

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**National Institutes of Health**

**Report to Congress:**

**The Fiscal Year 2013 Pediatric Research Initiative**

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## Report to Congress: Fiscal Year 2013 Pediatric Research Initiative

### PEDIATRIC RESEARCH AT THE NATIONAL INSTITUTES OF HEALTH

National Institutes of Health (NIH) research advances have transformed the diagnosis, treatment, and prevention of disease. Children have benefitted greatly from revolutionary progress in biomedical research. Infant death rates have dropped precipitously in the United States over the past 50 years. Survival rates for respiratory distress syndrome have gone from 5 percent in the 1960s to 95 percent today. Transmission of HIV from infected mother to fetus and infant has fallen to less than 1 percent. *Haemophilus influenzae* type B (Hib), once the leading cause of acquired intellectual and developmental disabilities, has been nearly eliminated after the introduction of an NIH-funded vaccine. Scientists' understanding of how children grow and develop has improved 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. The NIH's strong basic research portfolio provides the foundation for pediatric research in a variety of scientific areas, including neurodevelopment, cardiology, cancer, and behavioral and social sciences. In fiscal year (FY) 2013, the NIH funded research grants and projects directed specifically at pediatric research for a total of \$3,266,413,748. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) funds the largest portion of pediatric research among the 27 NIH Institutes and Centers (ICs), taking a leadership role in many pediatric research efforts that involve trans-NIH collaborations. However, the NICHD alone accounts for only 20 percent of the total NIH support for pediatric research. This reflects the breadth of the research portfolio at the NIH dedicated to improving the health of children everywhere.

### THE PEDIATRIC RESEARCH INITIATIVE

In the Children's Health Act of 2000 (the Act), Congress directed the Secretary of Health and Human Services (HHS) to establish a Pediatric Research Initiative (PRI) in the Office of the Director (OD) of the NIH. 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.”

—Section 409D(c)(3), Public Health Service Act

In response to this request, the NIH has prepared the following report for FY 2013.

The overall purpose of the PRI is to “conduct and support research that is directly related to diseases, disorders, and other conditions in children” (Section 409D(a), Public Health Service Act). 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, 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.

—Section 409D(b), Public Health Service Act

Congress did not appropriate any funds to the NIH specifically for carrying out the PRI. Consequently, the NIH has funded the initiative through (1) a one-time, \$5 million distribution from the NIH Director's Discretionary Fund (FY 2002); and (2) individual and collaboratively funded IC grants and contracts (FY 2002 and thereafter). For reporting purposes, the NIH has defined PRI research as including new or significantly expanded pediatric research projects funded in the reporting year. (The technical definition of research reported for PRI purposes is included in the Appendix.) It should be noted that the PRI reporting definition provides an incomplete picture of the NIH's total investments in pediatric research. Table 2 in the Appendix of this report provides funding amounts for the NIH's total investment in pediatric research by IC.

In addition to establishing the PRI, other related sections of the Act required increased NIH investment in training pediatric biomedical investigators; a review of the federal regulations for protection of children as research subjects; and a national longitudinal study of environmental influences (including physical, chemical, biological, and psychosocial factors) on children's health and development.

A core component of the NICHD's mission is to improve and promote children's health and development. Therefore, the Director of the NIH requested that the Director of the NICHD oversee and coordinate the PRI at the NIH and coordinate preparation of the report on the Initiative.

## **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 the NIH's scientific portfolio in pediatrics. Advances in early development, rare diseases, HIV/AIDS, treatment of serious pediatric illnesses, prevention, and global health research are emphasized. Several of these advances resulted from programs that are supported by multiple NIH ICs, and a total of 17 NIH ICs and Offices are represented.

### **Early Development**

*Uncovering the Origins of Congenital Heart Disease:* Findings from the National Heart, Lung, and Blood Institute (NHLBI) Pediatric Cardiac Genomics Consortium, an international multicenter collaborative research effort, have led to an improved understanding of the causes of congenital heart disease, the most common type of birth defect. The researchers found that about 10 percent of the 362 participants with congenital heart disease had spontaneous, or de novo, mutations that arise during fetal development. Many of the mutated genes were involved in a

specific pathway that controls and regulates gene expression, providing some insight into how the defects arise. <http://www.nature.com/nature/journal/v498/n7453/full/nature12141.html>

*Controlling the Size of the Heart During Fetal Development:* Organ size is important in cardiac development. The heart must be large enough to generate strong cardiac output but not so large as to hamper efficient blood flow, as in the case of obstructive cardiac disorders. In fruit flies, a cellular signaling protein known as Hippo is a key component of a molecular pathway that controls organ size by inhibiting excessive organ growth. To determine whether Hippo controls heart size in mammals, NICHD-funded researchers inactivated components of the Hippo pathway in the developing mouse heart. Hippo-deficient embryos had overgrown hearts, and additional experiments revealed that Hippo acts to inhibit a common growth pathway. This finding highlights the importance of proper heart size and reveals how this critical developmental pathway is maintained by the Hippo protein in organisms ranging from flies to mammals. <http://www.ncbi.nlm.nih.gov/pubmed/21512031>

*Identifying Children with Prenatal Exposure to Alcohol:* Fetal alcohol syndrome (FAS) involves a specific pattern of well-defined facial abnormalities, including small eye width, smoothing of the ridges between the base of the nose and the upper lip, and a thin upper lip border. FAS-affected children also exhibit growth deficits and cognitive impairments. The ability to detect facial features across the spectrum of alcohol-induced birth defects could enable earlier identification of children who are at high risk for cognitive impairments, especially those who are heavily exposed but lack the hallmark facial features of FAS. In a recent study conducted in collaboration with the National Institute on Alcohol Abuse and Alcoholism (NIAAA) Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD), researchers used three-dimensional photography and image analysis to examine facial characteristics of children either not exposed or heavily exposed to alcohol and compared their observations with clinically determined FAS categorizations. The researchers used a sample of children from a community clinic in Cape Town, South Africa, where the incidence of heavy alcohol use during pregnancy and FAS are among the highest in the world. The researchers found that three-dimensional facial image analyses substantially enhanced the ability to detect a broad range of alcohol-induced facial changes in children. Further testing of the techniques is planned in the United States, South Africa, and Ukraine. <http://www.nichd.nih.gov/news/releases/pages/072412-fetal-alcohol-exposure.aspx>

### **Rare Pediatric Diseases**

*New Treatment Approved for Rare Inflammatory Disease:* Neonatal-onset multisystem inflammatory disease (NOMID) is a rare but debilitating disease that strikes within the first weeks of life. If untreated, individuals with NOMID may develop hearing and vision loss, cognitive impairment, and physical disability. Previous research showed that the symptoms of NOMID were facilitated through the immune system's interleukin-1 (IL-1) signaling pathway and that blocking IL-1 with the Food and Drug Administration (FDA)-approved rheumatoid arthritis drug anakinra relieved symptoms of NOMID. Recently, intramural researchers at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) conducted a successful clinical trial demonstrating that anakinra not only improved the signs and symptoms of NOMID but also worked over the long term to stop the progression of organ damage. Based

on the trial results, in March 2013, anakinra became the first FDA-approved treatment for NOMID.

[http://www.niams.nih.gov/News\\_and\\_Events/Spotlight\\_on\\_Research/2013/anakinra\\_nomid.asp](http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2013/anakinra_nomid.asp)

*Advancing Efforts to Treat a Rare Kidney Disease:* National Human Genome Research Institute (NHGRI) scientists have overcome a major biological hurdle in an effort to find improved treatments for patients with a rare pediatric-onset disease called methylmalonic acidemia (MMA). Children with MMA are unable to properly metabolize certain amino acids in their diet, damaging a number of organs, most notably the kidneys. Using genetically engineered mice created for their studies, the research team identified a set of biomarkers of kidney damage—a hallmark of the disorder—and demonstrated that antioxidant therapy protected kidney function in the mice. Researchers validated the same biomarkers in MMA patients at the NIH Clinical Center. The biomarkers offer new tools for monitoring disease progression and the effects of therapies, both of which will be valuable in the researchers' design of clinical trials for this disease. <http://www.ncbi.nlm.nih.gov/pubmed/23898205>

*Moving Toward a New Treatment for Rare Childhood Disorder:* Neuronal ceroid lipofuscinoses, also known as Batten disease, constitute a group of hereditary neurodegenerative disorders that mostly affect children. Mutations in more than 10 genes underlie various types of Batten disease, and this list continues to grow. The infantile form of Batten disease, although rare, is a devastating, and ultimately fatal, childhood disorder. Children with this condition appear normal at birth but experience a gradual, steady loss of brain tissue. By 11 to 18 months, they have difficulty with physical coordination and begin to lose their vision. By age 4, they are typically blind and have no apparent brain activity. They may live in a vegetative state for several more years before dying. Currently, there is no effective treatment for any type of the Batten disease. Infantile Batten disease is caused by a genetic deficiency of a certain enzyme, PPT1. Scientists at the NICHD tested a new potential treatment on a strain of mice genetically modified to lack the PPT1 enzyme. When they added this new substance to the animals' drinking water, scientists observed several promising benefits to the treatment. Although the treatment did not prevent all of the damage that typically occurs in the mouse form of the disease, the treatment protected the neurons in the animals' brains, slowed the deterioration in motor coordination, and extended the animals' lifespan. Researchers will continue developing the treatment, and they hope to test it in humans ultimately.

<http://www.ncbi.nlm.nih.gov/pubmed/24056696>

*Identifying a Novel Pediatric Inflammatory Disease:* National Institute of Allergy and Infectious Diseases (NIAID) researchers and collaborators identified a novel pediatric inflammatory disease (PID) they have named PASLI (p110 delta activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency) disease. PASLI disease has been confirmed in 14 patients seen at the NIAID PID Clinic. The patients have experienced recurring infections since childhood, and some have developed Epstein-Barr virus (EBV)-associated lymphoma. Based on the cellular pathway affected by the mutation, the researchers identified rapamycin, already FDA-approved for the prevention of transplant rejection, as a treatment and are studying additional therapies. <http://www.ncbi.nlm.nih.gov/pubmed/24165795>

## *Advancing Diagnosis and Treatment for Pediatric Diseases and Conditions*

*Understanding and Treating a Common Cause of Visual Impairment in Children:* Scientists funded by the National Eye Institute (NEI) have made progress in understanding and improving treatment for amblyopia, a condition of poor vision in an otherwise healthy eye. Amblyopia, which occurs when the brain ignores one eye in favor of the other, is the most common cause of visual impairment in childhood. A study in mice revealed an elegant circuit within the developing visual system that helps to dictate how the eyes connect to the brain. By manipulating this circuit, the NEI-funded researchers were able to prevent ocular dominance in young mice and induce it in older mice. The research has implications for treating amblyopia, possibly later in life than is currently possible. Currently, the standard treatment for amblyopia is patching—covering a child’s better-seeing eye with a patch for 2 hours a day to improve vision in the weaker eye. Doctors often suggest increasing the daily duration of patching if children stop making progress, even though there have been limited data showing this approach actually works. The NEI-funded Pediatric Eye Disease Investigators Group (PEDIG) recently reported evidence that increasing patching from 2 to 6 hours a day is effective at treating persistent amblyopia. <http://www.nei.nih.gov/news/pressreleases/082613.asp>; <http://www.ncbi.nlm.nih.gov/pubmed/23975100>; [http://www.nei.nih.gov/news/briefs/eye\\_patching.asp](http://www.nei.nih.gov/news/briefs/eye_patching.asp); <http://www.ncbi.nlm.nih.gov/pubmed/?term=10.1016/j.optha.2013.04.008>

*Uncovering Genetic Factors Involved in Gliomas (Brain/Spinal Tumors):* National Cancer Institute (NCI)-supported researchers analyzed 45 tissue samples and found that the gene *MYBL1*, a transcription factor important for controlling other genes, was rearranged and missing part of its genetic message in nearly 30 percent of the diffuse low-grade gliomas categorized as grade 2 in terms of aggressiveness. The scientists went on to show that the mutated version of *MYBL1* can cause tumors in mice. *MYBL1* was not previously known to cause cancer, but a closely related gene, *MYB*, is one of the oldest “proto-oncogenes”—a normal gene that can become a cancer-causing gene. <http://www.ncbi.nlm.nih.gov/pubmed/23633565>

*Improving Chemotherapy for Children with Acute Myeloid Leukemia:* Gemtuzumab ozogamicin is an antibody-drug conjugate that targets CD33, a surface antigen that is expressed on most acute myeloid leukemia (AML) cells. An NCI-supported clinical trial for children with newly diagnosed AML found that at 3 years, event-free survival was 46.9 percent for children who received standard chemotherapy, compared with 53.1 percent for children who received standard chemotherapy plus gemtuzumab ozogamicin. <http://www.bloodjournal.hematologylibrary.org/content/122/21/355>

*Identifying Virulence of Respiratory Syncytial Virus:* Scientists supported by the NIH Office of Research in Women’s Health (ORWH) investigated the relationship between infant respiratory viral infection, particularly respiratory syncytial virus (RSV), and asthma development. They identified a novel RSV genotype that correlates with clinical disease severity, confirmed that the mutation confers pathogenicity in an animal model, and identified the molecular mechanism. The data confirm the hypothesis that some RSV strains are more virulent than others. <http://www.ncbi.nlm.nih.gov/pubmed/24455766>

*Faster Way to Measure Cortisol Could Save Time in Treating Critically Ill Children:* When critical illness stresses the body, the body responds by increasing production of cortisol, a hormone made by the adrenal gland. It is very important to identify these patients quickly, because they are at risk for critical illness-related cortisol insufficiency and could benefit from cortisol replacement therapy. One way to identify these patients is to determine the level of free cortisol in their blood. NICHD-funded researchers studied 165 critically ill children in pediatric intensive care units to find the most efficient way to measure free cortisol in blood. They compared two techniques: equilibrium dialysis and centrifugal ultrafiltration. Equilibrium dialysis is considered to be the gold standard, but it requires relatively large blood samples that must be sent to outside labs, and it takes days to get results. Centrifugal ultrafiltration requires only a small amount of blood and has a turnaround time of just 2 hours. The researchers demonstrated that centrifugal ultrafiltration provided faster results and is just as accurate as equilibrium dialysis. With a reliable, real-time way to measure cortisol, clinicians can make faster decisions about giving cortisol replacement therapy to critically ill children.

