DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Report to Congress:
The Fiscal Year 2016 Pediatric Research Initiative

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PEDIATRIC RESEARCH AT THE NATIONAL INSTITUTES OF HEALTH

Research advances supported by the National Institutes of Health (NIH) have transformed the diagnosis, treatment, and prevention of disease. Children 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 improved from 5 percent in the 1960s to 95 percent today. The rates of Sudden Infant Death Syndrome (SIDS) have declined considerably, with the mortality rate in 2014 being one-third the rate of 1990. The risk of transmission of HIV from infected mothers to fetus and infant has fallen from greater than 30 percent in the 1990s to less than 1 percent in the United States and higher income countries. Haemophilus influenzae type B (Hib), once the leading cause of acquired intellectual and developmental disabilities, has been nearly eliminated after the introduction of a vaccine partially funded by the NIH. Scientists’ understanding of how children grow and develop has improved immensely, informing 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) 2016, the NIH funded research grants and projects directed specifically at pediatric research for a total of $3,958,646,745, as detailed in Table 1 in the Appendix. The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) funds the largest portion of pediatric research among the 27 NIH Institutes, Centers, and Offices (ICOs), taking a leadership role in many pediatric research efforts that involve trans-NIH collaborations. However, all of the ICos support various aspects of pediatric research, such that the NICHD alone accounts for only 19 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 2016. 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 (FDA), to increase the development of adequate pediatric clinical trials and pediatric use information to promote the safer and more effective use of prescription drugs in the pediatric population.”

– Section 409D(b), Public Health Service Act
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 ICO 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 ICO.

In addition to establishing the PRI, other related sections of the Act required increased NIH investment in training pediatric biomedical researchers (PHS Act Sec. 452G); the pediatric research loan repayment program (PHS Act Sec. 487F); and a national longitudinal study of environmental influences (including physical, chemical, biological, and psychosocial factors) on children’s health and development (42 U.S.C. 285g, Subpart 7, Footnote 34).

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. This report emphasizes advances in child and adolescent development, rare diseases, treatment of serious pediatric illnesses, prevention, and global health research. Many of these advances resulted from programs that are supported by multiple NIH ICOs.

Child Development

**Telomere length in newborns.** Discoveries in a study of newborn infants’ “telomeres” – that is, the DNA repeats at the ends of chromosomes – challenge the widely-accepted hypothesis that the aging process is reflected in the naturally-occurring attrition of telomeres over the life span. Leucocyte (white blood cell) telomere length (LTL) has been seen as a “telomeric clock” that captures the aging process, primarily in the form of the accumulating burden of inflammation and oxidative stress. However, while measuring LTL in newborns and in their parents, researchers found the same variability in newborn LTL as is known to occur in adult populations. That is, some newborns had short LTL, while others had long LTL. According to these researchers, LTL seems to be a “poor index” of biological age. Rather, short or long LTL may be largely determined at birth. [Supported by NIEHS, NICHD]


**A molecular switch in human sex development.** A set of 46 chromosomes with two X chromosomes results in a typically female appearance; however, some individuals with these chromosomes develop testes or ovotestes, which is known as testicular or ovotesticular disorder of sex development (TDSD/OTDSD). A collaborative effort has discovered that this disorder can be caused by a single genetic mutation that acts as a molecular switch for sex determination, causing XX individuals to develop physically as males and XY individuals to develop as females. Therefore, a specific variant in development can switch organs from developing into either ovary or testis in mammals. [Supported by NIH Common Fund, NHGRI, NICHD]


**Long-term effects of preschool.** A new study of the long-term effects of preschool found strong positive impacts on school performance and earnings capacity. The study results showed that young students who experienced high-quality preschool were more likely to grow up healthy, continue their education, and earn higher incomes as adults. The study is not the first to demonstrate lasting, positive effects of preschool experiences, but earlier studies generally have not used nationally representative samples of children and have been otherwise limited. The authors of the new study developed a more sophisticated model of preschool’s effects and validated this model using longitudinal data from long-standing surveys that follow individuals from the time they are children through young adulthood. [Supported by NICHD]


**Effect of math anxiety depends on motivation.** Both children and adults may experience math anxiety – a feeling of tension, worry, or fear in situations involving math-related activities. Researchers conducted a series of related experiments in college students and in 262 pairs of same-sex twins, on average about 12 years old. For students who were highly motivated and valued math, moderate math anxiety seemed to improve their performance, but both low and high levels of anxiety worsened performance. For students who had lower math motivation, higher math anxiety seemed to worsen their performance. The effects were similar across age groups, but girls generally tended to have higher math anxiety than boys. This
study indicates that educators, parents, and students may want to consider both motivation and anxiety in developing individualized approaches to helping students learn. [Supported by NICHD]

**Social development and patterns of brain activity in young children.** Children who are shy in their preschool years may become more social as they grow older, or may remain more reticent into their preteen and adolescent years. To help understand how social abilities develop, researchers used a functional magnetic resonance imaging (fMRI) brain scan to measure brain activity during a classroom simulation, as children responded to various social roles and circumstances. Scientists gathered these data on children from age two to seven, then repeated the experiment with the same children at age eleven. This allowed the researchers to compare changes in brain activity among highly social children and children who were more reticent. The scientists found that the 11-year-olds who were more reticent in their early years showed greater brain activation patterns in areas associated with regulating distress and emotions, compared to highly social children. If replicated in larger studies, this finding could help scientists better understand how early social behavior may predict brain development during childhood. [Supported by NIMH, NICHD]

**Brief activity breaks may benefit children’s health.** Researchers assessed whether interrupting sitting with short, moderate-intensity walking bouts could improve glucose tolerance in children. The children came to the NIH Clinical Center after an overnight fast. During one visit, they remained seated for three hours (except to use the bathroom) with limited movement. They watched movies, read, did homework, or engaged in other sedentary activities. On another visit, they interrupted their sitting by walking on a treadmill for three minutes every 30 minutes. They walked six times for a total of 18 minutes during the three-hour time frame. During each visit, the children drank a glucose solution at the start and then had blood samples taken periodically. This procedure, known as an oral glucose tolerance test, measures the body’s ability to use glucose and is often used to test for diabetes. The researchers found that during the interrupted sitting day, the children averaged 7 percent lower glucose levels and 32 percent lower insulin levels compared to when they sat for three hours continuously. Their blood levels of free fatty acids (high levels of which are linked to type 2 diabetes) were also lower. So were levels of C-peptide, an indicator of how hard the pancreas is working to control blood sugar. At the end of each visit, the children were allowed to choose their lunch from food provided on a buffet table. The researchers calculated the calorie and nutrient content of what each child ate. They found that the children consumed roughly the same amounts of calories and kinds of foods after each of the sessions. This suggested that the brief walking sessions did not stimulate the children to eat more than they normally would. [Supported by NICHD, NIEHS, NCI, NIDDK, NIH Clinical Center]

**Environmental and Social Influences**

**Air pollution and its effects on pregnancy.** To assess how air pollution affects pregnant women and their children, researchers analyzed data from a group of pregnant women in Boston to assess whether exposure to fine particulate matter (a form of air pollution) was associated with intrauterine inflammation (IUI) – a risk factor for both preterm birth and low birth weight. The results suggested a relationship between even relatively low levels of the airborne particulate matter and higher levels of IUI, suggesting that pregnant women are a sensitive subpopulation that should be considered during review of environmental standards. (PMID 27120296) [Supported by NIEHS, NICHD] In another study, scientists observed that for women with asthma, the risk of preterm birth increased with both ongoing and short-term exposure to nitrogen oxides and carbon monoxide, particularly when women were exposed to those
pollutants just before conception and in early pregnancy. Exposure to high levels of particulate matter was also associated with higher preterm birth risk. (PMID 26944405) [Supported by NICHD]

Environmental and genetic risk factors for pediatric autoimmune diseases. Researchers have identified environmental risk and severity factors for juvenile dermatomyositis (a disease in children causing skin rash and weak muscles) and other pediatric systemic rheumatic diseases, including juvenile idiopathic arthritis (chronic arthritis in children) and juvenile systemic lupus erythematosus (a chronic autoimmune disease that can involve any organ system and shares characteristics with many other autoimmune diseases). Both ultraviolet light exposure based on residential location at diagnosis and infections within six months of illness onset have been identified as possible risk factors for a chronic illness course, and these are the first environmental factors associated with illness outcomes in pediatric autoimmune diseases. [Supported by NIEHS, NIDDK]

Prenatal phthalate exposures and body mass index among four- to seven-year-old children. Phthalates are a family of chemicals used in many plastics and scented products. Recent research has linked prenatal and early childhood phthalate exposure with a variety of adverse health effects. For example, phthalates are hypothesized to cause obesity, but few studies have assessed whether prenatal phthalate exposures are related to childhood body mass index (BMI). Researchers studied 707 children from three prospective cohort studies enrolled in the United States between 1998 and 2006 who had maternal urinary phthalate metabolite concentrations measured during pregnancy, and with weight and height measured at ages four to seven years. Maternal urinary measurements containing a chemical (mono-3-carboxypropyl phthalate, a nonspecific metabolite of several phthalates) was positively associated with childhood overweight/obesity. Metabolites of diethyl phthalate and DEHP were associated with lower BMI in girls but not in boys, suggesting that prenatal exposures may have sexually dimorphic effects on physical development. [Supported by NIEHS, NCATS, NICHD]

