liquid Crystal Glasses, they're programmed to alternate between clear to opaque every 30 seconds—have proven as effective as eye patches in treating amblyopia. Spectacle treatment with prescription eyeglasses is also used to treat—and sometimes eliminate–other conditions such as mild strabismus, where the eyes are misaligned, and myopia, also known as nearsightedness, which is caused by a misshapen cornea. In some children, the benefits of spectacle treatment plateau after several weeks, which can lead to a more permanent impairment. To understand why this plateau occurs, it is necessary to measure how often and how long children keep their eyeglasses on; previously this relied on parents monitoring and reporting their child's compliance. To more accurately quantify this variable, researchers incorporated a temperature sensor into the eyeglasses to assess compliance with the spectacle treatment in children younger than 3 years of age. This technology can readily be incorporated into future clinical studies to better correlate compliance with outcomes.
Supported by: NEI
Grants: UG1EY029657
Publications: https://pubmed.ncbi.nlm.nih.gov/34427625/

SELECTED NEW AND EXPANDED RESEARCH EFFORTS IN PEDIATRIC RESEARCH

Selected New Pediatric Research Efforts

NIH ICOs launched a range of new and expanded research programs and efforts related to pediatrics in FY21 and FY22. Selected highlights of new initiatives and funding opportunities are listed below. Several programs focus on understanding risk factors for complex conditions in children, including underrepresented populations in research, gauging environmental and social factors, and examining pain. Overall, many programs focus on developing and delivering evidence-based interventions.

Juvenile Myositis Pathogenesis and Translational Medicine
The Juvenile Myositis Therapeutic and Translational Studies Unit is a research group focused on better understanding the pathogenesis of juvenile myositis—particularly inflammatory and immune mechanisms—and improved therapy. Researchers are discovering biomarkers through broad analytic approaches such as transcriptomic and proteomic analysis in juvenile dermatomyositis—a rare autoimmune system disease with notable involvement of blood vessels, characteristic rashes, and muscle inflammation. They also are looking at how biomarkers in juvenile myositis compare to Mendelian autoinflammatory disease and further analyzing juvenile myositis patients separated by myositis autoantibody subgroups that have some distinct patterns of features. Novel treatments for juvenile myositis will be evaluated in small clinical trials with the goal of establishing more targeted therapy, ideally with fewer side-effects and greater efficacy.
Supported by: NIAMS
Grants: Intramural research (NIAMS), ZIAAR041215

Infrastructure for Musculoskeletal Pediatric Acute Care Clinical Trials
Pediatric medial epicondyle fractures (MEF) and displaced distal radius fractures (DRF) are two common injuries that lack consensus and adequate evidence to guide clinical decision-making. Children are either unnecessarily undergoing costly procedures with added risks or are being undertreated if their bone is not reduced to its original place, which may result in long-term disability. To address such clinical dilemmas, the Infrastructure for Musculoskeletal Pediatric Acute Care Clinical Trials (IMPACCT) consortium was organized to develop the infrastructure and experience necessary for multicenter randomized clinical trials. The central hypothesis is that children treated with reduction under general anesthesia (MEF) or conscious sedation (DRF) will have higher patient-reported outcome scores compared with those treated with simple immobilization alone. Trials on both fractures will be conducted simultaneously to take advantage of the economy of scale, because the injuries are similar in terms of anatomic location, outcome measures, and whether an intervention is necessary. The completion of these trials will provide a framework, infrastructure, and experience for future prospective multicenter clinical trials in pediatric orthopaedics, and the study results will guide clinical decision-making.
Supported by: NIAMS, NICHD
Grants: U01AR079113
Funding Opportunities: RFA-PAR-18-594

Cell-Based Therapy for Duchenne Muscular Dystrophy
Despite recent progress in developing treatments for Duchenne muscular dystrophy (DMD), current therapies are not effective for all DMD patients, and many patients still lose ambulation and have a reduced life expectancy. The grant supports plans for a phase 1 trial of the safety and tolerability of intramuscular injections of induced pluripotent stem cell (iPSC)–derived myogenic progenitors. The planned trial would build on previous preclinical investigations of stem cell therapy for DMD, which

found that iPSC–derived myogenic progenitors contribute to long-term skeletal muscle regeneration in dystrophic mice.
Supported by: NIAMS
Grants: R34AR081536

Media-enhanced Technology for Promoting the Behavioral Health and Family Relationships of Typically Developing Young Siblings
Siblings play an important and lifelong role in the lives of their brothers and sisters who have disabilities. Research documents health risks to family caretakers of people with special needs, and racial and ethnic minority family caretakers are disproportionately likely to suffer these risks. The Sibling Support Project (SSP) has developed a national and international network that provides innovative workshops for siblings and parents to share their challenges and concerns, and to learn effective social-emotional and behavioral-health strategies. This project aims to develop and test assistive mobile app technology to develop knowledge, skills, and routines for siblings' social-emotional health and well-being, as access to these in-person workshops is limited by geographic, socioeconomic, cultural, and other factors. Researchers will test one module, with a focus on establishing and monitoring family routines that include parent/child connection experiences among an ethnically diverse group of 50 parent/child pairs in a four-week pilot test of the app.
Supported by: NIMHD
Grants: R43MD015947

Impact of Technology and Digital Media Exposure/Usage on Child and Adolescent Development
Technology and digital media (TDM) exposure and use have become ubiquitous facets of modern childhood from an early age, underscoring the urgent need to understand how this exposure and usage affects multiple developmental domains and health outcomes, as well as alters neurocognitive development and the very nature of social interactions between family members, peers, and society at large. NICHD launched the TDM exposure/usage initiative to support integrated, multiproject research programs, creating a locus of research that examines the pathways by which TDM exposure and usage impact developmental trajectories and health outcomes in early childhood and adolescence.
Supported by: NICHD
Funding Opportunities: RFA-HD-22-009

Systems Biology of Early Atopy (SUNBEAM)
The Systems Biology of Early Atopy (SUNBEAM) study is a general population birth cohort study in which pregnant women, the offspring's biological father, and the offspring are enrolled at one of 12 study sites. SUNBEAM's objective is to study the role and interrelationships of novel and established clinical, environmental, biological, and genetic prenatal and early-life factors in the development of allergic diseases through 3 years of age, with an emphasis on food allergy and atopic dermatitis. SUNBEAM's goal is to enroll at least 2,500 pregnant women. The study will collect biological and environmental samples for rigorous analyses, including extensive omics approaches.
Supported by: NIAID
Grants: UM2AI130836

Stopping Eczema and Allergy
Stopping Eczema and Allergy (SEAL) is a clinical trial for children who have already developed atopic dermatitis (AD, also known as eczema) by 12 weeks of age. The primary objective is to test whether the combined use of regular tri-lipid skin barrier cream with topical steroids early in life (proactive care) decreases the prevalence of food allergy in infants with atopic dermatitis compared with those treated with reactive care.
Supported by: NIAID
Grants: U01AI147462

Binational Early Asthma and Microbiome Study
The Binational Early Asthma and Microbiome Study (BEAMS)—a birth cohort study conducted in Nogales, Mexico, and Tucson, Arizona—is designed to identify pre- and postnatal microbial exposures, gene pathways, and microbe-derived molecules associated with protection against the appearance of early markers of asthma such as wheezing. Furthermore, the study aims to understand the mechanisms by which these microbial exposures exert asthma-protective immunity.
Supported by: NIAID
Grants: P01AI048104

Tuberculous Meningitis Research
Central nervous system (CNS) tuberculosis (TB), most often tuberculous meningitis (TBM), is the most severe form of TB and disproportionately affects children, causing death or neurologic disability in more than half despite treatment. Studies are using different methodologies to elucidate TBM pathogenesis and develop new anti–TBM therapies. One study is utilizing access to some of the largest clinical studies in TBM globally and integrating multi-omics and deep-phenotyping data. Another study is using an animal model to optimize dosing of new TB antimicrobial drugs at the site of infection and multimodality position emission tomography (PET) imaging to evaluate neurologic outcomes.
Supported by: NIAID
Grants: R01AI165721, K08AI139371

A Solid-State Biosensor for Rapid Detection of Mycobacterium Tuberculosis Antigens in Pediatric Blood Samples
Tuberculosis (TB) can be difficult to diagnose and manage in pediatric patients due to the weak performance of current diagnostic tools, which function even worse for patients co-infected with human immunodeficiency virus (HIV). To address these issues, of a solid-state nanopore biosensor assay is being developed that can rapidly diagnose pediatric TB by measuring *Mycobacterium tuberculosis* (*Mtb*)–secreted antigens in patient serum samples. The robust portability of this platform also allows its use in resource-limited areas that are subject to high TB prevalence.
Supported by: NIAID
Grants: K22AI136686

Pediatric Immune System Ontogeny and Development
Worldwide, mortality in children under the 5 years of age is predominantly due to infectious diseases and immune modulations associated with these infections. The pediatric immune system is remarkably different from the adult immune system while also forming the basis for development of a robust and efficient immune system into adulthood. Understanding the variations between pediatric and adult immune systems offers insight into strategies for developing immune-therapeutics and vaccines against infections. The Pediatric Immune System Ontogeny and Development (INTEND) initiative was launched to foster research to understand the development of the human immune system across infancy, childhood, adolescence, and adulthood. It also studies how various factors such as an individual's microbiome or environmental factors affect development.
Supported by: NICHD, NIEHS, NIAID
Funding opportunities: PAR-21-248

Immune Development in Early Life
The purpose of the Immune Development in Early Life (IDEaL) initiative is to support research to define the mechanisms regulating the establishment, development, and maintenance of immunity throughout childhood (from birth to less than 18 years of age), including the impact of pathogenic or commensal microbes or vaccination against infectious diseases, allergens, and environmental pollutants on immune development and function.

Supported by: NIAID, NIEHS, NICHD
Funding opportunities: RFA-AI-20-077, RFA-AI-20-078

Consortium for Design of TB Drug Regimens
This consortium will establish a collaborative, multidisciplinary research platform to systematically evaluate new candidate agents in combination for their potential for incorporation into new TB drug regimens across the human lifespan including young children. It will incorporate pediatric-focused research to stimulate pre-clinical, translational activities that can enable accelerated clinical testing and earlier introduction of new TB drugs and regimens in pediatric populations, with an emphasis on young children (aged 6 years or younger).
Supported by: NIAID
Funding opportunities: RFA-AI-22-059

Pilot Study to Monitor Prevalence of EV-D68 and Other Infectious Diseases
The Pandemic REsponse REpository through Microbial and Immune Surveillance and Epidemiology (PREMISE) program and collaborators began a pilot study on enterovirus D68 (EV-D68)—a virus that can cause a polio-like neurologic disease in children called acute flaccid myelitis (AFM). The pilot study is enrolling children 10 years of age and younger and will monitor them for a minimum of three years for EV-D68 and other infectious diseases of interest using blood samples and nasal swabs. Study findings will aid in understanding the epidemiology of EV-D68 and other childhood infectious diseases. The resulting analyses will be shared to generate research and data resources for early detection and diagnosis, and to inform the identification of monoclonal antibody therapies and immunogens for vaccine discovery and development.
Supported by: NIAID
Website: PREMISE
Publications: https://pubmed.ncbi.nlm.nih.gov/35036969/

The Pediatric Lupus Nephritis Mycophenolate Mofetil Study
The Pediatric Lupus Nephritis Mycophenolate Mofetil (PLUMM) Study is comparing the current standard of treatment for children with proliferative lupus nephritis (LN), which is mycophenolate mofetil (MMF) dosed based on patient weight or body-surface area, with pharmacokinetically guided precision dosing of MMF. Researchers will assess the proportion of patients achieving at least partial renal remission, as well as the proportion achieving complete renal remission using the standard versus precision dosing approaches. The study holds potential to improve long-term disease outcomes in children with LN through rapid control of kidney inflammation.
Supported by: NIAMS
Grants: R01AR079124

Situation Awareness to Improve Infant Sepsis Recognition in the Presence of Clinical Uncertainty
Sepsis has a high mortality in infants, is associated with severe long-term morbidities, and burdens health care resources with prolonged hospitalization and complex interventions. Rapid identification of sepsis and timely initiation of antimicrobial therapy are critical for reducing neonatal mortality and improving morbidity. There is an urgent need for strategies to improve the early detection of sepsis in infants to improve outcomes. Researchers aim to improve sepsis recognition by developing an infant sepsis early recognition system that combines patient data with predictive model outputs to deliver timely and relevant information to clinicians and nurses.
Supported by: NLM
Grants: R01LM013526

The Research Expanding Access to Child Health Center

The Research Expanding Access to Child Health (REACH) Center is a recently established Centers of Biomedical Research Excellence (COBRE) site, located in an Institutional Development Award (IDeA)–eligible state. The center was designed to build capacity in pediatric health care delivery research in Delaware. Rooted in the principles and methods of pediatric health care delivery science, this center will bridge biomedical research and health care systems, in addition to ensuring equitable access to high-quality pediatric health care. To accomplish these goals, the REACH Center operates through three primary objectives: (1) Expand innovative programs of community-engaged, intervention-focused research using advances in technology to counter negative social ecological focuses and improve child health; (2) Enhance existing expertise and expand research infrastructure through core resources supportive of health equity research for children; and (3) Establish a critical mass of independently funded investigators who investigate pediatric health care delivery and address health disparities related to child health. As a starting point, interventions for improving equity in child health focus on children with obesity in rural Delaware, type 1 diabetes in Hispanic youth, and families with a prenatal diagnosis of congenital heart disease.
Supported by: NIGMS
Grants: P20GM144270
Funding opportunities: PAR-19-313

Pediatric COVID-19 Data Challenge
While most children with COVID-19 are asymptomatic or have mild symptoms, health care providers have difficulty determining which of their pediatric patients will progress to moderate or severe COVID-19. Some of these patients develop multisystem inflammatory syndrome in children (MIS-C), a life-threatening inflammation of organs and tissues. Methods to distinguish children at risk for severe COVID-19 complications, including conditions such as MIS-C, are needed for earlier interventions to improve pediatric patient outcomes. A data challenge competition will leverage de-identified electronic health record (EHR) data to develop, train, and validate computational models that can predict severe COVID-19 complications in children, equipping health care providers with the information and tools they need to identify pediatric patients at risk. Participants have been asked to develop, train, and validate computational models to predict pediatric patients at risk for hospitalization, need for ventilation, and cardiovascular interventions, utilizing deidentified EHR data available through the National COVID Cohort Collaborative (N3C) Data Enclave.
Supported by: NCATS
Grants: U24TR002306

Safe Return to School
The Safe Return to School Diagnostic Testing Initiative is a part of the Rapid Acceleration of Diagnostics Underserved Populations (RADx-UP) initiative. It addresses the needs of children with unequal access to COVID-19 testing, as well as those facing barriers to attending school remotely. This includes children who lack access to computers and internet connectivity, or who may not have family members available to help with virtual learning. Without in-person schooling, many children will miss out on school-based meals, speech or occupational therapy, and afterschool programs. Loss of such services disproportionately affects minorities, socially and economically disadvantaged children, children with disabilities, and those with medical complexities. Projects took place in rural, urban, and tribal communities and focused on several topics related to the safe return of students and teachers to school; implementing COVID-19 testing regimens for students younger than 12 years of age; exploring the influence of vaccination for eligible staff and students; addressing vaccine hesitancy; and seeking information on circulating variants and breakthrough infections. An initiative connecting scientists and physicians with school and community leaders across 18 states published a suite of research on COVID-19 and the return to in-person learning in underserved K–12 schools. “Safe Return to School For All” summarizes current evidence and best practices to help administrators, educators, and families and students—including students with disabilities—return to school safely in the context of COVID-19.

Supported by: NICHD
News Links: How Kids Can Go Back to School Safely, COVID-19 Testing Initiative Aims Safely Return Children Person School, New RADx-UP Research Effort, Suite of Research on COVID-19 and Schools, Safe Return to School for All

Researching COVID-19 to Enhance Recovery
The Researching COVID to Enhance Recovery (RECOVER) Initiative seeks to understand, prevent, and treat post-acute sequelae of SARS-CoV-2 (PASC), including Long COVID. *PASC* is a term scientists are using to study the potential consequences of a SARS-CoV-2 infection. The RECOVER Initiative aims to follow up to 1,500 pregnant patients with COVID-19 and their offspring for four years. The pediatric RECOVER cohort will establish the incidence, prevalence, and long-term sequelae of SARS-CoV-2 infection, characterize the clinical course and recovery, determine risk factors, and define the pathophysiology and biologic mechanisms of PASC.
Supported by: NICHD, OD, NEI, NHLBI, NHGRI, NIA, NIAAA, NIAID, NIAMS, NIBIB, NIDCD, NIDCR, NIDDK, NIDA, NIEHS, NIGMS, NIMH, NINDS, NINR, NIMHD, NLM, NCCIH, NCATS, OD/DPCPSI/ORIP, NCI, OD/DPCPSI/ODP, OD/DPCPSI/ORWH
Website: RECOVER: Researching COVID to Enhance Recovery

Pediatric COVID-19 and MIS-C Long-Term Follow-Up
Pediatric COVID-19 and MIS-C Long-Term Follow-Up (PECOS) is a prospective observational study designed to evaluate the long-term clinical manifestations and outcomes associated with SARS-CoV-2 infection. Children and young adults (0–21 years of age) who have recovered from infection will be invited to participate, and will be followed for three years. Household contacts will be encouraged to participate as controls. Participants will have a comprehensive cardiac, pulmonary, and neurodevelopmental evaluation at each visit, including the completion of validated questionnaires to assess the social and psychological impact of the disease for them and their families. Blood samples will be collected as part of a biorepository and evaluated for potential genetic and immunological factors associated with long-term manifestations.
Supported by: NIAID
Website: Pediatric SARS-CoV-2 and MIS-C Long-Term Follow-up

COVID-19 Impacts on Mental Health of Pregnant Women, Mothers, and Infants
Several studies are examining how COVID-19 stress may be shaping long-term mental health risks for families and children born during the pandemic. For example, researchers are combining measures of pandemic-related stress with neuroimaging and biological samples to determine mothers' and infants' risks for developing mental illnesses. Additionally, other researchers are examining how pandemic-related stress, including SARS-CoV-2 infection, modifies immune system function, maternal mental health, olfaction (which may play an important role in mother-infant bonding), and infant behaviors. These projects aim to improve our understanding of the social and biological factors that shape neurodevelopment and underlie an individual's level of risk and resilience to stress.
Supported by: NIMH
Grants: R01MH126468, R01MH125870, R01MH126531,
Funding Opportunities: RFA-PA-20-072 , NOT-OD-21-071

Fever Etiology and Point-of-Care Biomarkers in African Children with Severe Febrile Illness
The causes of severe febrile (fever) illnesses in children are seldom determined because of the inadequate availability of diagnostics at the point-of-care in less developed settings. Using highly sensitive methods for pathogen detection, whole-genome sequencing, host serum biomarkers, and clinical characteristics of children presenting with severe fever, this study will develop point-of-care biomarker tests and develop a treatment algorithm incorporating clinical signs and biomarkers that will guide management of children presenting with febrile illnesses in sub-Saharan Africa.