<http://www.ncbi.nlm.nih.gov/pubmed/21057361>

*Hydroxyurea Treatment for Toddlers with Sickle Cell Reduces Hospitalizations and Medical Care Costs:* NHLBI-funded researchers found that administering hydroxyurea therapy to infants and toddlers with sickle cell anemia reduced hospitalization and cut medical costs. Hydroxyurea has been approved for adults and adolescents with sickle cell disease, and the BABY HUG trial, which involved 193 children ages 9 to 18 months old when they enrolled, supported expanded use of the drug to patients across all ages. Continued concern over rising health care costs prompted the BABY HUG researchers to retrospectively assess hydroxyurea's impact on treatment cost. They calculated the estimated annual cost reduction to be 21 percent. This saving is estimated to grow as patients age and their symptoms increase in severity and frequency. The BABY HUG trial was funded by the NHLBI and the NICHD through the Best Pharmaceuticals for Children Act. <http://www.ncbi.nlm.nih.gov/pubmed/23999955>

*HIV/AIDS:* The combined efforts of the NIAID and the NICHD have continued to improve the prevention of HIV transmission from mother to child and to advance HIV/AIDS treatment in infected children. An NIAID- and NICHD-supported study identified a superior antiretroviral therapy (ART) regimen for HIV-infected children. Researchers found that a ritonavir-boosted lopinavir-based regimen was more effective for prevention of mother-to-child transmission than a nevirapine-based regimen in HIV-infected children who were not previously exposed to nevirapine. The PREDICT study is the first randomized, controlled trial to evaluate immediate versus delayed ART in children from 1 to 12 years of age first presenting for treatment. The researchers found that immediate ART did not confer a substantial benefit over delayed ART in older children with moderate immune suppression.

<http://www.ncbi.nlm.nih.gov/pubmed/23059199>

*Air Pollution Associated with Autism:* National Institute of Environmental Health Sciences (NIEHS)-funded researchers found that traffic-related air pollution and particulate matter could be associated with autism. The researchers used data from the Childhood Autism Risks from Genetics and the Environment study in California and modeled levels of traffic-related air pollution exposures using address information and Environmental Protection Agency (EPA) Air Quality System data. They found that exposure to traffic-related air pollution, nitrogen dioxide,

and particulate matter less than 2.5  $\mu\text{m}$  and 10  $\mu\text{m}$  (PM<sub>2.5</sub> and PM<sub>10</sub>) during pregnancy and the first year of life was associated with autism in children.

<http://www.ncbi.nlm.nih.gov/pubmed/23404082>

*Air Pollution and Cognitive Development:* Investigators supported by the National Institute on Minority Health and Health Disparities (NIMHD) and the NHLBI assessed the effects of perinatal exposure to traffic-related air pollution on neurobehavioral and cognitive development in urban children. Investigators examined associations between black carbon (BC), a marker of traffic particles, and attention measures at 7 to 14 years of age among 174 children in the Boston, Massachusetts, area. Investigators found that higher BC levels were associated with greater attention difficulties and slower reaction time, particularly for boys. Findings indicate the need to address childhood exposure to air pollution that may have a negative impact on children's cognitive development, which in turn may have detrimental effects on their long-term health, educational, and occupational outcomes. <http://www.ncbi.nlm.nih.gov/pubmed/23665743>

*Predicting Risk for Mental Health Problems in Children:* Problems with emotion regulation and behavior in children can indicate risk for later mental health disorders, but science's ability to predict which children will develop mental health problems is limited. In addition, behaviors that may indicate risk, such as temper tantrums or irritable mood, are a normal part of a child's development. National Institute of Mental Health (NIMH)-funded researchers recently developed a multidimensional measure that may be able to help identify where behaviors fall on the full spectrum from normal to at-risk to clinically concerning. The approach will allow parents, teachers, and clinicians to better understand when "watchful waiting," prevention efforts, or treatment may be warranted. <http://www.ncbi.nlm.nih.gov/pubmed/24342388>

*Brief Interventions for Adolescent Substance Use:* An estimated 25 percent of 12- to 18-year-olds are at risk of or in need of prevention and treatment services for "moderate" substance involvement, yet, in an overburdened treatment system, these teens often do not receive services. Adolescents who participated in two motivational interviewing sessions in addition to a cognitive behavioral-based session reported increased abstinence from alcohol and marijuana. Those who received separate counseling for parents/caregivers in addition to this treatment paradigm reported even better outcomes. This study illustrates the important role that parents/caregivers have in the life of adolescents with moderate substance involvement, and it also demonstrates the benefit of brief, cost-effective interventions. <http://www.ncbi.nlm.nih.gov/pubmed/22000326>

*Teacher-Delivered Intervention for Adolescents:* A teacher-delivered intervention program promoting healthy lifestyles improved health behaviors, social skills, severe depression, and academic performance in high school adolescents, a National Institute of Nursing Research (NINR)-supported study has found. It is one of the first studies to report multiple immediate improvements that were sustained over time using a teacher-delivered, cognitive behavioral skills-building intervention program incorporated into a high school health education class. Cognitive-behavioral skills training teaches coping techniques, social functioning skills, and problem-solving skills. Routine integration of such programs into health education curricula in high school settings may be an effective way to prevent high-risk teen populations from becoming overweight or obese and could lead to improved physical health, psychosocial skills, and academic outcomes. <http://www.ncbi.nlm.nih.gov/pubmed/24050416>

*Graduated Drivers Licensing Programs Reduce Fatal Teen Crashes:* Programs that grant privileges to new drivers in phases—known as graduated licensing programs—dramatically reduce the rate of teen driver fatal crashes, according to three studies funded by the NICHHD. Graduated licensing laws were adopted by all 50 states and the District of Columbia between 1996 and 2011. Researchers found that such programs reduced the rate of fatal crashes among 16- to 17-year-olds by eight to 14 percent. The greatest reductions in young driver crashes were seen in states that had adopted graduated driver licensing laws in combination with mandatory seat belt laws or laws requiring a loss of the driver’s license as a penalty for possession or use of alcohol by youth age 20 or younger. Limiting driving at night or with teenage passengers, in combination with graduated licensing laws, led to greater reductions in overall crash rates involving teen drivers than graduated licensing laws alone.  
<http://www.ncbi.nlm.nih.gov/pubmed/21972851>

*New Computational Model to Aid in Weight Management:* A new mathematical model predicts how weight and body fat in children respond to adjustments in diet and physical activity. NIDDK-funded researchers modified and successfully validated an existing computational model, originally designed for adults, to account for children’s unique physiology, including changes in body composition (the amounts of body fat and other body tissues) as they grow. The model suggests that there may be therapeutic windows of weight management when children can “outgrow” obesity without requiring weight loss, especially during periods of high growth potential in males who are not severely obese at the onset of treatment.

*Use of Child Safety Seats in American Indian Communities:* A community-level program to increase use of child safety seats in six northwest American Indian tribal communities has been developed with support from the NIMHD. To inform development of the program, investigators examined the use of child restraints in vehicles in Oregon, Washington, and Idaho in 2003 and 2009. Investigators observed 1,853 children age 12 years and younger in 1,207 vehicles; 49 percent rode properly restrained. Although proper restraint increased between 2003 and 2009, it remained low, and American Indian children were more likely to ride improperly restrained than were non-American-Indian children in the same communities, indicating the need for further intervention for these populations.  
<http://www.ncbi.nlm.nih.gov/pubmed/23237177?dopt=Citation>

*Reducing Unnecessary CT Scans in Children Could Cut Cancer Risk:* An NCI-supported study that examined trends in X-ray computed tomography (CT) use in children in the United States has found that reducing unnecessary scans and lowering the doses for the highest-dose (top quartile) scans could lower the overall lifetime risk of future imaging-related cancers by 62 percent. <http://www.ncbi.nlm.nih.gov/pubmed/23754213>

*Practices in Coordinated Care:* NINR-funded researchers analyzed how advanced practice registered nurses coordinated care for children with medical complexity, a subgroup of children with special health needs who suffer from complex conditions that require the use of multiple service providers. The researchers found that most episodes of care coordination were initiated by parents. The number of care coordination episodes increased during the 3-year period

analyzed, which may explain the reduction in hospitalizations that these researchers had previously reported for this group of children. <http://www.ncbi.nlm.nih.gov/pubmed/23988611>

### **Global Pediatric Health**

*Iron Supplements Did Not Increase Malaria Risk Among Children in Malaria-Prone Areas:* In sub-Saharan Africa, malaria is a major cause of childhood death and illness. Children in this region are also at risk for iron deficiency, which can impair the development of the brain and muscles. For children with iron deficiency, iron-fortified foods and supplements can enhance development and prevent severe anemia. However, research had suggested that, in areas where malaria is common, providing iron supplements could also increase the risk of malaria in young children. In 2006, the World Health Organization and the United Nations Children's Fund recommended limiting use of iron supplements among children in areas where malaria is common. This recommendation was modified in 2011; iron-fortified foods were recommended but in conjunction with measures to prevent and treat malaria. Researchers supported by the NICHD and the Gates Foundation conducted a randomized controlled trial to determine whether providing powdered nutritional supplements that included iron would increase the risk of malaria. The study was conducted among children living in a high malaria-burden area in central Ghana, West Africa. One group of children received powdered nutritional supplements that included iron, and another group received similar supplements that did not include iron. For all children in the study, insecticide-treated bed nets were provided at enrollment, as was malaria treatment when indicated. The scientists found no significant difference in the rates of malaria between the no-iron group and the group whose supplements contained iron. The results suggest that iron supplementation should be reconsidered to prevent anemia among children in areas where malaria is common. <http://jama.jamanetwork.com/article.aspx?articleid=1734705>

*New Rotavirus Vaccine for Use in India:* The NIAID partnered with the government of India, Bharat Biotech, the Program for Appropriate Technology in Health, and others to develop ROTAVAC®, the first rotavirus vaccine developed entirely in India. Results from a phase III clinical trial showed ROTAVAC® to be safe and effective. Bharat Biotech plans to file for registration of the vaccine in India. If approved, ROTAVAC® will provide a safe, effective, and affordable option for protecting infants and children in India against severe rotavirus-induced gastroenteritis. <http://www.niaid.nih.gov/news/newsreleases/2013/Pages/ROTAVAC.aspx>

*Addressing Severe Malnutrition in the Developing World:* A study of young twin pairs in Malawi showed the important role that gut microbes may play in causing severe malnutrition in children that persists in spite of nutritional interventions. The study's finding—that the combination of dietary deficiency with a particular gut microbial profile causes severe malnutrition—has far-reaching implications for developing sustainable interventions for childhood malnutrition. For example, biomarkers of microbial metabolism may need to be taken into account for the design of effective nutritional interventions in some individuals. These and other insights will be helpful in developing more effective approaches to treating and preventing the huge domestic and global challenge of childhood malnutrition. <http://www.ncbi.nlm.nih.gov/pubmed/23363771>

*Macrosomia and Birth Outcomes in South Africa:* With support from the NIH Common Fund's Medical Education Partnership Initiative, researchers have investigated risks associated with delivery of high birth weight babies in Zambia. Potential complications from high birth weight (macrosomia) delivery include perinatal mortality, birth asphyxia, and shoulder dystocia (obstruction of the infant's shoulder by the maternal pelvis). Although macrosomia is a growing concern in developed countries, much less information is available for low-income countries, where limited access to cesarean delivery may result in increased rates of maternal death from obstructed labor, sepsis, or postpartum hemorrhage. Researchers found that macrosomia was associated with increased risk for cesarean delivery and perinatal complications, including infant death and neonatal intensive care unit (NICU) admission. Risk factors for macrosomia included gestational diabetes, maternal weight, and delivery after 40 weeks of gestation. These results suggest that public health campaigns, targeted screening for risk factors, and early intervention for high-risk pregnancies may significantly reduce morbidity and mortality associated with macrosomia in sub-Saharan Africa, particularly in rural areas with limited access to medical facilities. <http://www.ncbi.nlm.nih.gov/pubmed/23669164>

*Global Cost of Lead Exposure:* Although children's blood lead levels have declined worldwide following the removal of lead in gasoline, significant exposure remains, particularly in low- and middle-income countries. NIEHS-supported researchers estimated a total cost of \$977 billion (range of \$728.6 billion to \$1162.5 billion) in low- and middle-income countries in economic costs attributable to lead exposure, amounting to approximately 1.2 percent of the world's gross domestic product (GDP). <http://science.time.com/2013/06/27/childhood-lead-exposure-may-cost-developing-countries-nearly-1-trillion/>

## **SELECTED NEW AND EXPANDED RESEARCH EFFORTS FOR FY 2013 IN PEDIATRICS**

### **Selected New Pediatric Research Efforts for FY 2013**

NIH ICs launched a range of new research programs and efforts related to pediatrics in FY 2013. Selected highlights of new initiatives are given below. Several programs are focused on understanding risk factors for complex conditions in children. However, the majority of the programs are concerned with developing and delivering evidence-based treatments.

*Autism Sequencing Consortium:* While there has been great progress in understanding the genetic differences in people with autism spectrum disorder (ASD), only a moderate number of the hundreds of genes and genomic regions thought to be involved in ASD have been identified. Starting in FY 2014, a group of NIMH-funded researchers will form the Autism Sequencing Consortium, combining forces to analyze data obtained using innovative sequencing methods to read the genomes of several different groups of individuals with ASD, to maximize the identification of genomic changes related to ASD. Understanding these changes will present opportunities for understanding the causes of ASD as well as for development of new treatments ([U01MH100233](http://www.nih.gov/research-conditions/autism-sequencing-consortium); [U01MH100229](http://www.nih.gov/research-conditions/autism-sequencing-consortium); [U01MH100209](http://www.nih.gov/research-conditions/autism-sequencing-consortium); [U01MH100239](http://www.nih.gov/research-conditions/autism-sequencing-consortium)).

*New Registry—Sudden Death in the Young:* A new collaboration between the Centers for Disease Control and Prevention (CDC), the NHLBI, and the National Institute of Neurological

Disorders and Stroke (NINDS) will create the Sudden Death in the Young (SDY) Registry by expanding the CDC's existing sudden unexpected infant death (SUID) case registry to include sudden cardiac death (SCD) and sudden unexpected death in epilepsy (SUDEP) in individuals up to age 24 in up to 15 states through 2018. By collecting comprehensive data, including biospecimens in a subset of cases, the registry will help define the scope of SCD and SUDEP in young people, develop standards for evaluating cases, and establish a resource for research on SCD and SUDEP causes and risk factors. A request for proposals (RFP) ([2013-N-15671](#)) for the registry's data coordinating center was issued by the CDC in FY 2013, and the contract was awarded to the Michigan Public Health Institute, which serves as the data coordinating center for the SUID registry. States will be able to apply for funding to participate in the registry in FY 2014, and scientists will be able to access registry data in the future to explore the causes and risk factors for sudden death in the young. <http://www.nhlbi.nih.gov/news/press-releases/2013/nih-and-cdc-launch-registry-for-sudden-death-in-the-young.html>

*Hemoglobinopathies:* The NHLBI Excellence in Hemoglobinopathies program is designed to accelerate high-impact multidisciplinary basic and translational research in hemoglobinopathies and to facilitate collaborations among basic and translational scientists and clinical hematologists. One study is fostering bench-to-bedside research to find treatment for acute chest syndrome, a complication of sickle cell disease. Researchers seek to find a drug or biological agent that will prevent, stop, or stem lung damage in children with sickle cell disease. <http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-13-005.html>

*Neurological and Kidney Problems in Infants Born Prior to 28 Weeks Gestation:* Infants born prior to 28 weeks of gestation are at high risk for death or neurodevelopmental impairment. In 2013-2014, the NINDS began funding a new clinical trial to determine whether neonatal treatment with recombinant erythropoietin (Epo) would decrease early mortality and neurodevelopmental disability in infants born prior to 28 weeks gestation. Epo is a widely available and affordable drug with promising neuroprotective properties, and it has been used safely in neonates to stimulate red blood cell production. ([U01NS077953](#); [NCT01378273](#)). The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has provided supplemental funding to collect data that will describe the natural progression of kidney function and development in this age group.