Health of Newly-Arrived Refugee Children. Each year, about 35,000 enter the United States as refugees. The Centers for Disease Control and Prevention (CDC) has used the best available data to develop screening guidelines that are specific for refugees. Many state and local departments of public health, as well as clinicians specializing in refugee health services, use these guidelines to identify infectious diseases, nutritional deficiencies, and other health problems in refugee children. Researchers combined data from refugee programs in Colorado, Minnesota, Washington state, and Philadelphia to assess the health of refugee children from Bhutan, Burma, the Democratic Republic of the Congo, Ethiopia, Iraq, and Somalia. The data showed that children had varying levels of anemia, high blood lead levels, and infectious diseases such as hepatitis B, depending on their age and country of origin. The health profile of children from Burma who entered the United States via Malaysia was significantly different from that of Burmese children who entered the United States via Thailand. This indicated that the living environment before departure plays a major role in these children’s health. Overall, the authors concluded that these data support the CDC’s current screening guidelines. [Supported by NICHD]

E-waste exposure on children's health. An emerging area of research is the impact of electronic waste (e-waste) exposure on children's health. E-waste includes the growing volume of cell phones and computers that end up in unregulated recycling facilities throughout the world. NIEHS (Superfund Research Program) co-sponsored a World Health Organization working group meeting to discuss e-waste exposure in children and develop a strategic plan for addressing this issue with future research. A
commentary from this meeting was published in 2015 and discusses e-waste from a global perspective and ways to reduce exposure. Ongoing NIEHS-sponsored research is evaluating the cognitive and behavioral outcomes of children exposed to e-waste in early life as well as exploring sources of early life lead exposure. [Supported by NIEHS, World Health Organization]

**Neighborhood and home food environment and children’s diet and obesity.** In neighborhoods with few sources of healthy foods, policy initiatives have tried to encourage establishment of supermarkets and to discourage proliferation of fast food outlets. Scientific evidence for such initiatives is limited, however. Researchers studied the neighborhood food environments and dietary behaviors of military teenagers, who move frequently. In addition to obtaining neighborhood data, the scientists collected information on child and family dietary behaviors, exercise, and potentially influential factors. The study found that neither the actual or perceived availability of supermarkets close to home was associated with lower probability of overweight or obesity or other positive outcomes for the teens. Similarly, availability of fast food outlets or convenience stores was not associated with negative outcomes. The healthiness of foods available in the home and parental behaviors, including supervision – such as limits on snack foods and meals eaten as a family – were associated with positive teen dietary behaviors. [Supported by NICHD]

**Adolescent susceptibility to peer influence in risky sexual behavior.** Identifying the factors that contribute to risky sexual-decision-making is critical to prevention efforts, especially during early adolescence when sexual behavior often starts. Researchers conducted a study examining young adolescents’ susceptibility to peer influence concerning risky sexual behavior. The study participants privately completed assessments about demographic information, sexual attitudes, and hypothetical high-risk sexual behavior scenarios. Then they participated in a simulated Internet chat room where they believed they were communicating with peers regarding the same hypothetical scenarios in the assessments. In reality, the “peers” were computer-programmed electronic companions. The results showed that 78 percent of the adolescents provided more risky responses in the chat room than in the private assessments. Boys were significantly more susceptible to social pressure regarding sexual behavior than girls. Boys with later pubertal development and African-American boys were the most susceptible. Both girls and boys who expected sex to increase their popularity showed greater levels of susceptibility to peer influences. The results confirm that not all adolescents are equally susceptible to peer influence concerning sexual behavior. The findings can help target interventions to adolescents who are most susceptible to social pressure regarding risky sexual behavior. [Supported by NICHD, NIAID]

**Pregnancy and the Health of the Newborn**

*Unintended and adolescent pregnancy rates declining in the United States, yet disparities remain.* Researchers compiled nationally representative data from several sources to compare rates of unintended pregnancy between 2008 and 2011, and across different groups of women. The unintended pregnancy rate continued to drop between 2008 and 2011 among women and girls in the United States aged 15 to 44, reaching its lowest level in 30 years. Unintended pregnancy rates declined among nearly all demographic subgroups, with the greatest percentage of reduction observed among poor and low-income women and girls, the Hispanic population, and women aged 20-24. However, despite the improvement, poor, Black, and Hispanic women and girls still have much higher rates of unintended pregnancy than white women and girls and those with higher incomes. (PMID 26962904) In another study, researchers confirmed that the reason United States adolescent pregnancy and births have been steadily going down is that adolescents are more frequently using contraceptives, and using them correctly. The researchers analyzed data on adolescent female sexual behaviors from a nationally representative survey and assessed data on
contraceptive failure rates. The results indicated that increases in overall contraceptive use are primarily responsible for the long-term decline of 57 percent in adolescent birth rates, from 1991 to 2013. (PMID 27595471) [Supported by NICHD]

**Predictors of pregnancy complications in patients with lupus.** Researchers studied pregnant women with lupus, and determined that most women who experienced pregnancy complications had one or more risk factors in the first trimester of the pregnancy. These risk factors included a specific type of anti-phospholipid (aPL) antibody in the blood, a history of high blood pressure requiring medications, and a low platelet count. The researchers determined that among women who did not have any of these risk factors in the beginning of their pregnancy, the chance of developing a problem was less than 8 percent. (PMID 26098843) In a second study of pregnant women with lupus, researchers discovered that specific angiogenic biomarkers detected in maternal blood early in pregnancy can signal who will or will not have an increased risk for developing severe complications. These biomarkers may enable physicians to better identify patients early in pregnancy who are likely to develop adverse pregnancy outcomes, and plan for appropriate care of these high-risk individuals. (PMID 26432463) [Supported by NIAMS]

**Development of non-human primate models for studying the effects of Zika virus on the developing fetus.** Researchers developed rhesus macaque model of Zika infection. In pregnant rhesus, the duration of Zika virus in the circulation was prolonged compared to non-pregnant rhesus. (PMID 27352279) [Supported by ORIP, NIAID] In addition, researchers demonstrated effects of Zika virus on the placenta and profound detrimental effects on fetal neural development in pigtail macaques. (PMID 27618651) [Supported by ORIP, NIAID, NICHD] These seminal findings are a critical first step for studying the effects of Zika virus in primates as well as development of vaccines and potential treatments.

**Discoveries in Zika virus pathology and transmission.** Using lab-grown human induced pluripotent stem cells, researchers found that Zika virus selectively infects cortical neural progenitor cells, making them more likely to die and less likely to divide normally and make new brain cells. (PMID 26952870) [Supported by NIAID, NINDS, NIMH] Additionally, scientists have identified the structure of mature Zika virus using cryo-electron microscopy, and found structural similarities between Zika and other flaviviruses. However, a variation was discovered in the glycoprotein structure of the outer envelope which may serve as an attachment site of the virus to the host cells. This discovery will help inform further research on disease pathogenesis and the development of effective diagnostics, therapeutics, and vaccines against Zika virus. (PMID 27033547) [Supported by NIAID] Studies funded by the BRAIN Initiative found that Zika may enter cells through a receptor that is highly expressed on the surface of neurons (human radial glial cells, astrocytes, endothelial cells, and microglia) in the developing human brain, as well as by progenitor cells in the retina. (PMID 27038591) [Supported by NINDS, NIMH]
Mouse model shows how Zika virus damages placenta and fetuses. Researchers discovered that Zika virus infects and crosses the placentas of pregnant mice, causing severe damage or death in fetal mice. These researchers have developed two mouse models of Zika infection in pregnancy. One mouse model was genetically engineered so that the mice could not mount an immune response, making them more susceptible to infection. Upon infection, Zika virus replicated much more in the placenta of these mice. In the second model, genetically normal pregnant mice were given an antibody that blocked their immune response to Zika virus. When these mice were infected with Zika virus, their fetuses survived, but with impaired growth. The viral genetic material stayed in the fetal heads and bodies for a long period throughout embryonic development, which is critical for the developing mouse brain. Mouse models of Zika virus infection will enable rapid testing of experimental drugs to prevent birth defects, ultimately allowing researchers to better understand how the virus affects pregnant women. [Supported by NICHD, NHGRI, NIAID, NINDS]


Risk of premature birth is tied to a mother’s mental health. Researchers used data from more than 200,000 women to study the effect of maternal depression, anxiety disorder, bipolar disease, and schizophrenia on the length of a pregnancy. Overall, 17.8 percent of women with a mental health disorder gave birth preterm, compared to 11.2 percent of women without a mental health condition. Women with anxiety disorder, bipolar disease, and depression with anxiety had higher rates of preterm births at 37, 34, and 28 weeks than women without mental health disorders. [Supported by NICHD]


Neuroprotective drugs have long-term positive effects in preterm infants. In a follow-up study of preschool children who were born preterm and treated early with medications to protect their developing brains, scientists found new evidence that the drugs had lasting positive effects on how the children functioned. In the original clinical trial, the newborns in the “treatment” group had been treated with drugs known as erythropoiesis-stimulating agents (ESAs), which stimulate production of red blood cells. Preterm newborns in the trial’s “control” group received placebo medication. Assessed at age two, toddlers who were treated with ESAs had significantly better neurocognitive outcomes than the placebo control group. At three and a half to four years of age, children who received the ESA treatment again had significantly better neurocognitive outcomes, compared with children who did not receive the treatment. [Supported by NICHD, NCATS]


Outcomes of antenatal corticosteroid treatment in extremely preterm, multiple gestation infants. For women in early labor, before 34 weeks of pregnancy, treatment with steroids is recommended to improve the infant’s lung function. However, it has been unclear how antenatal corticosteroids affect the health of multiple infants, late preterm babies, and infants with low birth weight. Researchers assessed the use of steroids in several populations to help identify which infants will benefit from the treatment and what risks may be involved.