Supported by: NIAID
Grants: K23AI144029

Defining the Inflammation and Immunity Transcriptome in Severe Malarial Anemia for Immunotherapeutic Discovery
Severe malarial anemia (SMA) is the most common manifestation of severe malaria in infants and young children; it accounts for the highest malaria-related morbidity and mortality worldwide. This research aims to identify gene profiles that result in severe malarial anemia in infants. The research team is investigating how changing gene expression profiles promote SMA during acute disease, as well as how they mediate disease severity throughout the development of naturally acquired immunity. The overall objective is to use this information to identify promising target genes and compounds for use in immunotherapy to achieve improved clinical outcomes.
Supported by: NIAID
Grants: R01AI130473

Pediatric Dose Optimization for Emergency Seizure Treatment
Seizures are among the most frequent reasons for Emergency Medical Services (EMS) calls for children. Benzodiazepines, such as midazolam, given in the nose or as a muscular injection, are the first-line treatment. But in a third of children, seizures continue on arrival to the emergency department, putting children at risk for respiratory failure or brain damage. Currently, paramedics must make a series of calculations in a stressful emergency situation to determine a weight-based dose—a process that can result in underdosing and delays to treatment. A new Phase III clinical trial will determine whether standardized, age-based dosing, which could be faster and simpler to implement, is more effective without compromising safety. The Pediatric Dose Optimization for Seizures in EMS (Pedi DOSE) study will measure the impact of standardized EMS midazolam dosing on seizure treatment effectiveness and safety in children in 20 EMS systems nationally.
Supported by: NINDS
Grants: U01NS114042

Effects of Light Exposure on Amygdala Plasticity During Adolescence: Implications for Anxiety and Well-Being
Anxiety and mood disorders are the most common mental health problem in adolescents, and are often associated with disruptions in both emotional processing and decision-making. Widespread exposure to light from electronic devices before bedtime is a possible risk factor for developing psychiatric disorders. Using a translational mouse model, this project will explore the effects of altered patterns of light exposure on amygdala plasticity and emotion-related behavior in adolescent mice, which will potentially lead to new complementary strategies to advance health and well-being in human adolescents.
Supported by: NCCIH
Grants: K99AT010903

Using Just-in-Time Adaptive Interventions to Optimize Established Adolescent Mental Health Treatments
Applications are now being sought for pilot research to develop and test just-in-time adaptive interventions, which are mobile and sensor-based technologies that monitor an individual's behavior and deliver responsive, tailored interventions at optimal times. Studies informed by developmental science and grounded in an empirical model of behavior change are of primary interest. Researchers will perform milestone-driven testing, refinement, and/or mechanistic validation of a mental health intervention geared toward adolescents. They may receive additional support to replicate pilot findings in a larger sample and examine the relationship between target mechanisms and clinical outcomes.
Supported by: NIMH
Funding Opportunities: RFA-MH-22-150

Family Navigator Models to Promote Early Access, Engagement, and Coordination of Mental Health Services for Youth
Research is being solicited to develop and test family navigator models—an intervention strategy in which health care professionals promote access, engagement, coordination, and optimization of treatment—for youth experiencing early symptoms of a mental illness. Researchers who aim to develop and test effective family navigator models and identify variables that can be optimized for the unique mental health needs of youth will be supported. There is also interest in emerging technologies to track and monitor the impact of family navigator models on clinical, functional, and behavioral outcomes in this population.
Supported by: NIMH
Funding Opportunities: PAR-21-291, PAR-21-292

Reducing Suicide Risk in Young People in Low- and Middle-Income Countries and Low-Resource Settings
Although suicide occurs across all ages, nearly one-third of all suicides occur among young people 10–24 years of age. Most data regarding risk factors for youth suicide come from high-income countries, including the United States, Canada, and those in the European Union. However, suicide is a significant global public health problem. Researchers are hoping to fill in gaps in our understanding of drivers of suicide among youth in low- and middle-income countries, and to develop and test interventions to reduce the global suicide rate.
Supported by: NIMH
Funding Opportunities: NOT-MH-21-090

Mechanisms and Predictors of Change in App-Based Mindfulness Training for Adolescents
Mindfulness-based smartphone apps have surged in popularity in recent years. An estimated 11% of U.S. adolescents have used mindfulness apps as a means of coping with symptoms of depression and anxiety, which increase substantially during the adolescent years and have been repeatedly linked to rumination in youth. The research activities will investigate the underlying neural and cognitive mechanisms that account for the beneficial effects of these apps on rumination, and a machine-learning algorithm will be developed to predict which specific adolescents are expected to benefit from app-based mindfulness training.
Supported by: NCCIH
Grants: R01AT011002
Funding Opportunities: PA-18-323

Sleep Biomarkers and Mental Health in Children
Children with behavioral and neurodevelopment disorders often have disorganized and dysfunctional sleep. Researchers are conducting a multisite, longitudinal study designed to answer questions relating sleep to mental health in children 6 months through 8 years of age. In addition to collecting neuronal recordings from the brain during sleep, these researchers are using genetics and clinical lab data to evaluate other physiological parameters of sleep. Physiological data are being compared alongside measures of cognition, behavior, and developmental milestones to determine which sleep-related measurements are most relevant for mental health outcomes. Researchers aim to develop a better understanding of sleep-related biomarkers that can identify children who will benefit from early therapeutic interventions.
Supported by: NIMH
Grants: ZIAMH002962

Evaluation of a Direct-to-Home Telemedicine Tool for ASD Diagnosis

Remotely delivered telemedicine tools have the potential to improve diagnostic services for infants exhibiting symptoms of autism spectrum disorder (ASD). Researchers recently validated TELE-ASD-PEDS (TAP), a parent-administered and clinician-guided diagnostic tool. Researchers are now examining TAP's range of assessments, diagnostic accuracy, family satisfaction, and accessibility in homes of a broader community sample, including populations that typically have unmet mental and behavioral health needs. TAP has the potential to improve access to care, eliminate the time lag between ASD symptom emergence and diagnosis, and reduce disparities for populations that are underserved.
Supported by: NIMH
Grants: R01MH127228
Funding Opportunities: PA-18-401

Combining Advances in Genomics and Environmental Science to Accelerate Actionable Research and Practice in ASD Network
This project will establish a network for the investigation of gene-environment (GxE) interactions in autism spectrum disorder (ASD) and outcomes among people with ASD across multiple studies. Robust evaluation of GxE requires a large sample size, harmonized data on both genetics and environmental exposures, and novel statistical methods for measuring and summarizing environments, genetics, and phenotypes. The Combining Advances in Genomics and Environmental Science to Accelerate Actionable Research (GEARs) and Practice in ASD will complement work in population studies with studies that leverage experimental models of 3D brain organoids reflecting different ASD–associated genetic backgrounds. Researchers will evaluate the impact of environmental risk factors on a range of ASD–relevant neurophysiology endpoints. The GEARs Network will also develop and implement a pipeline for outreach and dissemination of findings to the ASD community.
Supported by: NIEHS, NICHD, NINDS
Grants: R01ES034554
Funding Opportunities: RFA-HD-22-007

Biological Measures for Prognosing and Monitoring of Persistent Concussive Symptoms in Early and Middle Adolescents
Preadolescent- and adolescent-age groups may be at increased risk for long-term neurobiological and behavioral consequences of concussion or repeated head impacts. As part of a new initiative, a multicenter, multidisciplinary research center will develop and validate objective biological measures for prognosing and monitoring the recovery of adolescents who have or are at risk for developing persistent symptoms following concussion or repetitive head impacts. The five-year Concussion Assessment, Research and Education for Kids (CARE4Kids) study will enroll more than 1,300 adolescents nationwide in two phases of research to first identify prognostic biomarkers of persistent post-concussion symptoms and validate whether these biomarkers accurately predict prolonged symptoms. The goal is to develop a practical algorithm for use in general clinical practice by doctors and other health professionals.
Supported by: NINDS
Grants: U54NS121688
Funding Opportunities: RFA-NS-20-016

Breastmilk Ecology: Genesis of Infant Nutrition Project
A deeper understanding of human milk biology is essential for addressing ongoing and emerging questions about infant feeding practices. Human milk is a complex biological system—a matrix of many interacting parts—that is more than the sum of those parts. Human milk production should be studied as an ecology that consists of inputs from the lactating parent, their breastfed baby, and their respective environments. The Breastmil Ecology: Genesis of Infant Nutrition (BEGIN) Project—an effort by federal and non-federal partners and extramural investigators—was designed to examine this ecology and its functional implications for both parent and infant. BEGIN aims to explore ways in which emerging knowledge can be expanded via a targeted research agenda and translated to support efforts to ensure

safe, efficacious, and context-specific infant feeding recommendations and practices in the United States and globally.
Supported by: NICHD
Website: Breastmilk Ecology: Genesis of Infant Nutrition (BEGIN) Project

A Hybrid Mobile Phone Family Intervention to Prevent Childhood Obesity
Young Hispanic or Latino children experience disproportionate impacts of obesity during childhood. Consumption of sweetened beverages, media-viewing, and physical activity patterns are often established during early childhood. Family-based obesity interventions have shown effectiveness in shaping healthy behaviors and weight outcomes for young children, including Hispanic or Latino children. However, these interventions often lack methods to increase accessibility and dissemination to multiple family caregivers. This project will evaluate the impact of a family-based early childhood obesity intervention for Hispanic or Latino families on child body mass index. The study will incorporate mobile phones and evidence-based strategies of in-person childhood obesity interventions. It will also leverage important determinants of Hispanic or Latino health, such as familism and language, to decrease ethnic disparities in childhood obesity and cardiovascular risk.
Supported by: NIMHD
Grants: R01MD017703
Funding Opportunities: PAR-20-310

Feasibility and Acceptability of Biofeedback-based Virtual Reality for Postoperative Pain Management in Children and Adolescents
The goal of this two-phase study is to understand how to implement a novel biofeedback-based virtual reality (VR-BF) therapy for postoperative pain management in children. The proposed research is relevant to the Federal Pain Research Strategy to find more effective, novel, nonpharmacologic approaches for pain management given the risks of tolerance, dependence, and addiction associated with opioids. This research is especially important for disparate populations (e.g., children) given the particular vulnerability to the adverse effects of opioids. If the long-term aims of this project are achieved, this innovative delivery of effective mind-body therapy could change routine clinical practice in the pre- and postsurgical care areas. Widespread implementation of VR-BF has the potential to improve postoperative analgesia, reduce opioid and other analgesic medication consumption, and assist in pain and stress management in a variety of patient populations.
Supported by: NCCIH
Grants: R34AT011218
Funding Opportunities: PAR-18-417

Pediatric Preclinical In Vivo Testing Consortium
This consortium collaborates with industry partners on rigorous preclinical testing of molecularly targeted agents developed for adult cancers to evaluate their applicability to the treatment of pediatric cancer using *in vivo* models. The Pediatric Preclinical In Vivo Testing Consortium (PIVOT) is an extension and expansion of two previous highly-successful programs: the Pediatric Preclinical Testing Program and the Pediatric Preclinical Testing Consortium. PIVOT consortium members have decades of experience in developing and using *in vivo* models to advance treatment options for the most common childhood cancers. A public-private partnership comprises a coordinating center and seven academic research programs. PIVOT supports the Research to Accelerate Cures and Equity (RACE) for Children Act of 2017, which requires companies developing targeted cancer drugs for adults to evaluate those drugs for applicability to pediatric cancer, providing data on safety and preliminary efficacy "to inform potential pediatric labeling."
Supported by: NCI
Websites: Pediatric Preclinical In Vivo Testing Consortium, Pediatric PIVOT Program

Early Intervention to Promote Cardiovascular Health of Mothers and Children
The Early Intervention to Promote Cardiovascular Health of Mothers and Children (ENRICH) program will tap into existing federal home-visiting programs that serve at-risk families to determine whether adding a cardiovascular intervention will enhance maternal and early childhood outcomes for approximately 3,000 mother-child pairs. The new ENRICH program is investigating whether incorporating heart-healthy lifestyle interventions into federally sponsored home-visiting programs can reduce cardiovascular disease (CVD) and its risk factors in mothers and their children (0–5 years of age) living in low-income, low-resource rural or urban communities, or in U.S. regions with a high burden of CVD.
Supported by: NHLBI
Funding Opportunities: RFA-HL-22-007, RFA-HL-22-008

Clinical Trials of Drugs Targeting Shared Molecular Etiologies Across Multiple Rare Diseases
There are thousands of rare diseases, and the majority of these are pediatric. Some diseases are so rare that it does not make financial sense to start a clinical trial, even if there is a promising drug candidate. However, the number of underlying causes (etiologies) of rare diseases is much smaller, and many of these are shared across different rare diseases. Therefore, this funding opportunity is intended to support clinical trials of drugs targeting shared etiologies that include patients from more than one disease. This general approach has already been accepted by the FDA for cancer drugs. The broader goal of this funding opportunity is to increase the number of rare disease patients, many of which are children, in clinical trials.
Supported by: NCATS
Grants: UG3TR003908, UG3TR003897

Pediatric and Reproductive Environmental Health Scholars Program
The goal of the Pediatric and Reproductive Environmental Health Scholars (PREHS) program is to create a strong network of health care professionals who possess the skills and knowledge to address the complexities of pediatric and reproductive environmental health. The PREHS program will bring together institutional expertise in environmental health science research with clinical and translational expertise at Pediatric Environmental Health Specialty Units (PEHSUs) to provide pediatric health care providers, obstetricians/gynecologists, nurses, and other interested health care professionals (PREHS Scholars) with research experiences that bridge clinical practice in environmental health, community-level engagement, and teaching. These K–12 programs will produce well-qualified and well-trained pediatric and reproductive environmental health leaders.
Supported by: NIEHS
Grants: K12ES033584, K12ES033594, K12ES033593
Funding Opportunities: RFA-ES-20-007

Risk and Strength: Determining the Impact of Area-Level Racial Bias and Protective Factors on Birth Outcomes
Preterm birth and low birth weight have considerable and consistent racial and ethnic disparities. The observed inequalities are not entirely explained by individual-level risk variables. Although there is growing evidence that area-level racial bias plays a role in explaining these disparities, scientific tools, techniques, and results to assess its impact are lacking. This project will advance research by improving insights into the potential consequences of racial bias on the risk of preterm birth and low birth weight at a population level, as well as find protective variables to mitigate its influence. In addition, the project will advance understanding of the potential effects of racial bias at a population level on the risk of preterm birth and low birth weight, and identify protective factors to buffer its impact. This study will: (1) track and detect changes in area-level racial bias and identify local and national race-related events during these time points; (2) determine the impact of changes in area-level racial bias on changes in adverse birth outcomes; and (3) identify protective factors for adverse birth outcomes.

Supported by: NIMHD
Grants: R01MD015716
Funding Opportunities: PA-18-935

Social Stress, Epigenetics, and Cardiometabolic Health Among Youth
Economic and social pressures impact the development of cardiovascular disease early in life, but little is known about how social or economic pressures influence biological processes, or whether these changes are visible in youth. This project will analyze how social stressors affect DNA methylation, mitochondrial DNA damage, and cardiometabolic health in children who are members of the Hispanic Community Health Study/Study of Latinos Youth Study. The study will address these gaps by examining how social and economic stressors experienced in childhood impact DNA methylation and mDNA damage in a diverse sample of Hispanic or Latino youth living in the United States, as well as how these factors may impact their cardiometabolic health.
Supported by: NIMHD
Grants: R01MD015204

Innovative Approaches to the Study of Social Determinants of Health in Children
Millions of children in the United States get the flu each year, and thousands are hospitalized due to complications. There is a lack of data on the connections between stress and antibody production following vaccination in children. This project will examine how chronic and acute stress exposure is linked to children's antibody response to vaccination by focusing on the influenza vaccine. Investigators aim to understand what kinds of chronic and acute stressors in childhood are most likely to be linked to children's antibody responses. The study will examine parents' and youths' stressful experiences and antibody responses. The participants joined the study at 11 years of age and are currently in their late 20s. This unique sample is extremely well characterized, with annual assessments of exposure to socioeconomic disadvantage, parental depression and substance use, and coping strategies. The project sheds light on risk factors in childhood and adolescence that might put certain individuals at risk for increased susceptibility to infection, despite vaccination.
Supported by: NIMHD
Grants: DP2MD013947
Funding Opportunities: RFA-RM-17-006

Screening and Functional Validation of Human Birth Defects Genomic Variants
This initiative promotes the screening, functional validation, and characterization of birth defects-associated genetic variants identified through public-facing databases and individual efforts using *in silico* tools, appropriate animal models, *in vitro* systems, or multipronged approaches. This initiative addresses a challenging gap between identifying sequence variations of potential interest and recognizing which of those genetic variations have functional effects on targeted traits related to birth defects.
Supported by: OD/DPCPSI/ORIP, NICHD, NIDCR
Funding Opportunities: PAR-21-229

Selected Expanded Pediatric Research Efforts

In addition to launching new research programs, NIH ICOs build on successful programs to expand research efforts related to pediatrics. Selected highlights of expanded research efforts are given below. As with the new programs, many of these expanded initiatives focus on developing and delivering evidence-based interventions.

The Panel Study of Income Dynamics

The Panel Study of Income Dynamics (PSID) is a longitudinal survey of a nationally representative sample of U.S. families—the longest running household study in the world. In April 2021, the researchers offered early access to new data from the Child Development Supplement (CDS) of the PSID, which provide caregiver-reported information on how children and teens fared during the first months of the COVID-19 pandemic. The CDS is a nationally representative, ongoing component of the main PSID that focuses on the health, development, and well-being of children and adolescents whose families are enrolled in the main study. During each "wave" of the CDS, the primary caregivers of the children answer questionnaires about children and how they are developing within their family, school, and neighborhood environments. As the children get older, their reports replace those of the primary caregivers. Researchers will also collect new data on children's mask use and exposure to school mask mandates.
Supported by: NICHD
Grants: R01HD052646

The Environmental Determinants of Diabetes in the Young
Insights about strategies to prevent type 1 diabetes could be identified through the ongoing Environmental Determinants of Diabetes in the Young (TEDDY) study, which is following more than 6,000 children at high genetic risk of developing type 1 diabetes to identify environmental factors that trigger or protect against disease development. Researchers aim to characterize type 1 diabetes progression through -omics studies to identify how genes, proteins, metabolic markers, and the microbiome change over time in those at high risk of developing the disease. In Fiscal Year (FY) 2021, TEDDY researchers received funding to begin a study to identify environmental triggers of autoimmunity and type 1 diabetes in children who develop the disease late in their childhood; a similar study of children who developed the disease at a young age is currently ongoing.
Supported by: NIDDK, NIAID
Grants: U01DK128847
Funding Opportunities: RFA-DK-20-503

Clinical Studies in Pediatric Stroke
Perinatal and pediatric stroke are potentially life-threatening conditions that can occur in newborns and throughout childhood. They can lead to chronic impairments, including changes in cognitive and motor function and epilepsy. Research is now underway on early life strokes to improve strategies for prevention and recovery. For example, I-ACQUIRE is an ongoing multisite randomized clinical trial investigating constraint-induced movement therapy (CIMT)—a type of rehabilitation that encourages use of a weak, stroke-affected limb by constraining the unaffected limb. I-ACQUIRE will assess whether CIMT and intensive play therapy designed for babies 8–36 months of age can improve upper extremity (arm) motor function after perinatal stroke. Researchers will also evaluate the intervention's effects on overall motor development and cognition. Other examples include the Vascular Effects of Infection in Pediatric Stroke (VIPS I and II) trials, which examine the role of infectious pathogens (such as the common cold) and inflammatory factors in stroke as well as the influence of vaccinations on stroke prevention. Additionally, a new study—Seizures and Children's Outcomes after Stroke (SCOUTS)— is leveraging the VIPS cohorts to understand how stroke-related inflammation is related to post-stroke seizures and epilepsy, which are associated with poorer cognitive and quality of life outcomes after pediatric stroke. Together, these and other studies on pediatric stroke should drive improvements in prevention and recovery.
Supported by: NINDS
Grants: U01NS106655, R01NS104094, R01NS119896, U01NS087748, U01NS086872

Evaluating a Parenting Evidence-Based Mental Health Intervention for Hispanic Youth in Primary Care
Familias Unidas, a family-centered online intervention for Hispanic youth and their families, has been effective in preventing and reducing youth substance use, sexual risk behavior, and rates of sexually

transmitted infections. Familias Unidas has also shown unintended effects on symptoms associated with mental disorders. Investigators are now evaluating the effectiveness of an expanded Familias Unidas program focused on reducing depressive and anxiety symptoms and suicide behaviors in Hispanic youth. Researchers plan to evaluate the intervention in primary care settings to understand the real-world barriers and facilitators of implementing this intervention. In addition to youth behavior, researchers also aim to identify how family communication and depressive and anxiety symptoms in parents mediate youth symptoms.
Supported by: NIMH
Grants: R01MH124718
Funding Opportunities: RFA-MH-20-505

Childhood Cancer Data Initiative (CCDI)
In 2019, the Childhood Cancer Data Initiative (CCDI)—in alignment with a presidential proposed federal investment of $500 million over 10 years—began working to make progress against childhood cancers. The CCDI aims to enable greater data sharing among the childhood cancer community, to ensure data is easily accessible for cancer researchers to learn from and inform future preventative, clinical, and survivorship care. The CCDI is complementary to other initiatives working to advance the study of childhood cancer, including the efforts aligned with the implementation of the Childhood Cancer STAR Act. Through CCDI's efforts to integrate different types of data from various sources—including biospecimen repositories, clinical trials, basic research, preclinical models, real-world patient data, and population studies—data use and sharing among the pediatric cancer research community will increase to improve understanding of childhood cancers and advance research to develop new and better treatments. In 2021, the National Childhood Cancer Registry (NCCR) was launched. NCCR contributes to the CCDI data ecosystem by serving as a linked infrastructure of central cancer registry data that will integrate various other childhood cancer data—from hospitals, research centers, heath care administrations, and other sources—to enhance access to and utilization of childhood cancer and survivorship data. Additional activities underway include but are not limited to: developing and refining computational methods and pipelines that can be shared to analyze a variety of data; creating frameworks to harmonize pediatric cancer data; investing in pilot projects to enhance efficiency of clinical trials data collection; and building a searchable online catalog of the data, tools, and resources available through the CCDI. The biggest expansion of CCDI in 2022 was the launch of the Molecular Characterization Initiative (MCI). The MCI is a national collaboration among the childhood cancer community, including the Children's Oncology Group, advocates, pediatric oncologists, researchers, data scientists, children and adolescents and young adults with cancer, and families. It provides state-of-the-art molecular characterization at the time of diagnosis that helps participants and doctors select the best and most appropriate treatment. The data collected will also later be made accessible to researchers for future studies to enable them to create better clinical trials, learn about the origins and drivers of childhood cancer, and make faster progress in the development of new and better treatments—especially for childhood cancers with limited effective treatment options. In its first year, the initiative returned results to more than 1,000 patients. Additionally, the Childhood Cancer Datasets Catalog was launched in 2022. This provides researchers, administrators, and the public with a comprehensive catalog of research studies in pediatric cancer that is searchable by facets of interest, such as diagnosis, subject demographics, and types of samples and data that have been acquired.
Supported by: NCI
Grants: CCDI (RePORTER), Childhood Cancer Data Initiative (CCDI) (RePORTER)
Website: Childhood Cancer Data Initiative

Developing New Therapeutics to Treat Children with Cancer
A number of pediatric clinical trials released updates or results in 2022. Results from a Children's Oncology Group (COG) Phase III clinical trial for pediatric and adolescent and young adults (AYA) patients with Hodgkin's lymphoma (AHOD1331), a cancer of the lymphatic and immune systems, found

that a specific antibody-drug conjugate treatment significantly improved event-free survival and is an effective agent to improve outcomes for recently diagnosed patients in this age group. A COG Phase III trial (AAML1031) characterized a critical biomarker and identified it as a promising future therapeutic target for pediatric patients with acute myeloid leukemia (AML), a cancer of the blood and bone marrow, and a poor prognosis. Additionally, from this study, researchers found that a multikinase tyrosine kinase inhibitor—a drug that targets multiple enzymes involved in cell functions such as signaling and growth—could be safely added to chemotherapy and may improve outcomes for a specific type of pediatric AML patient population. A Phase I clinical trial (NCT03448393) found that therapy with a chimeric antigen receptor (CAR) T-cell targeting two antigens was safe, feasible, and effective for children and AYAs with B-cell acute lymphoblastic leukemia (B-ALL). While this approach may overcome some of the limitations of CAR T-cells with one target, treatment persistence needs to be improved—as well as targeting for one of the antigens—to maintain remission in patients. However, there is clinical promise for this therapeutic approach. Li-Fraumeni syndrome (LFS) is a genetic condition that increases the risk for some types of cancer. The only known cause of LFS is a change (mutation) in a gene known as *TP53*, but not all people with LFS have a *TP53* mutation. A federal LFS natural-history study (NCT01443468) found that individuals with LFS have a 24 times higher cancer incidence compared with the general population, with the highest incidence from childhood to 3 years of age. The granularity of this study—such as cancer incidence rates by age and cancer-free survival by the type of TP53 mutation—will be important when developing screening and management strategies for these patients.
Supported by: NCI
Grants: U10CA180886, K08CA230218, K08CA263192, R21CA261877, UM1CA228823

Collaborative Centers in Children's Environmental Health Research and Translation
The goal of this funding opportunity is the creation of a national network of children's environmental health (CEH) translation centers. Through external collaboration with the children's environmental health community, Collaborative Centers in Children's Environmental Health Research and Translation (CEHRT) will protect and improve children's health by developing and testing new scientific questions and public health interventions strategies, with an eye toward translation, and mentoring a pipeline of new investigators interested in translational CEH. CEHRT Centers will serve as leaders in CEH translational research and research methodology development, with a focus on creating actionable steps to move evidence-informed biomedical, behavioral, psychosocial, and environmental research findings in children's environmental health to the wider community. The collective, collaborative center program will also serve as a national research resource to support response efforts to emerging environmental exposures affecting children.
Supported by: NIEHS
Grants: P2CES033415, P2CES033430, P2CES033423, P2CES033432, P2CES033428, P2CES033433
Funding Opportunities: RFA-ES-20-001

Resources To Advance Pediatrics and HIV Prevention Science
This request for proposals seeks contractors to support preclinical HIV research, develop pediatric formulations, and advance next-generation HIV prevention and treatment products. These contractors will provide preclinical and nonclinical drug development support to HIV researchers and product developers for activities ranging from initial product discovery to clinical trials and licensure. NIAID may also use the contracts to advance therapeutic and preventive strategies for other infectious diseases. Promising single or combination therapeutic or non-vaccine biomedical prevention products will include those with activity against HIV or associated co-infections (e.g., Mycobacterium tuberculosis). These products may be sustained-release drug delivery platforms or multipurpose prevention technologies that incorporate contraceptives.
Request for proposals: 75N93021R000200
Website: Resources to Advance Pediatrics and HIV Prevention Science

SELECTED MAJOR ONGOING NIH PROGRAMS IN PEDIATRIC RESEARCH

NIH supports a large number of ongoing programs in pediatric research. Many, but not all, pediatric research programs focus exclusively on child health. For example, the Collaborative Pediatric Critical Care Research Network links pediatric intensive-care units at hospitals across the country to conduct clinical studies to improve research practice in pediatric critical care. The center/network programs supporting pediatric research at NIH include some that are targeted to a specific disease or condition, such as the Autism Centers of Excellence. Some, such as the pediatric component of the Clinical and Translational Science Awards Program, are not specific to any one condition. Other pediatric research programs are funded using research project grant mechanisms, such as R01 grants. This report highlights selected key ongoing NIH programs in pediatric research, funded through a variety of research grant and contract mechanisms.