*Concussion and Head Trauma in Youth:* As a result of a \$30 million partnership between the Foundation for the NIH and the National Football League, the NIH is embarking on a series of studies focused on the long-term risks of concussion. Together, NINDS, the NICHD, and the National Institute on Deafness and Other Communication Disorders (NIDCD) will award grants totaling \$1 million for pilot and exploratory studies in new directions for research on concussion in sports. Five of the awarded projects focus on pediatric populations, including studies to better characterize sports concussion and recovery in youth, to develop applications for rapid diagnosis in athletic-event settings, to identify risk factors for poor outcomes, and to establish evidence to inform guidelines for concussion management and safe return to play. [http://www.ninds.nih.gov/news\\_and\\_events/news\\_articles/pressrelease\\_nfl\\_tbi\\_12162013.htm](http://www.ninds.nih.gov/news_and_events/news_articles/pressrelease_nfl_tbi_12162013.htm)

*Traumatic Brain Injury:* Traumatic brain injury (TBI) is a leading cause of death and disability in children and young adults. In 2013, the NINDS funded a new five-year observational study

that will enroll 1,000 children at about 40 treatment centers. Scientists will compare the effectiveness of six major critical care guidelines for which evidence is lacking and for which practices vary across centers. Findings from this study could improve clinical care for children with severe TBI and provide the foundation for more effective clinical trials of interventions. [U01NS081041-01A1](#)

*Pediatric Oncology Trials:* The following new pediatric oncology clinical trials were activated with NCI support in FY 2013:

- A phase I study of the safety and effectiveness of adoptive transfer of activated natural killer (NK) white blood cells and IL-15 in children and young adults with advanced solid tumors ([NCT01875601](#));
- A phase II study of vandetanib in children and adults with c-KIT wild type gastrointestinal stromal (GIST) tumors that will assess clinical activity of a multi-tyrosine kinase inhibitor in GIST tumors that are deficient in succinate dehydrogenase ([NCT02015065](#));
- A phase II trial of a CD30-targeted antibody-drug conjugate (brentuximab vedotin) with gemcitabine for children with relapsed/refractory Hodgkin lymphoma ([NCT01780662](#));
- An additional randomized phase II trial evaluating how well two different chemotherapy regimens (busulfan, cyclophosphamide, and melphalan or busulfan and fludarabine phosphate) work when given before donor hematopoietic cell transplant in young children with juvenile myelomonocytic leukemia ([NCT01824693](#));
- A clinical trial for children with anaplastic large cell lymphoma (ALCL) to evaluate the addition of either the ALK inhibitor crizotinib or the CD30-targeted antibody drug conjugate brentuximab vedotin to standard chemotherapy ([NCT01979536](#)); and
- A phase I trial studying the side effects and best dose of cabozantinib, which may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth, in treating younger patients with recurrent or refractory solid tumors ([NCT01709435](#)).

*New Partnership for Childhood Cancer Research:* In 2013, Stand Up To Cancer (SU2C) and the St. Baldrick's Foundation, along with the American Association for Cancer Research (AACR), SU2C's scientific partner, announced the formation of a Dream Team dedicated to childhood cancer research. John M. Maris, M.D., director of the Center for Childhood Cancer Research at the Children's Hospital of Philadelphia, will lead the Dream Team, along with co-leader Crystal L. Mackall, M.D., chief of the NCI Pediatric Oncology Branch. The project is called Immunogenomics to Create New Therapies for High-Risk Childhood Cancers. The grant will provide \$14.5 million in funding over four years and involves a team of seven leading pediatric oncology institutions within North America.

[http://www.standup2cancer.org/dream\\_teams/view/su2c\\_st\\_baldricks\\_pediatric\\_cancer\\_dream\\_team](http://www.standup2cancer.org/dream_teams/view/su2c_st_baldricks_pediatric_cancer_dream_team)

*Management Strategies for Children with Type 1 Diabetes:* The NIDDK recently released a new initiative to support research to develop, refine, and pilot test innovative strategies to improve diabetes management and quality of life in families with young children with type 1 diabetes. Given the unique challenges of managing type 1 diabetes in young children, there is a need to develop innovative and effective interventions to help families. Improved family coping, communication, and practices around diabetes management in the early stages may also provide

a buffer for some of the declines in glucose control frequently seen in adolescents and young adults. <http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-13-022.html>

*Orthotics in Pediatric Populations:* The National Center for Medical Rehabilitation Research, housed at the NICHD, developed a new initiative to support small businesses that could design, build, and test novel orthotics that capitalize on the plasticity of the neuromuscular and skeletal systems in growing children. Specially designed orthotics could help improve function for children with disabilities such as cerebral palsy, spina bifida, and muscular dystrophy. Currently, children with disabilities use as few as half of prescribed medical devices because the child outgrows them, refuses to use them, or finds them unhelpful. This number may be partly reflective of the minimal innovation in the orthotics field. Many devices have changed little in the past 40 years; they are often aesthetically unpleasing, rigid plastic and metal devices that limit clothing and shoe choices. However, innovations in plastics, sensors, and other materials show promise for improved orthotics that could benefit large numbers of children. <http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-14-029.html>

*Down Syndrome Registry:* The CDC estimates that there are about 250,000 people living with Down syndrome in the United States. The NIH Down Syndrome Working Group has partnered with public and private organizations to create a centralized, secure national resource, DS-Connect™, for storing and sharing health information about Down syndrome. The registry allows people with Down syndrome and their family members, researchers, and parent and support groups to share information and health history in a safe, confidential, online database. Users can create and edit their customizable online profiles, share their profiles with Down syndrome investigators and biorepositories, and view information about medical research and Down syndrome-related events. DS-Connect™ also provides access to general information about Down syndrome, as well as aggregate, de-identified data based on user responses to survey questions. People with Down syndrome and their families create password-protected profiles after providing online informed consent to participate in the registry. If registered users give permission to be contacted about a research study, the registry coordinator may invite eligible users to contact the clinician or researcher directly to sign up for the study or trial. The registry complies with all regulations and laws governing privacy, personally identifiable information, and health data and has been created on a Federal Information Security Management Act (FISMA) moderate platform to ensure that the health and demographic information is protected. Launched in September 2013, the registry is now planning an official launch of the professional portal to support investigators who request access to the de-identified data in the registry. <https://dsconnect.nih.gov/>

*mHealth Initiatives in Pediatrics:* Mobile devices can offer important benefits to medical practice and public health. For example, a growing body of evidence supports the effectiveness of cognitive behavioral therapy (CBT) for treatment of anxiety disorders in children and adolescents, yet access to evidence-based CBT treatments is limited. The NIMH has funded a study to assess the feasibility of a smartphone application for the delivery of CBT, paired with a web-based portal that allows therapists to monitor and communicate with patients from a distance. The goal of the intervention is to extend the availability of evidence-based strategies to children with the most commonly occurring anxiety disorders, including those in underserved communities. Similarly, parent management training is an established approach to treating

conduct problems in young children. While parent training is often delivered within therapy sessions, evidence suggests that between-session practice of new parenting skills promotes better outcomes. NIMH-funded scientists will develop and test a mobile health application that is designed to promote between-session homework and to help families practice the skills they learn in therapy. [R01MH100482](#); [R01MH100377](#);

*Juvenile Justice Initiative:* The National Institute on Drug Abuse (NIDA) Juvenile Justice Translational Research on Interventions for Adolescents in the Legal System (JJ-TRIALS) is a multisite cooperative agreement that launched in 2013. JJ-TRIALS is a seven-site cooperative research program designed to identify and test strategies for improving the delivery of evidence-based substance abuse and HIV prevention and treatment services for justice-involved youth. Virtually all justice-involved youth could benefit from HIV and substance abuse prevention and/or treatment interventions. Many evidence-based interventions targeting adolescent substance abuse and HIV screening, assessment, prevention, and treatment currently exist. Unfortunately, implementation of these interventions within juvenile justice settings is variable, incomplete, and nonsystematic at best. Seven research centers were funded as part of the JJ-TRIALS collaborative. Awardees will develop and execute collaborative multisite studies across a variety of juvenile justice settings, including juvenile probation and drug courts. These studies will provide insight into the process by which juvenile justice and other service settings can successfully adopt and adapt existing evidence-based programs and strategies to improve drug abuse and HIV service delivery for at-risk youth. <http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-13-009.html>

*Palliative Care:* In FY 2013, the NINR pilot-tested Palliative Care: Conversations Matter—a campaign to raise awareness of and improve communications about pediatric palliative care—with two hospital systems. The campaign aims to increase the use of palliative care for children living with a serious illness and their families. The campaign’s evidence-based materials (a series of video vignettes and a customizable tear-off pad in both English and Spanish) are designed to help health care providers initiate palliative care conversations with pediatric patients and their families as soon as possible following diagnosis and to continue these discussions throughout an illness to meet changing needs of patients and families. The NINR used feedback from the pilot sites to refine the materials. The health care provider materials and web resources are now available at <http://www.ninr.nih.gov/conversationsmatter>.

### **Selected Expanded Pediatric Research Efforts for FY 2013**

In addition to launching new research programs, NIH ICs built on successful programs to expand research efforts related to pediatrics. Selected highlights of expanded research efforts are given below. As with the new programs, the majority of these expanded initiatives are concerned with developing and delivering evidence-based treatments.

*Expanding Research in Undiagnosed Pediatric Diseases:* The NIH Common Fund’s [Undiagnosed Diseases Network](#) (UDN) is establishing clinical sites at academic centers across the country to aid in the diagnosis of rare and new diseases. The UDN builds upon the experience and expertise of the NIH intramural Undiagnosed Diseases Program, established in 2008, which has conducted state-of-the-art genetic and functional studies on almost 700 patients

and provided diagnoses in approximately 25 percent of the cases. Approximately 40 percent of the patients seen in the Undiagnosed Disease Program are children, many of whom present with complex pediatric genetic disorders. With the expansion of UDN to multiple clinical sites around the country, it is anticipated that many more children with rare diseases will have access to the most advanced medical and genomic approaches for diagnosis and disease management. The insights gained from understanding rare diseases may also provide important clues about the pathology and potential treatments of a host of common diseases, for both pediatric and adult patients.

*Children's Environmental Health Centers:* In FY 2013, the NIEHS and the EPA funded eight Children's Environmental Health Centers, building on previous efforts in this program. Each center includes three research projects, a community outreach translation core, and a pediatric health specialist to coordinate and translate the research within the center. The program's objectives are to capitalize on research findings and resources from epidemiological and clinical studies, enhancing application of novel findings and approaches to improve children's health; to develop and apply new or improved biomarkers, environmental measurements, models, and consideration of different exposure factors; to train new junior investigators to address emerging children's environmental health issues; and to ensure active participation of stakeholders and the broader community in the research process and translation of findings.

<http://epa.gov/ncer/childrenscenters/>

*Autism Centers of Excellence:* The NIH created the Autism Centers of Excellence (ACE) Program in 2007 with a series of five-year awards to launch an intense and coordinated research program into the causes of ASD and to find new treatments. The ACE program is funded by five NIH ICs: the NICHD, NIDCD, NIEHS, NIMH, and NINDS. The second iteration of the ACE program, launched in FY 2012, comprises (1) three centers focused on possible causes of ASD, risk and resilience in ASD, and children with ASD who have limited speech and communication; and (2) six networks focusing on causes, preventive interventions, and improved treatment, as well as ASD among females and how genetic and environmental factors are associated with the development of ASD. Two additional ACE network programs received awards in FY 2013, for a total of eight networks. One of these network projects will examine how the style, intensity, and long-term effects of an intervention benefit the development of young children with ASD. The second project will investigate gene variants associated with ASD, specifically among a subpopulation of African Americans. Data from the ACEs, along with all new NIH-funded ASD research involving human subjects, will be submitted to the NIH National Database for Autism Research. The NIH will convene the annual meeting of the principal investigators of the ACEs in the summer of 2014 to discuss research approaches and information on core instrumentation.

<http://www.nichd.nih.gov/research/supported/Pages/ace.aspx>

*Expansions in Pediatric Oncology Clinical Trials:* The NCI has expanded or activated pediatric clinical trials in 2013 through existing NCI networks or programs. For example, in 2013, the NCI's Pediatric Brain Tumor Consortium (PBTC) began a phase II clinical trial studying how well the telomerase inhibitor imetelstat sodium works in treating younger patients with recurrent or refractory brain tumors ([NCT01836549](#)), as well as a phase I trial of p28, a peptide inhibitor of p53 ubiquitination, in children with relapsed/refractory brain tumors ([NCT01975116](#)). The PBTC also activated a phase II trial of the MEK inhibitor selumetinib, focusing on low-grade

gliomas with BRAF mutations, by amending the phase I trial to include phase II expansions for molecularly designed patient cohorts ([NCT01089101](#)). The NCI-funded New Approaches to Neuroblastoma Therapy (NANT) Consortium initiated a phase I trial of lenalidomide given with ch14.18 (a monoclonal antibody targeting GD2 expressed on neuroblastoma cells) for children with refractory or recurrent neuroblastoma ([NCT01711554](#)).

*Expanding Research on a Promising Potential Treatment for Acute Lymphoblastic Leukemia (ALL):* In 2013, the NCI substantially expanded clinical experience with chimeric antigen receptor therapy for acute lymphoblastic leukemia. Using T cells genetically engineered to recognize CD19, which is universally expressed on B-ALL, an impressive complete response rate of about 70 percent was observed for patients with refractory or multiple relapsed disease treated with a single infusion of T cells. This represents a breakthrough therapy for pediatric ALL and is one of the most active immune-based therapies ever tested for cancer ([NCT01593696](#)).