• To determine whether the dosage used for single pregnancies is adequate for women who are pregnant with more than one infant, researchers analyzed data on nearly 7,000 multiple gestation, extremely preterm infants (gestational age 22 to 28 weeks) born from 1988 through 2013. The results suggested positive effects of the treatment overall. However, surviving newborns of multiple gestations who were small for gestational age continued to have higher risks when compared to those who were at an appropriate weight. [Supported by NICHD]


• Researchers assessed whether a steroid given to women who were in their 34th through 36th week of pregnancy, and at risk for preterm birth, would decrease respiratory and other neonatal
complications. The 2,831 women who participated in the study were randomly assigned to receive two injections, 24 hours apart, of either a steroid or a placebo. The results showed that the steroid decreased the need for substantial respiratory support during the first 72 hours after birth and also resulted in reduced rates of longer term severe respiratory complications. [Supported by NICHD, NHLBI, NCATS]


• Research shows that treating mothers who are at risk for preterm delivery with steroids reduces their babies’ risk for intraventricular hemorrhage (IVH). However, these studies were conducted decades ago, when IVH was more common. Researchers analyzed data from California hospitals on 26,000 very-low-birth-weight infants who were 22 to 32 weeks old at delivery. They found that treating mothers with steroids reduced the infants’ overall risk of IVH, as well as their risk of severe IVH. Current guidelines recommend steroids only for mothers expecting to deliver at 24 to 34 weeks of pregnancy, because scientists did not previously know whether younger babies benefit from the treatment. This study found that steroid treatment also helped protect infants born at 22 weeks of pregnancy. [Supported by NICHD]


Treating high blood pressure in late pregnancy and risks to newborn health. Treating high blood pressure (hypertension) in pregnant women with beta blockers (one type of antihypertensive drug) may pose significant health risks for their newborn infants, according to a study of Medicaid data from approximately 2.2 million pregnancies in 46 states and the District of Columbia. Scientists found an estimated 70 percent increased risk of low blood sugar (hypoglycemia) in newborns of women taking the medications around the time of birth, compared to newborns of non-medicated mothers. Moreover, the research showed a 30 percent increased risk of abnormally low heart rate (bradycardia) in these newborns. The scientists recommended increased surveillance, including routine glucose monitoring and prompt treatment if needed, for newborn infants of women who have been treated with beta blockers. [Supported by NICHD]


E. coli bacteria is associated with necrotizing enterocolitis (NEC) and death among infants. NEC is a disease in which the intestines are injured or begin to die. It affects about 10 percent of very preterm infants, especially those who are fed formula instead of breastmilk, and is a significant cause of death in these babies. About one-third of affected infants need surgery, and survivors face a number of health problems, including higher risk for abnormalities in intelligence and motor skills. Scientists do not know the cause of NEC, but it seems to be related to the types of bacteria in the intestines. To learn more, researchers used genomic sequencing techniques to identify bacterial species in 144 preterm and 22 term infants. The researchers found that of the 27 infants who developed NEC, 13 had higher relative numbers of a particular type of Escherichia coli in their gut bacteria, and 10 of those 13 infants died. These findings suggest that the presence of these strains of E. coli in premature infants could indicate increased risk for NEC and death. Detecting these strains could allow health care providers to identify infants at higher risk and treat them with appropriate antibiotic therapies. [Supported by NICHD, NHGRI, NCATS, NIAID]


Safety of histamine-2 receptor blockers in hospitalized very low birth weight infants. A type of medication that reduces stomach acid and reduce gastric acid reflux (movement of stomach acid from the stomach into the esophagus) is called histamine-2 receptor blockers (brand names include Zantac and Pepcid). Because of concerns about the adverse effects of gastric reflux like poor weight gain and breathing problems, the drugs have been commonly used in very low birth weight infants, although the
drugs’ efficacy and safety have not been tested specifically in these fragile babies. Increasingly since the early 2000s, smaller studies have raised safety questions about the use of the drugs in infants with very low birth weight. Many of these infants are susceptible to NEC, an infection-triggered intestinal inflammation, as well as sepsis, an overwhelming, systemic inflammatory reaction to infection. Both conditions are difficult to prevent or treat and can swiftly prove fatal. Researchers analyzed electronic medical record data from 348 North American neonatal intensive care units between 1997 and 2012. The results showed that use of the histamine-2 receptor blockers in very low birth weight infants was associated with significantly increased risk of death, NEC, or sepsis. The scientists also reported a steady decline in the histamine-2 blocker drug use, from 23 percent of very low birth weight infants in 2005 to 8 percent in 2012, an apparent response to reports about safety concerns and the lack of efficacy data.

[Supported by NICHD, FDA, NCATS, NIAID]

Association between ampicillin and seizures in neonates. Ampicillin has long been the most commonly-used medication in hospitalized infants, including newborns, yet FDA approval for this antibiotic does not include dosing or safety information for children at such a young age. Researchers recently used a novel method to develop some of the missing information about the safety of ampicillin for infants. Using data from electronic health records of more than 131,700 infants hospitalized from 1997 to 2012, they calculated levels of ampicillin exposure – the amount of the drug in the infants’ blood serum over time – that were associated with specific doses and safety events, as noted in the records. The very large number of infants in the study allowed the researchers to identify a rare but important association between higher doses of ampicillin and seizures, a rare but dangerous side effect known to occur with this drug in adults.

[Supported by NICHD]

Preventing candidiasis in premature infants. Invasive candidiasis (IC) is an important cause of sepsis in premature infants and is associated with a high risk of death and neurodevelopmental impairment. Prevention of IC has become a major focus in very low birth weight infants, with the drug fluconazole increasingly used as a preventative measure. Scientists analyzed all randomized, placebo-controlled trials evaluating preventive fluconazole in premature infants that were conducted in the United States. This review showed that fluconazole reduced the odds of IC or death, IC, and Candida colonization during the drug exposure period compared with infants given placebo. [Supported by NCATS, NICHD, FDA, NIAID]

Screening programs may miss many cases of life-threatening infection in newborns. Staphylococcus aureus (S. aureus) is a common bacterium that typically lives on the skin and inside the nostrils. In healthy people, S. aureus usually doesn’t cause disease. However, it can cause serious and sometimes life-threatening infections, especially in preterm and undersized infants or in people who have weakened immune systems. In recent years, some strains of the bacterium have become immune, or resistant, to the antibiotic used to treat the infection. In adult patients, concerns have focused on these resistant strains because they more difficult to treat. Researchers analyzed hospital records of newborns who had S. aureus infections in 348 intensive care units in 34 states to determine the predominant source of the infection: methicillin-resistant S. aureus (MRSA) or methicillin-susceptible S. aureus (MSSA). MSSA infections made up slightly more than 72 percent of the total, while MRSA infections comprised nearly 28 percent. Overall, the infections were most common in very low birth weight infants, which are the smallest, most fragile class of preterm infants. For cases in which death records were available, 9.6 percent of infants with MSSA and 11.6 percent of infants with MRSA died before leaving the hospital. The study authors note that some hospitals have programs to detect patients who are harboring MRSA, before they become infected. However, most newborn care facilities with programs limit these programs to only MRSA. Based on these findings, researchers suggest that newborn care facilities consider
expanding their screening programs to include MSSA, which appears to pose an equally serious threat to preterm infants. [Supported by NIAID, NICHD, AHRQ, NCATS, FDA]

**Advising moms not to share a bed with their infants does not discourage breastfeeding.** Infants who sleep in a bed with their mothers are at higher risk for unintentional sleep-related infant deaths. However, room-sharing without bed sharing reduces the risk of Sudden Infant Death Syndrome by 50 percent. The American Academy of Pediatrics (AAP) recommends that infants sleep in the parent’s room, but in a separate sleep space. Exclusive breastfeeding to six months of age is also recommended. However, some infant care and public health experts have feared that instructing mothers to avoid bed sharing could discourage them from breastfeeding. Researchers surveyed more than 3,000 mothers in the United States to gather information about breastfeeding and infant sleep locations. The majority of women (66 percent) reported room sharing without bed sharing, while 21 percent reported bed sharing. Exclusive breastfeeding was reported by 30 percent of the women, and among these women over half shared a room but not a bed. The researchers found that the mothers were more likely to follow recommendations for room sharing and exclusive breastfeeding if they received advice to do so. Receiving advice to share a room and not share a bed did not discourage breastfeeding. [Supported by NICHD]