Bone and Muscle Health

Senator Paul D. Wellstone Muscular Dystrophy Specialized Research Centers
The six currently supported Wellstone Centers promote collaborative basic, translational, and clinical research on muscular dystrophies, including those affecting children. They also provide resources, including outstanding training environments, community outreach, a national registry, and shared core facilities.
Supported by: NINDS, NIAMS, NICHD, NHLBI
Grants: U54AR052646, U54NS053672, U54HD060848, U54NS048843, U54AR065139, U54HD087351
Funding Opportunities: RFA-AR-23-001, RFA-NS-19-031, RFA-AR-21-008

Engineering Clinical Trials on a Chip for Muscular Dystrophy
New therapies are needed for the treatment of Duchenne and Becker types of muscular dystrophy. Better tools can help researchers understand how these genetic disorders affect cardiac and skeletal muscle tissues and speed the development of new therapies. As part of the Clinical Trials-on-a-Chip initiative, this project will develop 3D–engineered muscular tissues to explore cardiac and skeletal muscle deficiencies and test potential therapies. The chip platform will allow real-time assessment of drug treatment efficacy. Researchers will use the platform to simulate protocols for running a Phase III–style clinical trial of a new cation-channel inhibitor.
Supported by: NCATS, NIAMS
Grants: UG3TR003271
Funding Opportunities: RFA-TR-19-014

Clinical Trial of Sodium Thiosulfate to Treat Calcinosis Associated with Juvenile Dermatomyositis
Calcinosis is a debilitating complication of dermatomyositis in up to 40% of patients, resulting in increased disability, frequent infections, and impaired quality of life. No known therapy exists to treat calcinosis after it occurs. Based on anecdotal experiences suggesting significant improvement in the calcifications of dermatomyositis with sodium thiosulfate treatment, researchers are in progress with a Phase II pilot study to evaluate the efficacy of intravenous sodium thiosulfate in juvenile and adult dermatomyositis with moderate to severe calcinosis. Sodium thiosulfate is approved by the FDA for the treatment of cyanide poisoning, but it also acts as a calcium chelator, an antioxidant, and a vasodilator. The study will also assess the safety of longer-term use of sodium thiosulfate in children and adults and evaluate the impacts of treatment on quantitative changes in calcium lesions by imaging, quality of life, functional disability, muscle strength, and laboratory values (including biomarkers of inflammation and endothelial activation), as well as overall myositis disease activity and damage.
Supported by: NIEHS, CC

Clinical Trials Study: NCT03267277
Website: Calcinosis Study

Child Development

Molecular Transducers of Physical Activity in Humans
The Molecular Transducers of Physical Activity Consortium (MoTrPAC) aims to uncover, at the molecular level, how exercise improves and maintains the health of the body's tissues and organs. The MoTrPAC is conducting a clinical research study designed to extensively catalogue the biological molecules affected by physical activity in people, identify some of the key molecules that underlie the systemic effects of physical activity, and characterize the function of these key molecules. One of the clinical sites is focusing on the molecular changes that occur when children and adolescents exercise. This portion of the study began recruitment in late November 2019, looking to enroll more than 320 participants through 2024. Study activities were paused in March of 2020 due to the COVID-19 pandemic, and resumed in March of 2021. Analysis and characterization of the samples from 23 pre-pandemic participants is planned, and a revised timeline for recruitment is pending. When combined with data from the six clinical sites actively recruiting adults, the research will show whether the molecular transducers of exercise's health benefits differ between children and adults and among different stages of development.
Supported by: OD/DPCPSI/OSC, NIAMS, NIA, NIDDK
Grants: U01AR071158

Research Center for Child Well-Being
The Research Center for Child Well-Being focuses on prevention and intervention research aimed at reducing risk for mental, emotional, and behavioral (MEB) disorders and problems that promote obesity in children 2–10 years of age. Key cross-cutting themes of the research projects and the center as a whole emphasize preventive intervention strategies to promote more nurturing environments for healthy child development, to strengthen children's self-regulation, to ensure that the interventions benefit children from lower socioeconomic backgrounds without stigmatizing them, and to study and bolster quality of implementation for the interventions. The center has considerable potential through innovative research to progress the scientific basis for joint prevention of mental/behavioral and obesogenic problems, leading to greater well-being of children.
Supported by: NIGMS
Grants: P20GM130420
Funding Opportunities: PAR-19-313

Reproductive Axis Maturation in the Early Post-Menarchal Years: A Pilot Study
Scientists launched the largest, most comprehensive study to date of the biological underpinnings of a girl's first few menstrual cycles. The study will chart the normal developmental path of the beginning of menstruation, with the goal of developing a way to differentiate between the girls who will go on to establish regular cycles from those who may be at high risk for infertility and other issues, including a condition called Polycystic Ovary Syndrome (PCOS). The study is enrolling 75 girls 10–14 years of age who will be followed for two years. The aim of this study is to obtain a better understanding of normal hormonal dynamics during the transition from menarche to the establishment of mature ovulatory cycles—a prerequisite for fertility. This will permit the more precise differentiation of girls with anovulatory cycles who will go on to establish regular cycles from those who may be at high-risk for long-term oligomenorrhea and infertility. The interval from menarche to regular ovulatory cycles represents a time of unopposed estrogen exposure; an established risk factor for endometrial cancer, even among adolescents; and a potential risk factor for breast cancer.
Supported by: NIEHS

Clinical Trials Study: NCT03986021
Website: Girl's Menstrual Health Study

Learning Disabilities Research Centers Consortium
The Learning Disabilities Research Centers (LDRC) Consortium develops knowledge on the causes, origins, and developmental course of learning disabilities. It addresses learning disabilities that affect reading and writing, including basic reading skills, reading fluency, reading comprehension, and written expression. Complementing the consortium, the Learning Disabilities Innovation Hubs (LD Hubs) focus on understudied research topics and projects that study people diagnosed with and at risk for learning disabilities. Projects also include mentorship of researchers who are in the early stages of their careers, with a particular focus on enhancing involvement of underrepresented groups in scientific careers. Previous findings from research on learning disabilities confirmed that reading ability is not related to IQ, identifying and understanding how reading ability typically develops, how the brain processes numbers, and how brain function and reading ability could improve with interventions.
Supported by: NICHD
Website: Learning Disabilities Research Centers (LDRC) Consortium

Childhood Diseases, Allergies, and Immunity

The Primary Immune Deficiency Clinic
The Primary Immune Deficiency (PID) clinic is dedicated to research on genetic mutations that result in inborn dysfunction of the immune system. The goal is to understand the immunological mechanisms of PIDs, which interfere with the normal functioning of the body's defenses against infection in infancy, childhood, or adulthood. The clinic typically sees about 50–60 new patients per year, in addition to 200–300 follow-up visits.
Supported by: NIAID
Website: Primary Immune Deficiency Clinic

Respiratory Syncytial Virus Vaccine Trials
Respiratory syncytial virus (RSV) is the leading global cause of severe lower respiratory illness in infants and young children. Investigators are developing RSV vaccines for the pediatric population. They are currently conducting three separate clinical trials to compare promising live-attenuated vaccine candidates for intranasal administration in seronegative infants and young children. This powerful trial design accelerates the generation of clinically relevant evidence. These vaccine candidates are based on different modes of viral inactivation and are designed to elicit a robust immune response.
Supported by: NIAID
Publications: https://pubmed.ncbi.nlm.nih.gov/36259542/

Pediatric Malaria
Scientists have several ongoing efforts to reveal fundamental factors in pediatric malaria disease and transmission and to develop novel vaccines and therapeutics for this population. Current malaria pediatric studies include testing a transmission blocking vaccine, determining host and parasite factors involved in susceptibility, and assessing malaria prevalence around Maferinyah, Guinea.
Supported by: NIAID
Clinical Trials Studies: NCT03917654, NCT01168271,NCT04105855

Impact of Initial Influenza Exposure on Immunity in Infants
The purpose of this program is to establish, follow, and characterize longitudinal cohorts of infants to determine how initial and repeated natural influenza infections and/or influenza vaccinations shape infant

and childhood immunity to future influenza exposures. The ultimate goal of this research is to provide key information to facilitate design of durable, broadly protective influenza vaccines.
Supported by: NIAID
Grants: U01AI144673, U01AI144616
Funding Opportunities: RFA-AI-18-010

The International Maternal Pediatric Adolescent AIDS Clinical Trials Network
The International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) will continue evaluating prevention and treatment interventions for HIV and HIV–associated complications and co-infections in infants, children, adolescents, and pregnant/postpartum women through the conduct of high-quality clinical trials. The network is led by a leadership and operations center and includes a laboratory center and a statistical and data management center. In FY 2021, IMPAACT 2007—a multi-center study of HIV-1–exposed infants—provided new pharmacokinetic and safety data for the antiretroviral maraviroc. The data were the basis of the FDA approval of this product for use in combination with other antiretroviral agents for the treatment of CCR5-tropic HIV-1 virus infection in adults and pediatric patients weighing at least 2 kilograms.
Supported by: NIAID, NICHD, NIMH
Grants: UM1AI068632, UM1AI106716, UM1AI068616
Funding Opportunities: RFA-AI-19-004, RFA-AI-19-002, RFA-AI-19-045

Pediatric Adolescent Virus Elimination (PAVE)
PAVE is a multidisciplinary, multicultural, and iterative pediatric-focused collaboratory which is using cutting edge science to deepen the understanding of the immunopathogenesis of pediatric HIV-1 reservoirs across the age spectrum, as well as to demonstrate preclinical safety and efficacy of novel therapeutics to eradicate HIV-1 reservoirs and control rebound in children.
Supported by: NIAID, NIDA, NICHD, OD
Grants: UM1AI164566
Website: https://www.pave-collaboratory.org/

Pediatric Centers of Excellence in Nephrology
Three centers focus on various aspects of translational research in pediatric nephrology, undiagnosed pediatric renal and urogenital disorders, and kidney development. The emphases for this program are severalfold: (1) to continue to attract new scientific expertise into the study of human pediatric physiology and kidney disorders in humans and in disease models; (2) to encourage multidisciplinary research in these areas; (3) to explore new areas with translational potential; and (4) to design developmental research pilot and feasibility studies that should lead to new and innovative approaches to study kidney disease in the pediatric population.
Supported by: NIDDK
Grants: P50DK096418, P50DK114786, P50DK096373
Funding Opportunities: RFA-DK-21-024 RFA-DK-16-032

Chronic Kidney Disease in Children Study
Chronic Kidney Disease (CKiD) in Children Study is defining risk factors that lead to the development of chronic kidney disease (CKD) in children and how CKD progression affects factors that raise the risk for cardiovascular disease or heart and blood vessel disease; cognitive development, or the brain's ability to think, remember, or reason; quality of life; and growth. A better understanding of the risk factors that lead to CKD may result in clinical trials to improve the health outcomes of children with CKD. Information from the CKiD Study is still being gathered. So far, the study has helped researchers develop better screening tools and treatments for CKD and its complications. It has also helped researchers better understand the causes of CKD and the relationship between CKD and the risk for cardiovascular disease, cognitive development, other complications, and racial disparities.

Supported by: NIDDK, NHLBI, NICHD
Grants: U01DK066174, U01DK066143, U24DK066116, U24DK082194
Funding Opportunities: RFA-DK-17-034, RFA-DK-17-502, RFA-DK-17-503

Improving Medication Adherence in Children Who Had a Liver Transplant
This multisite study being conducted at leading pediatric liver-transplant centers in the United States and Canada is testing a tailored telemetric intervention to reduce transplant rejection rates by improving adherence to immunosuppressant medication. Nonadherence to such medication is the leading cause of organ rejection in adolescent transplant recipients. Such interventions are a particular need for transplant recipients in rural areas.
Supported by: NIDDK
Grants: U01DK119200

Nonalcoholic Steatohepatitis Clinical Research Network
The Nonalcoholic Steatohepatitis Clinical Research Network (NASH) is composed of multiple clinical sites across the United States that have conducted several clinical trials to test potential treatments for forms of nonalcoholic fatty liver disease. These forms of the disease include NASH in children and adults. The trials are made possible through public-private partnerships. The overriding objective of this research program is to pursue clinical research on adult and pediatric NASH, with a secondary objective to encourage reverse translational research to understand disease origins. Such understanding will provide the basis for understanding the natural history of disease and developing means for its diagnosis, treatment, and clinical management.
Supported by: NIDDK
Grants: U01DK061737, U01DK061732, U01DK061713, U01DK061728, U01DK061734, U01DK061718, U01DK061731, U01DK061738, U01DK061730
Funding Opportunities: RFA-DK-18-505, RFA-DK-18-506

International Study Group of Pediatric Pancreatitis: In Search for a CuRE
The INternational Study Group of Pediatric Pancreatitis: In Search for a CuRE (INSPPIRE), a multinational study group, was established to investigate risk factors for, and outcomes of, pediatric pancreatitis—an inflammation of the pancreas often accompanied by severe pain that can increase risk for diabetes and pancreatic cancer. It is currently part of the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC) and has enrolled the largest cohort of pediatric pancreatitis patients to date, collecting genetic, demographic, and clinical data from children with acute, recurrent, or chronic forms of pancreatitis. The goal of this program is to develop improved diagnostic, disease prognostic, and treatment approaches for pancreatitis in children.
Supported by: NIDDK, NCI
Grants: U01DK126300, U01DK126365, U01DK108327, U01DK108326, U01DK108323, U01DK108320, U01DK108314, U01DK108300, U01DK108334, U01DK108288, U01DK108306, R01DK118752, U01DK108328,
News Link: Story of Discovery: Pancreatitis in Children
Funding Opportunities: RFA-DK-19-009

Prevention of Lower Urinary Tract Symptoms
From childhood to menopause and beyond, bladder health is a concern for all women. Health issues related to the bladder and/or urination range from acute infections to chronic, sometimes painful, conditions, and can have far-reaching negative effects on health and well-being for girls and women. The Prevention of Lower Urinary Tract Symptoms (PLUS) consortium is conducting transdisciplinary studies necessary to establish the evidence base that will lead to recommendations that promote bladder health and inform prevention of lower urinary tract symptoms in girls and women. The consortium has developed an instrument to assess bladder health in adults, but a corresponding measure does not exist for

adolescents. PLUS is currently drafting plans to develop a survey instrument specifically for adolescent girls and young women 13–17 years of age, which will utilize standard processes including translatability review, cognitive interviewing in English and Spanish, and psychometric testing.
Supported by: NIDDK, OD/DPCPSI/ORWH
Grants: U01DK126045, U01DK106827, U01DK106858, U01DK106893, U01DK106898, U01DK106892, U01DK106908, U01DK106853
Funding Opportunities: RFA-DK-19-015, RFA-DK-19-016

An Asthma Collaboration to Reduce Childhood Asthma Disparities on the Navajo Nation
This cooperative agreement is focused on improving asthma care for Navajo children through interventions at the level of the medical provider, family, and schools. The study design, approved by the Navajo Nation Human Research Review Board (NNHRRB), sequentially provides the interventions in three agencies: Chinle, Tuba City, and Fort Defiance. Health care providers receive training and tools to provide evidence-based asthma care, education materials for the families of children with asthma have been adapted to make them contextually appropriate, and efforts are underway to ensure stock inhalers are available for any child needing one at school, in addition to the asthma education provided when children are in school. During the pandemic, researchers have remained in (remote) contact with the team on the reservation, as well as conducting telephone interviews with families. Publications describing some of the work on the grant are under review by NNHRRB.
Supported by: NHLBI
Grants: U01HL138689
Funding Opportunities: RFA-HL-17-001

The Microbiome and Juvenile Rheumatic Diseases
The Twin Sibling Study has enrolled 300 twins and same-gender (close in age) sibling pairs—where one sibling has been diagnosed with juvenile or adult myositis, rheumatoid arthritis, lupus, or scleroderma and the other sibling has not—to examine environmental risk factors common to patients recently diagnosed with these systemic rheumatic diseases. To date, this study has identified peripheral blood gene and proteomic signatures common to these diseases, found epigenetic changes in a number of immune response genes in systemic lupus erythematosus patients, and identified herpes virus expression to be increased in the peripheral blood of affected patients. In one of the first studies of microbiome in pediatric rheumatic diseases, the oral and stool microbiome in children with juvenile dermatomyositis is being compared with their unaffected siblings and parents to see if changes in the microbiome may be associated with oral changes or disease outcomes.
Supported by: NIEHS
Website: Rheumatic Disorders in Siblings

Multi-Omics Studies of Childhood Complex Traits in Diverse Populations
The Childhood Complex Disease Genomics Section within the Center for Precision Health is a translational genomics research lab using human genetics and genomics to better understand the pathophysiology of childhood diseases, particularly in diverse populations. The unique developmental context and reduced environmental exposure of children over time provides fertile ground for genetic discovery and therapeutic investigation. At the same time, there is a general lack of diversity among genomic studies, with populations of African ancestry being particularly underrepresented—despite harboring an abundance of genomic diversity and unique clinical presentations. The lab's approach is to start with epidemiological evidence for differences between individuals and formulate plausible genetic models of disease. They then work with global and national collaborators to recruit well-phenotyped cohorts, to which they apply genomic, epigenomic, and transcriptomic technologies alongside population and quantitative genetics to identify the genes and gene pathways that drive disease. Newly discovered genes are then validated, and the underlying mechanisms probed. This approach facilitates the group's

ultimate goal of translating mechanistic understanding into therapeutic strategies—providing personalized medicine by going from bedside to bench and back.
Supported by: NHGRI
Grants: ZIAHG200414, ZIAHG200412

Center for Translational Pediatric Research: COBRE Phase I
The Center for Translational Pediatric Research (CTPR) is a Center of Biomedical Research Excellence (COBRE) in Phase 1 supported by the Institutional Development Award (IDeA) Program. The scientific theme of the CTPR is the study of how pediatric diseases develop from systems biology and mechanistic standpoints; the ultimate goal of identifying intersections of disease and development, which in turn, will produce targets for therapeutic intervention and the development of new treatments. The centerpiece of the CTPR is the use of state-of-the-art systems biology approaches to uncover and mechanistically explore the basis of pediatric diseases.
Supported by: NIGMS
Grants: P20GM121293

Center for Pediatric Research: COBRE Phase II
Many pediatric diseases have their origins from altered developmental programming related to the processes of cell proliferation, morphogenesis, migration, differentiation, and programmed death. These developmental processes are at the root of pediatric disease and are disrupted through genetic disorders, aberrant fetal programming, altered growth and development, and environmental pressures. The multidisciplinary Center for Pediatric Research (CPR) applies genetic, biochemical, cell, and molecular approaches across several model organisms to characterize alterations during development as they pertain to pediatric diseases and disorders.
Supported by: NIGMS
Grants: P20GM103620

Clinical Care, Outreach, and Services

Pediatric Research at the NIH Clinical Center
The NIH Clinical Center (CC) provides patient care, services, training, and the environment in which NIH clinician-scientists creatively translate emerging knowledge into better understanding, detection, treatment, and prevention of human diseases. In fiscal year 2021, 1,568 children on 249 research protocols were treated at the center. This included 161 patients who had a combined 3,272 inpatient hospital days. The average length of stay for inpatients decreased 3% to 12.5 days. Overall, 9% of patients were under 18 years of age. Natural-history studies, often in patients with rare diseases, make up about half of the pediatric clinical research conducted at the center. Understanding the basis for rare diseases often leads to new approaches to common problems. Most of the other clinical research studies are the early Phase I and II trials that are the first studies of new treatments and therapies.
Supported by: CC
Websites: Kids In Research, Info For Parents

Creating an Artificial Intelligence Therapy-to-Data Feedback Loop for Child Developmental Health Care
A shortage of autism specialists limits timely access to therapy for children with an autism diagnosis. Researchers intend to address this problem through the use of a machine learning–enabled wearable that delivers social cues to children during real-time interactions and provides several engagement modes for families. This solution may enable greater access to care for children with an autism diagnosis and their families.
Supported by: NLM

Grants: R01LM013083

Oral Health Disparities and Inequities in Children Research Consortium
A federal research consortium and data coordinating center are working to reduce inequities in access to dental and oral health care, and to improve the oral health of children in underserved and underrepresented groups. Current studies include: using financial incentives and technology to improve oral health behaviors; conducting oral health interventions in primary care settings; using text message–based interventions to reduce caries in children; and promoting preventive oral health behaviors via family-focused oral health education and support from community health workers. All four studies have completed participant recruitment and are undergoing follow-up activities or data analyses.
Supported by: NIDCR
Grants: U01DE025507, UH3DE025514, UH3DE025487, UH3DE025492, UH3DE025483

Improving Oral Health and Reducing Disparities in Adolescents
Research is needed to improve the oral health of adolescents in the United States and reduce observed oral health disparities and inequities. Research proposed through this funding opportunity will help to elucidate key common risk and protective factors that contribute to adolescent oral and overall disease development or health promotion, and to evaluate oral health promotion and disease-prevention strategies in adolescents.
Supported by: NIDCR
Funding Opportunities: PAR-20-058, PAR-20-059

A New Model of Rehabilitation to Meet the Cultural Needs of American Indian/Alaska Native Children with Disabilities
American Indian and Alaska Native (AI/AN) persons report disability at higher levels than the general population. Social connection through participation in traditional cultural activities is an important part of AI/AN health and wellness and a valuable element to incorporate in rehabilitation services for AI/AN children with disabilities to attain optimal functional and wellness outcomes. This study will integrate community perspectives into a novel model of culturally centered rehabilitation and test the acceptability and feasibility of this model during rehabilitation services for AI/AN children with neurological impairments. The study will: (1) develop and administer a survey to understand pediatric rehabilitation professionals' knowledge, attitudes, and behaviors when serving AI/AN children and their perceived barriers and facilitators for culturally-centered care; (2) develop a culturally centered rehabilitation services model with community members to better meet the cultural and functional needs of AI/AN children with disabilities; and (3) test the acceptability and feasibility of the novel model during pediatric neurological rehabilitation services, using quantitative and qualitative evaluations.
Supported by: NIMHD
Grants: K23MD014157
Funding Opportunities: PA-19-118

Investigating the Role of Care Retention in Lupus Disease Outcomes and Disparities in Young Adult and Pediatric Patients
Systemic Lupus Erythematosus (SLE/lupus) is a chronic systemic autoimmune disease that affects more than a million Americans, with 20% of those diagnosed being children. Racial and ethnic minority populations, especially young women, are more likely to develop SLE, while individuals of African descent in the United States experience disproportionate lupus-related complications. This study will evaluate care retention and disease outcome disparities in young patients with SLE and investigate the role of care retention gaps in mediating health disparities and poor clinical outcomes in these patients. The findings of the study will help to quantify disparities and expand understanding of modifiable risk factors that lead to poor lupus outcomes in young, racial and ethnic minority, and low socioeconomic status patients, allowing for targeted interventions to improve outcomes and reduce disparities.