*Pediatric Kidney Disease:* The NIDDK's Chronic Kidney Disease in Children (CKiD) study is a prospective cohort study of kidney disease in children and adolescents that seeks to identify risk factors for progression of disease, as well as the impact of chronic kidney disease on neurocognitive development, cardiovascular disease, and growth. The study has identified several risk factors for pediatric kidney disease, as well as early manifestations of disease. An ancillary study to CKiD to investigate genetic factors associated with progression of kidney disease in the study population has been funded. CKiD has been renewed through 2018 and expanded to allow for the recruitment of additional patients. <http://www.statepi.jhsph.edu/ckid/>

*Pediatric Liver Disease:* The NIDDK recently released a solicitation to continue its Childhood Liver Disease Research Network (ChiLDReN), which supports clinical and translational research on rare pediatric liver diseases, such as biliary atresia, Alagille syndrome, alpha-1-antitrypsin deficiency, progressive familial intrahepatic cholestasis syndromes, bile acid synthesis defects, mitochondrial hepatopathies, idiopathic neonatal hepatitis, and cystic fibrosis liver disease. The Network's efforts have been strengthened by partnerships with the Alpha-1 Foundation, the Cystic Fibrosis Foundation, and private industry. <http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-13-011.html>

*Type 1 Diabetes Network Launches New Prevention Study:* The NIDDK-led Type 1 Diabetes TrialNet is an international clinical trials network that screens large numbers of individuals (over 100,000 people to date) and conducts trials of agents to prevent type 1 diabetes in at-risk people and to slow progression of the disease in people who are newly diagnosed. TrialNet started patient enrollment in a new trial testing CTLA-4 Ig (abatacept) in the prevention of type 1 diabetes. The new prevention trial is the first prevention trial to use a nondiabetes primary endpoint—in this case, progression to dysglycemia. Use of risk progression as a trial endpoint is a novel approach and could decrease the time needed to test promising new interventions for prevention. TrialNet has two other ongoing prevention trials testing an anti-CD3 monoclonal antibody (teplizumab) and oral insulin. <https://www.diabetestrialnet.org/>

*Safe to Sleep Campaign:* Safe to Sleep® began in 1994 as the Back to Sleep campaign, with the goal of educating parents, caregivers, and health care providers about ways to reduce the risk of

sudden infant death syndrome (SIDS). The campaign works closely with and within communities to spread safe sleep messages and help reduce the risk of SIDS. In 2012-2013, the NICHD, with the support of its campaign collaborators, created the Safe to Sleep® campaign as an expansion of the Back to Sleep campaign. While the overall SIDS rate has declined, rates of other sleep-related causes of infant death—deaths that are related to where a baby sleeps or slept—have been rising. Communities saw increases in “accidental suffocation or strangulation in bed (ASSB),” strangulation, entrapment (when a baby gets caught between two objects, such as a mattress and a wall, and cannot breathe), and other accidental causes of infant death, partly because of unrecognized dangers in the baby’s sleep environment. The expanded Safe to Sleep® messages address some prenatal care and infant care issues as they relate to SIDS and provide information on ways to make babies’ sleep areas safer in terms of risks for accidental sleep-related deaths. <http://www.nichd.nih.gov/sts/Pages/default.aspx>

*Pediatric Chronic Fatigue Syndrome:* Researchers funded by the NIH ORWH will determine the prevalence of pediatric chronic fatigue syndrome (CFS) in a demographically diverse sample of participants unbiased by illness, help-seeking behaviors, or differential access to the health care system. Additionally, the researchers will assess orthostatic intolerance symptoms in a community-based sample of children with pediatric CFS, who are unbiased by help-seeking behaviors or differential access to the health care system. This is a novel approach, as existing published pediatric epidemiologic CFS studies have had limited sampling plans, resulting in systematic biases and exclusion of certain populations, impeding efforts to understand the true prevalence and nature of pediatric CFS. [R01MH072208-01A1](#)

### **Funding Opportunities in FY 2013 for Pediatric Research**

In FY 2013, the NIH issued 148 Funding Opportunity Announcements (FOAs) that specifically called for applications related to pediatric research. These FOAs are listed in Table 3 of the Appendix to this report. Much of the NIH’s pediatric research portfolio comes from investigator-initiated research, and a large number of funded grants are associated with funding opportunities that do not have a pediatric focus. However, the FOAs listed in Table 3 provide information about the range of areas that NIH ICs have taken steps to address in pediatric research. In FY 2013, the NIH issued FOAs in pediatric health disparities, diabetes, violence, underage drinking, asthma, nutrition, pediatric drug formulations, and autism, among other areas.

### **SELECTED MAJOR ONGOING NIH PROGRAMS IN PEDIATRIC RESEARCH**

The NIH supports a large number of ongoing programs in pediatric research. In FY 2013, at least 100 NIH-supported center or network programs supported pediatric research, and many other additional programs support pediatric research outside of center/network grant mechanisms. Many, but not all, pediatric research programs were focused exclusively on child health. For example, the NICHD’s 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 the NIH include some that are targeted to a specific disease or condition—the Autism Centers of Excellence, for example—and others, like the pediatric component of the Clinical and Translational Science Awards, that are not specific to any one condition. This

report highlights selected key ongoing NIH programs supporting the pediatric research community.

### **Early Development**

*Obstetric-Fetal Pharmacology Research Units (OPRU) Network:* A number of factors influence pharmacology during both normal and abnormal pregnancies, such as a lengthened period of intestinal transfer, increased cardiac output, and altered composition of plasma sex hormones. However, very little is known about the effects of these variables on drugs that are necessary for the health and well-being of pregnant women and their fetuses. The OPRU Network, funded by the NICHD, provides the expert infrastructure needed to test therapeutic drugs during pregnancy. The OPRU Network allows researchers to conduct safe, technically sophisticated, and complex studies that will help clinicians protect women's health, improve birth outcomes, and reduce infant mortality. [http://www.nichd.nih.gov/research/supported/Pages/opru\\_network.aspx](http://www.nichd.nih.gov/research/supported/Pages/opru_network.aspx)

*Studies of Epilepsy During Pregnancy:* Epilepsy is one of the most common neurological disorders affecting women of childbearing age, and poor pregnancy outcomes are more common in women with epilepsy and their children. The Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs study, supported by the NINDS and the NICHD, follows over 300 women with epilepsy recruited during pregnancy to determine the effects of common epilepsy drugs (alone or in combination) on long-term neurodevelopment in children, as well as on maternal outcomes. Results from the initial funding period of this project—associating valproate exposure with adverse cognitive and other outcomes in children—are already informing clinical practice for managing epilepsy in women of childbearing age to optimize outcomes for both mother and child ([U01NS038455](https://www.nichd.nih.gov/research/supported/Pages/epilepsy_study.aspx)).

*Birth Defects Initiative:* Funded by the NICHD, the NIAAA, the National Institute of Dental and Craniofacial Research (NIDCR), the NIDDK, the NIEHS, and the NINDS, the goal of the Birth Defects Initiative is to capitalize on genomic and other biomedical discoveries to further the understanding of the mechanisms responsible for structural birth defects, which affect almost four percent of all live births in the United States each year. The ultimate goal is to develop new, innovative, and valuable strategies for the molecular diagnosis, treatment, and prevention of human structural birth defects. The Birth Defects Initiative supports basic scientists and clinicians whose research projects span basic, translational, and clinical approaches to understanding the developmental biology and genetics of structural birth defects. Every year at their annual meeting, researchers discuss the plans for and progress of their research, exchange ideas and information, share resources, and foster synergistic collaborations that enhance Initiative goals. <http://www.nichd.nih.gov/research/supported/Pages/bdiwg.aspx>

*Prenatal Alcohol and SIDS and Stillbirth (PASS) Network:* The PASS Network is funded by the NICHD, the NIAAA, and the NIDCD. The Network is designed to conduct community-linked studies to investigate the role of prenatal exposure to alcohol in SIDS and adverse pregnancy outcomes, such as stillbirth and fetal alcohol spectrum disorders (FASDs). The Safe Passage Study, the main study conducted by the PASS Network, will enroll approximately 12,000 pregnant women from the United States and South Africa and will follow the development of their babies through pregnancy and the infants' first year of life. The long-term goals of the Safe

Passage Study are to reduce fetal and infant mortality and improve child health in communities at high risk of prenatal maternal consumption of alcohol. Another substudy within the PASS Network is designed to address hearing loss in Native American populations. The study includes auditory tests that may reveal deficits in auditory conduction and neural processing and may help scientists assess the association of hearing loss in children with possible risk factors, including prenatal exposure to alcohol. <http://www.nichd.nih.gov/research/supported/Pages/pass.aspx>

*Neonatal Abstinence Syndrome:* When newborns are exposed to opioids before birth, they can display withdrawal symptoms, such as difficulty feeding, irritability, diarrhea, and tremors, known collectively as neonatal abstinence syndrome (NAS). Current NAS treatment consists of morphine administered for four to six weeks in the hospital. Researchers funded by NIDA are conducting a clinical trial to determine whether, and what dose of, buprenorphine—an opioid medication used to treat opioid addiction in adults—is more effective than the standard morphine treatment for symptoms of NAS. Recent research demonstrating the value of buprenorphine in reducing the severity of NAS symptoms when the medication is given to pregnant opioid-addicted mothers suggests its viability as an alternative treatment. [R01DA029076](https://www.nida.nih.gov/research/supported/Pages/R01DA029076.aspx)

*Nulliparous Pregnancy Outcomes Study—Monitoring Mothers-to-Be (nuMoM2b):* nuMoM2b, which began in 2010, studies pregnant women who will be delivering for the first time (nulliparous women). This large prospective cohort study evaluates the underlying, interrelated mechanisms of several common adverse pregnancy outcomes, which can be unpredictable in women who have little or no pregnancy history to help direct their treatment. This initiative addresses a critical group of at-risk women who are currently understudied and represent 40 percent of the four million births in the United States each year. The study is primarily funded by the NICHD, with cofunding from the ORWH. An NHLBI-funded substudy of 3,600 nuMoM2b participants is examining the relationship between sleep disorders during pregnancy and adverse pregnancy outcomes. nuMoM2b is enrolling racially, ethnically, and geographically diverse pregnant women through eight clinical research sites and 12 subsites around the country. Ultimately, the study's 10,000 participants will take part in a variety of tests to identify potential mechanisms of adverse outcomes and predictive factors for the outcomes at four points during pregnancy. <http://www.nichd.nih.gov/research/supported/Pages/nuMoM2b.aspx>

*Maternal-Fetal Medicines Unit (MFMU) Network:* The MFMU Network is designed to conduct rigorous clinical trials in maternal-fetal medicine and obstetrics, particularly with respect to the continuing problem of preterm birth. The aims of the Network are to reduce maternal, fetal, and infant morbidity related to preterm birth, fetal growth abnormalities, and maternal complications, and to provide the rationale for evidence-based, cost-effective obstetric practice. The network is primarily funded by the NICHD, with cofunding from other ICs for specific projects. Current projects include an observational study of hepatitis C in pregnancy, a clinical trial to determine whether administering hyperimmune globulin for congenital cytomegalovirus (CMV) can reduce mother-to-child transmission of CMV infection, and a study to determine whether thyroxine treatment of women with subclinical hypothyroidism or hypothyroxinemia diagnosed during the first half of pregnancy is associated with an intellectual improvement in their children at age five years. <http://www.nichd.nih.gov/research/supported/Pages/mfmua.aspx>

*Neonatal Research Network (NRN):* The NRN is a collaborative network of neonatal intensive care units across the United States, comprising 18 clinical centers and a data coordinating center. Focused on newborns, particularly extremely low-birth-weight (ELBW) infants, the NRN conducts clinical trials and clinical studies in such areas as sepsis and other infections, bronchopulmonary dysplasia and other lung conditions, and necrotizing enterocolitis (NEC), a condition in which the intestines lack oxygen or blood flow. The NRN is funded primarily by the NICHD, with cofunding from other ICs for specific projects.

<http://www.nichd.nih.gov/research/supported/Pages/nrn.aspx>

*Pediatric Devices:* The NICHD and the NHLBI have joined forces on a program to foster collaboration between the clinical and bioengineering research communities to help develop safe and effective instruments and medical devices for use in newborn infants and children of all ages. The program supports the small business community in conducting innovative research that can lead to development of noninvasive or minimally invasive instruments, devices, and monitors that improve assessment, monitoring, and treatment of neonates, infants, and children of all ages who require routine as well as intensive care treatments.

<http://grants.nih.gov/grants/guide/pa-files/PAR-13-090.html>

*Global Network for Women's and Children's Health Research:* The Global Network, funded by the NICHD, supports and conducts clinical trials in resource-limited countries by pairing foreign and U.S. investigators, with the goal of evaluating low-cost, sustainable interventions to improve maternal and child health and simultaneously 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.

<http://www.nichd.nih.gov/research/supported/Pages/globalnetwork.aspx>

*Retinopathy of Prematurity:* The NEI studies a wide range of vision disorders in children. Retinopathy of prematurity (ROP) is the leading cause of treatable childhood blindness. An ongoing multicenter clinical study funded by the NEI is comparing the effectiveness of screening for ROP in at-risk infants with a telemedicine evaluation system versus the standard care performed by an ophthalmologist. Babies with low birth weights undergo both digital retinal imaging and clinically indicated indirect ophthalmoscopic examinations on the same day. The results of this study will attempt to answer the question of whether such a telemedicine system can help improve access and quality of care for ROP. [U01EY017014](#)

*Newborn Screening Translational Research Network:* Newborn screening programs across the United States currently screen more than four million infants per year. This public health program has saved countless lives through the early identification of infants who may appear healthy but who are at risk for serious disorders for which early interventions and treatments can be beneficial. After babies are born, they routinely receive a simple heel stick within the first 24 to 48 hours of life. A few drops of blood are collected on a filter paper card; using those dried

blood spots, states routinely screen newborns for at least 30 congenital disorders. The NICHD's Newborn Screening Translational Research Network (NBSTRN) is a resource for investigators engaged in newborn screening related research. It enables biomedical investigators, with appropriate institutional review board (IRB) permission and privacy protections, to access dried blood spots and other biological specimens for research, and it facilitates the development and assessment of new methods and technologies for newborn screening.

<http://www.nichd.nih.gov/research/supported/Pages/nbstrn.aspx>

### **Advancing Diagnosis and Treatment for Pediatric Diseases and Conditions**

*Food Allergy:* The NIAID supports several major food allergy clinical trials, including trials involving pediatric populations, through the Consortium of Food Allergy Research (CoFAR) (cosponsor: NIDDK), the Asthma and Allergic Diseases Cooperative Research Centers (AADCRCs) (cosponsor: NIH ORWH), and the Immune Tolerance Network (ITN).