**Nutrition and Obesity in Pregnancy and Childhood**

**In mice, poor maternal diet affects multiple future generations.** Children born to obese mothers are at risk of developing obesity, cardiovascular disease, and diabetes in adulthood. Grandchildren and great-grandchildren of obese women may also inherit risk of metabolic disease – a cluster of conditions, such as elevated blood pressure and blood glucose (sugar) – associated with the development of cardiovascular disease and type 2 diabetes. Researchers fed female mice a high calorie diet from before conception until after their offspring were weaned. Then, they fed the next three generations of mice a normal diet. Although only the first generation of mice had been born to mothers with poor diets, each generation following developed mitochondrial abnormalities associated with metabolic disease. The daughters and granddaughters of the obese mothers were found to have abnormal mitochondria in their eggs. The researchers surmised that a mother’s diet-induced metabolic disorders may be passed on through her eggs. [Supported by NICHD, NIDDK]

**Preterm infants born to diabetic women using insulin before pregnancy are at risk for complications.** Researchers have found that extremely preterm infants whose mothers had insulin-dependent diabetes during pregnancy were at significantly greater risk of two swift-moving, potentially fatal disorders, compared with extremely preterm peers whose mothers do not have this form of diabetes. The disorders are necrotizing enterocolitis (NEC), a condition in which immature intestine tissue is damaged and begins to die, and late-onset sepsis, systemic infection that can trigger potentially fatal systemic responses and that can occur 7 to 90 days after birth. Surviving preterm infants of the diabetic mothers also had a smaller than average head size. The rates of neurodevelopmental problems in this high risk premature group did not differ among infants of diabetic mothers compared to the non-diabetic mothers. [Supported by NICHD]
**Association of cesarean delivery and formula supplementation with the intestinal microbiome of six-week-old infants.** The intestinal microbiome plays a critical role in infant development, and how a baby is delivered (vaginally vs caesarian) and fed (breast milk vs formula) determine the microbiome composition. A study identified six individual bacterial genera that were differently abundant depending on delivery and feeding modes, and found that differences in microbial community composition between infants delivered vaginally and by cesarean birth were equivalent to or significantly larger than such differences between feeding groups. These results may inform feeding choices and shed light on the mechanisms behind the lifelong health consequences of delivery and infant feeding modalities.

[Supported by NIEHS, NLM, NIGMS]


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**Donor breast milk can reduce risk of deadly disease without discouraging breastfeeding.** Infants born too early or a low birth weight are at particularly high risk for necrotizing enterocolitis (NEC), a potentially fatal inflammation of the intestines. Breastfeeding can help protect infants against NEC, but mothers of these fragile, preterm infants may find it difficult to breastfeed. Some clinicians have suggested that making donated breast milk available might be helpful, but others have expressed concern that having donated milk available might discourage breastfeeding. Researchers tracked the availability of donated human breast milk in very low birthweight (VLBW) infants in California hospitals. They found that the availability of donated milk markedly increased from 2007 to 2013. By the end of the study period, the availability of the donated breast milk had risen from 32.2 percent to 81.3 percent of VLBW infants born in regional neonatal intensive care units (NICUs). As was hoped, the availability of the donated milk was associated with significant decreases in NEC. Breastfeeding rates were higher in the hospitals where donated human breast milk was available, compared with hospitals without the donated breast milk.

[Supported by NICHD]


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**A comparison of three vitamin D dosing regimens in extremely preterm infants.** A small, pilot study of different levels of vitamin D supplements for extremely preterm infants has found positive results with a dose that lies between the levels recommended by United States and European experts. Vitamin D is critically involved in fetal developmental processes, including lung development and maturation of the immune system. Vitamin D supplementation is recommended for preterm infants because their early arrival means that they have low levels of the vitamin. The American Academy of Pediatrics recommends that preterm infants receive daily vitamin D doses of 200-400 IU (international units) while the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition recommends daily supplementation of 800 to 1,000 IU. The pilot study, designed to identify an optimum vitamin D dosage for a larger clinical trial, found that daily doses of 200 IU had reduced vitamin D deficiency in extremely preterm infants by the 28th day after birth, and that larger doses of 800 IU prevented the deficiency altogether.

[Supported by NICHD]


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**In teens with severe obesity, bariatric surgery improved health and quality of life three years after the surgeries.** The Teen Longitudinal Assessment of Bariatric Surgery (Teen-LABS) observational study found that teens who undergo bariatric surgery often see improved health and quality of life, although some risks remain. Three years post-surgery, participants’ weight decreased by an average of 90 pounds, or 27 percent, among 242 enrolled teens; 95 percent of the teens who had type 2 diabetes had reversal of their disease; 86 percent of those with kidney damage experienced improvements in kidney function; and most of the participants with elevated blood pressure or lipid abnormalities saw improvements in their conditions. Some risks were identified: 13 percent of participants needed additional abdominal surgery, most commonly gallbladder removal, and more than half had low iron levels.

[Supported by NIDDK, NCATS]

Program improves overweight and depressive symptoms in high school adolescents. Scientists evaluated the long-term efficacy of a program for teens to encourage positive mental attitudes, exercise, and healthy nutrition. The results showed that a year after completing the program, there was a significant decrease in the proportion of overweight and obese students. In addition, students who had begun the program with severely elevated depressive symptoms had significantly lower depression a year after completing the program. [Supported by NINR]  

School in-class breakfast program not linked to obesity. For 50 years, the federally-funded School Breakfast Program has provided breakfast for children from low-income families. However, concerns have been raised that serving a breakfast in the classroom would contribute to student obesity. In two separate studies, researchers found no evidence that the program contributed to obesity or increased body-mass index (BMI). [Supported by NICHD]

- In several schools implementing breakfast in the classroom, researchers examined school breakfast and lunch participation, student weight measurements, and data on demographics, attendance, and academic test scores in grades 4 through 8. The study results showed a substantial increase in school breakfast participation when breakfast was served in the classroom, with no impact on the lunch program participation. There was no evidence that the program contributed to obesity or increased BMI, or that attendance was affected. However, there was no significant improvement in academic achievement.  

- Researchers conducted a study to explore eating patterns and weight status among 5th to 7th graders in a medium-sized urban school district. The results showed that the weight change of children who ate breakfast both at home and at school was no different over time than the average weight change of all other students. However, children that frequently skipped breakfast altogether were more likely, not less likely, to be overweight or obese compared with children eating breakfast both at home and at school.  

Diabetes

Birth weight affects weight gain and type 2 diabetes for African American women. African American women are more likely to develop obesity and type 2 diabetes (T2D) than other racial and ethnic groups. African American women are also more likely to have been born preterm and with a low birth weight, compared to White women in the United States. Researchers examined the relationship between birth weight, genetic variation, and adult body mass index in a sample of 2,215 African American women from the Black Women's Health Study. The study found three genetic variants which were associated with higher body mass index, among women who had low birth weights. These findings suggest that low birth weight may disrupt mechanisms of body weight regulation in African American women, leading to higher incidence of obesity and T2D later in life. [Supported by NIMHD]  

TODAY data helps researchers identify youth whose diabetes will progress more quickly. The 4-year Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) clinical trial found that: (1) the disease often progressed more rapidly in young people than in middle-aged and older people; (2) the standard first-line drug metformin was insufficient to control blood glucose adequately in about half of the participants; and (3) metformin combined with another drug, rosiglitazone, was only slightly better. However, a new analysis of TODAY data showed that most of the adolescents whose diabetes was not well controlled by metformin (or both drugs) saw their blood glucose rise outside the prescribed range.
very early. These young people should be carefully monitored in case more aggressive treatment is needed to control blood glucose levels. [Supported by NIDDK, NCATS]

**Helping adolescents with type 1 diabetes control blood sugar levels.** Glycemic (“blood sugar”) control typically worsens during adolescence as teens’ bodies are rapidly changing. Researchers developed the “WE-CAN manage diabetes” program for young people ages 9-15 and their families, and the program was successful in improving glycemic control. The clinic-based intervention facilitates family problem-solving and communication skills, as well as responsibility-sharing in managing a young person’s glycemic level. Because of concerns that programs such as this may be less helpful for families with fewer resources, researchers analyzed data to see whether family income determined how well the program worked for young people. The scientists found that the program was similarly effective in improving glycemic control of youth with type 1 diabetes, regardless of annual family income. [Supported by NICHD]

**Structural Anomalies and Birth Defects**

**Prior use of oral contraceptives not associated with risk of birth defects.** A very large new study from Denmark indicates that the use of oral contraceptives around the time of conception does not increase the risk of having a child with a major birth defect. Researchers analyzed data on more than 880,000 live births recorded in Danish registries between 1997 and 2001, together with data in pharmacy records of oral contraceptive prescriptions that were filled. [Supported by NICHD] https://www.ncbi.nlm.nih.gov/pubmed/26738512 [Jan 2016]