Supported by: NIMHD
Grants: F30MD015211

Delaware Clinical and Translational Research ACCEL Program
The Delaware Clinical and Translational Research ACCEL Program is an Institutional Development Award (IDeA) network for clinical and translational research (CTR). The Nemours Children's Hospital, Delaware is one of five partners in this statewide consortium supporting clinical and translational research. Most pediatric research projects at Nemours supported by this grant focus on gaining a better understanding of the biological underpinnings of pediatric disease or testing the implementation and effectiveness of health care interventions for children. ACCEL also provides Nemours with bioinformatics infrastructure and support, such as making the hospital an integral part of PEDSnet, a large-scale external pediatric data network that cuts across all pediatric diseases. During the COVID-19 pandemic, researchers in the ACCEL program also conducted research on improving pediatric COVID-19 vaccine awareness, access, and accountability in underrepresented communities.
Supported by: NIGMS
Grants: U54GM104941, U54GM104941-09S1
Funding Opportunities: PAR-17-304

Clinical Sequencing Evidence-Generating Research
The Clinical Sequencing Evidence-Generating Research (CSER) consortium is a national, multisite study that investigates the efficacy of integrating genomic sequencing into the clinical care of minority and underserved populations. Through the work of seven clinical sites and one coordinating center, the CSER consortium has made advancements in the areas of discovery and interpretation of genomic variants, return of results, and evaluation of health outcomes and metrics, among others. Five of the seven CSER sites work with pediatric populations, from studies of cancer to developmental genetic disorders. Examples of advancements made by the consortium include examining the extent to which exome-sequencing can assist in the prenatal diagnosis of nonimmune hydrops fetalis, understanding how genomic sequencing fits into the broader context of a child's therapeutic odyssey, and developing a web-based platform to deliver genetic test results in an understandable and personalized manner to families, which is of particular concern in pediatric cases.
Supported by: NHGRI, NIMHD, NCI
Grants: U01HG009610, U01HG006485, U01HG007301, U01HG007292, U01HG006487, U01HG009599, ZIAHG200387, U24HG007307,
Funding Opportunities: RFA-HG-16-011, RFA-HG-16-012

Suicide Risk Screening in Youth Using the Ask Suicide Questions Tool
The majority of youth 10–24 years of age who die by suicide visit a health care provider within months, sometimes weeks, before their death. These health care visits represent a tremendous opportunity to identify those at risk and connect them with mental health resources. The Ask Suicide-Screening Questions (ASQ) is a tool to screen medical patients 10 years of age and above for suicide risk. Researchers continue to validate the ASQ and integrate suicide risk screening across various medical settings (EDs, inpatient medical units, and outpatient care clinics) and with new populations (e.g., adolescents with type 1 diabetes and youth in the child welfare system), in addition to translating the ASQ into more than 15 languages.
Supported by: NIMH
Grants: ZIAMH002922

Coronovirus Disease 2019 (COVID-19)

Pediatric SARS-CoV-2 infection, COVID-19, and MIS-C

Several important studies concerning pediatric SARS-CoV-2 infection, COVID-19, and multisystem inflammatory syndrome in children (MIS-C) are underway. In FY 2021, investigators launched a multisite prospective observational study to evaluate the clinical consequences of symptomatic and asymptomatic SARS-CoV-2 infection in the participants 21 years of age and younger—including COVID-19 and MIS-C—and characterize the immune response associated with these clinical presentations. Another study focuses on T-cells from persons previously infected with SARS-CoV-2 and aims to develop antibody tests to evaluate persons for infection with COVID-19, measure changes in antibody levels over time, and understand the T-cell response to SARS-CoV-2 infection. Scientists are also conducting a long-term analysis of specimens, clinical, and laboratory data from more than 1,300 multinational adult and pediatric patients hospitalized with acute COVID-19, to better understand immune dysfunction associated with COVID-19 and MIS-C. There is an ongoing study of responses of T-cells from patients with MIS-C, using cells from subjects with acute SARS-CoV2 infection and age-matched healthy volunteers as comparators.
Supported by: NIAID
Grants: ZIAAI001270, ZIAAI001258, ZIAAI001274
Clinical Trials Study: NCT04830852

Collaboration to Assess Risk and Identify Long-Term Outcomes for Children with COVID-19
The Collaboration to Assess Risk and Identify Long-term Outcomes for Children with COVID (CARING for Children with COVID) program aims to better understand SARS-CoV-2 infection, which leads to COVID-19, in children. The collaboration allows the supporting institutes to coordinate research related to COVID-19 in children and to capitalize on well-established infrastructure. CARING studies aim to understand why some children are more likely to get infected with SARS-CoV-2, differences in COVID-19 symptoms, development of more severe illness like Multisystem Inflammatory Syndrome in Children (MIS-C), and the long-term outcomes for children who have become infected with SARS-CoV-2. The program aligns multiple cohort studies to improve understanding of the effects of SARS-CoV-2 infection and MIS-C on children. The Long-Term Outcomes After the Multisystem Inflammatory Syndrome In Children (MUSIC) study focuses on cardiovascular complications of MIS-C, but also collects data on all aspects of childhood and adolescent health in affected participants. The Pharmacokinetics, Pharmacodynamics, and Safety Profile of Understudied Drugs Administered to Children per Standard of Care (POP02) study focuses on understanding the treatment of children diagnosed with COVID-19 or MIS-C with medicines that have shown promise in adults with COVID-19. The Pediatric Research Immune Network on SARS-CoV-2 and MIS-C (PRISM) study aims to evaluate the short- and long-term health outcomes of SARS-CoV-2 infection in children, including MIS-C, and to characterize the immunologic pathways associated with different disease presentations and outcomes. The Predicting Viral-Associated Inflammatory Disease Severity in Children with Laboratory Diagnostics and Artificial Intelligence (PreVAIL kIds) focuses on development of innovative approaches for understanding the underlying factors that influence the range of symptoms present in children infected with SARS-CoV-2. Research will include studies of genetic, immune, viral, environmental, and other factors that influence the severity of childhood COVID-19 and will help understand risk factors for developing MIS-C. CARING for Children with COVID is also supporting the collection of a core set of clinical data across all protocols to ensure robust and interoperable cloud-based data sharing on three platforms. And the Fast Healthcare Interoperability Resources (FHIR) will enable the exchange of health care-related information. These resources will facilitate data analysis between research cohorts, enabling researchers to construct a bigger "virtual" cohort or to identify smaller cohorts or subpopulations to answer specific research questions. Datasets on these platforms will be made widely available to allow more researchers to conduct additional analyses and make more discoveries.
Supported by: NICHD, OD, NHLBI, NIAID, NIAMS, NIDA, NIMHD, FIC
Website: Caring 4 kids with COVID
News Links: COVID-19 in Children, NIH Project Seeks Identify Children at Risk for MIS-C, Observational Study Coronavirus Infection and Multisystem Inflammatory Syndrome in Children Begins,

NIH Funds Eight Studies to Uncover Risk Factors for COVID-19-Related Inflammatory Syndrome Children
Clinical Trial Study: NCT04588363

Diabetes

Type 1 Diabetes TrialNet
Type 1 Diabetes TrialNet is an international clinical trials network that screens thousands of individuals yearly and conducts trials of agents to prevent clinical diagnosis of type 1 diabetes in people with early-stage disease and to slow disease progression in the newly diagnosed. Blood tests can accurately identify relatives of people with type 1 diabetes who are at early stages of the disease (at high or moderate risk of developing clinical symptoms within five years), enabling TrialNet to initiate clinical trials of promising prevention strategies.
Supported by: NIDDK, NIAID
Grants: TrialNet (RePORTER)
Website: TrialNet
News Link: Progress on the Pathway to Prevention of Type 1 Diabetes
Funding Opportunities: RFA-DK-18-509, RFA-DK-19-506, RFA-DK-20-508

Global Pediatric Health

NICHD Domestic and International Pediatric and Maternal HIV and Other High-Priority Infectious Diseases Clinical Studies Network (NICHD Network)
The NICHD network conducts trials related to preventing and treating HIV infection and its complications in newborns, infants, children, adolescents, and pregnant women. It is currently composed of 15 domestic sites in 11 states and territories and 14 international sites in Argentina, Brazil, Kenya, Tanzania, and Thailand, plus a data coordinating center. Recently, network researchers have broadened their focus to include tuberculosis, malaria, hepatitis, and investigation of vaccines that might prevent HIV-related or other high-priority infectious diseases in children, adolescents, and pregnant women, in addition to treatment of HIV infection. This network has collaborated closely with the International Pediatric Maternal Adolescent AIDS Clinical Trials (IMPAACT) Network, which has made it possible to conduct an expanded clinical trial portfolio advancing pediatric HIV/AIDS clinical research.
Supported by: NICHD
Websites: NICHD Network, NICHD Clinical Studies

Prevention and Treatment through a Comprehensive Care Continuum for HIV-affected Adolescents in Resource Constrained Settings
Prevention and Treatment through a Comprehensive Care Continuum for HIV-affected Adolescents in Resource Constrained Settings (PATC3H) is a consortium of eight research teams conducting clinical research and evaluation of a variety of combination interventions—aimed at the individual, family, community, structural and education, and health systems levels—to improve health outcomes among adolescents with, or at risk for, HIV. PATC3H's primary goal is to generate the needed scientific innovation that will yield effective public health interventions for adolescents and young adults 10–24 years of age (with emphasis on 20 years of age or younger) affected by HIV in resource-limited settings in Brazil and sub-Saharan Africa. The program will research any needs or interventions that may help reduce the HIV incidence rates among adolescents while maximizing the impact of research in adolescent prevention and care for youth with HIV within these countries.
Supported by: NICHD, NIMHD, OD/DPCPSI/OBSSR, OD/DPCPSI/OAR
Grants: RFA-HD-18-032 (RePORTER)
Website: PATC3H

Funding Opportunities: RFA-HD-23-013, RFA-HD-23-014

Human Heredity and Health in Africa
The Human Heredity and Health in Africa (H3Africa) Initiative aims to facilitate a contemporary research approach to the study of genomics and environmental determinants of common diseases, with the goal of improving the health of African populations. H3Africa supports multiple projects focused on pediatric conditions and populations, including the microbiome and respiratory disease in African children, host genetic factors in pediatric HIV disease progression, sickle cell disease, developmental disorders, hereditary neurological disorders, genetics of hearing loss, transgenerational effects of maternal stressors and trauma, and breast milk microbiota influence on infant immunity and growth.
Supported by: FIC, OD/DPCPSI/OSC, NHGRI, NHLBI, NIAID, NICHD, NIMH, NIDCD, NCI, OD/DPCPSI/ORWH, NIDDK, NIEHS, NEI, NLM
Grants: H3Africa (RePORTER)
Website: H3africa

Global Network for Women's and Children's Health Research
The Global Network for Women's and Children's Health Research **(**Global Network) supports and conducts clinical trials in resource-limited countries by pairing international and U.S. researchers with the goal of evaluating low-cost, sustainable interventions to improve maternal and child health while building local research capacity and infrastructure. Today, the Global Network focuses on community-based common protocols—conducted at three or more sites—that address major maternal and newborn health challenges, with the goal of evaluating low-cost, sustainable interventions to improve maternal and child health. This unique position allows scientists to identify gaps between science and practice and disseminate the research findings to inform local and national health policy. Each study examines either a novel, evidence-based treatment or an innovative use of a proven treatment to improve the health, well-being, and survival of pregnant women and infants. In 2020, the eight sites within the Global Network conducted a study to estimate the prevalence and impact of SARS-CoV-2 infection during pregnancy. Using antibody testing at delivery, the study sought to compare the maternal, fetal, and neonatal outcomes of women infected with SARS-CoV-2 with those of noninfected women. The study will enroll approximately 2,000 pregnant women for each site in Kenya, Zambia, Guatemala, India (Belagavi and Nagpur), Democratic Republic of the Congo, Pakistan, and Bangladesh.
Supported by: NICHD
Grants: U24HD092094, RFA-HD-17-010 (RePORTER), RFA-HD-23-009 (RePORTER)
Website: Global Network

Injuries, Maltreatment, and Violence

CAPSTONE Centers for Multidisciplinary Research in Child Abuse and Neglect
Over the past two decades, the NIH has funded research on the prevalence, causes, course, and consequences of child abuse and neglect. These efforts have led to a better understanding of the nature, scope, and extent of child maltreatment, as well as the effect of abusive behavior on both the immediate and long-term health of its victims. Results of this research indicate that child and adolescent victims of physical or sexual abuse are likely to have a legacy of physical and mental illness well into adulthood. The CAPSTONE Centers for Multidisciplinary Research in Child Abuse and Neglect address child maltreatment as a significant public health concern. This program—which currently includes three centers—allows researchers to assess the efficacy and effectiveness trials of child abuse and neglect interventions, examine the long-term impact of specific and understudied types of maltreatment, study the neurobiology of abuse and neglect and implications for health outcomes, and develop screening tools and assessment measures for early identification and treatment of specific types of abuse and neglect.
Supported by: NICHD

Grants: RFA-HD-18-012 (RePORTER)
Funding Opportunities: RFA-HD-23-007

Intellectual and Developmental Disabilities, Neurological Disorders, and Mental Health

Intellectual and Developmental Disability Research Centers

The Intellectual and Developmental Disability Research Centers (IDDRCs) employ advanced technologies to support a broad range of research projects related to intellectual and developmental disabilities (IDDs). The centers have cores to provide infrastructure support and must support new research component projects that use the center cores, focusing on comprehensive -omic approaches to IDDs, outcome measures for interventions or treatments, multimodal treatment approaches, shared resources across IDDRCs for treatment or assessment, and/or public health approaches. Examples of disabilities that the IDDRCs study include chromosomal conditions that cause IDDs, such as Prader-Willi (PWS), Angelman (AS), Williams (WS), and Down (DS) syndromes ; X chromosome disorders, such as Rett and Fragile X syndromes (FXS); and disorders that involve biochemical processes and metabolic issues related to brain functioning, such as hypoxia and phenylketonuria (PKU).
Supported by: NICHD
Grants: IDDRC (RePORTER)
Website: Eunice Kennedy Shriver Intellectual & Developmental Disabilities Research Centers

Research on Prenatal and Pediatric Hydrocephalus

Hydrocephalus is a condition in which excess cerebrospinal fluid accumulates in the brain, resulting in enlargement of the ventricles and functional impairments. Two funding opportunities sought to support research on the molecular, cellular, and developmental mechanisms involved in prenatal and/or pediatric hydrocephalus, and to develop new and improved research tools that will advance such research as well as efforts to develop new therapies. New and ongoing projects supported through these initiatives aim to understand genetic and molecular mechanisms of congenital hydrocephalus and the physiological consequences of surgical treatments for hydrocephalus, to develop new animal models for hydrocephalus research, and to apply new imaging methods to pediatric hydrocephalus management.
Supported by: NINDS
Grants: R01NS123168, R21NS116484, R01NS111029, R21NS111249, R01NS110793, R21NS121642
Funding Opportunities: PA-18-622, PA-18-623

Basic Neurodevelopmental Biology of Circuits and Behavior

Multiple initiatives aim to understand how interactions within and among brain regions change over pre- and postnatal development, allowing for the emergence of cognitive, affective, and social behaviors. Researchers will focus on the mechanistic links between the maturation of brain circuits and behaviors across development in rodents and nonhuman primates. To this end, researchers will investigate neurodevelopmental processes through measures of neural activity in awake, behaving animals.
Supported by: NIMH
Funding Opportunities: PAR-22-066, PAR-22-067, PAR-19-027, PAR-19-028

Understanding Genetic Causes of Epilepsy

The Centers Without Walls for Collaborative Research in the Epilepsies (CWOW) program supports projects spanning multiple institutions to address targeted challenges in epilepsy research. Two current CWOWs focus on understanding the basis of genetic epilepsies, which often emerge in childhood. One center focuses primarily on the role of sodium and potassium channel genes, which are among the most common genetic causes of severe pediatric epilepsy. Hundreds of other genetic variants have been

associated with different types of epilepsy, but the extent to which these variants cause disease is often unclear. Another CWOW is developing a multipronged approach to determining the functional, pharmacological, neuronal network, and whole animal consequences of genetic variants in non-ion channel genes associated with a range of clinical epilepsy types, including pediatric epilepsies. Both programs stand to improve the accuracy of epilepsy diagnoses and inform therapy development and treatment selection for specific disease-causing mutations.
Supported by: NINDS
Grants: U54NS117170, U54NS108874
Funding Opportunities: RFA-NS-19-019, RFA-NS-18-001

Investigation of Co-Occurring Conditions Across the Lifespan to Understand Down Syndrome
The INvestigation of Co-occurring Conditions across the Lifespan to Understand Down syndromE (INCLUDE) project was launched in June 2018 in support of a congressional directive that called for a new NIH-wide research initiative on individuals with Down syndrome (DS). INCLUDE researchers are investigating conditions that affect individuals with DS and the general population, including Alzheimer's disease/dementia, autism, cataracts, celiac disease, congenital heart disease, and diabetes. Applying the expertise and resources from multiple organizations, INCLUDE supports targeted, high-risk, high-reward, basic science studies on chromosome 21 and promotes the inclusion of individuals with DS in new and existing clinical trials.
Supported by: NICHD, OD
Grants: INCLUDE project (RePORTER)
Funding Opportunities: RFA-OD-20-006, RFA-OD-20-005, RFA-OD-20-004, RFA-OD-20-003, FRA-OD-21-007, RFA-OD-22-008, RFA-OD-22-009, RFA-OD-22-007, RFA-OD-22-010

DS-Connect®
DS-Connect is a web-based health registry that serves as a national health resource for individuals with Down syndrome (DS) and their families, researchers, and health care providers. The registry facilitates communication and online resource-sharing through a secure, confidential database. With more than 5,100 registrants to date, DS-Connect has received more than 80 requests for analysis or recruitment support from researchers, including 10 projects funded at least partially by the INCLUDE project. An e-tool kit is now available in Spanish, and the website features a clinical trial search page for participants to find DS–related research projects.
Supported by: NICHD, NCI, NHLBI, NHGRI, NIA, NIAID, NIDCD, NIDCR, NIDDK, NIMH, NIMHD, NINDS, NCATS
Grants: DS-Connect (RePORTER)
Websites: https://dsconnect.nih.gov/, The Down Syndrome Registry

Centers for Collaborative Research in Fragile X and FMR1-Related Conditions
This program supports research to improve the diagnosis and treatment of Fragile X syndrome (FXS)—the most common inherited form of intellectual and developmental disability—and its related conditions. The centers are geared toward stimulating multidisciplinary, multi-institutional research, with the common goal of facilitating the translation of basic research findings from bench to bedside and bedside to community. In fiscal year (FY) 2022, there were 18 active projects, including research on mechanisms of development, biomarkers and therapeutic targets, and measuring emotional well-being.
Supported by: NICHD, NINDS, NIMH
Grants: RFA-HD-20-003 (RePORTER)
Website: Centers for Collaborative Research in Fragile X and FMR1-Associated Conditions

Autism Centers of Excellence
Since 2007, this NIH-wide initiative has supported large-scale multidisciplinary studies on autism spectrum disorder (ASD), with the goal of determining the disorder’s causes and best treatments.