<http://www.niaid.nih.gov/topics/foodallergy/Pages/default.aspx>

*Childhood Nutrition:* Programs in the NICHD and the NIDDK, among other NIH ICs, focus on the role of nutrition throughout the life cycle. Many of these programs include an emphasis on the needs of women of reproductive age (including pregnant and lactating women), preterm and term infants, and children through adolescence. Scientists are exploring the role of nutrients in reproduction, immune function, cognition, and behavioral development; improving understanding of the causes, potential prevention, and treatment of childhood obesity; and assessing the nutritional and developmental origins of health and disease. In addition, scientists are continuing to assess the nutritive and other qualities of breast milk. Among the important components of breast milk is a group of compounds called oligosaccharides, short chains of sugar molecules joined together by chemical bonds. Previous research, including NICHD-supported work, has indicated that these compounds play an important role in developing an infant's natural defenses against bacteria and viruses that infect the intestines. Oligosaccharides and their related components may also prove useful as a basis for developing novel preventive and therapeutic agents that inhibit disease by various pathogens.

<http://www.nichd.nih.gov/about/org/der/branches/pgnb/Pages/overview.aspx>;

<http://www.niddk.nih.gov/about-niddk/research-areas/Pages/digestive-diseases-nutrition.aspx>

*Obesity in Pregnancy and Childhood:* The Hyperglycemia and Adverse Pregnancy Outcome Follow-Up Study (HAPO-FUS), cosponsored by the NIDDK and the NICHD, is determining whether maternal glucose levels during pregnancy are associated with later obesity or adverse metabolic or cardiovascular status in offspring of mothers with well-characterized pregnancies, in addition to looking at maternal outcomes. Because maternal obesity and excessive weight gain during pregnancy are linked to adverse health consequences in mothers and offspring, the NIDDK, with other IC partners, started the Lifestyle Interventions for Expectant Moms (LIFE-Moms), a set of studies of lifestyle interventions in overweight and obese pregnant women designed to control gestational weight gain and improve metabolic outcomes for the women and their offspring. The NIDDK continues to support a multicenter observational study in teens, called the Teen Longitudinal Assessment of Bariatric Surgery (Teen-LABS), to collect data on the longer-term risks and benefits of bariatric surgery in obese adolescents. In addition to investigating surgical outcomes, another broader goal of Teen-LABS is to understand better the

etiology, pathophysiology, and behavioral aspects of severe obesity in youth and how this condition affects human beings over time. [U01DK094830](#)

*Childhood Diabetes:* The NIDDK study, The Environmental Determinants of Diabetes in the Young (TEDDY), is working to determine the infectious agents, dietary factors, or other environmental conditions that trigger type 1 diabetes in genetically susceptible individuals, which could inform future efforts to prevent type 1 diabetes. This long-term study is following more than 8,000 genetically susceptible children from birth until age 15. Children enrolled in the study are developing autoimmunity and type 1 diabetes at the predicted rates. Pilot studies to address questions related to the etiology and pathogenesis of islet immunity and type 1 diabetes are under way in the following areas: diet, microbiome, and virome; genes and gene expression; and metabolome. The Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) study was a randomized, controlled, comparative effectiveness trial with three treatment arms (metformin alone, metformin with lifestyle intervention, or metformin with rosiglitazone). NIDDK will continue to follow the TODAY cohort to track the progression of type 2 diabetes and related comorbidities and complications as the participants transition to young adulthood. This research is critical for preventing a potential public health crisis since the TODAY data suggest that individuals who develop type 2 diabetes during adolescence may be at risk for developing vascular complications, including cardiovascular disease, in the prime of their lives. <http://teddy.epi.usf.edu/>; <http://www.niddk.nih.gov/news/research-updates/Pages/course-type-2-diabetes-complication-onset-youth-today.aspx>

*HIV/AIDS:* The NICHD, the NIAID, and other ICs support and conduct domestic and international research related to HIV infection and its complications in infants, children, and adolescents. For example, the NICHD and other ICs support the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN), the only national, multicenter research network devoted to the health and well-being of HIV-infected and at-risk adolescents and young adults. As the HIV epidemic has evolved in the United States and globally, the NIH has ensured that research reflects these changes and addresses important research opportunities and gaps as they arise. The NICHD and the NIAID address research gaps related to many HIV-associated co-infections—such as tuberculosis, hepatitis, and malaria—in children and pregnant women. The NIAID and the NICHD support studies to determine the optimal antiretroviral regimen for reducing mother-to-child HIV transmission during pregnancy, labor and delivery, and breastfeeding ([NCT01061151](#)). The International Maternal Pediatric Adolescent AIDS Clinical Trial Network (IMPACT) includes both a domestic research agenda and an international research agenda. The domestic research agenda includes a focus on evaluating the pharmacokinetics, safety, optimal dosing, and long-term complications of new antiretroviral (ARV) therapies for HIV/AIDS in pediatric and adolescent populations. The international research agenda includes a focus on the prevention of mother-to-child HIV transmissions and reduction of maternal and infant HIV/AIDS morbidity and mortality through studies such as Promoting Maternal and Infant Survival Everywhere (PROMISE). <http://www.nichd.nih.gov/research/supported/Pages/atn.aspx>; <http://www.nichd.nih.gov/research.supported.pages.impact.aspx>

*Pediatric Cancer:* The NCI supports a comprehensive research program for children with cancer, ranging from basic molecular projects to preclinical testing and clinical trials to

epidemiological studies to identify potential factors associated with childhood cancer development. One of this research program's ultimate goals is to identify more effective and less toxic treatments so that all children diagnosed with cancer can survive their cancer and grow to become healthy adults. Ongoing research initiatives include the following:

- The Pediatric Brain Tumor Consortium (PBTC), a multidisciplinary cooperative research organization devoted to identifying superior treatment strategies for children with primary brain tumors (recently approved for an additional five-year funding period that started in April 2014); <http://www.pbtc.org/>
- The International Childhood Cancer Cohort Consortium, which allows researchers to follow 11 cohorts of more than 70,000 children to explore risk factors for cancer; <https://communities.nci.nih.gov/i4c/default.aspx>
- The Childhood Cancer Survivor Study (CCSS), which addresses the long-term effects of cancer and cancer therapy in more than 14,000 survivors of childhood cancer and approximately 4,000 siblings of survivors; <https://www.cancer.gov/cancertopics/copying/survivorship/ccss>
- The Pediatric Preclinical Testing Program (PPTP), which identifies new, more effective agents for treating childhood cancers and has tested more than 50 agents in the past 5 years, with several PPTP-tested agents moving into clinical testing; <http://pftp.nchresearch.org/>
- The Pediatric Oncology Branch in the NCI's Center for Cancer Research, which conducts high-risk, high-impact basic, translational, and clinical studies; <http://pediatrics.cancer.gov/>
- The Children's Oncology Group, part of the NCI National Clinical Trials Network, that develops and coordinates pediatric cancer clinical trials that are available at over 200 member institutions, including cancer centers throughout the United States and Canada; <http://www.childrensoncologygroup.org/> and
- The Childhood Cancer TARGET (Therapeutically Applicable Research to Generate Effective Treatment) Initiative, a public-private partnership harnessing genomics technology to identify molecular targets to diagnose and treat childhood cancers more precisely, effectively, and safely than ever before. To date, the initiative has led to two clinical trials for new drugs against childhood tumors and identified numerous new mutations and chromosomal abnormalities associated with pediatric tumors. <http://ocg.cancer.gov/programs/target>

*Organ Transplantation:* Cofunded by the NIAID and the NHLBI, the Clinical Trials in Organ Transplantation in Children (CTOT-C) is a multisite consortium established to focus on specific problems associated with transplantation in children. The CTOT-C conducts clinical trials with associated studies of immune mechanisms for all types of pediatric solid organ transplantation. The goal of these studies is to improve short- and long-term graft and patient survival in children who have undergone heart, lung, or kidney transplantation. <https://www.ctotc.org>

*Collaborative Pediatric Critical Care Research Network (CPCCRN):* The technology, therapeutic agents, and strategies for treatment and life support in childhood critical illness and injury have evolved rapidly during the past 2 decades. Children with illnesses and injuries who were once thought to be beyond the reach of modern medicine now survive in large numbers in multidisciplinary pediatric intensive care units (PICUs). Although mortality in U.S. PICUs has

fallen precipitously, survivors of childhood critical illness and injury remain at risk for morbidity and disability. Pediatric critical care practice has evolved rapidly, but most of this development has occurred without the benefit of descriptive studies that might enable translational understanding of the pathophysiology of life-threatening illnesses and injuries in childhood. Focused on critically ill infants and children, the NICHD's 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. The 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. <http://www.nichd.nih.gov/research/supported/Pages/cpccrn.aspx>

*Febrile Seizures:* the NINDS supports an ongoing, prospective study following approximately 200 children who experienced a prolonged seizure during fever, called febrile status epilepticus (FSE). The study seeks to clarify the association between FSE and subsequent epilepsy or other adverse neurological outcomes, as well as to identify biomarkers that may predict which children are most at risk. So far, the study has reported brain imaging (magnetic resonance imaging [MRI]) and activity (electroencephalography [EEG]) features indicating that for some children, FSE may injure the brain; and for others, pre-existing abnormalities could increase susceptibility to FSE. The investigators will continue to follow the children to determine how these or other markers relate to long-term outcomes, including the development of epilepsy. ([R37NS043209](#))

*Pediatric Migraine:* More than six million children and adolescents experience migraine headaches, which can result in significant disability due to absence from school and impacts on family and social function. No medication is FDA-approved for preventing migraine in children and adolescents, and treatment is often based on what works in adult populations, with limited evidence regarding the most effective approaches for younger patients. The Childhood and Adolescent Migraine Prevention (CHAMP) study is a multisite, randomized, controlled trial that aims to determine the safety, tolerability, efficacy, and comparative efficacy of two commonly prescribed medications—amitriptyline and topiramate—for preventing migraine headaches in children and adolescents. ([U01NS076788](#); [NCT01581281](#))

*Primary Immune Deficiency Diseases:* Pediatric research in the NIAID intramural research program is primarily focused on investigations of congenital immune defects, development of vaccines for childhood diseases, and studies of infectious diseases with increased severity in children. The NIAID Primary Immune Deficiency (PID) Clinic is the focal point for studies of the genetics, pathophysiology, and treatment of chronic granulomatous disease, common variable immunodeficiency, DiGeorge syndrome, hyperimmunoglobulin E syndrome, severe combined immunodeficiency, and many other PID diseases. Research and development of vaccines against rotaviruses, herpesviruses (varicella-zoster virus, cytomegalovirus, and EBV), malaria, and major pediatric respiratory pathogens for which no vaccines currently exist (RSV, parainfluenza viruses) are ongoing in NIAID labs. The NIAID also conducts basic and clinical investigations of allergic diseases, pediatric-onset mastocytosis, and the immunology and pathogenesis of severe malaria in children. <http://www.niaid.nih.gov/topics/immunodeficiency/Pages/Default.aspx>

*Pediatric Rheumatology Clinic:* The NIH Pediatric Rheumatology Clinic, supported by the NIAMS, is a specialty-care medical facility dedicated to evaluating and treating children with pediatric rheumatic diseases who are enrolled in clinical trials. Since the causes of these diseases are unknown, the NIH also seeks a better understanding of why some children develop them. In the clinic, medical staff diagnose and treat children with arthritis, periodic fever syndromes, lupus, and other rheumatic diseases.

[http://www.niams.nih.gov/Health\\_Info/Pediatric\\_Diseases/default.asp](http://www.niams.nih.gov/Health_Info/Pediatric_Diseases/default.asp)

*Asthma:* The NIAID supports the Inner-City Asthma Consortium to develop clinical trials that evaluate the safety and efficacy of immune-based therapies to reduce asthma severity and prevent disease among children living in inner-city environments. A longitudinal, prospective study of a birth cohort of 606 inner-city children (the Urban Environment and Childhood Asthma study) is examining the immunologic causes of recurrent wheezing and asthma. Another clinical trial, to be completed in early 2014, is comparing short-term (four to five months) use of Xolair (omalizumab) with short-term boosts of inhaled steroids to protect against seasonal exacerbations of asthma. The Asthma Phenotype in the Inner City (APIC) study, a yearlong longitudinal study of more than 700 children and adolescents with asthma, is collecting information on response to treatment and clinical and immunology markers to identify different types of asthma. <http://www.niaid.nih.gov/topics/asthma/Pages/default.aspx>

*Otitis Media:* Otitis media (OM), or middle ear infection, is one of the most common reasons for an infant to visit a doctor: 75 percent of children experience at least one episode of OM by their third birthday, and almost half of these children will have three or more ear infections during their first three years, leading to billions of dollars in medical costs and lost wages. The NIDCD supports a wide variety of studies to develop new treatments for chronic and recurrent OM. These studies examine the bacterial pathogenesis and human immune responses following infection, how genetic risk factors make individuals more or less susceptible to OM, and whether environmental factors could reduce OM risks in children with genetic predisposition. The NIDCD also supports research on the delivery of drugs to the middle ear and studies that seek to develop vaccines against OM.