**Antipsychotic use in pregnancy and the risk for congenital malformations.** The use of antipsychotic drugs during the early stages of pregnancy has doubled in the last decade, at a time when there have been only limited and conflicting research findings on whether the drugs increase the risk of birth defects in the developing fetus. However, a recent analysis of nationwide Medicaid data has found a relatively small risk, both of overall congenital malformations and congenital heart problems specifically. Researchers analyzed medical records of well over a million women. More than 9,000 of these women had been prescribed a class of drugs known as atypical antipsychotics during the first trimester of their pregnancy. The drugs are used to manage serious psychotic symptoms, such as hallucinations, paranoia, or disordered thoughts. The size of the study enabled the scientists to assess possible risks associated with each individual drug. As the researchers noted, medications should be avoided if possible during pregnancy. Avoidance is frequently not possible, however, in the case of serious disorders like schizophrenia or bipolar disorders, where the illness also poses a risk to mother and child and where few alternative treatments exist. [Supported by NICHD, NIMH]

**Selection criteria and pre-operative treatment used for fetal spina bifida surgery.** In 2012, researchers reported success in a landmark clinical trial of fetal surgery, to repair a type of spina bifida (myelomeningocele) before an affected child is born. Scientists have now assessed how specialized fetal medicine centers are following voluntary guidelines for this high-risk, high-benefit procedure. Their survey at specialized centers found considerable variation from the guidelines in identifying candidates for the procedure, conducting preoperative evaluation, and monitoring the fetus during the surgery. The scientists recommended ongoing evaluation of the criteria for patient selection, as well as operative techniques, to ensure the continued safety, efficacy, and ethical appropriateness of the procedure. [Supported by NICHD]
A variant in the transcription factor gene GRHL3 associated with non-syndromic cleft palate. Non-syndromic cleft palate is a common birth defect, with complex underlying causes. Researchers performed a genome-wide association study (GWAS) on a diverse study population and identified a significant association with a variant in the gene Grainyhead-like 3 (GRHL3), which was also replicated in an independent study population of European individuals. Additional experiments in a zebrafish model system demonstrated that this altered GRHL3 protein did not function normally. This new variant in GRHL3 demonstrates that a single amino acid change can increase risk for non-syndromic forms of cleft palate and is the first genetic variant identified for non-syndromic cleft palate. The identification of genetic variants associated with craniofacial disorders offer new avenues to diagnose and potentially treat these conditions. [Supported by NIDCR, NIMHD, CDC, NIEHS] https://www.ncbi.nlm.nih.gov/pubmed/27018472 [Apr 2016]

Second hand smoke is a risk factor for cleft lip and/or palate. Previous studies have demonstrated that maternal smoking increases the risk of a child being born with cleft lip/cleft palate (CLP), but the effects of second hand smoking on mothers are not well understood. Scientists demonstrated that second hand smoking was significantly associated with CLP and the increased risk was consistent for different populations and types of CLP. [Supported by NIDCR, NICHD, NIEHS, CDC] https://www.ncbi.nlm.nih.gov/pubmed/27045073 [May 2016]

Intellectual and Developmental Disabilities

Enrollment in early intervention programs among children conceived with Assistive Reproductive Technology (ART). To learn whether children conceived with ART are at risk of poor developmental and behavioral outcomes, researchers examined an indirect indicator of risk by comparing children's enrollment in early intervention (EI) programs. These programs serve infants and children, from shortly after birth through age three, who have developmental delays or are at risk of such delays. Researchers found that single infants conceived with ART – and also single infants born to sub-fertile women who had not used ART – were more likely than other children to be enrolled in an EI program, even after accounting for whether or not the children were born preterm. [Supported by NICHD] https://www.ncbi.nlm.nih.gov/pubmed/26908668 [Mar 2016]

Improving cognitive function in Down syndrome. Previous experiments in mice have shown that the group of genes called the Down syndrome critical region on human chromosome 21 is an important region underlying cognitive deficits. Scientists defined the genetic region and identified two particularly important genes in a mouse model of Down syndrome. One of the critical products of these genes is the protein Dyrk1a, which is particularly noteworthy because a number of clinical studies are currently aiming to lower Dyrk1a levels, hoping to improve cognitive function in individuals with Down syndrome. [Supported by NINDS, NIGMS, NHLBI, NCI] https://www.ncbi.nlm.nih.gov/pubmed/26374847 [Nov 2015]

Trisomy conditions can disrupt overall gene regulation pathways in fetal development. People are normally born with 23 pairs of chromosomes, with a total of 46, which are numbered by size from largest to smallest. Trisomies are rare conditions in which people have three versions of a particular chromosome instead of two. For example, trisomy 13, or three copies of chromosome 13, results in severe intellectual disability and physical abnormalities, with many infants dying within their first weeks of life. Trisomy 18 occurs in about 1 in 5,000 live births, and many affected fetuses do not survive. Trisomy 21, also known as Down syndrome, causes intellectual disability, and may also involve other conditions such as heart defects, digestive abnormalities, and onset of Alzheimer’s disease in middle age. Generally, older mothers are at higher risk of having a baby with a trisomy. Researchers sought to understand how three copies of chromosomes 13, 18, or 21 disrupt normal development. They used microarray technology to examine...
how genes are expressed at the interface between pregnant mothers and their developing fetuses. Scientists had previously theorized that a higher number of chromosomes results in a higher number of genes, resulting in an abnormal amount of proteins. However, these researchers found that, in fetuses who had these trisomy conditions, genes on chromosomes with multiple copies caused differences in how genes throughout the entire genome were regulated. This “dysregulation” results in different signals to express other genes, disrupting processes that are critical to normal placental and fetal development, including the formation or functioning of brain cells, immune system, heart and blood vessels, and overall growth. [Supported by NICHD]

Adding choline to diet of pregnant mice improves brain function in Down syndrome model. One mouse model of Down syndrome, the Ts65Dn mouse, shows characteristics that are similar to humans with Down syndrome. In particular, these mice have damaged brain systems involving the production of acetylcholine, which is a chemical that controls signaling and transmits information throughout the brain. These systems affect sleep and learning. Researchers supplemented the diets of pregnant Ts65Dn mice with choline, a nutrient that helps in normal fetal brain development. The researchers measured the offspring’s cognitive skills through behavioral tests. They also measured brain signaling activity by examining the hippocampus, which controls aspects of learning and memory, and is often affected in Alzheimer’s disease. The researchers found that mice whose mothers had diets supplemented with choline had improved hippocampal function, even into later adulthood, compared to mice whose mothers had not received choline during pregnancy. By identifying specific pathways that affect premature aging changes, researchers hope to develop effective treatments for the early Alzheimer’s disease-like changes that impact people with Down syndrome. [Supported by NICHD, NIA]

Tumors and Down syndrome in a mouse model. People with Down syndrome have intellectual disabilities, and many also have heart defects and/or early dementia. However, people with Down syndrome are typically less likely than the general population to develop solid tumors. Scientists recently discovered an interesting exception to this apparent protective effect. After being exposed to certain cancer-promoting chemicals, mice bred to mimic the genetic basis of Down syndrome were more likely to develop hyperkeratosis (a thickening of the skin) and papillomas (wart-like skin tumors) than their unaffected littermates. These experiments suggest that certain changes in gene expression in Down syndrome may be responsible for the growth and overgrowth of certain types of cells. Therefore, the processes that suppress or promote tumor formation in Down syndrome may be more complex than previously appreciated, which may ultimately have clinical implications for people with Down syndrome. [Supported by NICHD]

Intellectual disability and obesity risk. Children in the United States with intellectual disability (ID) are almost twice as likely as their peers to be obese, according to an analysis of nationally-representative data collected in the CDC’s National Survey of Children’s Health. In children ages 10-17 years, 28.9 percent of children with ID were reported to be obese, compared with 15.5 percent of children without ID. This difference remained after controlling for age, sex, race/ethnicity, and poverty level. Less frequent physical activity was associated with higher rates of obesity in children both with and without ID, though the difference was significant only for children without ID. The prevalence of obesity was higher in all children who ate family meals every day, compared to fewer days per week, and this effect was significantly more pronounced in children with ID. [Supported by NICHD, NIDDK]
Injury-related emergency department visits for children with autism or intellectual disability. Parents of children with autism spectrum disorder (ASD) are often concerned about their children becoming injured. Analyzing nationwide 2008 data on emergency room visits, researchers found that over a quarter of all visits among those with ASD were related to injury. Children with ASD had higher injury rates compared to youth with intellectual disability, but were less likely to be injured than youth who had neither ASD nor intellectual disability. Compared to all other pediatric injury-visits in the US, visits among children with ASD were more likely to be due to self-inflicted injury and poisoning, and were more likely to result in hospitalization. Children with intellectual disability were more likely to experience injuries inflicted by someone else, compared to children with ASD or typically developing children. [Supported by NICHD] https://www.ncbi.nlm.nih.gov/pubmed/27241347 [Aug 2016]

Labor induction not associated with risk of ASDs in children. Previous research has suggested that children born when labor is induced may be at elevated risk of ASDs. However, it has been unclear whether labor induction somehow caused ASD, or if children with ASD and who were born when labor was induced share some other unknown genetic or environmental risk factor. Researchers analyzed data from more than 1.3 million births from Sweden’s medical register of births, which is linked to Swedish population, health, and education records. The researchers investigated outcomes in siblings of children with ASD whose birth had not involved labor induction. By studying the siblings, the researchers were able to account for more of the environmental and genetic factors that could contribute to ASD risk. The analyses of sibling outcomes showed no association between labor induction and ASD risk. These findings suggest that concern for ASD should not strongly factor into clinical decisions on whether to induce labor. [Supported by NICHD] https://www.ncbi.nlm.nih.gov/pubmed/27454803 [Sep 2016]