Research efforts are coordinated by the NIH Autism Coordinating Committee. Through the Autism Centers of Excellence (ACE) program, large research projects aim to understand ASD and develop interventions, and facilitate innovative and cost-effective services for people with ASD throughout their lifespan. These awards seek to build upon prior knowledge by supporting the most innovative, multidisciplinary science. ACE projects are focused on studying the earliest brain and behavioral markers of ASD, identifying its subtypes, understanding the differences between males and females with this disorder, evaluating screening practices, and developing innovative treatments. In fiscal year 2022, nine ACEs received $100 million over five years to support research at individual centers (which feature collaboration between teams of experts) and at research networks (which involve multiple institutions) dedicated to the study of ASD.
Supported by: NIMH, NICHD, NIDCD, NINDS, NIEHS
Grants: Autism Centers of Excellence (RePORTER)
Website: Autism Centers of Excellence (ACE) Program
News Link: NIH Awards 100 Million for Autism Centers of Excellence Program

The Autism Biomarkers Consortium for Clinical Trials
Autism spectrum disorder (ASD) is known as a spectrum disorder because there is wide variation in the type and severity of symptoms people experience, which makes testing new treatments complicated. There is a need for objective biological measures, called biomarkers, that can separate individuals with ASD into subgroups for clinical trials, leading to more predictive and personalized treatment. The Autism Biomarkers Consortium for Clinical Trials **(**ABC-CT) was established in 2015 to test and refine a set of reliable biomarkers of the variations in social impairment seen in people diagnosed with ASD. Primary analyses of the ABC-CT data were completed in June 2020, and two biomarkers based on the neural processing of, and visual attention to, faces were found to be promising. Both were successfully submitted into the FDA biomarker program in 2020—the first two biomarkers for a neurodevelopmental or psychiatric disorder to be accepted into this program. ABC-CT was awarded new funding in 2020 to replicate and examine the long-term stability of these measures and conduct a feasibility study using these same biomarkers.
Supported by: NIMH, NICHD, NIDCD, NINDS
Grants: U19MH108206
News Link: Testing and Refining Biomarkers to Support Intervention Research for Children with Autism

Developmental Synaptopathies Consortium
According to current estimates, autism spectrum disorder (ASD) affects 1 in 36 children in the United States. Research on individually rare genetic conditions associated with a high prevalence of ASD provides an opportunity to learn about causes and mechanisms shared across different forms of ASD; they may also pave the way for new, broadly applicable treatments. For example, the Developmental Synaptopathies Consortium (DSC) aims to explore underlying causes of ASD by focusing on three rare genetic disorders with high penetrance for ASD and intellectual disability, including tuberculosis sclerosis complex (TSC), PTEN hamartoma tumor syndrome (PHTS), and Phelan-McDermid syndrome (PMS). Part of the NIH Rare Diseases Clinical Research Network, the DSC involves experienced physician-researchers, genetic counselors, and strong institutional and patient advocacy group support. In a recent report, researchers characterized autism and epilepsy profiles identifiable in young children with TSC using longitudinal data from clinical studies that enrolled infants with the condition. These profiles may facilitate the use of early, targeted interventions to improve outcomes for children with TSC.
Supported by: NINDS, NCATS, NICHD, NIMH
Grants: U54NS092090

Understanding Suicide Risk in Children and Preteens
Investigators, clinicians, and various communities are working to understand suicide risk and risk trajectories for youth under 12 years of age. On January 14, 2022, a webinar shared new and innovative

practices in school-based suicide prevention. School administrators, researchers, practitioners, policymakers, and representatives from funding agencies gathered to discuss risk identification, follow-up care, and referral for additional services for youth at high risk for suicide. Attendees also learned about preliminary research efforts and ways to overcome common barriers to implementing suicide prevention in schools, including data collection and evaluation. Research on youth suicide—particularly suicide amongst African American or Black youth—continues across a variety of settings, including schools. Further, future studies will aim to characterize risk trajectories and protective factors and better understand systems-level risk detection and interventions that can reduce self-harm and suicidal thoughts and behaviors in African American or Black youth.
Supported by: NIMH, NIDA, NIMHD, OD/DPCPSI/OBSSR
Grants: R01MH129786, R34MH129789, R34MH129782, R34MH121639, R01MH118382, R01MH122214, R01MH124438, R01MH116052, R01MH122213
Funding Opportunities: NOT-MH-22-086, NOT-MH-22-195, RFA-MH-22-140, RFA-MH-22-141

Child Neurologist Career Development Program
Developmental disorders of the nervous system affect roughly 15% of the population. The Child Neurologist Career Development Program (CNCDP) was established to foster and support the research careers of new child neurology physician-scientists who have made a commitment to pursue crucial, innovative research in the field. The CNCDP is a single national program that provides up to three years of structured oversight and support for emerging scientists. Led by accomplished physician-scientists with a breadth of expertise, the CNCDP provides new child neurologist-scientists with the knowledge, tools, and research experience they need to develop a research project for which they can obtain subsequent funding. More than 80% of program participants have obtained subsequent funding to continue their research, enhancing the pipeline of child neurologists performing research to tackle disorders of the developing nervous system.
Supported by: NINDS
Grants: K12NS098482
Funding Opportunities: RFA-NS-19-010

Nutrition and Obesity

Improving Methods to Assess Body Composition in Infants and Young Children
Obesity in children continues to increase and remains a major public health problem. Accelerated growth patterns and the development of obesity during infancy and early childhood are associated with a higher risk of overweight/obesity in adolescence and adulthood, as well as greater risk for developing various health complications such as type 2 diabetes. This initiative seeks to fill technological gaps by improving methods to assess body composition in infants and young children. This opportunity is specifically for small-business innovation research and small-business technology transfer applications to explore technological potential in this research area.
Supported by: NIDDK, NIBIB
Funding Opportunities: NOT-DK-20-036

Obesity and Caries in Young South Asian Children: A Common Risk-Factor Approach
The Child Health Action to Lower Obesity and Oral Health Risk (CHALO) project is a multilevel strategy to reduce pediatric obesity and dental caries risk in South Asian children. This study employs a common risk/health factors approach to dental caries and obesity in a low-income South Asian immigrant community. CHALO has enrolled 176 participants, interviewed 21 physicians working with South Asian patients for a qualitative study, and designed and developed educational modules for the Knowledge Translation—a two-pronged campaign that will target pediatric and oral health professionals and local communities.

Supported by: NIMHD
Grants: R01MD010460

Center for Childhood Obesity Prevention (COBRE, Phase II)
Childhood obesity is a national public health threat that is disproportionately worse in Arkansas, where 23% of school-age youth have obesity and 17% are classified as overweight. The Center for Child Obesity Prevention (CCOP) is working to reduce the prevalence of child obesity and related comorbidities. The multidisciplinary CCOP brings together research in complex disease origins, epidemiology, and social systems to both find causes of childhood obesity and test interventions that can address the childhood obesity crisis and improve child health.
Supported by: NIGMS
Grants: P20GM109096
Funding Opportunities: PAR-19-312

Teen Longitudinal Assessment of Bariatric Surgery
Teen Longitudinal Assessment of Bariatric Surgery (Teen-LABS) is a multicenter prospective observational study that began in 2006 to assess the risks and benefits of bariatric (weight-loss) surgery in adolescents with severe obesity and serious health-related problems, such as prediabetes, type 2 diabetes, cardiovascular disease, or other conditions. Researchers have found that weight-loss surgery earlier in life may have greater benefits compared with surgery later in life; though some risks associated with the surgery have also been identified.
Supported by: NIDDK
Grants: UM1DK072493, UM1DK095710
Funding Opportunities: RFA-DK-15-508, RFA-DK-15-509

Implementation of Decision Support for the Management of Obesity in a National Pediatric Primary Care Research Network
Children with lower socioeconomic status, racial and ethnic minority children, and rural children are disproportionately impacted by overweight or obesity, which affects nearly 1 in 3 children and adolescents in the United States. Children with obesity are at greater risk of obesity in adulthood, placing them at higher risk of obesity-related cancers, cardiometabolic disease, and early mortality. This study will evaluate the dissemination and implementation of an effective intervention using electronic health records (HER) to improve the management of overweight and obesity in pediatric primary care within different practice settings serving low income children, racial and ethnic minority children, and rural children. The results from the study will provide invaluable evidence on the effectiveness of the intervention package and implementation-facilitation strategy in settings that serve populations most heavily burdened by obesity.
Supported by: NIMHD
Grants: R01MD014853
Funding Opportunities: PAR-19-093

Pediatric Cancer

Childhood Cancer Survivor Study
The Childhood Cancer Survivor Study (CCSS) examines the long-term adverse effects of cancer and cancer therapy on approximately 35,000 survivors of childhood cancer who were diagnosed between 1970–1999. The study was also created to educate survivors and the medical community about the potential impacts of a cancer diagnosis and treatment. The results obtained from CCSS are used to help design treatment protocols and interventions, to increase survival, and to develop and expand programs for early detection and prevention of late effects in children and adolescent cancer survivors. One study

looked at the clinical benefits and cost-effectiveness of breast cancer screening among childhood cancer survivors treated without chest radiation; it reported that, among survivors of childhood leukemia or sarcoma, early initiation of breast cancer screening at 40 years of age may reduce breast cancer deaths by half and is cost-effective. Researchers are continuing to conduct whole-exome sequencing of samples from childhood cancer survivors to identify other types of genetic variants that may be related to the development of childhood cancer and late effects following childhood cancer diagnosis. Other studies are examining subsequent cancers or conditions that pediatric cancer survivors may develop as well as contributing risk factors, including breast, lung, and thyroid cancer; neuromuscular dysfunction; esophageal disease; hypertension; and kidney failure.
Supported by: NCI
Websites: Childhood Cancer Survivor Study, Changing Lives Through Research

Childhood Cancer Survivorship, Treatment, Access, and Research Act Implementation Efforts
Pediatric survivorship research is ongoing, as is biospecimen collection and enhancement, in alignment with the provisions of the Childhood Cancer Survivorship, Treatment, Access, and Research (STAR) Act of 2018. "Research to Reduce Morbidity and Improve Care for Pediatric, and Adolescent and Young Adult (AYA) Cancer Survivors" was issued, and 24 projects have been funded as of FY22. Additionally, building upon prior collaboration with the Agency for Healthcare Research and Quality (AHRQ) focused on identifying best practices in survivorship care, several grant supplement awards went to cancer centers to conduct research to understand and address organizational factors that contribute to disparities in outcomes among childhood cancer survivors. Support continued for several biobanking projects in FY21 and FY22 through the Children's Oncology Group (COG). The COG Rare and Under-Represented Cancer Tissue Banking project is collaborating closely with the Childhood Cancer Data Initiative (CCDI) to conduct clinically relevant molecular profiling through the CCDI Molecular Characterization Protocol. The data generated will help guide the diagnosis and treatment of patients; the data will additionally be stored and made available to the research community through CCDI data platforms. In addition to rare cancer populations, the protocol is supporting characterization of tumors from children with central nervous system tumors and from children with soft-tissue sarcomas. Through CCDI, tumor specimens from diagnosis and from relapse are being molecularly characterized through the Pediatric MATCH Precision Medicine Trial to identify the changes in gene mutations and gene expression that occur between diagnosis and relapse. This project will enable more in-depth study of the molecular changes that occur between diagnosis and relapse, which could then inform better treatments. Implementation of the Childhood Cancer STAR Act provisions—through activities that will expand emphasis on these research areas for pediatric and AYA patients in the upcoming year—is anticipated.
Supported by: NCI
Website: STAR Act

Research to Reduce Morbidity and Improve Care for Pediatric, and Adolescent and Young Adult Cancer Survivors
This funding opportunity aligns with survivorship research priorities emphasized in the Childhood Cancer STAR Act and is focused on improving care and health-related quality of life for childhood, and adolescent and young adult (AYA) cancer survivors. Specifically, this funding opportunity solicits mechanistic, observational, and intervention applications that focus on six key domains: (1) disparities in survivor outcomes; (2) barriers to follow-up care (e.g. access, adherence); (3) impact of familial, socioeconomic, and other environmental factors on survivor outcomes; (4) indicators for long-term follow-up needs related to risk for late effects, recurrence, and subsequent cancers; (5) risk factors and predictors of late/long-term effects of cancer treatment; and (6) development of targeted interventions to reduce the burden of cancer for pediatric/AYA survivors.
Supported by: NCI
Grants: RFA-CA-20-028 (RePORTER), RFA-CA-20-027 (RePORTER),
Funding Opportunities: RFA-CA-20-028, RFA-CA-20-027

The Children's Oncology Group
The Children's Oncology Group (COG) is part of the NCI National Clinical Trials Network and develops and coordinates pediatric cancer clinical trials that are available at more than 200 member institutions, including cancer centers throughout North America, Australia, New Zealand, and Europe. COG member institutions care for more than 90% of the children and adolescents diagnosed with cancer in the United States, and COG consistently has almost 100 active open clinical trials. COG's goal is to cure pediatric patients with cancer, reduce the short and long-term complications of cancer treatments, and determine the causes of childhood cancer and find ways to prevent it. Many clinical trials of high-priority novel agents are now under way, including trials of targeted therapies and immunotherapies. The types of cancers addressed include relapsed/refractory solid tumors and lymphomas, newly diagnosed high-risk Hodgkin lymphoma, certain relapsed leukemias, osteosarcoma, Ewing sarcoma, and certain pediatric brain tumors. Three COG clinical trials opened in 2021 for children, adolescents, and young adults: a Phase II trial studying how to best combine chemotherapy and radiation therapy for patients with a certain type of brain cancer (non-germinomatous germ cell tumors); a Phase III trial looking at chemotherapy with and without monoclonal antibodies for a specific rare non-Hodgkin lymphoma; and a Phase III trial investigating potential combination therapy and dosing for patients with the brain cancer low-grade glioma. Building upon the success of the COG Phase I and Pilot Consortium, the Pediatric Early Phase Clinical Trials Network (PEP-CTN) conducts early phase clinical trials of new agents that are relevant to one or more childhood cancers. In addition, the PEP-CTN conducts pilot studies of novel agents and regimens to determine their tolerability, so that promising regimens can proceed to definitive testing in Phase III clinical trials. There were eleven active PEP-CTN clinical trials as of FY 2022 (5 active/recruiting and 6 active/not recruiting).
Supported by: NCI
Grants: U10CA180886, UM1CA097452,UM1CA228823
Website: Childrens Oncology Group

Pediatric Cancer Immunotherapy Trials Network
In 2017, the Cancer Immunotherapy Trials Network (CITN) received a grant to support immunotherapy clinical trial development for children and young adults with cancer, and the Pediatric Cancer Immunotherapy Trials Network (PedsCITN) was formed. PedsCITN utilizes the clinical trials infrastructure of CITN to conduct clinical trials of immunotherapy agents of specific relevance to children and adolescents with cancer, to speed up pediatric approval for immune-based therapies and identify innovative treatments sooner. PedsCITN consists of 10 universities, institutes, and hospitals across North America. The most promising therapies identified through PedsCITN trials are further tested through partners including the Children's Oncology Group. Additionally, PedsCITN focuses on developing and implementing best practices for measuring and managing patient side effects and outcomes for new therapies identified.
Supported by: NCI
Grants: P30CA015704, UM1CA154967

Beau Biden Cancer Moonshot
Since the initial launch of the Cancer Moonshot in 2016, the cancer community has made measurable progress toward three ambitious goals: (1) to accelerate scientific discovery in cancer, (2) foster greater collaboration, and (3) improve the sharing of cancer data. Early in 2022, President Biden announced a reignition of the Cancer Moonshot, highlighting new goals: to reduce the cancer death rate by half within 25 years and improve the lives of people with cancer and cancer survivors. Several Moonshot activites focus on children and adolescents. The Fusion Oncoprotein Childhood Cancer Consortium (FusOnC2) is a collaborative network of multidisciplinary investigators focused on uncovering the mechanisms governing how fusion oncoproteins drive childhood cancers. The success of this program lead to the development of the Targeting Fusion Oncoproteins in Childhood Cancer (TFCC) Network in 2022. The

Pediatric Immunotherapy Discovery and Development Network (PI-DDN) is another highly collaborative network that aims to advance pediatric immunotherapies to treat children and adolescents with high-risk cancers. As a follow-up to this initiative, a funding announcement was released in 2022 for the Pediatric Immunotherapy Network (PIN), which will address current challenges in pediatric cancer immunotherapy and accelerate the pace at which effective immunotherapies are realized for pediatric solid tumors. Other relevant Moonshot activities include the Center for a Pediatric Tumor Cell Atlas, which works on three high-risk cancer subtypes that account for a combined 50% of all pediatric cancer deaths: high-grade glioma, high-risk neuroblastoma, and very high risk acute lymphoblastic B-cell precursor leukemia. An additional program called MyPART (Moonshot Pediatric, Adolescent, and Adult Rare Tumors Network) is focused on research on a range of pediatric, adolescent, and young adult rare solid tumors, specifically teaming with advocacy groups to raise awareness about rare tumors among researchers and increase access to biospecimens for research. The initiative will translate findings to new clinical trials for cancer therapy and symptom management, and improve access to clinical trials for patients. A new network is also directly engaging cancer patients and post-treatment cancer survivors as partners in generating a shared database of clinical, genomic, molecular, and patient-reported data, which should accelerate treatments and help develop new standards of care. This network includes the Count Me In research initiative, which will engage adult and pediatric participants with osteosarcoma and leiomysarcoma.
Supported by: NCI
Grants: Moonshot (RePORTER),
Website: Moonshot Cancer Initiative

Pediatric Brain Tumor Consortium
The Pediatric Brain Tumor Consortium **(**PBTC) is a multidisciplinary cooperative research organization devoted to the identification of superior treatment strategies for children with primary brain tumors. Since its inception, in 1999, PBTC has focused on rapidly evaluating novel therapeutic agents in Phase I/II clinical studies. To validate results of these studies, PBTC has worked closely with the Children's Oncology Group, which carries out confirmatory Phase III clinical trials. PBTC also aims to improve treatment delivery technologies and radiation treatments. PBTC is composed of 15 competitively selected institutions across the United States, including academic centers and children's hospitals. The consortium is being expanded to include up to an additional six sites to support more clinical trials.
Supported by: NCI
Grants: Pediatric Brain Tumor Consortium (PBTC) (RePORTER)
Website: Pediatric Brain Tumor Consortium

Pediatric Genomic Data Inventory
Pediatric cancer is a genetic disease that can largely differ, especially genomically, from similar malignancies in an adult population. To fuel new discoveries and treatments specific to pediatric cancers, a dynamic resource known as the Pediatric Genomic Data Inventory (PGDI) will allow investigators to more easily locate genomic datasets, which is often a challenge for pediatric cancers. This resource lists known ongoing and completed sequencing projects of pediatric cancer cohorts from the United States and other countries, along with some basic details and reference metadata. This inventory is an evolving list that will be continually updated as new information is deposited by the research community; the success of this resource to improve outcomes for pediatric patients relies on researcher participation and data submission. As of January 2021, PGDI contained 49 projects available for review.
Supported by: NCI
News Link: Finding Pediatric Cancer Genomic Data through PGDI

Specialized Programs of Research Excellence in Pediatric Oncology
Specialized Programs of Research Excellence (SPOREs) in Pediatric Oncology are a cornerstone of efforts to promote collaborative, interdisciplinary translational cancer research. SPORE grants involve both basic and clinical/applied scientists working together, and support projects that will result in new and

diverse approaches to the prevention, early detection, diagnosis, and treatment of human cancers. Each SPORE focuses on a specific organ site; currently 21 organ sites, systems, or pathway-specific themes are represented in the SPORE portfolio. SPOREs focused on pediatric cancers include pediatric astrocytoma, pediatric glioma, and pediatric melanoma. In particular, the Developmental and Hyperactive RAS Tumor SPORE focuses on developing better treatment for cancers and premalignant conditions associated with Neurofibromatosis 1 (NF1) mutations, including plexiform neurofibroma (pNF), malignant peripheral nerve sheath tumors (MPNST), juvenile myelomonocytic leukemia (JMML), and the biology of NF1-associated brain tumors.
Supported by: NCI
Grants: PAR-20-305 (RePORTER)
Funding Opportunities: PAR-20-305

The RASopathies Study
The RASopathies are a clinically defined group of disorders caused by mutations in genes encoding components of the Ras/mitogen-activated-protein kinase (Ras/MAPK) pathway, which helps regulate a variety of responses in the body, including cell differentiation, cell growth, and tissue development. These disorders have overlapping clinical features due to Ras/MAPK dysfunction, including a predisposition to the development of certain malignancies. The goal of this program is to accelerate the understanding of RASopathies/RAS–mutated tumors and to develop effective therapies and prevention strategies. This included opening a RASopathy clinic at the NIH Clinical Center (CC) for a natural-history study and parallel trials with RAS-targeting agents for RASopathies and pediatric cancers with somatic RAS mutations/Ras pathway activation. The aims of the prospective longitudinal cohort study called the Clinical, Genetic, and Epidemiologic Study of Children and Adults with RASopathies are to determine the incidence of malignancy in patients with RASopathies and underlying differences in those who develop tumors as compared with those who do not, in order to inform cancer screening recommendations. In addition, this longitudinal cohort study will provide a better understanding of non-tumor RASopathy manifestations. In fiscal year 2021, the protocol was approved; recruitment began in 2022.
Supported by: NCI
Website: RASopathies Study

Linking the Provider Recommendation to Adolescent HPV Vaccine Uptake
This funding opportunity encourages research on how the health care delivery system enhances or inhibits the effectiveness of a provider's recommendation of the adolescent human papillomavirus (HPV) vaccine. Characteristics of the provider, parent/patient, and clinical setting can all affect whether a provider makes a recommendation, and whether that recommendation results in uptake of the HPV vaccine. This research requires expertise in cancer prevention, adult and childhood behavior, immunization promotion, and health care delivery.
Supported by: NCI
Grants: PAR-19-358 (RePORTER), PAR-19-359 (RePORTER), PAR-19-360 (RePORTER)
Funding Opportunities: PAR-19-358, PAR-19-359, PAR-19-360

Gabriella Miller Kids First Pediatric Research Program
The goal of the Gabriella Miller Kids First Pediatric Research Program (Kids First) is to help researchers uncover new insights into the biology of childhood cancer and structural birth defects, including the discovery of shared genetic pathways between these disorders. Kids First is achieving this goal through two initiatives: (1) identifying children with childhood cancer and structural birth defects and their families for whole-genome sequencing performed by the Kids First sequencing centers; and (2) developing the Gabriella Miller Kids First Data Resource—a large-scale database of clinical and genetic data from patients with childhood cancers and structural birth defects and their families. In 2015–2022, the program selected 63 childhood cancer and structural birth defects cohorts for whole-genome

sequencing through a peer-review process. The cohorts selected in 2022 will add approximately 9,000 new genomes representing about 3,000 families. Genomes for more than 20,900 participants among affected children and their families are available today—via the Kids First Data Resource Portal and the Genotypes and Phenotypes (dbGaP) database—to enable new findings in birth defects and childhood cancers. In addition, the Kids First program is engaging with the Common Fund Data Ecosystem (CFDE) to help harmonize data and workflows from multiple Common Fund program Data Coordinating Centers (DCCs) and create an ecosystem for working within and across Common Fund data sets. In 2022, the program also funded five small projects to enhance the utility of genomic datasets it generated. Awarded projects included an effort to link Kids First studies to relevant animal models and projects to integrate Kids First data with other large childhood cancer and structural birth defect studies.
Supported by: OD/DPCPSI/OSC, NICHD, NCI, NHLBI
Website: https://commonfund.nih.gov/KidsFirst
Funding Opportunities: RFA-RM-22-006