<http://www.nidcd.nih.gov/health/hearing/pages/earinfections.aspx#11>

*Oral Health Disparities Centers:* Early childhood caries (ECC) is the most prevalent chronic childhood disease in the United States, particularly among economically disadvantaged, underserved children. Three centers, supported by the NIDCR, are conducting four large community-based randomized clinical trials to understand, prevent, and reduce oral health disparities, with a focus on preventing ECC. The studies are enrolling participants from American Indian communities, Hispanic communities in Southern California, and public housing projects in Boston. [http://nidcr.nih.gov/Research/NIDCR\\_Centers\\_and\\_Research\\_Networks/CentersforResearchtoReduceDisparities/](http://nidcr.nih.gov/Research/NIDCR_Centers_and_Research_Networks/CentersforResearchtoReduceDisparities/)

*Children with Cleft Palate:* Individuals with cleft lip and/or palate (CLP) have multiple special needs including speech and language problems, facial differences, atypical dental development, malocclusion, learning disabilities, chronic ear infections, and associated psychosocial sequelae. The goal of one NIDCR-supported study is to improve the understanding of quality of life (QoL) and related issues among youth with CLP who are between 8 and 18 years old and who are

undergoing secondary corrective surgery. This study may provide insight into how effective cleft habilitation is at improving oral health-related QoL and overall QoL, and it may identify subgroups where targeted interventions are most needed. Another NIDCR study explores provider and family communication as they decide on treatment options for children with CLP. [R01DE018729](#)

*Rare Diseases Clinical Research Network:* Led by the National Center for Advancing Translational Sciences (NCATS) and cofunded by six other ICs, the Rare Diseases Clinical Research Network conducts collaborative clinical research in rare diseases, including longitudinal studies of individuals with rare diseases, clinical studies, and/or clinical trials. Many of the rare diseases studied under this network occur primarily or frequently in children, including primary immune deficiency diseases, urea cycle disorders, mitochondrial diseases, lysosomal diseases, and Angelman, Rett, and Prader-Willi syndromes. <http://rarediseases.info.nih.gov/research/pages/41/rare-diseases-clinical-research-program>

*Intellectual and Developmental Disabilities Research Centers (IDDRCs):* The NICHD's IDDRCs program supports researchers whose goals are to advance understanding of a variety of conditions and topics related to intellectual and developmental disabilities (IDDs). The program relies on a core grant mechanism to fund infrastructure research cores that support independently funded, IDD-relevant projects, as well as a small portion of new program projects. This structure allows the centers to support substantially more projects and investigators than would be possible using NICHD support alone. Centers offer different research services, including information technology, bioinformatics, and biostatistics, as well as gene array, proteomics, and behavioral and clinical core services. Many studies involve collaborations with researchers outside the program to leverage multiple funding sources. <http://www.nichd.nih.gov/research/supported/Pages/eksidddrc.aspx>

*Muscular Dystrophy Research Centers:* Cofunded by the NICHD, NINDS, NIAMS, and NHLBI, the Wellstone Muscular Dystrophy Research Centers are designed to foster the translation of new scientific findings and technological developments into novel treatments for muscular dystrophies (MDs). The Centers promote basic, translational, and clinical research and provide important resources that can be used by the national muscle biology and neuromuscular research communities. Each Center serves as a focal point for research collaborations in the field and provides training and advice about MDs for basic and clinical researchers. The Centers also engage patients and patient advocates in educational programs. Centers include one or more scientific research resource cores that support the specific projects and serve as a resource for the international research community. <http://www.nichd.nih.gov/research/supported/Pages/mdcrc.aspx>

*Learning Disabilities:* The NICHD supports the Learning Disabilities Research Centers (LDRC) Consortium, a program to develop knowledge on the causes, origins, and developmental course of learning disabilities. The LDRC Consortium addresses learning disabilities that affect reading and writing, including basic reading skills, reading fluency, reading comprehension, and written expression. Complementing the LDRC Consortium, the Learning Disabilities Innovation Hubs focus on understudied research topics and on 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. <http://www.nichd.nih.gov/research/supported/Pages/ldr.aspx>; <http://www.nichd.nih.gov/research/supported/Pages/ldhubs.aspx>

*Vaccine Research:* NIAID's Vaccine and Treatment Evaluation Units (VTEUs) conduct studies of seasonal and pandemic influenza vaccines in at-risk populations, including children and pregnant women. The VTEUs are also evaluating the combined tetanus, diphtheria, and pertussis (Tdap) vaccine in pregnant and postpartum women. In 2012, NIAID VTEUs completed a clinical trial that found that the Tdap vaccine is safe and immunogenic in pregnant women, and babies born to women vaccinated antepartum had higher levels of antibodies than did babies born to women vaccinated postpartum. Another VTEU study is evaluating Tdap in postpartum women ([NCT01711645](https://clinicaltrials.gov/ct2/show/study/NCT01711645)). Pediatric Research in the NIAID intramural research program focuses on the development of vaccines for childhood diseases, as well as studies of infectious diseases with increased severity in children. Research and development of vaccines against rotaviruses, herpesviruses (varicella-zoster virus, cytomegalovirus, and EBV), malaria, and major pediatric respiratory pathogens for which no vaccines currently exist (RSV, parainfluenza viruses) are ongoing in NIAID labs. Building on their previous work describing the atomic structure of a metastable viral surface protein, scientists at the NIAID Vaccine Research Center used the structural information to design stabilizing mutations and produced a vaccine antigen that elicited high levels of RSV-specific neutralizing antibodies when tested in animals. Early-stage human clinical trials of the candidate vaccine are planned in the next several years.

*Substance Abuse:* The NIDA and the NIAAA continue to fund multiple programs addressing substance abuse specifically among adolescents. For example, in the Neurobiological Mechanisms and Impulse Control in Adolescence study, NIDA-funded researchers seek to identify the relationships between brain maturation (frontostriatal circuitry), impulse control, and substance use involvement across adolescent development to predict onset and severity of substance use. Integrating knowledge about brain development, adolescent behavior, and substance abuse can advance scientists' understanding of risks and consequences of adolescent substance use to inform effective treatment and prevention strategies. Other research programs in this area have a more clinical focus. For example, a treatment modality for adult substance abuse, known as adaptive treatment (AT), has demonstrated the value of giving people who respond poorly to an initial evidence-based treatment a different or more enhanced version of the same treatment. An ongoing study is now expanding AT to research on youth substance abuse treatment, addressing factors such as differing responses to treatment, poor responders, and relapse prevention across various treatment modalities. [R01DA033997](https://clinicaltrials.gov/ct2/show/study/R01DA033997); [R01DA030454](https://clinicaltrials.gov/ct2/show/study/R01DA030454)

### **Cross-Cutting Areas of Pediatric Research**

*Pediatric Pharmacology and the Best Pharmaceuticals for Children Act:* Federal legislation and FDA regulations require that drugs be tested for safety and efficacy in a specific population, at a specific dosage, and for a specific time period before the drugs are approved for clinical use. Use of drugs without appropriate testing is considered "off-label" use. Testing drugs in children presents considerable 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 incentives for companies to study drugs in neonates, infants, and children; lack of necessary technology to monitor patients and assay very small amounts of blood; and lack of a suitable infrastructure for conducting pediatric pharmacology drug trials. As a result, the majority of drugs used in children today are used off label, without adequate understanding of appropriate dose, safety, or efficacy.

The Best Pharmaceuticals for Children Act (BPCA), signed into law in 2002 (P.L. 107-109) and reauthorized in 2007 and 2012, directs the Secretary of HHS, acting through the Director of the NIH, to establish a program for pediatric drug testing and development. The NIH Director delegated the authority and responsibility for establishing and conducting this program to the Director of the NICHD. In 2012, the BPCA was reauthorized as part of the FDA Safety and Innovation Act (P.L. 112-144). Among other things, the legislation refined the earlier BPCA mandate, directing the Secretary, acting through the Director of the NIH and in consultation with the Commissioner of Food and Drugs and experts in pediatric research, to develop and publish a priority list of needs in pediatric therapeutics, including drugs or indications that require study (Section 409I, Public Health Service Act). In the prioritization of drugs and pediatric conditions, the NICHD consults annually with experts in pediatrics, colleagues at the participating ICs at the NIH, and colleagues at the FDA to identify drugs that are used in pediatric care and for which studies would have public health benefit. The NICHD continues to seek collaborative opportunities and to establish partnerships with other ICs to achieve the stated goal of the Act—“to improve the safety and efficacy of pharmaceuticals for children”—by increasing knowledge of the conditions affecting children and the drugs used to treat those conditions (P.L.107-109). BPCA activities are authorized at the NIH through FY 2017 at \$25,000,000 annually (Section 409I(e)(1), Public Health Service Act).

The NICHD supports the Specialized Centers in Research in Pediatric Developmental Pharmacology (RPDP) program to advance the science of pediatric pharmacology. The program’s overall goals are to:

- Investigate the fundamental mechanisms of changes in drug disposition and response over the course of human development from birth through adolescence.
- Provide an arena for multidisciplinary interactions between basic and clinical scientists who are interested in establishing high-quality translational research programs in pediatric pharmacology.
- Serve as national resource for training and career development of new scientists electing to pursue careers in the conduct of translational research in high-priority areas of pediatric developmental pharmacology.
- Facilitate important community outreach and education efforts to increase awareness and convey the importance and implications of the research activities to the general public.

The RPDP program is designed to establish predictive nonclinical models, including animal studies; cell-, tissue-, and organ-based systems; computational and systems modeling; and integration of signals and information from multiple systems to evaluate response- and age-specific toxicity, particularly neurologic and behavioral effects. The program performs nonclinical and clinical research to understand mechanisms of age- and developmentally related changes in metabolism and response to medicinal products, and it develops outcome and assessment measures that are age-appropriate to determine response or toxicity. The FDA is

working closely with the NIH to maximize the success of this important program.  
<http://bpca.nichd.nih.gov/Pages/Index.aspx>; <http://www.nichd.nih.gov/research/supported/Pages/scrpdp.aspx>

*Development of Pediatric Outcomes Measures:* The Common Fund's Patient-Reported Outcomes Measurement Information System (PROMIS) program aims to develop a rigorously tested and validated system for measuring patient-reported outcomes across a variety of physical, mental, and emotional dimensions. One aspect of the PROMIS program is a focus on the development of measures that are appropriate and relevant for pediatric patients suffering from a variety of diseases, including cancer, asthma, and pediatric chronic pain syndromes. Pediatric patient-reported outcome measures will advance the science of pediatric clinical trials, inform our understanding of childhood diseases, and elucidate the effects of pediatric health care.  
<http://www.nihpromis.org/science/pediatricmethodology>

*Pediatric Research at the NIH Clinical Center:* The NIH Clinical Center continues to support a broad clinical research portfolio in pediatrics. In FY 2013, fifteen Institutes admitted 3,326 pediatric patients to the Clinical Center as part of 262 research protocols. These children were seen in 12,575 pediatric outpatient visits on 10,354 outpatient days and accounted for 578 inpatient admissions, for 5,486 pediatric inpatient days. Compared with FY 2012, this was a 3-percent increase in outpatient appointments, a 4.3-percent increase in admissions to the pediatric psychiatric unit, and a 10-percent increase in average length of stay for inpatients. Children under age 18 years represent more than 10 percent of all Clinical Center inpatient activity and approximately 11 percent of all Clinical Center outpatient visits. The Clinical Research Center's pediatric unit, which supports multiple NIH ICs, includes 22 beds and 14 day hospital stations, a six-bed pediatric behavioral health inpatient unit plus room for two day patients, and a multi-Institute pediatric outpatient clinic with 21 patient care rooms. In FY 2004, to accommodate the growing number of pediatric intramural research subjects, the Children's Inn at the NIH completed its first expansion. Now almost doubled in size, the family-centered residence can care for 59 families every night. In FY 2013, 1,566 families stayed 13,000 nights at the Inn and its associated facility, the Woodmont House, a transitional home that was opened in FY 2011 to accommodate up to seven families requiring longer stays. Since 1990, over 12,000 families, from all 50 states and 84 countries, have stayed at the Inn and the Woodmont House.  
<http://www.cc.nih.gov/>

*Clinical and Translational Science Awards:* The NCATS Clinical and Translational Science Award (CTSA) program offers academic homes for translational sciences and supporting research resources needed by local and national research communities to improve the quality and efficiency of all phases of translational research, including clinical trials. CTSA centers also support the training of clinical and translational scientists and the development of all disciplines needed for a robust workforce for translational research. The CTSA program includes a special provision to support pediatric research, allowing a pediatric principal investigator to be appointed within a single CTSA with a separate budget and infrastructure for child health clinical research. Eight CTSA centers are headed by principal investigators who are also pediatricians, and 51 centers included children's hospitals conducting pediatric research as partners in their CTSA applications. Of the 62 CTSA, 57 support one or more pediatric investigators' participation in the CTSA Consortium Child Health Oversight Committee, a leadership

committee charged with sharing best practices and promoting collaboration. The CTSA program has supported a large number of pediatric studies, including scientific areas and conditions such as peanut allergy, newborn screening, Niemann-Pick type C1, fragile X, rare muscle diseases, cystic fibrosis, and Charcot-Marie-Tooth disease (a rare neurological disorder with no known cure). <http://www.ncats.nih.gov/research/cts/cts.html>

### **Research Training, Career Development, and Loan Repayment**

*Child Health Research Career Development Awards (CHRC):* The CHRC program was created to fill the gap in training for junior faculty who intend to devote their careers to academic pediatrics. The program provides funding for sustained mentoring and laboratory-based training and offers the vital foundation to compete for grant funding. During the past two decades, the NICHD has funded 780 pediatric investigators working in 15 different subspecialty areas of pediatrics in 38 pediatric departments throughout the United States. A majority of the scholars have remained in academic pediatrics and, through their independent research programs, they have trained countless undergraduate, graduate, and postdoctoral trainees who have contributed substantially to knowledge of childhood diseases. Many hold important leadership positions in their fields. <http://www.nichd.nih.gov/research/supported/Pages/chrcda.aspx>

*Pediatric Scientist Development Program (PSDP):* The NICHD established the PSDP to provide scientific research experience (particularly in basic science areas) for pediatricians wishing to pursue careers in academic medicine. The PSDP has provided research training for more than 175 scholars across the country. Many PSDP scholars have gone on to strong research careers and have received subsequent NIH funding in pediatric research. <http://www.cincinnatichildrens.org/education/research/psdp/default/>

*Neurological Sciences:* The NINDS Neurological Sciences Academic Development Award is designed to support the research career development of pediatric neurologists at educational institutions or professional organizations who have made a commitment to independent research careers. The FOA for this initiative was reissued in FY 2013, following prior releases in FYs 2003, 2008, and 2010. The NINDS currently funds awards to nine institutions through this program, and each institution may support up to three research scholars. [http://www.ninds.nih.gov/funding/k12\\_institutions.htm](http://www.ninds.nih.gov/funding/k12_institutions.htm)

*Pediatric Research Training in Pakistan:* Infectious diseases are the biggest killers of children in Pakistan, causing 60 percent of all deaths of children under five years of age. Since 2006, the John E. Fogarty International Center (FIC) has supported a grant with the Department of Pediatrics and Child Health at the Aga Khan University in Pakistan, that also includes the CDC and Emory University, to train Pakistani master's students to conduct research related to vaccine-preventable childhood illnesses and neonatal infections. The goal is to create a cadre of individuals who will provide the research, leadership, and passion needed to reduce the burden of childhood infections in Pakistan. The efforts of the team were recognized in December 2013 when FIC researcher Dr. Anita Zaidi was awarded the Caplow Children's Prize, the largest award dedicated to reducing global child mortality. <http://childrensprize.org/>

*Pediatric Critical Care and Trauma Scientist Development Program:* The NICHD Pediatric Critical Care and Trauma Scientist Development Program is a national faculty training program that develops successful pediatric critical care and pediatric trauma physician scientists. The goal of the program is to increase the number of highly trained, successfully funded, and sustainable pediatric critical care and pediatric trauma physician scientists who will conduct research to enhance the scientific understanding, clinical management, and long-term outcome of critical illness and trauma in children. <http://www.pccsdp.org/>

*Pediatric Loan Repayment Program:* The NIH's Loan Repayment Program is designed to further recruitment and retention of highly qualified health professionals in careers in scientific research. Within the overall NIH Loan Repayment Program, there is a special program to promote pediatric research. Under the program, the NIH repays a portion of the educational loan debt incurred to pay for the researcher's undergraduate, graduate, and/or health professional school educational expenses. More than 1,000 individuals received assistance under this program from 2008 to 2013. [http://www.lrp.nih.gov/about\\_the\\_programs/pediatric.aspx](http://www.lrp.nih.gov/about_the_programs/pediatric.aspx)

## **APPENDIX**

Table 1: All NIH Pediatric Research, FY 2013

Table 2: Pediatric Research Initiative, FY 2013

Table 3: NIH Funding Opportunity Announcements That Solicited Applications for  
Pediatric Research, FY 2013

Table 4: Acronyms for NIH Institutes, Centers, and Offices and Other Federal Agencies  
Referred to in This Report

**Table 1: All NIH Pediatric Research, FY 2013**

The totals below were derived from NIH's 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 the NIH's best estimates based on the category definitions. The 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. A list of NIH-funded grants and projects in pediatric research is available at

<http://report.nih.gov>

[/categorical\\_spending\\_project\\_listing.aspx?FY=2013&ARRA=N&DCat=Pediatric](http://report.nih.gov/categorical_spending_project_listing.aspx?FY=2013&ARRA=N&DCat=Pediatric). The term "Roadmap" refers to research funded through the Office of Strategic Coordination, OD, NIH, to address key scientific issues that no one IC is positioned to address alone.