Researchers discover role of peripheral sensory system involvement in ASDs. Scientists recently uncovered a critical role for two genes that are expressed in somatosensory neurons – MECP2 and GABRB3 – for development of tactile and behavioral deficits in an animal model of ASD. MECP2 mutations cause Rett syndrome, and GABRB3 has been associated with ASD. Deletion of MECP2 or GABRB3 in peripheral somatosensory neurons in mice caused synaptic and mechano-sensory dysfunction, as well as tactile impairments. Deletion of these genes during development led to social interaction deficits and anxiety-like behaviors, and restoring MeCP2 expression in MECP2-deficient mice rescued the impairments. These data strongly indicate a role for mechano-sensory processing dysfunction in behavioral impairments in mouse models of ASD, and have broader implications for peripheral sensory system involvement in brain development and autism. [Supported by NINDS, NIDCR] https://www.ncbi.nlm.nih.gov/pubmed/27293187 [Jul 2016]

Researchers uncover mechanisms of gene related to ASDs and Phelan McDermid syndrome. Mutations of the SHANK3 gene are associated with ASDs. SHANK3 is expressed in most cells and is particularly enriched at excitatory synapses. Scientists discovered that SHANK3 mutations were associated with impaired Ih (hyperpolarization-activated cation) channels in human neurons. The impaired function of these ion channels resulted in decreased length and branching of the neuronal projections, and it also altered the electrical properties of the neuron and its connections with other neurons. The study also indicates that the SHANK3 protein is involved in organization of the Ih channels during neuronal development. [Supported by NINDS, NIMH] https://www.ncbi.nlm.nih.gov/pubmed/27293187 [Jul 2016]

Improving empathic communication skills in adults with ASD. Researchers examined the effectiveness of a video-feedback intervention with a visual framework component to improve verbal empathetic statements and questions during conversation for adults with ASD. The intervention improved empathy and confidence in communication skills. [Supported by NIDCD] https://www.ncbi.nlm.nih.gov/pubmed/26520148 [Mar 2016]
Identifying target in FMRP in mouse model of Fragile X. In Fragile X syndrome (FXS), the most common inherited form of intellectual disability, mutations in the fragile X mental retardation gene (FMR1) prevent cells from producing fragile X mental retardation protein (FMRP). However, the mechanism by which loss of FMRP leads to the developmental and neurological problems seen in FXS is poorly understood. In recent experiments, researchers used a mouse model of FXS to identify a molecular target of FMRP. They treated these mice with a promising small molecule called Nutlin-3, which acts on this molecular target of FMRP. They found that the treated mice had better growth and development of nerve tissue and fewer cognitive deficits. This work suggests that Nutlin-3 merits further study as a potential treatment for fragile X syndrome. [Supported by NICHD, NIMH, NINDS]


New mouse model for muscular dystrophies shows defects in repairing muscles. Muscular dystrophy refers to a group of more than 30 genetic diseases characterized by muscle weakness and muscle loss that progressively worsens over time. One group of muscular dystrophies is thought to be caused by a mutation in a protein called “dysferlin,” which is associated with skeletal muscle repair. Reduction or loss of dysferlin has been linked to a mutation in the ANO5 gene, which causes two types of muscular dystrophies, limb-girdle muscular dystrophy and Miyoshi myopathy dystrophy. The ANO5 gene usually contains instructions for repairing muscles. Researchers have created an Ano5 mouse model with a disrupted ANO5 gene. These Ano5 mice have tissues that appear and function similarly to those of muscular dystrophy patients, as well as an inability to exercise or repair muscle cells. [Supported by NICHD, NIAMS, NEI, NHGRI, NCATS]


Genome editing restores dystrophin protein in mouse model of muscular dystrophy. Duchenne muscular dystrophy (DMD) is a fatal muscle disease that affects 1 in 3500 to 5000 boys, often resulting in heart attacks or heart failure. The disease is caused by mutations in the gene for dystrophin, a protein that supports muscle cells when they contract. Recently, a genomic editing technique called “myoediting” has enabled researchers to specifically modify the genome, presenting a potential new way to correct disease-causing mutations. A mouse model of DMD, called the mdx mouse, has a genetic mutation that is similar to DMD in humans. Using myoediting, researchers were able to specifically target dystrophin genes in muscle cells of the mdx mouse and introduce specific modifications to the DNA. This led to an increase in the level of normal dystrophin in the treated mouse muscle over time. The mice who received this therapy also had more grip strength in their legs than mice who did not. Although this is experimental science in an animal model, this technique may form the basis for developing treatments for patients with muscular dystrophy. [Supported by NICHD, NHLBI, NIDDK, NEI]


Neurological Disorders and Mental Health

Uncorrected farsightedness linked to literacy deficits in preschoolers. The Vision in Preschoolers study found that children with moderate uncorrected farsightedness (hyperopia) did significantly worse in preschool literacy tests than peers with normal vision. Moderate hyperopia may affect up to 14 percent of pre-school children; it makes it difficult to see things up close. While refractive errors can lead to literacy deficits that affect grade school readiness, early detection with screening can lead to correction with glasses. [Supported by NEI]

**Computer-aided diagnosis in Retinopathy of Prematurity.** Retinopathy of prematurity (ROP) is a leading cause of blindness in children. ROP primarily affects premature infants weighing about 2½ pounds or less that are born before 31 weeks of gestation. Diagnosis depends on reviewing images of the eyes for growth of abnormal blood vessels. In severe cases, the abnormal vessels become enlarged and twisted, a condition known as plus disease, which can lead to detachment of the light-sensitive retina. In about 90 percent of ROP cases, the disease improves and leaves no permanent damage, but severe cases require time-sensitive treatment. The recent Telemedicine Approaches to Evaluating Acute-phase ROP (e-ROP) study demonstrated that trained readers could accurately detect severe ROP from images remotely sent from a clinic. Telemedicine provides new options for rural and underserved communities where a pediatric ophthalmologist is unable to evaluate infants in person. However, diagnosis of plus disease can differ between experts, as some ophthalmologists deviate from published definitions in their treatment decisions. The e-ROP consortium has now developed computer-based image analysis to diagnose plus disease. They found that when incorporating additional factors used by experts the algorithm could diagnose plus disease with 95 percent accuracy (compared to an average 87 percent diagnosis agreement between 11 experts in the study). [Supported by NEI]


**EEG as a biomarker for epileptogenesis in infants with tuberous sclerosis complex (TSC).** Epilepsy affects approximately 80 percent of individuals with TSC and almost half of all infants with TSC develop epileptic spasms, which is associated with poor neurological outcomes. Scientists recently demonstrated that serial routine EEGs in infants with tuberous sclerosis complex is a feasible strategy to identify individuals at high risk for epilepsy. Such a predictive biomarker may be useful in allowing for earlier intervention to alter or prevent epileptogenesis in these patients. [Supported by NINDS, NCATS]


**Understanding common neurodevelopment disorders (NDDs) through rare genetic syndromes.** Researchers applied advanced computational methods to brain scans from individuals with NDDs to identify subtle structural changes in specific brain regions associated with increased risk for NDDs. These efforts pinpointed specific genetic effects in brain networks important for planning, communications, and social interaction. For example, neuroimaging a rare cohort of humans with different numbers of sex chromosomes showed that X- and Y-chromosomes exert effects on the proportional size and organization of the brain systems involved in adaptive social functioning. (PMID 25146371, PMID 26911691). Scientists are also using analogous approaches in mice with abnormal sex chromosome counts (PMID 25146308). Another study showed that MRI scans can detect a difference in cortical thickness (changes in anatomy of the surface of the brain) in children with ASD. As these children were better able to communicate, their cortical thickness increased at a faster rate than children who had not been diagnosed with ASD. (PMID 27061356) [Supported by NIMH]

**Longitudinal studies of childhood-onset schizophrenia (COS).** COS is a rare and severe disorder, with more pronounced biological and genetic factors than for the adult-onset form of schizophrenia. Recent findings include abnormal structural brain connectivity in patients with COS and more subtle abnormalities in brain growth in healthy siblings of COS patients. These findings indicate genetically influenced developmental abnormalities in schizophrenia, particularly delayed maturing of connections between the occipital and temporal lobes of the brain of COS patients. (PMID 26176706) COS may also affect connections in how brain regions function. Analysis of resting-state brain imaging in patients with COS, their siblings, and healthy controls found striking abnormalities in the integration of activation in cognitive/social and motor/sensory circuits in the brain. (PMID 26493637) [Supported by NIMH]