Pediatric Critical Care and Emergency Care

Collaborative Pediatric Critical Care Research Network
Pediatric critical care—or the effective and efficient care of children with critical or unstable conditions—is an important and growing subspecialty in pediatrics. Much of the technology and many therapies in pediatric critical care have evolved without adequate study, or have been adopted uncritically from adult, neonatal, or anesthetic practice. As a result, the risks and benefits of much of intensive-care practice remain largely unknown. Research is needed to make optimal decisions regarding effective critical care practices. Focusing on critically ill infants and children, the Collaborative Pediatric Critical Care Research Network (CPCCRN) aims to reduce morbidity and mortality from pediatric critical illness and injury by enhancing knowledge of the scientific bases of pediatric critical care practice. Established in 2004, CPCCRN conducts a wide range of research activities, reaching across traditional disciplinary lines and transcending customary thinking and organizational structures to achieve innovative research in the care of critically ill and injured children. Research topic areas include bereavement and grief, functional outcomes, intensive-care clinical processes and protocols, infection, sepsis, and multiple organ dysfunction syndrome (MODS).
Supported by: NICHD
Grants: CPCCRN (RePORTER)
Website: Collaborative Pediatric Critical Care Research Network

Pediatric Pharmacology

Pediatric Pharmacology and the Best Pharmaceuticals for Children Act
Testing the safety and efficacy of drugs in children presents significant scientific, clinical, ethical, technical, and logistical challenges. Over the years, several practical challenges have discouraged the testing of drugs in pediatric populations. These challenges include lack of technology to monitor patients and assay very small amounts of blood from neonates, infants, and children; and lack of a suitable infrastructure for conducting pediatric pharmacology drug trials. The Pediatric Pharmacology and the Best Pharmaceuticals for Children Act (BPCA) established a process for NIH, FDA, and pediatric experts to identify drugs that are used in pediatric care, and for which studies would have public health benefit. The goal of the act is to provide rigorous clinical data to improve pediatric-specific information in prescription drug labeling. If industry does not fund studies on drugs prioritized under the BPCA, NIH ICOs support research to address the need. As of 2022, BPCA activities produced 17 labeling changes to improve pediatric labeling (dosage, safety, and/or efficacy information).
Supported by: NICHD
Grants: BPCA (RePORTER)

Website: Best Pharmaceuticals for Children Act (BPCA)

Pregnancy and Newborn Health

Maternal and Pediatric Precision in Therapeutics Hub
Maternal and Pediatric Precision in Therapeutics (MPRINT) aims to expand the available knowledge, tools, and expertise in maternal and pediatric therapeutics. It will serve as a national resource for conducting and fostering therapeutics-focused research in obstetrics, lactation, and pediatrics while enhancing inclusion of people with disabilities. MPRINT's coordination hub will aggregate and identify knowledge deficits in the principles of maternal and pediatric therapeutics, including pharmacokinetics, pharmacodynamics, genetics, proteomics, and metabolomics that inform drug development and regulatory science. MPRINT's clinical centers will conduct cutting-edge clinical, translational, basic, and/or data sciences research; provide resources; and generate novel tools and approaches to advance and accelerate research and regulatory science in maternal and pediatric therapeutics.
Supported by: NICHD
Grants: MPRINT (RePORTER),
Funding Opportunities: RFA-HD-21-025, RFA-HD-21-026
Website: Maternal and Pediatric Precision in Therapeutics (MPRINT) Hub

Neonatal Research Network
The Neonatal Research Network (NRN) is a collaborative network of neonatal intensive-care units across the United States that is composed of 15 clinical centers and a data coordinating center. Focused on newborns—particularly infants with extremely low birth weight—the network aims to facilitate the advancement of neonatal care. This network conducts clinical trials and clinical studies with common protocols, which can study the required numbers of patients and provide answers more rapidly than individual centers acting alone. To fulfill this mission, the NRN has completed or is implementing 22 observational studies and 40 interventional trials in areas such as preterm birth complications and outcomes; sepsis and other infections; bronchopulmonary dysplasia and other lung conditions; anemia; and necrotizing enterocolitis, a condition in which the intestines lack oxygen or blood flow.
Supported by: NICHD
Grants: NRN (RePORTER)
Website: Neonatal Research Network (NRN)
Funding Opportunities: RFA-HD-23-001, RFA-HD-23-002

Prenatal Treatment of Down Syndrome to Improve Brain Development and Neurocognition
Primarily due to three copies of chromosome 21, Down syndrome (DS) causes functional alterations of the developing brain and is associated with intellectual disability. Routine screening for DS may provide a unique opportunity to begin prenatal therapy as soon as the diagnosis is made. Researchers are identifying several drug candidates that can be used in preclinical safety and efficacy studies in a mouse model of DS to determine whether prenatal treatment with drug candidates, given during pregnancy, can rescue transcriptomic changes in DS and result in improved fetal brain growth and connectivity. The overall goal is to identify and repurpose FDA–approved drugs that could be given to a pregnant woman to treat her fetus with DS. The ultimate hope is to improve neurocognition and independent life skills in people who have DS.
Supported by: NHGRI
Grants: ZIAHG200399
Publications: https://pubmed.ncbi.nlm.nih.gov/32029743/, https://pubmed.ncbi.nlm.nih.gov/33766516/

Ensuring Patients' Informed Access to Noninvasive Prenatal Testing

Noninvasive prenatal genetic testing is rapidly expanding. Researchers are studying an evidence-based communication tool to support patient decisions by focusing on the interaction between the patient and provider. Initial findings suggest that primary drivers in patient decision-making about use of these technologies were outdated or inaccurate perceptions of advanced maternal age and procedure-related risks to the fetus, and financial considerations. Researchers also found many patients felt a mismatch between their priorities at the first prenatal visit and those of their providers.
Supported by: NHGRI
Grants: R01HG010092
Publications: https://pubmed.ncbi.nlm.nih.gov/32441820/

University of Utah Center of Excellence in ELSI Research
The University of Utah Center for Excellence in ELSI Research (UCEER) explores issues relevant to population testing and screening for genetic conditions in the health care of women and children, as well as ethical, legal and social implications (ELSI) arising from testing and screening in the broader family context and responses to disabilities identified through genetic technologies. In fiscal year 2021, the center completed two research projects focused on the use of visual media to improve education for pregnant women about carrier testing for genetic disorders. An additional study created video resources based on prior data and participant feedback to meet the parent-expressed need for meaningful messages about what life may be like for parents who have a child with a disability. The center also published a study using qualitative methods to demonstrate the important of perinatal palliative-care programs for women who received a life-limiting diagnosis for their child. Taken together, these studies assessed effective strategies to educate families about prenatal genetic testing and provide resources for families facing difficult prenatal or fetal genetic diagnoses.
Supported by: NHGRI
Grants: RM1HG009037

Rare Pediatric Diseases

Undiagnosed Diseases Network
The Undiagnosed Diseases Network (UDN) is a research study designed to improve the level of diagnosis of rare and undiagnosed conditions. By bringing a nationwide network of top clinicians and laboratory researchers together, the UDN is able to generate diagnoses for some of the most complex medical cases. Also, by promoting research into the biological mechanisms of these rare conditions, the likelihood of designing treatments and, hopefully, cures for these diseases will be increased. Many of the participants enrolled in the UDN are pediatric. In fiscal year 2021, UDN researchers doing gene function studies in animal models on genetic variants identified in program participants uncovered the biological foundations of several developmental disorders. They showed that variants in the *TPO2* gene could cause abnormalities in the development of neurons and delay development overall, while a new variant identified in the *NBEA* gene contributed to seizures in addition to neurodevelopmental delays. In another study, UDN researchers nearly doubled the number of people studied with a rare form of early infantile epileptic encephalopathy. The increased study size allowed the researchers to make suggestions for treatment approaches that may benefit other individuals with the disorder who share variations in the same *ALG13* gene. In June of 2021, the program as a whole was featured in *Discover* magazine, including the stories of two pediatric participants.
Supported by: OD/DPCPSI/OSC
Grants: UDN (RePORTER)

Clinical Trial Readiness for Rare Neurological and Neuromuscular Diseases
New research will aim to fill gaps in the design of upcoming clinical trials in rare neurological or neuromuscular diseases, including pediatric disorders. Through the support of trial-readiness studies—

such as efforts to validate clinical outcome measures or biomarkers or characterize patient cohorts— an acceleration of the initiation of clinical trials for rare diseases and an increased likelihood of success in those trials is expected. In 2021, this program supported a new project focused on CDKL5 deficiency disorder (CDD), an early onset genetic epilepsy, as well as ongoing studies on Aicardi-Goutières syndrome (AGS) and juvenile neuronal ceroid lipofuscinosis (JNCL), a form of Batten disease.
Supported by: NINDS, NCATS
Grants: U01NS101946, U01NS114312, U01NS106845
Funding Opportunities: PAR-19-220

Rare Diseases Clinical Research Network
The Rare Diseases Clinical Research Network (RDCRN) conducts collaborative clinical research in rare diseases, including longitudinal studies of individuals with rare diseases, clinical studies, and clinical trials. The RDCRN is composed of 20 distinctive research consortia and a central Data Management and Coordinating Center, which work in concert to improve availability of rare disease information, treatment, clinical studies, training of new scientists, and general awareness for both patients and the medical community. The RDCRN researchers work in tandem with patient advocacy groups. One-half to two-thirds of rare diseases manifest in children, so many of the rare diseases studied by this network occur primarily or frequently in children. Current consortia that study such disorders cover primary immune deficiency diseases; urea cycle disorders; mitochondrial diseases; lysosomal diseases; rare lung, bone, kidney, and metabolic disorders; neurodevelopmental and degenerative disorders; congenital and perinatal infections; disorders of glycosylation; leukodystrophies; myasthenia gravis; and hyperphenylalaninemia.
Supported by: NCATS, NIAID, NIDDK, NICHD, NHLBI, NIDCR, NINDS, NIMH, NIAMS
Grants: RDCRN (RePORTER)
Funding Opportunities: RFA-TR-18-020

Natural History of Glycosphingolipid Storage Disorders and Glycoprotein Disorders
This project, initiated in 2008, tracks the disease progression of children and adult patients with glycosphingolipid storage disorders (GM1 and GM2 gangliosidosis; the latter disorder includes Tay-Sachs and Sandhoff diseases) and glycoprotein storage disorders (sialidosis and galactosialidosis). Both classes of disorders feature progressive and relentless neurodegeneration, and there are no approved therapies for any of these diseases. The study has accrued 56 children, mostly with GM1 disease—the largest prospective study of such patients. The study is providing important markers of disease progression, particularly in type 2 (late-infantile and juvenile) GM1 patients, that will be used as controls for our ongoing gene-therapy trial (10-HG-0101).
Supported by: NHGRI
Grants: ZIAHG200409
Publications: https://pubmed.ncbi.nlm.nih.gov/24156116, https://pubmed.ncbi.nlm.nih.gov/34539759, https://pubmed.ncbi.nlm.nih.gov/33807817, https://pubmed.ncbi.nlm.nih.gov/34450229

Social and Environmental Influences

Environmental influences on Child Health Outcomes
Environmental influences on Child Health Outcomes (ECHO) investigators study the effects of a broad range of early environmental influences on child health and development. The program consists of 72 existing and ongoing observational studies and a pediatric clinical trials network. Research conducted through ECHO focuses on five key pediatric outcomes that have a high public health impact: (1) pre-, peri- and postnatal outcomes; (2) upper and lower airway health; (3) obesity; (4) neurodevelopment; and (5) positive health, a sense of wellbeing. The ECHO program has implemented an evaluative planning approach to ensure success in developing a consortium-wide high-quality data platform and biorepository

with data and specimens from more than 50,000 children and their families, which it will make available to the research community as a national resource for studying child health. As of November 2021, the ECHO Cohorts had data from 96,049 participants from 72 cohort studies, including 58,863 children, with 27,244 in active follow up. The program has 40,650 biospecimens collected from 19,900 participants. ECHO participants are diverse in age, socioeconomic status, geography, and race/ethnicity: 26% Hispanic, 43% non-Hispanic White, 12% Black, 4% Asian, 3% American Indian or Alaska Native, 4% more than one race, and 8% unknown/not reported/other.
Supported by: OD, NICHD, NIGMS
Funding Opportunities: RFA-OD-16-004, RFA-OD-16-006, RFA-OD-16-005, RFA-OD-16-003, RFA-OD-19-026, RFA-OD-19-025

IDeA States Pediatric Clinical Trials Network
Environmental influences on Child Health Outcomes (ECHO)'s IDeA States Pediatric Clinical Trials Network (ISPCTN) consists of interventional research sites in 18 states historically underrepresented in biomedical research, providing access to state-of-the art clinical trials. The ECHO ISPCTN includes children from rural or underserved areas in clinical trials while building capacity by supporting professional development and infrastructure. The ECHO ISPCTN currently has three trials underway, and has completed four large trials, including a trial related to building evidence for best practices to care for newborns with opioid withdrawal syndrome. Results from this randomized controlled clinical trial showed that newborns cared for with the Eat, Sleep, Console (ESC) approach were medically ready for discharge approximately 6.7 days earlier; they were also 63% less likely to receive medication as part of their treatment, compared with newborns cared for with the Finnegan Neonatal Abstinence Tool (FNAST).
Supported by: OD/ECHO, NICHD, OD/HEAL
Grants: U2COD023375, U24OD024957, U24HD095254
Website: ECHO IDeA States Pediatric Clinical Trials Network
Publications: https://pubmed.ncbi.nlm.nih.gov/37125831/
Funding Opportunities: RFA-OD-19-025

Structural Congenital Anomalies and Newborn Screening

Newborn Screening Translational Research Network
The Newborn Screening Translational Research Network (NBSTRN) seeks to improve the health outcomes of newborns with genetic or congenital disorders through an infrastructure that provides the research community with access to resources for newborn screening. The NBSTRN has developed three tools to facilitate newborn-screening research: (1) Virtual Repository of Dried Blood Spots (VRDBS), a secure web-based tool that provides a centralized and deidentified view of dried blood spots stored in all participating states; (2) Longitudinal Pediatric Data Resource (LPDR), a data collection tool and management system that allows the collection of follow-up screening data for data-sharing and dissemination to screening programs; and (3) Laboratory Performance Database (R4S), a database application for the collection and reporting of analytical newborn screening and diagnosis data. As part of the Newborn Screening Saves Lives Act (in 2007 and 2013) and the Newborn Screening Saves Lives Reauthorization Act (Public Law 113-240), the Hunter Kelly Newborn Screening Program was established, with the NBSTRN Coordinating Center as a key component. Current research projects include: research and assay development for lysosomal storage disorders and severe combined immunodeficiency disorders; studies of inborn errors of metabolism and effectiveness of current interventions; characterization of disorders of sex development and effective screening methods; and testing of spinal muscular-atrophy screening methods.
Supported by: NICHD
Grants: NBSTRN (RePORTER)

Hunter Kelly Newborn Screening Research Program
Under the provisions of the Newborn Screening Saves Lives Act, Congress established The Hunter Kelly Newborn Screening Research Program. The program is authorized to carry out, coordinate, and expand research in newborn screening. This program funds an array of research related to newborn screening that focuses on developing systematic methods to identify additional conditions appropriate for newborn screening, developing, and testing innovative interventions and treatments to improve outcomes; educating the provider workforce; developing and implementing appropriate information and communication systems for parents and providers; and sponsoring ongoing programs of research and research training in newborn screening.
Supported by: NICHD
News Links: NIH Newborn Screening Research Program Named in Memory of Hunter Kelly, Hunter Kelly

Newborn Screening and Health Data Standards
Several state newborn screening programs and federal partners are reviewing and revising guidance for using health information technology to electronically report 1) newborn screening test results for conditions newly targeted by screening tests, 2) strategies for improving newborn screening procedures, and 3) new health data standards.
Supported by: NLM
Website: Newborn Screening Coding and Terminology Guide

Implementation of Whole-Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants.
The BabySeq Project was the first randomized controlled trial (RCT) to study the clinical use and cost effectiveness of genome sequencing (GS) as a screening tool in infants. However, the BabySeq population was not diverse, and thus the findings were not generalizable. In order to disseminate this technology equitably, it is important to understand its impact on ethnically, racially and socioeconomically diverse populations and their health care providers. The goals of this project are to use the infrastructure and protocols developed in the BabySeq Project to study medical, behavioral, and economic outcomes associated with implementing GS in underrepresented, primarily African American and Hispanic populations of infants at several Clinical and Translational Science Awards (CTSA) sites. They will return pathogenic GS and copy number variation results and study the impact on families and health care providers, as well as the medical and economic impact. This project will focus on a topic that is important and address central questions that need to be answered before GS becomes routine in pediatric care. Through this research, the project will develop, implement, and evaluate a sustainable approach to GS as screening that leverages underserved community.
Supported by: NCATS, NICHD, NHLBI, NHGRI
Grants: U01TR003201, R01HL143295, R01HD090019, U19HD077671, K01HG009173, K99HG011491, R01HG009922, OT2OD026553
Publications: https://pubmed.ncbi.nlm.nih.gov/35571041/

A Study Evaluating the Safety and Efficacy of Second-Generation Tissue Engineered Vascular Grafts
A safety and efficacy trial of tissue-engineered vascular grafts (TEVG) for single-ventricle congenital heart disease, created from the patient's own cells—which, unlike conventional grafts, would be able to grow and remodel with growth or other structural changes of the patient's heart—has been funded.
Supported by: NHLBI
Grants: UH3HL148693

Substance Use and Misuse

Alcohol's Effects on the Developing Brain

The National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) is a longitudinal study examining brain structure and function in approximately 800 youths (12–21 years of age) before and after they begin using alcohol and other substances. NCANDA helped lay the foundation for the Adolescent Brain Cognitive Development (ABCD) study—the largest long-term study of brain and cognitive development in children and adolescents. Complementing NCANDA and ABCD, the Neurobiology of Adolescent Drinking in Adulthood consortium is enabling researchers to examine, in animal models, the mechanisms by which adolescent drinking leads to changes in brain structure and function that persist into adulthood.
Supported by: NIAAA
Funding Opportunities: RFA-AA-21-007, RFA-AA-21-008, RFA-AA-21-009

Technology and Tools

4D Nucleome

The 4D Nucleome program is an NIH-wide initiative that aims to study the three-dimensional organization of the nucleus in space and time (the fourth dimension). The first phase of this initiative began in 2015 and focused on delivering tools, resources, and reference data to the broader scientific community. The second phase kicked off in late 2020, with emphasis on applying these tools and resources to investigate the role of nuclear organization in human health. Several supported projects focus on pediatric issues such as brain development, Friedreich's ataxia (FA), congenital heart defects (CHDs), Down syndrome (DS), and fetal development.
Supported by: OD/DPCPSI/OSC, NHGRI, NCI, NIDA, NIDDK, NHLBI
Grants: 4D Nucleome (RePORTER)
Website: 4D Nucleome (4DN)

Developmental Genotype-Tissue Expression

Organs and tissues are made up of a complex mixture of different cell types, each with essentially the same genetic code but distinct biology, due presumably, in part, to differences in gene expression patterns. Just as some genes are differentially expressed across different cell types, some are turned on and off at different times during development within the same cell type. Despite considerable variation in expression patterns across tissues and across individuals, these patterns are relatively stable throughout adulthood, when most human gene expression studies have been done. The changes in gene expression that occur during postnatal development are largely unstudied, and yet lead to important milestones in health and disease such as the onset or cessation of growth spurts or puberty, and the development of childhood conditions such as asthma or attention-deficit/hyperactivity disorder (ADHD). The primary goal of the Developmental Genotype-Tissue Expression (dGTEx) Project is to establish a resource database and associated tissue bank to study gene expression patterns in multiple relatively healthy reference neonatal, pediatric, and adolescent tissues, and to make this resource broadly available for further research. The dGTEx will be a powerful tool to provide a comprehensive dataset of gene expression across a wide range of human tissues throughout development, filling a gap in genomic databases across developmental stages.
Supported by: NHGRI, NICHD
Grants: U24HG012090, U24HG012108, U24HD106537
Funding Opportunities: RFA-HG-21-026

Developmental NeuroToxicity Data Integration and Visualization Enabling Resource

Research shows that a child's developing nervous system is far more vulnerable to chemical exposures than an adult nervous system. The National Toxicology Program (NTP) has developed more rapid screening tools that use human cell-based assays, as well as alternate animal models such as zebrafish and planaria, to identify toxicants with potential for developmental neurotoxicity (DNT). Multiple tests are often required to represent the complexity of the developing nervous system, but that can make it challenging to compare and summarize results. NTP designed the Developmental NeuroToxicity Data Integration and Visualization Enabling Resource (DNT-DIVER), a free public resource to analyze, compare, and visualize multiple DNT assays in an interactive web application.
Supported by: NIEHS
Websites: Developmental NeuroToxicity Data Integration and Visualization Enabling Resource (DNT-DIVER), NTP DNT-DIVER

FaceBase: Comprehensive Craniofacial Data and Resources
FaceBase, the primary public data resource for craniofacial researchers worldwide, solicits, curates, and disseminates a variety of molecular, cellular, -omic, imaging and other phenotypic datasets on craniofacial development and related developmental disorders. First established in 2009, FaceBase is building on its robust computational system to enhance the findability, accessibility, interoperability, and reusability (the FAIR principles) of the data that it disseminates. FaceBase is also engaging with its data contributors and users to increase the volume and variety of data related to craniofacial development and malformation, and to improve curation, organization, and preparation of FaceBase data for its use in machine learning (ML) and artificial intelligence (AI)–based investigations. In the era of Big Data, FaceBase will play a significant role in enhancing craniofacial research and data science to speed new scientific discoveries and accelerate development of diagnostics and therapies.
Supported by: NIDCR
Grants: U01DE028729