	Fiscal Year 2013
FIC	\$4,789,110
NCATS	\$32,171,132
NCCAM	\$4,497,781
NCI	\$276,880,479
NEI	\$37,908,035
NHGRI	\$49,194,858
NHLBI	\$289,531,157
NIA	\$13,060,884
NIAAA	\$111,655,560
NIAID	\$246,905,283
NIAMS	\$47,408,907
NIBIB	\$7,151,813
NICHD	\$651,447,718
NIDA	\$168,617,306
NIDCD	\$71,184,886
NIDCR	\$64,596,885
NIDDK	\$160,501,488
NIEHS	\$116,559,552
NIGMS	\$50,519,550
NIMH	\$367,227,490
NIMHD	\$27,468,641
NINDS	\$161,964,612
NINR	\$25,031,690
NLM	\$1,429,164
OD	\$158,447,570
Roadmap	\$29,015,460
Type 1 Diabetes	\$91,246,737
NIH Total	\$3,266,413,748

***Table 2: Pediatric Research Initiative, FY 2013***

*Definition of PRI research:* Congress did not appropriate any funds to the NIH specifically for carrying out the PRI. For reporting purposes, PRI research is defined as new or significantly expanded pediatric research funded in the reporting year under FOAs for which ICs had set aside specified amounts of available funds. “Significant expansions” may include substantial increases in funding to expand an existing IC initiative beyond that for which funds were originally committed. For example, an expansion could add another grant or site to an existing initiative, expand or add a pediatric population to an existing intramural or extramural study, or launch a new pediatric clinical drug trial or other pediatric research within an established research infrastructure. This definition is consistent with congressional intent that the PRI be supported with dedicated, identifiable dollars that expand support for pediatric research. Table 2 below provides funding by NIH IC for research that meets this definition. A list of NIH-funded grants and projects for the PRI is available at [http://report.nih.gov/categorical\\_spending\\_project\\_listing.aspx?FY=2013&ARRA=N&DCat=Pediatric%20Research%20Initiative](http://report.nih.gov/categorical_spending_project_listing.aspx?FY=2013&ARRA=N&DCat=Pediatric%20Research%20Initiative).

	Fiscal Year 2013
FIC	\$10,000
NCATS	\$396,180
NCCAM	\$54,750
NCI	\$17,465,341
NEI	\$243,265
NHGRI	\$6,203,729
NHLBI	\$8,090,271
NIA	\$11,051,148
NIAAA	\$1,355,240
NIAID	\$4,115,159
NIAMS	\$1,154,696
NIBIB	\$29,822
NICHD	\$26,587,988
NIDA	\$28,716,576
NIDCD	\$111,620
NIDCR	\$12,616,651
NIDDK	\$6,506,881
NIEHS	\$20,247,840
NIGMS	\$290,499
NIMH	\$20,811,518
NINDS	\$818,879
NINR	\$2,615,733
OD	\$2,646,077
Roadmap	\$6,558,190
Type 1 Diabetes	\$79,305,524
NIH Total	\$258,003,577

**Table 3: NIH Funding Opportunity Announcements That Solicited Applications for Pediatric Research, FY 2013**

	<b>Announcement Number</b>	<b>Issuing Organization</b>	<b>Activity Code</b>	<b>Title</b>
1	<a href="#">PAR-13-366</a>	NIDDK	R18	Pragmatic Research in Healthcare Settings to Improve Diabetes Prevention and Care (R18)
2	<a href="#">PAR-13-367</a>	NIDDK	R34	Planning Grants for Pragmatic Research in Healthcare Settings to Improve Diabetes Prevention and Care (R34)
3	<a href="#">PAR-13-365</a>	NIDDK	R18	Evaluating Natural Experiments in Healthcare to Improve Diabetes Prevention and Treatment (R18)
4	<a href="#">PA-13-363</a>	NIAAA	R01	Research on the Health Determinants and Consequences of Violence and its Prevention, Particularly Firearm Violence (R01)
5	<a href="#">PA-13-368</a>	NIAAA	R03	Research on the Health Determinants and Consequences of Violence and its Prevention, Particularly Firearm Violence (R03)
6	<a href="#">PA-13-369</a>	NIAAA	R21	Research on the Health Determinants and Consequences of Violence and its Prevention, Particularly Firearm Violence (R21)
7	<a href="#">PAR-13-364</a>	NIMH	R01	Development of Assays for High-Throughput Screening for Use in Probe and Pre-therapeutic Discovery (R01)
8	<a href="#">PA-13-359</a>	NIAAA	R01	Nutrition and Alcohol-Related Health Outcomes (R01)
9	<a href="#">PA-13-360</a>	NIAAA	R03	Nutrition and Alcohol-Related Health Outcomes (R03)
10	<a href="#">PA-13-361</a>	NIAAA	R21	Nutrition and Alcohol-Related Health Outcomes (R21)
11	<a href="#">PA-13-352</a>	NIDDK	R01	Translational Research to Improve Diabetes and Obesity Outcomes (R01)
12	<a href="#">PAR-13-346</a>	NICHD	R41	Development of Appropriate Pediatric Formulations and Drug Delivery Systems STTR (R41)
13	<a href="#">PAR-13-345</a>	NICHD	R43	Development of Appropriate Pediatric Formulations and Drug Delivery Systems (R43)

	<b>Announcement Number</b>	<b>Issuing Organization</b>	<b>Activity Code</b>	<b>Title</b>
14	<a href="#">PAR-13-325</a>	NICHD	R01	Development of Appropriate Pediatric Formulations and Pediatric Drug Delivery Systems (R01)
15	<a href="#">PAR-13-326</a>	NICHD	R21	Development of Appropriate Pediatric Formulations and Pediatric Drug Delivery Systems (R21)
16	<a href="#">PAR-13-344</a>	NICHD	R03	Development of Appropriate Pediatric Formulations and Drug Delivery Systems (R03)
17	<a href="#">RFA-AI-13-036</a>	NIAID	UM1	Inner City Asthma Consortium (UM1)
18	<a href="#">RFA-TR-13-002</a>	NCATS	U54	Rare Diseases Clinical Research Consortia (RDCRC) for Rare Diseases Clinical Research Network (U54)
19	<a href="#">PA-13-328</a>	NINR	R01	Health Promotion Among Racial and Ethnic Minority Males (R01)
20	<a href="#">PA-13-331</a>	NINR	R21	Health Promotion Among Racial and Ethnic Minority Males (R21)
21	<a href="#">RFA-DK-13-022</a>	NIDDK	DP3	Improving Diabetes Management in Young Children with Type 1 Diabetes (DP3)
22	<a href="#">PAR-13-306</a>	NICHD	R01	Developmental Pharmacology and Toxicology: Role of Ontogeny (R01)
23	<a href="#">PAR-13-307</a>	NICHD	R03	Developmental Pharmacology and Toxicology: Role of Ontogeny (R03)
24	<a href="#">PAR-13-308</a>	NICHD	R21	Developmental Pharmacology and Toxicology: Role of Ontogeny (R21)
25	<a href="#">RFA-MH-14-210</a>	NIMH	R01	Research to Improve the Care of Persons at Clinical High Risk for Psychotic Disorders (Collaborative R01)
26	<a href="#">RFA-MH-14-211</a>	NIMH	R01	Research to Improve the Care of Persons at Clinical High Risk for Psychotic Disorders (R01)
27	<a href="#">RFA-MH-14-212</a>	NIMH	R34	Research to Improve the Care of Persons at Clinical High Risk for Psychotic Disorders (R34)
28	<a href="#">RFA-RM-13-012</a>	Roadmap	UH2/UH3	NIH Health Care Systems Research Collaboratory - Demonstration Projects for Pragmatic Clinical Trials Focusing on Multiple Chronic Conditions (UH2/UH3)
29	<a href="#">PA-13-314</a>	NIAID	R03	Small Grants on Primary Immunodeficiency Diseases (R03)

	<b>Announcement Number</b>	<b>Issuing Organization</b>	<b>Activity Code</b>	<b>Title</b>
30	<a href="#">PA-13-315</a>	NIAID	R21	Exploratory/Developmental Investigations on Primary Immunodeficiency Diseases (R21)
31	<a href="#">PAR-13-309</a>	NICHD	R01	Translational Research in Pediatric and Obstetric Pharmacology and Therapeutics (R01)
32	<a href="#">PAR-13-310</a>	NICHD	R03	Translational Research in Pediatric and Obstetric Pharmacology and Therapeutics (R03)
33	<a href="#">PAR-13-311</a>	NICHD	R21	Translational Research in Pediatric and Obstetric Pharmacology and Therapeutics (R21)
34	<a href="#">PA-13-288</a>	OBSSR	R21	Behavioral and Social Science Research on Understanding and Reducing Health Disparities (R21)
35	<a href="#">PA-13-292</a>	OBSSR	R01	Behavioral and Social Science Research on Understanding and Reducing Health Disparities (R01)
36	<a href="#">RFA-DK-13-506</a>	NIDDK	U01	Limited Competition: Chronic Kidney Disease (CKD) Biomarkers Consortium Data Coordinating Center (U01)
37	<a href="#">PAR-13-295</a>	NICHD	R21	Biomarkers: Bridging Pediatric and Adult Therapeutics (R21)
38	<a href="#">PAR-13-296</a>	NICHD	R01	Biomarkers: Bridging Pediatric and Adult Therapeutics (R01)
39	<a href="#">PAR-13-299</a>	NICHD	R03	Biomarkers: Bridging Pediatric and Adult Therapeutics (R03)
40	<a href="#">PAR-13-285</a>	NICHD	P01	Developmental Mechanisms of Human Structural Birth Defects (P01)
41	<a href="#">RFA-AI-13-006</a>	NIAID	U01	Clinical Trials in Organ Transplantation (CTOT) (U01)
42	<a href="#">RFA-FD-13-035</a>	FDA	R01	Predictive Methods for Characterizing Product Performance in Pediatric Patients, Case Study: Furosemide (R01)
43	<a href="#">RFA-DK-13-011</a>	NIDDK	U01	Continuation of ChiLDReN, the Childhood Liver Disease Research Network (U01)
44	<a href="#">RFA-DK-13-503</a>	NIDDK	U01	Limited Competition: Continuation of the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN)(U01)
45	<a href="#">RFA-DK-13-004</a>	NIDDK	P30	Diabetes Research Centers (P30)
46	<a href="#">RFA-AR-13-021</a>	NIAMS	U54	Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (U54)

	<b>Announcement Number</b>	<b>Issuing Organization</b>	<b>Activity Code</b>	<b>Title</b>
47	<a href="#">RFA-HL-14-010</a>	NHLBI	R43, R44	Developing a Point-of-Care Device for the Diagnosis of Sickle Cell Disease in Low Resource Settings SBIR (R43/ R44)
48	<a href="#">PA-13-262</a>	NIAAA	R01	Implications of New Digital Media Use for Underage Drinking, Drinking-Related Behaviors, and Prevention Research (R01)
49	<a href="#">PA-13-263</a>	NIAAA	R21	Implications of New Digital Media Use for Underage Drinking, Drinking-Related Behaviors, and Prevention Research (R21)
50	<a href="#">RFA-CA-13-502</a>	NCI	UM1	Limited Competition: Pediatric Brain Tumor Consortium (UM1)
51	<a href="#">RFA-DK-13-009</a>	NIDDK	U01	Type 1 Diabetes TrialNet Clinical Network Hub (U01)
52	<a href="#">RFA-DK-13-010</a>	NIDDK	U01	Type 1 Diabetes TrialNet Clinical Centers (U01)
53	<a href="#">RFA-DA-14-010</a>	NIDA	R01	HIV/AIDS and Substance Use among Black/African American Women and Young MSM (R01)
54	<a href="#">RFA-MH-14-100</a>	NIMH	R01	Services Research for Autism Spectrum Disorder across the Lifespan (ServASD): Research on Early Identification and Linkage to Services for ASD (R01)
55	<a href="#">RFA-MH-14-101</a>	NIMH	R34	Services Research for Autism Spectrum Disorder across the Lifespan (ServASD): Pilot Research on Services for Transition-Age Youth (R34)
56	<a href="#">RFA-MH-14-102</a>	NIMH	R34	Services Research for Autism Spectrum Disorders across the Lifespan (ServASD): Pilot Studies of Services Strategies for Adults with ASD (R34)
57	<a href="#">PAR-13-231</a>	NICHD	R01	Phenotyping Embryonic Lethal Knockout Mice (R01)
58	<a href="#">RFA-HD-14-004</a>	NICHD	R41, R42	In-vivo Methods for Assessing Placental Development and Function (R41/R42)
59	<a href="#">RFA-HD-14-005</a>	NICHD	R43, R44	In-vivo Methods for Assessing Placental Development and Function (SBIR) (R43/R44)
60	<a href="#">RFA-TW-13-002</a>	FIC	R21	Research on the Role of Epigenetics in Social, Behavioral, Environmental and Biological Relationships, throughout the Life-Span and Across Generations (R21)