**Movement helps improve focus in children with attention-deficit/hyperactivity disorder (ADHD).** About 11 percent of all children between the ages of 4 and 17 have ADHD. ADHD is characterized by impulsivity, hyperactivity, and inattentiveness. Physical activity, like bouncing on a ball chair or even chewing gum, seems to allow these children to focus on difficult tasks. Researchers analyzed 26 teens and pre-teens diagnosed with ADHD, and compared them to a control group of 18 with typical development, examining how the intensity and frequency of movement affected the students’ ability to do tests that demanded focus. The ADHD students with the highest number of correct answers showed the greatest degree of movement. The typically-developing group did not show any within-group differences. The findings suggest that excessive movement may reflect compensatory efforts in children with ADHD to modulate attention and alertness. [Supported by NIMH, NICHD] https://www.ncbi.nlm.nih.gov/pubmed/26059476 [2016]

**Variants associated with opioid-related respiratory depression in children.** Morphine is commonly used to treat postoperative pain in children, but opioids like morphine also have serious side effects such as respiratory depression. In a recent study, scientists found that certain genetic variants were associated with an increased risk of respiratory depression (2.36 to 3.7 times greater risk, depending on the variant in question). [Supported by NHGRI, NCATS, NICHD] https://www.ncbi.nlm.nih.gov/pubmed/26810133 [Jan 2016]

**Substance Use**

**Improved clinical guidelines for diagnosing fetal alcohol spectrum disorders.** Prenatal alcohol exposure is a leading preventable cause of birth defects and developmental abnormalities in the United States. Recently, researchers issued improved guidelines for diagnosing fetal alcohol spectrum disorders. The new guidelines provide a more precise definition of documented prenatal alcohol exposure, advice for evaluating facial anomalies and physical deformities characteristic of fetal alcohol spectrum disorders, and new information about the extent of cognitive and/or behavioral impairments seen in different subtypes of fetal alcohol spectrum disorders and in children less than three years old. [Supported by NIAAA]


**Screening, brief intervention, and referral to treatment (SBIRT) for adolescent alcohol and other substance misuse.** SBIRT by primary care providers has been shown to be effective in reducing alcohol misuse and related problems in adults, and some evidence has supported the use of SBIRT in preventing the initiation and escalation of substance use by adolescents.

- Physicians often face barriers to providing these services, including time constraints and a lack of training in SBIRT. Recently, researchers found that pediatricians who are provided with brief training on implementing substance use and mental health SBIRT were significantly more likely
to conduct screening, assessment, and brief interventions with adolescent patients than pediatricians who were not provided with this training. [Supported by NIAAA] 

- To encourage screening for alcohol problems in youth, researchers developed a very brief, empirically-based alcohol screener and guide to help primary care providers identify 9 to 18-year-olds who are at risk for alcohol use, are using alcohol, or have alcohol use disorder (AUD). Researchers used a computer-administered assessment to examine alcohol involvement in a large sample of adolescents seen in rural primary care settings. The researchers found that a single question on past year drinking frequency – as recommended in the youth screening tool – could help identify youth whose AUD risk ranged from moderate to the highest level of risk. [Supported by NIAAA] 

Adolescent alcohol exposure leads to brain and behavior changes in adulthood. Researchers found that exposing rats to alcohol during adolescence led to anxiety-like behavior, increased drinking, and changes in the amygdala – an area of the brain involved in the regulation of emotion, anxiety, and alcohol use – during adulthood. The epigenetic modifications observed in these animals were associated with changes in the expression of genes involved in synaptic plasticity, a neurobiological mechanism underlying learning and memory, and in synaptic changes in amygdala neurons. In adult animals, administering compounds that block certain epigenetic processes normalized gene expression patterns and reduced the anxiety-like and drinking behaviors produced by adolescent alcohol exposure. [Supported by NIAAA] 

Opioid prescriptions to children and teens were low and stable over time. Prescription opioid misuse is the fastest growing drug problem among adolescents in the United States. As many as 8-9 percent of 12th grade students have reported that they had misused opioids in the past year. Researchers used a nationally representative dataset, the Medical Expenditure Panel Surveys, to assess trends in opioid prescriptions made to children and adolescents, to their families, and to adults in the United States from 1996 to 2012. The researchers found that, from 1996 to 2012, opioid prescriptions to children and adolescents remained stable and low (from 2 to 3 percent). In contrast, opioid prescriptions to family members of children and adolescents (and adults in general) significantly increased during this period. The most common opioid prescriptions to children and adolescents in 2012 were codeine, hydrocodone, and oxycodone. This high rate of codeine prescriptions was unexpected, as codeine can lead to toxicity or inadequate pain relief. Safer alternatives exist for many children and adolescents. [Supported by NICHD, NIGMS] 

Rural-urban differences in prescription opioid misuse among adolescents. Researchers used data from a 2011-2012 nationally representative survey of over 30,000 adolescents to assess prescription opioid misuse in adolescents age 12-17. An estimated 6.8 percent of rural teens and 5.3 percent of teens in large urban areas reported misusing opioids in the previous year. Rural adolescents perceived substance use to be less risky, and were more likely to smoke and engage in binge drinking. However, they were less likely to use marijuana. Regardless of whether they lived in a rural or urban area, teens that misused opioids most commonly reported the source of the drug as friends and family. However, rural teens were more likely than urban teens to report having received opioids from a physician or dealer. These results may help public health officials improve programs to decrease opioid misuse, particularly in rural areas. [Supported by NICHD] 
**Teens using e-cigarette devices not just for nicotine.** In a recent study of 8th, 10th, and 12th graders, researchers found that of the teens who ever used a vaporizer, 65 percent reported that the last time they used the device they inhaled just flavoring, 20 percent inhaled nicotine, 6 percent inhaled marijuana, and 6 percent were unsure what substance they were using. Although the FDA recently expanded its tobacco regulatory authority to include e-cigarettes, many of these types of devices may be used for other purposes. [Supported by NIDA]  

**E-cigarettes increase likelihood of smoking among adolescents.**
- In the first national longitudinal study of e-cigarettes and young adults in the United States, scientists found that youth who used e-cigarettes were more likely than their peers to start smoking traditional cigarettes within a year than peers who didn't smoke e-cigarettes. [Supported by NCI, NCATS] [https://www.ncbi.nlm.nih.gov/pubmed/26348249](https://www.ncbi.nlm.nih.gov/pubmed/26348249) [Nov 2015]
- Researchers analyzed data from the Children’s Health Study, which includes periodic surveys that assess smoking behavior among high school juniors and seniors in southern California. Although use of conventional cigarettes in this population has declined steadily over the past two decades, the study showed an increase in the percentage of students who reported using cigarettes and/or e-cigarettes in 2014 (the most recent year that data were collected) compared with the percentage of students using cigarettes in 2004. [Supported by NCI, FDA] [https://www.ncbi.nlm.nih.gov/pubmed/27401102](https://www.ncbi.nlm.nih.gov/pubmed/27401102) [Aug 2016]

**Methamphetamine use and the adolescent brain.** Scientists have found that adolescent methamphetamine users exhibited more significant and widespread gray and white matter alterations, particularly affecting the frontostriatal system, and greater executive dysfunction compared with adult users. These findings highlight that the adolescent brain is more vulnerable to methamphetamine than the adult brain, and may explain the severe behavioral complications and relapses that are common in adolescent-onset drug addiction. [Supported by NIDA]  

**Bone and Muscle Health**

**Markers for bone health in adults are apparent in children.** More than 53 million people either already have osteoporosis – which commonly occurs in older women – or are likely to develop osteoporosis because of low bone density. This potentially debilitating disease has its origins in childhood, when low bone density and fractures can first become clinically apparent. Previously, a study of European adults identified specific changes near two genes, EN1 and SOX6, that appeared to be linked to low bone density. Researchers set out to determine whether similar genetic changes were apparent in children and whether they were more common in girls or boys. Leveraging genome-wide genotyping data on over 1,400 teens from the Bone Mineral Density in Childhood Study, researchers identified genetic changes that are associated with increased bone density in children and adolescent females, but not in males. The researchers also reported, for the first time, associations between rare genetic variants near EN1 and bone density in childhood. This provides evidence that the genetic variants previously identified in adults also affect bone mass density in childhood. [Supported by NICHD, NIDDK, NCATS, NHLBI]  

**Refining understanding of enzymes in bone and cartilage formation.** Researchers are currently building upon knowledge gained in previous work on a rare condition known as soft bones. In this previous study, the scientists discovered that enzyme replacement therapy can rectify some of the clinical conditions in infants. In this new extension of their work, the team is seeking to determine how the two phosphatase enzymes that are deficient in this genetic condition interact with each other and work cooperatively in the
initiation of mineralization. Understanding the molecular mechanism of mineralization is key to developing new treatment approaches for genetic skeletal abnormalities. [Supported by NIDCR, NIAMS] https://www.ncbi.nlm.nih.gov/pubmed/26457330 [Dec 2015]

**Uncovering a new pathway in bone developmental defects.** Scientists sought to unravel how a specific transport protein found in cilia, which are short, hair-like, rhythmically beating cellular appendages that provide cellular mobility, directs bone cell precursors to develop into bone, and how the absence of this protein leads to growth retardation and decreased bone mass. Through the power of genetics, the scientists discovered that this ciliary protein affects the cellular ultrastructural framework, and that the loss of this protein leads to inhibition of bone formation. These findings present novel opportunities for therapeutic targeting in skeletal abnormalities. [Supported by NIDCR, NIAMS, NCI, NIA] https://www.ncbi.nlm.nih.gov/pubmed/26996322 [Mar 2016]