NIH Baby Toolbox
The NIH Infant and Toddler Toolbox (aka the NIH Baby Toolbox, or NBT) is a comprehensive developmental assessment tool for infants and toddlers 1–42 months of age. With this tool, researchers and clinicians will be able to evaluate brain development in infants and toddlers using a computer tablet to assess their thinking (cognition), social functioning, spoken and understood language, ability to understand numbers (numeracy), self-regulation, and ability to accomplish a task (executive function). Children will be able to provide most of the responses themselves, and parents or legal guardians may give answers for them, as needed. Current developmental assessment tools are time-intensive and expensive; require highly trained personnel for administration, scoring, and interpreting; and often rely on outdated norms. The NBT is an innovative solution that will be easy to administer, score, and interpret within a relatively brief time frame, and will be able to capture multiple areas of neurodevelopment across this age range.
Supported by: NICHD, NIMH, NINDS
Grants: Baby Toolbox (RePORTER)
Website: NIH Infant and Toddler (Baby) Toolbox

Vision, Hearing, and Speech

Communication Development in Children with Cerebral Palsy
Dysarthria is a communication disorder caused by impairments to the parts of the brain that control the muscles in the lips, tongue, vocal folds, and diaphragm. Weakened muscles result in slurred or slow speech, making an individual’s speech difficult to understand. Researchers are now developing tools for better diagnosis and interventions for individuals with dysarthria. For example, one research study is investigating speech and language development in children with cerebral palsy (CP). Speech impairments

may affect over 80% of children with CP ; however, very little is known about the specific nature of these problems, how they change as children grow, or how to treat them. Scientists observed speech development in children with CP between the ages of 4 and 10 years. They aim to compare longitudinal trends of Viking Speech Scale (VSS) ratings—a scale measuring speech severity—among a wider age range, spanning throughout early childhood and into young adulthood to observe the long-term impact of speech impairment in CP with the goal of developing the predictive ability to determine speech and language outcomes for children. These outcome trajectories are necessary to develop interventions that improve speech, language, and communication—and ultimately quality of life—for children with CP.
Supported by: NIDCD
Grants: R01DC009411
Publications: https://pubmed.ncbi.nlm.nih.gov/35262181, https://pubmed.ncbi.nlm.nih.gov/34767477/

Developing New Standardized Treatment Options for Children with Asymmetrical or Single Sided Hearing Loss
In a clinical trial, clinicians are treating children with asymmetric hearing loss (AHL, defined as severe to profound hearing loss in one ear and mild to moderate hearing loss in the other ear) or single sided deafness (SSD, defined as severe to profound hearing loss in one ear and normal hearing function in the other) with a cochlear implant. Since 2020, the FDA has approved cochlear implants for use in eligible children with bilateral severe-to-profound hearing loss beginning at 9 months of age. Children who receive a cochlear implant followed by intensive therapy before they are 18 months of age typically are better able to hear and speak compared to their peers who receive implants when they are older. Many of these children also develop spoken language skills at a rate comparable to children with typical hearing, and many succeed in mainstream classrooms. Recently, the FDA granted approval to implant a subset of children with AHL or SSD; however, the approval is restrictive, as it is limited to children with profound hearing loss and very low word recognition in the poorer hearing ear. This longitudinal, prospective, multicenter clinical trial will help provide evidence for expanded cochlear implant candidacy criteria, appropriate assessment tools, and performance outcomes over time for children with AHL or SSD. This evidence-based approach is integral to the establishment of standardized and equitable treatments for these children.
Supported by: NIDCD
Grants: U01DC018942

Improving Language and Cognition in Children with Down Syndrome
Part of the INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE Project (INCLUDE) is a clinical trial in children and young adults with Down syndrome (DS) who have severe, obstructive sleep apnea. While continuous positive airway pressure (CPAP), or sleep masks, may be a common treatment option for obstructive sleep apnea, the majority of children with DS are noncompliant with CPAP due to co-occurring sensory conditions. In a Phase I clinical trial, investigators first looked at hypoglossal nerve stimulation (HGS), a therapy that involves implanting a device that stimulates nerve-controlling tongue movement for moderate to severe obstructive sleep apnea in adults for whom CPAP treatment is not successful. The researchers sought to determine whether HGS implantation was safe for the treatment of obstructive sleep apnea in children and young adults with DS, and to identify changes in sleep quality and evaluate compliance. Interestingly, parents reported their children were more attentive and doing better in school; many also reported their children were speaking with more clarity. The scientists performed a pilot study in five children with DS. These children showed improvements in IQ scores, diversity of vocabulary, and complexity in spoken language. Because of these improvements in articulation and language expression, the study has moved on as a Phase II multicenter trial. The results of this study are particularly meaningful because of the potential improvements in cognitive and expressive language outcomes. Researchers will track brief attention, sustained attention, processing speed, verbal intelligence, and executive functioning; they will also measure the diversity of

vocabulary and syntactic complexity. If the intervention trial is successful, it could mean rapid translation to inform immediate changes for how children with DS and sleep apnea can improve their quality of life.
Supported by: NIDCD
Grants: U01DC019279

Early Hearing Detection and Intervention Program
The federal Early Hearing Detection and Intervention **(**EHDI) program is continuing to ensure early identification of, and improved outcomes for, deaf and hard-of-hearing newborns, infants, and children. Resources have been developed for parents about hearing screening in children, hearing loss, and communication development. National progress on infant hearing screening, deaf, and hard of hearing diagnosis, and enrollment in early intervention is tracked by the CDC through state-level reporting. The Health Resources and Services Administration (HRSA) awards project grants to states and territories to implement and improve EHDI programs.
Supported by: NIDCD
Websites: Your Baby's Hearing Screening and Next Steps, Your Baby's Hearing and Communicative Development Checklist, CDC Early Hearing Detection and Intervention (EHDI) Program, HRSA Early Hearing Detection Intervention (EHDI)

Behavioral Intervention for Families with Deaf and Hard of Hearing Preschoolers
Children who are deaf and hard of hearing (DHH) demonstrate twice the prevalence of disruptive behavior problems seen in normal hearing children, yet rarely get behavioral interventions. Researchers are adapting an evidence-based behavioral intervention to prevent the long-term costly outcomes of behavior problems for parents of young children who are DHH. Under a one-year supplement to this project, scientists will also describe the impact of COVID-19 on quality of life and access to hearing health care for these children, their parents, and their families in the context of social determinants of health.
Supported by: NIDCD
Grants: R01DC016957

Bifocal Lenses In Nearsighted Kids
The prevalence of myopia (nearsightedness) among children worldwide is increasing at alarming rates. Myopic patients, especially those with severe cases, are at increased risk for a variety of blinding conditions including retinal detachment, cataract, and glaucoma. As children grow, the interaction of genetic and environmental factors regulate signals that control the axial length of the eye, and hence the point at which objects appear in focus. Recent findings from a three-year clinical trial, Bifocal Lenses in Nearsighted Kids (BLINK), showed that multifocal contact lenses slowed the progression of visual impairment in nearsighted children by 43% compared with single-vision contact lenses. Multifocal contact lenses correct the focus for central vision, which is needed for reading and recognizing faces, but do not correct the focus for peripheral vision. Continued research efforts will lead to important information regarding features of the eye and factors in the environment that may affect myopia progression.
Supported by: NEI
Grants: UG1EY023204, UG1EY023206, UG1EY023208, UG1EY023210, P30EY007551, UL1TR001070,

Pediatric Eye Disease Investigator Group
The Pediatric Eye Disease Investigator Group (PEDIG) is as network of doctors and scientists from academia and private practice dedicated to facilitating multicenter clinical research and developing community-based practices studying eye disorders that affect children. PEDIG studies have helped change the practice of pediatric eye care worldwide. Recent PEDIG research revealed that a large proportion of children with amblyopia or “lazy eye” can be successfully treated with less intense

treatment regimens than previously thought. Amblyopia, a condition where the brain ignores input from one eye, can be treated during a critical window of vision development with eyedrops or by patching one eye. These positive findings reduce amblyopia treatment burden and increase care for millions of children. PEDIG also recently completed a study to identify the lowest possible therapeutic dose of a drug to treat retinopathy of prematurity (ROP), and has launched a clinical trial to establish optimal standard of care (drug vs. laser treatment) for ROP. ROP is one of the leading causes of blindness in children and is caused by abnormal blood vessel growth that—when left unchecked—can cause scarring and retinal detachment.

Supported by: NEI
Grants: UG1EY011751
Funding Opportunities: PAR-21-041

ADDITIONAL PEDIATRIC COLLABORATIONS

Pediatric research at NIH involves various collaborations between NIH ICOs, as well as other Department of Health and Human Services (HHS) and federal agencies. During FY21 and FY22, NIH spearheaded and participated in a broad array of workshops, committees, working groups, and task forces encompassing many aspects of pediatric health. A selection of additional NIH–supported collaborative efforts for pediatric populations follows, but these examples represent only a small fraction of the collaborative efforts underway within NIH, with HHS, and across the federal government.

The NIH, the Office of the U.S. Global AIDS Coordinator (OGAC), and the CDC are members of the Adolescent HIV Prevention and Treatment Implementation Science Alliance (AHISA), which facilitates collaboration and communication to address implementation challenges related to prevention, screening, and treatment of human immunodeficiency virus (HIV) in adolescents [participating ICOs: Fogarty, NIAID, NICHD, NIMH, OAR]. The Gabriella Miller Kids First Pediatric Research Program fosters collaborative research to uncover the causes of childhood cancers and structural birth defects and support data sharing within the pediatric research community [NICHD, NCATS, NCI, NIDA, NHGRI, NHLBI, NIAAA, NIAID, NIAMS, NIDCR, NIDDK, NIEHS, OD, NINDS, ORIP, CDC].

Development, assessment, and optimization of pediatric drugs and devices are the subjects of many collaborative activities at NIH. NIH and FDA have joined forces on the Best Pharmaceuticals for Children Act (BPCA) Working Group, which provides safety oversight for the development and testing of pediatric medications [NICHD, NHLBI, NCI]. NICHD and FDA work with the American Academy of Pediatrics (AAP) Committee on Drugs to review all aspects of pediatric pharmacology. NICHD and FDA also participate in the Pediatric Device Consortia Program to facilitate the development, production, and distribution of pediatric medical devices via funding of nonprofit consortia.

NIH collaborations also address multiple aspects of nutrition and obesity among children, adolescents, and pregnant people. The NIH Nutrition Research Task Force (NRTF) guided the development of the 2020–2030 Strategic Plan for NIH Nutrition Research—the first NIH–wide strategic plan for nutrition research—and is infused with strategies that pay close attention to the role of diet in the health of women and children due to the formative role of nutrition in pregnancy and infancy and throughout childhood [NIDDK, NICHD, NHLBI, NCI, CSR, Fogarty, NHGRI, NIA, NIDA, NIDCR, NIEHS, NIMHD, NINR, NIAMS, OBSSR, ODP, ODS]. NIH collaborates with the U.S. Department of Agriculture (USDA), CDC, HRSA, FDA, and HHS Office of the Secretary (OS) on the Pregnancy and Birth to 24 Months project, which conducts dietary reviews, makes dietary recommendations, and examines topics of public health importance for pregnant women, infants, and toddlers less than 2 years of age [NIDDK, NCI, NICHD, NHLBI]. The National Collaborative on Childhood Obesity Research (NCCOR)—a collaboration between the CDC, USDA, NIH, and private foundations—speeds progress in reducing childhood obesity through surveillance, policies, research, and interventions [NICHD, NCI, NHLBI, NIDDK, OBSSR, ODP].

With the emergence of the COVID-19 pandemic, several NIH ICOs initiated collaborations to understand the effects of the SARS-CoV-2 virus on the health and safety of children. The NIH Multisystem Inflammatory Syndrome in Children (MIS-C) Task Force was tasked to develop and implement a research program to investigate the spectrum of SARS-CoV-2 illness in children and the novel MIS-C [NHLBI, NIAID, NICHD]. The NIH Pediatric Research Consortium (N-PeRC) COVID-19 subgroup is an NIH-wide working group that discusses current activities and opportunities to coordinate and advance COVID-19 and MIS-C research in maternal and pediatric populations across all 27 NIH ICOs. Several ICOs participate in the NIH-wide Long-Term Follow-Up Working Group to establish appropriate longitudinal follow-ups among hospitalized children with MIS-C [NICHD, NHLBI, NIAID, NIDA, NIDDK, NIMH, NINDS, NEI, OBSSR]. Collaborations strengthen pediatric research at NIH.

APPENDIX

Table 1: NIH Pediatric Research, Fiscal Years 2021 (FY21) and 2022 (FY22)

The totals below were derived from the NIH Research, Condition, and Disease Categorization (RCDC) system, which uses sophisticated text data mining (categorizing and clustering using individual words and multiword phrases) in conjunction with NIH–wide definitions for matching extramural and intramural research grants and projects to categories. The RCDC use of data mining is designed to improve consistency and eliminate wide variability in defining the research categories reported. The reported levels represent NIH's best estimates based on the category definitions. NIH does not expressly budget by category. The annual estimates reflect amounts that change as a result of science, actual research projects funded, and the NIH budget. Full lists of FY21 and FY22 NIH–funded grants and projects in pediatric research is available at https://report.nih.gov/funding/categorical-spending#/. The term "Common Fund" refers to research funded through the Office of Strategic Coordination (OSC), Office of the Director (OD), NIH, to address key scientific issues that no one ICO is positioned to address alone.

NIH ICO	FY21	FY22
Common Fund	$53,691,821	$40,261,847
Fogarty	$10,059,774	$10,465,384
NCATS	$51,854,734	$47,963,196
NCCIH	$8,223,888	$9,977,578
NCI	$664,044,625	$656,539,680
NEI	$94,816,184	$102,555,872
NHGRI	$76,773,356	$79,346,383
NHLBI	$499,221,786	$569,013,780
NIA	$41,105,884	$41,654,138
NIAAA	$126,152,518	$133,230,145
NIAID	$609,014,480	$570,123,566
NIAMS	$79,280,082	$71,160,747
NIBIB	$19,497,747	$24,866,130
NICHD	$885,348,456	$918,543,600
NIDA	$229,641,294	$226,464,770
NIDCD	$93,452,101	$102,593,298
NIDCR	$115,775,960	$124,922,114
NIDDK	$285,761,250	$314,254,729
NIEHS	$155,732,847	$168,281,979
NIGMS	$132,883,791	$137,109,864
NIMH	$495,482,327	$540,911,671
NIMHD	$77,360,973	$97,663,583
NINDS	$311,447,217	$324,543,331
NINR	$36,091,231	$37,780,316
NLM	$3,942,933	$4,126,725
OD	$268,420,458	$276,815,592
Type 1 Diabetes	$39,603,445	$75,415,165
Grand Total	**$5,464,681,162**	**$5,706,585,183**

Table 2: NIH Requests for Applications That Solicited Applications for Pediatric Research, Published in Fiscal Year 2021 (FY21) and FY22

Number	URL	Issuing Org.	Participating Orgs.	Activity Code	Title
RFA-HD-23-023	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-23-023.html	NICHD	None	K12	Pediatric Clinical Pharmacology Research Career Development Award (K12 Clinical Trial Not Allowed)
RFA-HD-23-003	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-23-003.html	NICHD	NIDA, ODS, PN	UC2	Elucidation and Validation of the role of Transporters in the Placenta, Lactating Mammary Gland, Developing Gut, and Blood Brain Barrier (UC2 Clinical Trial Not Allowed)
RFA-OD-22-022	https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-22-022.html	OD	NCATS, NCCIH, NHLBI, NIA, NIAAA, NIAID, NICHD, NIDA, NIDCR, NIDDK, NIEHS, NIMH, NIMHD, NINDS, NINR, NLM, OBSSR, ODP	U24	Environmental influences on Child Health Outcomes (ECHO) Data Analysis Center (U24) Clinical Trial Not Allowed
RFA-OD-22-021	https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-22-021.html	OD	NCATS, NCCIH, NHLBI, NIA, NIAAA, NIAID, NICHD, NIDA, NIDCR, NIDDK, NIEHS, NIMH, NIMHD, NINDS, NINR, NLM, OBSSR, ODP	U2C	Environmental influences on Child Health Outcomes (ECHO) Coordinating Center (U2C) (Clinical Trial Not Allowed)

Number	URL	Issuing Org.	Participating Orgs.	Activity Code	Title
RFA-OD-22-019	https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-22-019.html	OD	NCATS, NCCIH, NCI, NHLBI, NIA, NIAAA, NIAID, NICHD, NIDA, NIDCR, NIDDK, NIEHS, NIMH, NIMHD, NINDS, NINR, NLM, OBSSR, ODP, ORWH	UG3/UH3	Limited Competition: Environmental influences on Child Health Outcomes (ECHO) Cohort Study Sites for Pediatric Follow Up. Clinical Trial Not Allowed (UG3/UH3)
RFA-OD-22-018	https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-22-018.html	OD	NCATS, NCCIH, NCI, NHLBI, NIA, NIAAA, NIAID, NICHD, NIDA, NIDCR, NIDDK, NIEHS, NIMH, NIMHD, NINDS, NINR, NLM, OBSSR, ODP, ORWH	UG3/UH3	Limited Competition: Environmental influences on Child Health Outcomes (ECHO) Pregnancy and Pediatric Cohort Study Sites. Clinical Trial Not Allowed (UG3/UH3)
RFA-OD-22-017	https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-22-017.html	OD	NCATS, NCCIH, NCI, NHLBI, NIA, NIAAA, NIAID, NICHD, NIDA, NIDCR, NIDDK, NIEHS, NIMH, NIMHD, NINDS, NINR, NLM, OBSSR, ODP, ORWH	UG3/UH3	Open Competition: Environmental influences on Child Health Outcomes (ECHO) Pregnancy Cohort Study Sites. Clinical Trial Not Allowed (UG3/UH3)

Number	URL	Issuing Org.	Participating Orgs.	Activity Code	Title
RFA-OD-22-016	https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-22-016.html	OD	NCATS, NCCIH, NHLBI, NIA, NIAAA, NIAID, NICHD, NIDA, NIDCR, NIDDK, NIEHS, NIMH, NIMHD, NINDS, NINR, NLM, OBSSR, ODP	U24	Environmental influences on Child Health Outcomes (ECHO) Laboratory Core (U24) Clinical Trial Not Allowed
RFA-HD-23-033	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-23-033.html	NICHD	NIAAA, NIDA, NIMH, NINDS	R21	HEAL Initiative: Opioid Exposure and Effects on Placenta Function, Brain Development, and Neurodevelopmental Outcomes (R21 Basic Experimental Studies with Humans Required)
RFA-HD-23-031	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-23-031.html	NICHD	NIAAA, NIDA, NIMH, NINDS	R21	HEAL Initiative: Opioid Exposure and Effects on Placenta Function, Brain Development, and Neurodevelopmental Outcomes (R21 Clinical Trial Not Allowed)
RFA-HD-23-030	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-23-030.html	NICHD	NIAAA, NIDA, NIMH, NINDS	R01	HEAL Initiative: Opioid Exposure and Effects on Placenta Function, Brain Development, and Neurodevelopmental Outcomes (R01 Clinical Trial Not Allowed)
RFA-HD-23-032	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-23-032.html	NICHD	NCCIH, NIAAA, NIDA, NIMH, NINDS	R01	HEAL Initiative: Opioid Exposure and Effects on Placenta Function, Brain Development, and Neurodevelopmental Outcomes (R01 Basic Experimental Studies with Humans Required)
RFA-CA-22-030	https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-22-030.html	NCI	None	U24	Cancer Adoptive Cellular Therapy Network (Can-ACT) Coordinating Center (U24 Clinical Trial Not Allowed)

Number	URL	Issuing Org.	Participating Orgs.	Activity Code	Title
RFA-CA-22-029	https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-22-029.html	NCI	None	UG3/UH3	Cancer Adoptive Cellular Therapy Network (Can-ACT) for Pediatric Cancers (UG3/UH3 Clinical Trial Required)
RFA-HD-23-018	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-23-018.html	NICHD	None	U24	MPRINT Translational Research Resource Platform (TRRP) (U24 Clinical Trial Not Allowed)
RFA-DA-23-050	https://grants.nih.gov/grants/guide/rfa-files/RFA-DA-23-050.html	NIDA	NCCIH, NIAAA	R01	HEAL Initiative: Development and validation of virtual assessments to study children and caregivers in their natural environment (R01- Clinical Trial Not Allowed)
RFA-DA-23-055	https://grants.nih.gov/grants/guide/rfa-files/RFA-DA-23-055.html	NIDA	NCCIH, NIAAA	R01	HEAL Initiative: Development and validation of virtual assessments to study children and caregivers in their natural environment (R01- Basic Experimental Studies with Humans Required)
RFA-AT-23-003	https://grants.nih.gov/grants/guide/rfa-files/RFA-AT-23-003.html	NCCIH	ODP	UG3/UH3	Fostering Mental, Emotional, and Behavioral (MEB) Health Among Children in School Settings: Opportunities for Multisite Trials of Complementary and Integrative Health Interventions (Clinical Trial Optional)

Number	URL	Issuing Org.	Participating Orgs.	Activity Code	Title
RFA-HD-23-037	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-23-037.html	NICHD	NCATS, NCCIH, NHGRI, NHLBI, NIAAA, NIAID, NIBIB, NIDA, NIDCR, NIDDK, NIEHS, NIMH, NIMHD, NINDS, NINR, OAR, OBSSR, ODP, ODS, ORWH, SGMRO	U24	Maternal Health Research Centers of Excellence Implementation Science Hub/Resource Center (U24 Clinical Trial Optional)
RFA-HD-23-035	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-23-035.html	NICHD	NCATS, NCCIH, NHGRI, NHLBI, NIAAA, NIAID, NIAMS, NIBIB, NIDA, NIDCR, NIDDK, NIEHS, NIMH, NIMHD, NINDS, NINR, OAR, OBSSR, ODP, ODS, ORWH, SGMRO	U54	Maternal Health Research Centers of Excellence (U54 Clinical Trial Optional)
RFA-HD-23-036	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-23-036.html	NICHD	NINDS, NINR, NLM, OAR, OBSSR, ODP, ODS, ORWH, SGMRO, NIMHD, NCATS, NCCIH, NHGRI, NHLBI, NIAAA, NIAID, NIBIB, NIDA, NIDCR, NIDDK, NIEHS, NIMH	U24	Maternal Health Research Centers of Excellence Data Innovation and Coordinating Hub/Resource Center (U24 Clinical Trial Not Allowed)