	<b>Announcement Number</b>	<b>Issuing Organization</b>	<b>Activity Code</b>	<b>Title</b>
61	<a href="#">PA-13-226</a>	NIMHD		Evidence-based Demonstration Projects in Immunization (Admin Supp)
62	<a href="#">RFA-HD-14-019</a>	NICHD	K12	Pediatric Critical Care and Trauma Scientist Development Program (K12)
63	<a href="#">RFA-MH-14-110</a>	NIMH	U19	Limited Competition: Mental Health Research Network II (U19)
64	<a href="#">RFA-MH-14-200</a>	NIMH	R03	Integration and Analysis of Diverse HIV-Associated Data (R03)
65	<a href="#">RFA-DA-14-005</a>	NIDA	R01	Substance Use Disorders and Molecular Regulation of Brain Energy Utilization (R01)
66	<a href="#">RFA-DA-14-006</a>	NIDA	R21	Substance Use Disorders and Molecular Regulation of Brain Energy Utilization (R21)
67	<a href="#">PA-13-216</a>	NIMH	R01	Research on Autism Spectrum Disorders (R01)
68	<a href="#">PA-13-217</a>	NIMH	R21	Research on Autism Spectrum Disorders (R21)
69	<a href="#">PA-13-218</a>	NIMH	R03	Research on Autism Spectrum Disorders (R03)
70	<a href="#">PAR-13-195</a>	NICHD	R01	Preclinical Research on Model Organisms to Predict Treatment Outcomes for Disorders Associated with Intellectual and Developmental Disabilities (R01)
71	<a href="#">PAR-13-208</a>	NINDS	U01	Countermeasures Against Chemical Threats (CounterACT) Cooperative Research Projects (U01)
72	<a href="#">PAR-13-213</a>	NICHD	R01	Outcome Measures for Use in Treatment Trials for Individuals with Intellectual and Developmental Disabilities (R01)
73	<a href="#">PAR-13-206</a>	NICHD	R21	Biophysical and Biomechanical Aspects of Embryonic Development (R21)
74	<a href="#">PAR-13-207</a>	NICHD	R01	Biophysical and Biomechanical Aspects of Embryonic Development (R01)
75	<a href="#">RFA-MH-14-070</a>	NIMH	U01	Pediatric Suicide Prevention in Emergency Departments (U01)
76	<a href="#">PA-13-193</a>	NIAAA	R21	Mechanisms of Alcohol and Nicotine Co-Addiction (R21)
77	<a href="#">PA-13-194</a>	NIAAA	R01	Mechanisms of Alcohol and Nicotine Co-Addiction (R01)
78	<a href="#">PA-13-191</a>	NIAAA	R01	Structural Interventions, Alcohol Use, and Risk of HIV/AIDS (R01)

	<b>Announcement Number</b>	<b>Issuing Organization</b>	<b>Activity Code</b>	<b>Title</b>
79	<a href="#">PA-13-192</a>	NIAAA	R21	Structural Interventions, Alcohol Use, and Risk of HIV/AIDS (R21)
80	<a href="#">PAR-13-187</a>	NIMH	R01	Reducing the Duration of Untreated Psychosis in the United States (R01)
81	<a href="#">PAR-13-188</a>	NIMH	R34	Reducing the Duration of Untreated Psychosis in the United States (R34)
82	<a href="#">RFA-DE-14-004</a>	NIDCR	U01	FaceBase 2: Craniofacial Development and Dysmorphology Dataset, Tool, and Resource Development (U01)
83	<a href="#">RFA-DE-14-005</a>	NIDCR	U01	FaceBase 2: Craniofacial Development and Dysmorphology Data Management and Integration Hub (U01)
84	<a href="#">PA-13-179</a>	NIAID	R03	Indo-U.S. Vaccine Action Program (VAP) Small Research Grant Program (R03)
85	<a href="#">PAR-13-178</a>	NIDCR	R03	NIDCR Small Research Grants for Secondary Analysis of FaceBase Data (R03)
86	<a href="#">PA-13-162</a>	NIAAA	R03	Alcohol Use Disorders: Treatment, Services, and Recovery Research (R03)
87	<a href="#">PA-13-161</a>	NIAAA	R21	Alcohol Use Disorders: Treatment, Services, and Recovery Research (R21)
88	<a href="#">PA-13-160</a>	NIAAA	R01	Alcohol Use Disorders: Treatment, Services, and Recovery Research (R01)
89	<a href="#">RFA-AA-13-003</a>	NIAAA	R01	Research on Comparative Effectiveness and Implementation of HIV/AIDS and Alcohol Interventions (R01)
90	<a href="#">RFA-AA-13-004</a>	NIAAA	R21	Research on Comparative Effectiveness and Implementation of HIV/AIDS and Alcohol Interventions (R21)
91	<a href="#">PA-13-153</a>	NIDDK	R01	Home and Family Based Approaches for the Prevention or Management of Overweight or Obesity in Early Childhood (R01)
92	<a href="#">PA-13-154</a>	NIDDK	R21	Home and Family Based Approaches for the Prevention or Management of Overweight or Obesity in Early Childhood (R21)
93	<a href="#">RFA-FD-13-010</a>	FDA	P50	Pediatric Device Consortia Grant Program (P50)
94	<a href="#">RFA-HL-14-007</a>	NHLBI	U01	Molecular Atlas of Lung Development - Human Tissue Core (HTC) (U01)
95	<a href="#">RFA-HL-14-008</a>	NHLBI	U01	Molecular Atlas of Lung Development - Research Center (RC) (U01)

	<b>Announcement Number</b>	<b>Issuing Organization</b>	<b>Activity Code</b>	<b>Title</b>
96	<a href="#">RFA-HL-14-009</a>	NHLBI	U01	Molecular Atlas of Lung Development - Data Coordinating Center (DCC ) (U01)
97	<a href="#">RFA-MH-14-060</a>	NIMH	R01	Improving Health and Reducing Premature Mortality in People with Severe Mental Illness (R01)
98	<a href="#">RFA-NS-13-014</a>	NINDS	R21	Pilot Projects on Sports-Related Brain and Spinal Cord Injury (R21)
99	<a href="#">RFA-NS-13-015</a>	NINDS	R03	Pilot Projects on Sports-Related Brain and Spinal Cord Injury (R03)
100	<a href="#">RFA-MH-14-030</a>	NIMH	R01	Advancing Eating Disorders Research through Dimensional Studies of Biology and Behavior (R01)
101	<a href="#">PAR-13-130</a>	OBSSR	R01	Understanding and Promoting Health Literacy (R01)
102	<a href="#">PAR-13-131</a>	OBSSR	R03	Understanding and Promoting Health Literacy (R03)
103	<a href="#">PAR-13-132</a>	OBSSR	R21	Understanding and Promoting Health Literacy (R21)
104	<a href="#">RFA-AR-14-005</a>	NIAMS	R43	Small Business Innovation Research on Rare Musculoskeletal, Rheumatic and Skin Diseases (SBIR) (R43)
105	<a href="#">RFA-HD-14-029</a>	NICHD	R43	Orthotics for Pediatric Populations (SBIR) (R43)
106	<a href="#">PA-13-120</a>	NIAAA	R03	Research on Alcohol and HIV/AIDS (R03)
107	<a href="#">PA-13-121</a>	NIAAA	R01	Research on Alcohol and HIV/AIDS (R01)
108	<a href="#">PA-13-122</a>	NIAAA	R21	Research on Alcohol and HIV/AIDS (R21)
109	<a href="#">PAR-13-112</a>	NICHD	T32	Postdoctoral Training Program in Obstetric and Pediatric Pharmacoepidemiology (T32)
110	<a href="#">RFA-HD-14-027</a>	NICHD	R01	Safety and Effectiveness of Triple Antiretroviral Drug Strategies for Prevention of Mother to Child HIV Transmission (R01)
111	<a href="#">RFA-NR-13-002</a>	NINR	R01	The Influence of the Microbiome on Preterm Labor and Delivery (R01)
112	<a href="#">RFA-NR-13-003</a>	NINR	R21	The Influence of the Microbiome on Preterm Labor and Delivery (R21)
113	<a href="#">PA-13-110</a>	NIDDK	R01	Obesity Policy Evaluation Research (R01)
114	<a href="#">PAR-13-109</a>	NIDDK	R01	Mechanistic Insights from Birth Cohorts (R01)

	<b>Announcement Number</b>	<b>Issuing Organization</b>	<b>Activity Code</b>	<b>Title</b>
115	<a href="#">RFA-HD-14-026</a>	NICHD	R01	Evaluation of the Latent Reservoir in HIV-Infected Infants and Children with Early Antiretroviral Treatment and Virologic Control (R01)
116	<a href="#">PA-13-098</a>	NICHD	R21	School Nutrition and Physical Activity Policies, Obesogenic Behaviors, and Weight Outcomes (R21)
117	<a href="#">PA-13-099</a>	NICHD	R03	School Nutrition and Physical Activity Policies, Obesogenic Behaviors and Weight Outcomes (R03)
118	<a href="#">PA-13-100</a>	NICHD	R01	School Nutrition and Physical Activity Policies, Obesogenic Behaviors and Weight Outcomes (R01)
119	<a href="#">RFA-RM-13-004</a>	OD	U01	Clinical Sites for an Undiagnosed Diseases Network (UDN) (U01)
120	<a href="#">PAR-13-094</a>	NICHD	R01	Differentiation and Integration of Stem Cells (Embryonic and Induced-Pluripotent) Into Developing or Damaged Tissues (R01)
121	<a href="#">PAR-13-095</a>	NICHD	R21	Differentiation and Integration of Stem Cells (Embryonic and Induced-Pluripotent) Into Developing or Damaged Tissues (R21)
122	<a href="#">PAR-13-090</a>	NICHD	R43, R44	Safe and Effective Instruments and Devices for Use in Neonatal and Pediatric Care Settings (R43/R44)
123	<a href="#">PAR-13-091</a>	NICHD	R41, R42	Safe and Effective Instruments and Devices for Use in Neonatal and Pediatric Care Settings (R41/R42)
124	<a href="#">RFA-HD-13-002</a>	NICHD	U54	Intellectual and Developmental Disabilities Research Centers 2013 (U54)
125	<a href="#">RFA-MH-14-010</a>	NIMH	R43, R44	Clinical Neuroscience and Entertainment Software Pilot Partnership Program to Develop Neuropsychiatric Interventions (R43/R44)
126	<a href="#">PAR-13-086</a>	NIMH	U19	National Cooperative Drug Discovery/Development Groups (NCDDG) for the Treatment of Mental Disorders, Drug or Alcohol Addiction (U19)
127	<a href="#">PAR-13-087</a>	NIMH	UM1	National Cooperative Drug Discovery/Development Groups (NCDDG) for the Treatment of Mental Disorders, Drug or Alcohol Addiction (UM1)

	<b>Announcement Number</b>	<b>Issuing Organization</b>	<b>Activity Code</b>	<b>Title</b>
128	<a href="#">RFA-MH-13-140</a>	NIMH	R24	Leveraging Existing Natural Experiments to Advance the Health of People with Severe Mental Illness (R24)
129	<a href="#">RFA-DK-12-023</a>	NIDDK	P30	Silvio O. Conte Digestive Diseases Research Core Centers (P30)
130	<a href="#">RFA-OD-12-007</a>	NIH	P30	NIH Revision Applications for Research Relevant to the Family Smoking Prevention and Tobacco Control Act (P30)
131	<a href="#">RFA-DK-13-001</a>	NIDDK	R43, R44	Small Business Innovation Research to Develop New Therapeutics and Monitoring Technologies for Type 1 Diabetes (T1D) Towards an Artificial Pancreas [SBIR (R43/R44)]
132	<a href="#">PA-13-043</a>	NIDDK	R01	Calcium Oxalate Stone Diseases (R01)
133	<a href="#">RFA-DK-12-511</a>	NIDDK	UC4	Limited Competition for Clinical Trials in Type 1 Diabetes (UC4)
134	<a href="#">RFA-NS-13-008</a>	NINDS	U01	International Traumatic Brain Injury Research Initiative: NIH Cooperative Program for Comparative Effectiveness of Clinical Tools and Therapies (U01)
135	<a href="#">RFA-DK-12-021</a>	NIDDK	DP3	Diabetes Impact Award-Closed Loop Technologies: Development and Integration of Novel Components for an Automated Artificial Pancreas System (DP3)
136	<a href="#">RFA-DK-12-020</a>	NIDDK	DP3	Diabetes Impact Award-Closed Loop Technologies: Clinical, Physiological and Behavioral Approaches to Improve Type 1 Diabetes Outcomes (DP3)
137	<a href="#">RFA-RM-12-020</a>	OD	U01	Coordinating Center for an Undiagnosed Diseases Network (UDN) (U01)
138	<a href="#">PAR-13-028</a>	NIDDK	DP3	Research Using Subjects From Selected Type 1 Diabetes Clinical Studies (Living Biobank) (DP3)
139	<a href="#">PAR-13-019</a>	NICHD	T32	Ruth L. Kirschstein National Research Service Award (NRSA) Institutional Predoctoral Training Program in Systems Developmental Biology (T32)
140	<a href="#">RFA-AI-12-043</a>	NIAID	UM1	Collaborative Network for Clinical Research on Immune Tolerance (UM1)
141	<a href="#">PA-13-015</a>	NIDA	R01	Prescription Drug Abuse (R01)
142	<a href="#">PA-13-016</a>	NIDA	R21	Prescription Drug Abuse (R21)

	<b>Announcement Number</b>	<b>Issuing Organization</b>	<b>Activity Code</b>	<b>Title</b>
143	<a href="#">PAR-13-013</a>	NIDDK	DP3	Research Using Biosamples from Selected Type 1 Diabetes Clinical Studies (DP3)
144	<a href="#">RFA-DK-12-510</a>	NIDDK	UC4	Limited Competition: Data Coordinating Center for The Environmental Determinants of Diabetes in the Young (TEDDY) Study (UC4)
145	<a href="#">PA-13-003</a>	NIAAA	R01	Epigenetic Inheritance and Transgenerational Effects of Alcohol (R01)
146	<a href="#">PA-13-004</a>	NIAAA	R21	Epigenetic Inheritance and Transgenerational Effects of Alcohol (R21)
147	<a href="#">RFA-HD-13-004</a>	NICHD	U01	Centers for Collaborative Research in Fragile X (U01)

**Table 4: Acronyms for NIH Institutes, Centers, and Offices and Other Federal Agencies Referred to in This Report**

Acronym	Organization
CC	NIH Clinical Center
CDC	Centers for Disease Control and Prevention
CF	NIH Common Fund
DPCPSI	Division of Program Coordination, Planning, and Strategic Initiatives, OD
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FIC	John E. Fogarty International Center for Advanced Study in the Health Sciences
HHS	Department of Health and Human Services
ICs	NIH Institutes and Centers
NCATS	National Center for Advancing Translational Sciences
NCI	National Cancer Institute
NCCAM	National Center for Complementary and Alternative Medicine
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	<i>Eunice Kennedy Shriver</i> 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
OBSSR	Office of Behavioral and Social Sciences Research, DPCPSI, OD
OD	Office of the Director, National Institutes of Health
ORWH	Office of Research on Women's Health, DPCPSI, OD