Number	URL	Issuing Org.	Participating Orgs.	Activity Code	Title
RFA-HD-23-034	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-23-034.html	NICHD	None	K12	Pediatric Scientist Development Program (PDSP) (K12 Clinical Trial Not Allowed)
RFA-AI-22-054	https://grants.nih.gov/grants/guide/rfa-files/RFA-AI-22-054.html	NIAID	None	U01	Allergy and Asthma Statistical and Clinical Coordinating Center (AA-SCCC) (U01 Clinical Trial Not Allowed)
RFA-HD-23-009	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-23-009.html	NICHD	None	U24	NICHD Global Network for Womens and Childrens Health Research: Data Coordinating Center (U24 Clinical Trial Optional)
RFA-HD-23-008	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-23-008.html	NICHD	None	UG1	NICHD Global Network for Womens and Childrens Health Research: Research Units (UG1 Clinical Trial Optional)
RFA-DK-22-022	https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-22-022.html	NIDDK	None	R01	Integrated Physiology of Exocrine and Endocrine Pancreas in Type 1 Diabetes (R01 - Clinical Trial Not Allowed)
RFA-DK-22-504	https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-22-504.html	NIDDK	NHLBI, NICHD	U01	Limited Competition for Continuation of the Prospective Study of Chronic Kidney Disease in Children Clinical Coordinating Centers (U01 Clinical Trial Not Allowed)
RFA-DK-22-010	https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-22-010.html	NIDDK	NHLBI, NICHD	U24	Chronic Kidney Disease in Children Central Biochemistry Laboratory (U24 Clinical Trial Not Allowed)
RFA-DK-22-505	https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-22-505.html	NIDDK	NHLBI, NICHD	U24	Limited Competition for Continuation of the Prospective Study of Chronic Kidney Disease in Children Data Coordinating Center (U24 Clinical Trial Not Allowed)

Number	URL	Issuing Org.	Participating Orgs.	Activity Code	Title
RFA-DK-22-021	https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-22-021.html	NIDDK	None	R01	Collaborative Research Using Biosamples from Type 1 Diabetes Clinical Studies (R01 - Clinical Trial Not Allowed)
RFA-AR-23-001	https://grants.nih.gov/grants/guide/rfa-files/RFA-AR-23-001.html	NIAMS	NHLBI, NICHD, NINDS	P50	Senator Paul D. Wellstone Muscular Dystrophy Specialized Research Centers (MDSRC) (P50 Clinical Trial Optional)
RFA-HD-23-004	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-23-004.html	NICHD	None	R01	Bioprinted Tissue Constructs for Obstetric, Gynecologic, and Pediatric Applications (R01 Clinical Trial Optional)
RFA-HD-23-016	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-23-016.html	NICHD	None	UG1	NICHD Maternal-Fetal Medicine Units (MFMU) Network: Clinical Centers (UG1 Clinical Trial Optional)
RFA-HD-23-017	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-23-017.html	NICHD	None	U24	NICHD Maternal-Fetal Medicine Units (MFMU) Network: Data Coordinating Center (U24 Clinical Trial Optional)
RFA-HD-23-001	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-23-001.html	NICHD	None	U24	NICHD Neonatal Research Network (NRN): Data Coordinating Center (U24 Clinical Trial Optional)
RFA-HD-23-002	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-23-002.html	NICHD	None	UG1	NICHD Neonatal Research Network (NRN): Clinical Centers (UG1 Clinical Trial Optional)
RFA-OD-22-008	https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-22-008.html	OD	NCI, NEI, NHGRI, NHLBI, NIA, NIAID, NIAMS, NICHD, NIDCD, NINDS	R03	Small Research Grants for Analysis, Curation, and/or Sharing of Down syndrome-related Research Data for the INCLUDE Project (R03 Clinical Trial Not Allowed)

Number	URL	Issuing Org.	Participating Orgs.	Activity Code	Title
RFA-OD-22-010	https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-22-010.html	OD	NCI, NEI, NHLBI, NIA, NIAMS, NICHD, NIDCD, NINDS	R61/R33	Clinical Trials Development for Co-Occurring Conditions in Individuals with Down syndrome: Phased Awards for INCLUDE (R61/R33 Clinical Trial Required)
RFA-OD-22-009	https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-22-009.html	OD	NCI, NEI, NHGRI, NHLBI, NIA, NIAID, NIAMS, NICHD, NIDCD, NIDCR, NIMH, NINDS, ORIP	R01	Transformative Research Award for the INCLUDE (Investigation of Co-occurring Conditions across the Lifespan to Understand Down syndrome) Project (R01 Clinical Trial Not Allowed)
RFA-OD-22-007	https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-22-007.html	OD	NCI, NEI, NHLBI, NIA, NIAMS, NICHD, NIDCD, NINDS	R21	INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE (INCLUDE) Clinical Trial Readiness (R21 Clinical Trial Not Allowed)
RFA-CA-22-016	https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-22-016.html	NCI	None	U01	Pediatric Immunotherapy Network (PIN) (U01 Clinical Trial Optional)
RFA-MH-22-141	https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-22-141.html	NIMH	None	R21	Understanding Suicide Risk and Protective Factors among Black Youth (R21 Clinical Trial Not Allowed)
RFA-MH-22-140	https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-22-140.html	NIMH	NIMHD, OBSSR	R01	Understanding Suicide Risk and Protective Factors among Black Youth (R01 Clinical Trial Not Allowed)
RFA-HD-23-007	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-23-007.html	NICHD	None	P50	CAPSTONE Centers for Multidisciplinary Research in Child Abuse and Neglect (P50) (Clinical Trial Optional)
RFA-OD-22-004	https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-22-004.html	ODP	NCI, NHLBI, NIDA, NIEHS	U54	Tobacco Centers of Regulatory Science (TCORS) for Research Relevant to the Family Smoking Prevention and Tobacco Control Act (U54 Clinical Trial Optional)

Number	URL	Issuing Org.	Participating Orgs.	Activity Code	Title
RFA-AI-22-015	https://grants.nih.gov/grants/guide/rfa-files/RFA-AI-22-015.html	NIAID	NICHD	R01	Biomarker Signatures of TB Infection in Young Children With and Without HIV (R01 Clinical Trial Not Allowed)
RFA-HD-22-024	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-22-024.html	NICHD	ORWH	UG3/UH3	Community Engaged Research on Pregnancy Related and Associated Infections and Sepsis Morbidity and Mortality (UG3/UH3 Clinical Trial Optional)
RFA-DK-21-020	https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-21-020.html	NIDDK	None	U01	Elucidating the heterogeneity of impaired awareness of hypoglycemia in Type 1 Diabetes (T1D) Clinical Centers (U01 Clinical Trial Required)
RFA-DK-21-036	https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-21-036.html	NIDDK	None	U01	Elucidating the heterogeneity of impaired awareness of hypoglycemia in Type 1 Diabetes (T1D) - Biostatistics Research Center (U01 Clinical Trial Not Allowed)
RFA-AI-21-079	https://grants.nih.gov/grants/guide/rfa-files/RFA-AI-21-079.html	NIAID	None	U19	Asthma and Allergic Diseases Cooperative Research Centers (U19 Clinical Trial Optional)
RFA-HD-23-021	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-23-021.html	NICHD	NIMH, NIDA	UM2	Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) Operations and Collaborations Center (UM2 Clinical Trial Optional)
RFA-HD-23-020	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-23-020.html	NICHD	NIMH, NIDA	UM2	Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) Scientific Leadership Center (UM2 Clinical Trial Optional)
RFA-HD-23-010	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-23-010.html	NICHD	None	K12	Child Health Research Career Development Award (CHRCDA) Program (K12 Clinical Trial Not Allowed)

Number	URL	Issuing Org.	Participating Orgs.	Activity Code	Title
RFA-RM-22-006	https://grants.nih.gov/grants/guide/rfa-files/RFA-RM-22-006.html	RMOD	None	R03	Expert-Driven Small Projects to Strengthen Gabriella Miller Kids First Discovery (R03 Clinical Trial Not Allowed)
RFA-MH-22-150	https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-22-150.html	NIMH	None	R61/R33	Using Just-in-Time Adaptive Interventions to Optimize Established Adolescent Mental Health Treatments (R61/R33 Clinical Trial Required)
RFA-HD-22-023	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-22-023.html	NICHD	None	R01	Elucidating the Role of Nutrition in Care and Development of Preterm Infants (R01 Clinical Trial Optional)
RFA-HD-23-005	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-23-005.html	NICHD	ORWH	R01	Promoting Reproductive Health for Adolescents and Adults with Disabilities (R01 Clinical Trial Optional)
RFA-MH-22-106	https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-22-106.html	NIMH	None	R34	Expanding Differentiated Care Approaches for Adolescents Living with HIV (R34 Clinical Trial Optional)
RFA-MH-22-105	https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-22-105.html	NIMH	None	R01	Expanding Differentiated Care Approaches for Adolescents Living with HIV (R01 Clinical Trial Optional)
RFA-MH-22-125	https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-22-125.html	NIMH	None	R34	Enhanced Interpersonal Focused Strategies for Suicide Prevention Interventions (R34 Clinical Trial Required)
RFA-MH-22-120	https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-22-120.html	NIMH	None	R34	Pilot Practice-based Research for Primary Care Suicide Prevention (R34 Clinical Trial Optional)
RFA-DK-21-025	https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-21-025.html	NIDDK	None	R01	Pediatric Obesity Discovery Science Research to Improve Understanding of Risk and Causal Mechanisms for Obesity in Early Life (R01 Clinical Trial Optional)

Number	URL	Issuing Org.	Participating Orgs.	Activity Code	Title
RFA-OD-21-007	https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-21-007.html	OD	NEI, NIDCD, NIAMS, NCI, NIDCR, NIAID, NCCIH, NHLBI, NIA, NICHD, ORIP	R21	INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE (INCLUDE) Exploratory/Developmental Research Grant Award (R21 Clinical Trial Not Allowed)
RFA-HD-22-009	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-22-009.html	NICHD	None	P01	Impact of Technology and Digital Media (TDM) Exposure/Usage on Child and Adolescent Development (P01 Clinical Trial Optional)
RFA-HD-22-005	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-22-005.html	NICHD	None	P20	Learning Disabilities Innovation Hubs (P20 Clinical Trial Optional)
RFA-RM-21-014	https://grants.nih.gov/grants/guide/rfa-files/RFA-RM-21-014.html	RMOD	None	U2C	Limited Competition: Continued Development of the Gabriella Miller Kids First Pediatric Data Resource Center (U2C Clinical Trial Not Allowed)
RFA-HD-22-007	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-22-007.html	NICHD	NIEHS, NIDCD, NIMH, NINDS	R01	Autism Centers of Excellence: Networks (R01 Clinical Trial Optional)
RFA-HD-22-008	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-22-008.html	NICHD	NIEHS, NIDCD, NIMH, NINDS	P50	Autism Centers of Excellence: Centers (P50 Clinical Trial Optional)
RFA-DK-21-018	https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-21-018.html	NIDDK	None	R01	Pilot and Feasibility Studies to Improve Technology Adoption and Reduce Health Disparities in Type 1 Diabetes Mellitus (R01 Clinical Trial Required)
RFA-DK-21-003	https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-21-003.html	NIDDK	None	U01	Understanding and Targeting the Pathophysiology of Youth-onset Type 2 Diabetes Biostatistics Research Center (U01 Clinical Trial Not Allowed)

Number	URL	Issuing Org.	Participating Orgs.	Activity Code	Title
RFA-DK-21-002	https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-21-002.html	NIDDK	None	U01	Understanding and Targeting the Pathophysiology of Youth-onset Type 2 Diabetes Clinical Centers (U01 Clinical Trial Not Allowed)
RFA-AA-21-009	https://grants.nih.gov/grants/guide/rfa-files/RFA-AA-21-009.html	NIAAA	NIDA	U24	Limited Competition for the Continuation of the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) Data Analysis Resource (U24 Clinical Trials Optional)
RFA-AA-21-007	https://grants.nih.gov/grants/guide/rfa-files/RFA-AA-21-007.html	NIAAA	NIDA	U01	Limited Competition for the Continuation of the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) Research Project Sites (U01 Clinical Trials Optional)
RFA-AA-21-008	https://grants.nih.gov/grants/guide/rfa-files/RFA-AA-21-008.html	NIAAA	NIDA	U24	Limited Competition for the Continuation of the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) Administrative Resource (U24 Clinical Trials Optional)
RFA-AA-21-014	https://grants.nih.gov/grants/guide/rfa-files/RFA-AA-21-014.html	NIAAA	None	UH2	Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD), Developmental Project (UH2 Clinical Trial Optional)
RFA-AA-21-013	https://grants.nih.gov/grants/guide/rfa-files/RFA-AA-21-013.html	NIAAA	None	U24	Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD), Data Coordination Resource (U24 Clinical Trial Not Allowed)

Number	URL	Issuing Org.	Participating Orgs.	Activity Code	Title
RFA-AA-21-012	https://grants.nih.gov/grants/guide/rfa-files/RFA-AA-21-012.html	NIAAA	None	U24	Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD), Diagnostic-Telemedicine Resource (U24 Clinical Trial Not Allowed)
RFA-AA-21-011	https://grants.nih.gov/grants/guide/rfa-files/RFA-AA-21-011.html	NIAAA	None	U24	Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD), Administrative Resource (U24) (Clinical Trial Not Allowed)
RFA-AA-21-010	https://grants.nih.gov/grants/guide/rfa-files/RFA-AA-21-010.html	NIAAA	None	U01	Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD), Research Project (U01 Clinical Trial optional)
RFA-HD-22-020	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-22-020.html	NICHD	None	R01	Human Milk as a Biological System (R01 Clinical Trial Optional)
RFA-DE-22-002	https://grants.nih.gov/grants/guide/rfa-files/RFA-DE-22-002.html	NIDCR	ODP, ORWH, OBSSR	UG3/UH3	Addressing Social Determinants of Health to Eliminate Oral Health Disparities (UG3/UH3 Clinical Trials Optional)
RFA-HD-22-004	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-22-004.html	NICHD	None	P01	Developmental Mechanisms of Human Structural Birth Defects (P01 Clinical Trial Not Allowed)
RFA-MH-21-230	https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-21-230.html	NIMH	None	R34	Pilot Effectiveness Trials of Interventions for Preschoolers with ADHD (R34 Clinical Trial Required)
RFA-MH-21-186	https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-21-186.html	NIMH	ODP, SGMRO	R34	Systems-Level Risk Detection and Interventions to Reduce Suicide, Ideation, and Behaviors in Black Children and Adolescents (R34 Clinical Trial Optional)

Number	URL	Issuing Org.	Participating Orgs.	Activity Code	Title
RFA-MH-21-185	https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-21-185.html	NIMH	ODP, SGMRO	R01	Systems-Level Risk Detection and Interventions to Reduce Suicide, Ideation, and Behaviors in Black Children and Adolescents (R01 Clinical Trial Optional)
RFA-MH-21-188	https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-21-188.html	NIMH	ODP	R34	Systems-Level Risk Detection and Interventions to Reduce Suicide, Ideation, and Behaviors in Youth from Underserved Populations (R34 Clinical Trial Optional)
RFA-MH-21-187	https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-21-187.html	NIMH	ODP, SGMRO	R01	Systems-Level Risk Detection and Interventions to Reduce Suicide, Ideation, and Behaviors in Youth from Underserved Populations (R01 Clinical Trial Optional)
RFA-HD-22-013	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-22-013.html	NICHD	None	P2C	Population Dynamics Centers Research Infrastructure Program FY 2022 (P2C Clinical Trial Not Allowed)
RFA-HD-22-014	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-22-014.html	NICHD	None	R24	Coordinating Center for the NICHD Population Dynamics Centers Research Infrastructure Program FY 2022 (R24 Clinical Trial Not Allowed)
RFA-DK-21-006	https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-21-006.html	NIDDK	None	R01	Development of New Technologies and Bioengineering Solutions for the Advancement of Cell Replacement Therapies for Type 1 Diabetes (T1D) (R01 Clinical Trial Optional)
RFA-HD-21-033	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-21-033.html	NICHD	None	UG3/UH3	Community Engaged Research on Pregnancy Related and Associated Infections and Sepsis Morbidity and Mortality (UG3/UH3 Clinical Trial Optional)

Number	URL	Issuing Org.	Participating Orgs.	Activity Code	Title
RFA-HD-22-006	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-22-006.html	NICHD	None	K12	Recompetition of the Pediatric Scientist Development Program (PSDP) (K12 Clinical Trial Not Allowed)
RFA-HL-22-008	https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-22-008.html	NHLBI	ODP, ORWH, NIMHD	U24	Early Intervention to Promote Cardiovascular Health of Mothers and Children (ENRICH) Multisite Resource and Coordinating Center (U24 Clinical Trial Required)
RFA-HL-22-007	https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-22-007.html	NHLBI	ORWH, NIMHD, ODP	UG3/UH3	Early Intervention to Promote Cardiovascular Health of Mothers and Children (ENRICH) Multisite Clinical Centers (Collaborative UG3/UH3 Clinical Trial Required)
RFA-DK-21-005	https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-21-005.html	NIDDK	NIAID	R01	Immune Cell Engineering For Targeted Therapy And Disease Monitoring in Type 1 Diabetes (R01 Clinical Trial Not Allowed)
RFA-TW-21-003	https://grants.nih.gov/grants/guide/rfa-files/RFA-TW-21-003.html	Fogarty	ORWH, NINDS	D43	Fogarty Global Trauma and Injury Research Training Program (D43 Clinical Trial Optional)
RFA-RM-21-011	https://grants.nih.gov/grants/guide/rfa-files/RFA-RM-21-011.html	RMOD	None	R03	Expert-Driven Small Projects to Strengthen Gabriella Miller Kids First Discovery (R03 Clinical Trial Not Allowed)
RFA-AI-20-078	https://grants.nih.gov/grants/guide/rfa-files/RFA-AI-20-078.html	NIAID	NICHD, NIEHS	U19	Immune Development in Early Life (IDEaL) (U19 Clinical Trial Not Allowed)
RFA-AI-20-077	https://grants.nih.gov/grants/guide/rfa-files/RFA-AI-20-077.html	NIAID	NICHD, NIEHS	U01	Immune Development in Early Life (IDEaL) (U01 Clinical Trial Not Allowed)

Number	URL	Issuing Org.	Participating Orgs.	Activity Code	Title
RFA-DA-21-022	https://grants.nih.gov/grants/guide/rfa-files/RFA-DA-21-022.html	NIDA	NIAAA, NIBIB, NICHD, NIEHS, NIMH, NIMHD, NINDS, OBSSR, ORWH	U24	HEAL Initiative: HEALthy Brain and Child Development Consortium Administrative Core (U24 - Clinical Trial Not Allowed)
RFA-DA-21-023	https://grants.nih.gov/grants/guide/rfa-files/RFA-DA-21-023.html	NIDA	NIMH, ORWH, OBSSR, NIBIB, NINDS, NIEHS, NIMHD, NIAAA	U24	HEAL Initiative: HEALthy Brain and Child Development Data Coordinating Center (U24)
RFA-DA-21-021	https://grants.nih.gov/grants/guide/rfa-files/RFA-DA-21-021.html	NIDA	NIMHD, NINDS, OBSSR, ORWH, NIAAA, NIBIB, NICHD, NIEHS, NIMH	U01	HEAL Initiative: HEALthy Brain and Child Development Study (U01 - Clinical Trial Not Allowed)
RFA-DA-21-020	https://grants.nih.gov/grants/guide/rfa-files/RFA-DA-21-020.html	NIDA	NINDS, OBSSR, ORWH, NIAAA, NIBIB, NICHD, NIEHS, NIMH, NIMHD	U01	HEAL Initiative: HEALthy Brain and Child Development Study (Collaborative U01- Clinical Trial Not Allowed)
RFA-HD-21-031	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-21-031.html	NICHD	None	UG1	HEAL Initiative: Neonatal Opioid Withdrawal Syndrome Pharmacological Treatments Comparative Effectiveness Trial - Clinical Sites (UG1 Clinical Trial Required)
RFA-HD-21-032	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-21-032.html	NICHD	None	U24	HEAL Initiative: Data Coordinating Center for the Neonatal Opioid Withdrawal Syndrome Pharmacological Treatments Comparative Effectiveness Trial (U24 Clinical Trial Required)

Number	URL	Issuing Org.	Participating Orgs.	Activity Code	Title
RFA-DK-20-508	https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-20-508.html	NIDDK	None	U01	Limited Competition: Revision to the Coordinating Center for Type 1 Diabetes TrialNet (U01 Clinical Trial Required)
RFA-DK-20-030	https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-20-030.html	NIDDK	None	R01	Understanding the Cellular and Molecular Mechanisms of Gastroparesis in Adults and Children (R01 Clinical Trial Not Allowed)
RFA-HD-21-030	https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-21-030.html	NICHD	None	R21	Using Archived Data and Specimen Collections to Advance Maternal and Pediatric HIV/AIDS Research (R21 Clinical Trial Not Allowed)

Table 3: Acronyms for NIH Institutes, Centers, and Offices and Other U.S. Federal Agencies Referred to in This Report

Acronym/ Abbreviation	Organization
AHRQ	Agency for Healthcare Research and Quality
CC	Clinical Center
CDC	Centers for Disease Control and Prevention
DPCPSI	Division of Program Coordination, Planning, and Strategic Initiatives, OD
FDA	U.S. Food and Drug Administration
Fogarty	Fogarty International Center
HHS	Department of Health and Human Services
HRSA	Health Resources and Services Administration
ICOs	NIH institutes, centers, and offices
NCATS	National Center for Advancing Translational Sciences
NCCIH	National Center for Complementary and Integrative Health
NCI	National Cancer Institute
NEI	National Eye Institute
NHLBI	National Heart, Lung, and Blood Institute
NHGRI	National Human Genome Research Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NIDA	National Institute on Drug Abuse
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NIMHD	National Institute on Minority Health and Health Disparities
NINDS	National Institute of Neurological Disorders and Stroke
NINR	National Institute of Nursing Research
NLM	National Library of Medicine
OAR	Office of AIDS Research, DPCPSI
OD	Office of the Director, NIH
OBSSR	Office of Behavioral and Social Sciences Research, DPCPSI
ODP	Office of Disease Prevention, DPCPSI
ODS	Office of Dietary Supplements, DPCPSI
ORIP	Office of Research Infrastructure Programs, DPCPSI
ORWH	Office of Research on Women's Health, DPCPSI
USDA	U.S. Department of Agriculture