**Childhood Disease, Allergies, and Immunity**

**FNDC1 as a disease contributing gene for acute otitis media (AOM).** AOM is one of the most common pediatric disease and the most frequent reason for antibiotic treatment in children. A genome-wide association study (GWAS) for AOM found that the gene *FNDC1* may play a role in the pathogenesis of AOM. *FNDC1*’s biological function is not well studied, but it is known to play a role in inflammation. This study is the largest genetic study of otitis media to date. [Supported by NHGRI] https://www.ncbi.nlm.nih.gov/pubmed/27677580 [Sep 2016]

**Gauging the correct dose of antibiotic to fight serious infections in children.** Pediatricians face a difficult challenge in gauging the right dose of the antibiotic cefepime for serious bacterial infections in children. This drug is widely used to treat certain potentially life-threatening infections, which are resistant to many other medications. Too low a dose of cefepime risks treatment failure in infants and children with infections, but using more than is needed increases the risk of new resistant strains of bacteria. To assess current dosing recommendations, researchers analyzed data from two published studies on intravenous cefepime use in pediatric patients with suspected or confirmed infections. The scientists found that the current standard regimen of cefepime may not be sufficient to avoid treatment failure in children more than 30 days old who have severe bacterial infections. [Supported by NICHD] https://www.ncbi.nlm.nih.gov/pubmed/26810655 [Mar 2016]

**Muscle mitochondrial dysfunction in severely burned children.** Severe burns over a large proportion of the body are known to increase a patient’s metabolism to abnormally high rates, with adverse effects that last long after the original burn injury. The long-term effects can include multi-organ dysfunction, degradation of muscle protein, insulin resistance (pre-diabetes) and increased risk for infection. To develop new approaches to blunt these long-term effects, however, scientists need to develop a more complete understanding of the biochemical processes involved in such burn-related “hypermetabolism.” Researchers found that after a burn injury in children, the functioning of the mitochondria (energy-producing structures within the muscle cells) is altered, compared with healthy mitochondrial functioning, and remains so for at least two years. These changes likely contribute to burn-induced hypermetabolism and its lasting adverse effects. [Supported by NICHD, NCATS, NIA, NIGMS, NIAMS] https://www.ncbi.nlm.nih.gov/pubmed/26361327 [Jan 2016]

**Hydroxyurea for children with sickle cell anemia.** Sickle cell anemia is a chronic and debilitating disease that affects an estimated 100,000 people in the United States, about a third of them children. The drug hydroxyurea has been approved by the FDA to treat adults, but not children, with sickle cell anemia. Although the drug has not been approved for use in children, it is frequently prescribed “off-label” for children, especially older children, in capsule form. Researchers measured children’s blood concentrations to hydroxyurea in both capsule and liquid form. The scientists found that the liquid and
capsule forms were equivalent, and that dosages based on a child’s weight provided consistent and predictable drug exposure. The results of the study may support approval of the drug in children, and will help develop a liquid form for children who are unable to swallow a capsule. [Supported by NICHD, NHLBI]


**Drug may reduce stroke in children with sickle cell disease (SCD).** SCD describes a group of inherited red blood cell disorders. People with SCD have abnormal hemoglobin, called hemoglobin S or sickle hemoglobin, in their red blood cells. Children with sickle cell disease (SCD) have an increased risk of stroke. Scientists found that the drug hydroxyurea can reduce blood flow velocities in the brain, a key predictor of stroke in these patients. Hydroxyurea is already prescribed to treat pain in children with SCD. [Supported by NHLBI, NCATS]


**Genes, congenital heart disease, and neurodevelopment.** Researchers have found several hundred genes that, when mutated, can lead to congenital heart disease. Many of these genes were recently found to play key roles in early development in both the heart and the brain, which is consistent with the observation that children with congenital heart disease are also at risk for neurodevelopmental disabilities. [Supported by NHLBI]


**Identifying risk factors for pancreatitis in children.** A large multinational group of scientists found that the most common risk factor for pancreatitis in children was at least one mutation in any of four genes that are known to be associated with pancreatitis. The researchers also identified pancreatic duct obstruction as another common risk factor, and that, overall, non-Hispanic children were more likely than Hispanic children to develop chronic pancreatitis. The results from this large study suggest that there are potential ways to screen for increased risk of pancreatitis in children, paving the way for early intervention. [Supported by NIDDK, NCI, NCATS]


**Genetic diversity and evidence for transmission of *Streptococcus mutans* (S. mutans).** Mother-to-child transmission is widely accepted as the primary route of infection with *S. mutans*, the primary bacteria causing caries (dental decay). Although other sources of transmission have been reported (i.e., from the father, nursery and/or school classmates), research investigating these other sources is rare. This study investigated the genetic diversity and transmission of *S. mutans* in children and participating household members. Overall, children had 1-9 genotypes and those with multiple genotypes were 2.3 times more likely to have dental caries currently or in the past. Children most frequently shared genotypes with their mothers (54 percent), siblings (46 percent) and cousins (23 percent). This study presents evidence that there is child-to-child and intra-familial transmission of *S. mutans*, in addition to mother-to-child transmission. Further research in this area could identify new strategies to prevent dental caries in high risk children. [Supported by NIDCR]


**Discovering the underlying causes of periodontal inflammation in children with leukocyte adhesion deficiency type 1 (LAD-1).** LAD-1 is a disease of the immune system that is often diagnosed in infancy or childhood. LAD-1 disrupts the body’s ability to fight infection and inflammation, increasing the risk of developing periodontitis, an infection of the tissues that surround and support the teeth. Compared to healthy individuals or individuals with other types of severe periodontal disease, the teeth of individuals with LAD-1 have different bacterial communities, which produce large complex molecules that move into periodontal tissues, potentially triggering the inflammation associated with periodontitis. Therefore, therapies to correct the balance of healthy and disease-causing bacteria and inhibit the molecules
responsible for causing the inflammation could help individuals with LAD-1 and those with severe periodontal disease. [Supported by NIDCR]

**Identifying causes of Amelogenesis Imperfecta (AI).** AI is a condition where the enamel of teeth does not form properly, leading to problems in early childhood, including increased susceptibility to dental decay. Researchers examined how mutations in two essential bone proteins needed in early tooth development result in AI. Their results showed that these proteins act through regulation of the expression of key enamel enzymes that are essential for formation of the proper tooth enamel architecture. These results will lead to further studies on the mechanisms of AI and greater understanding of this disease. [Supported by NIDCR]

**Respiratory Syncytial Virus (RSV) vaccine candidate shows promise in early clinical trial.** Each year in the United States, RSV leads to an average of about 55,000 hospitalizations among children younger than 5 years, with most hospitalizations occurring among infants younger than 6 months. There is currently no approved vaccine to prevent RSV infection. Scientists have developed an attenuated RSV vaccine. In a Phase I trial, the researchers found that when compared to the previous leading RSV candidate, the new candidate more effectively elicits protective antibodies in children who have not been exposed to RSV. [Supported by NIAID, NCATS]

**Prevention of recurrent, severe lower respiratory tract illnesses (LRTIs) in preschool children.** Many preschool children develop recurrent, severe episodes of LRTIs. Although viral infections are often present, bacteria may also contribute to these illnesses. Researchers set out to evaluate a strategy of treating children with recurrent severe LRTIs with the drug azithromycin, started prior to the onset of severe LRTI symptoms. Among young children with histories of recurrent severe LRTIs, children who received azithromycin early during an apparent RTI were less likely to have a severe LRTI, compared with children who received a placebo. [Supported by NHLBI] https://www.ncbi.nlm.nih.gov/pubmed/26575060 [Nov 2015]

**Acetaminophen is safe for children with asthma.** In a new clinical trial, researchers found that use of acetaminophen to manage pain or fever in young children with asthma is not associated with worsening asthma. This is an important finding because some prior observational studies suggested acetaminophen use might exacerbate asthma, which led some doctors to recommend against its use in children with asthma. The findings provide assurance to doctors and parents for providing acetaminophen to children with asthma who have fever, pain, or other discomfort. [Supported by NHLBI, NIAID, NCATS]

**Preseasonal treatment decreased colds in inner-city children with asthma.** A study conducted within the Inner-City Asthma Consortium showed that pre-seasonal treatment with Omalizumab, an injectable antibody sold under the brand name Xolair, significantly decreased the number of colds in inner-city children with allergic asthma. [Supported by NIAID, NCATS]

**Better sleep might improve quality of life for children with asthma.** To better understand how nighttime sleep quality and daytime sleepiness affect children with asthma, researchers collected information on asthma control, sleep, and health-related quality of life from 229 children and their parents. Because the study took measurements multiple times over two years, the researchers were able to look at individual
children’s changes, as well as to compare children with each other. Unsurprisingly, poorer asthma control was associated with lower health-related quality of life. However, the researchers found that daytime sleepiness explained the effect of asthma control on quality of life at the individual level, and both nighttime sleep quality and daytime sleepiness could explain this effect at the between-children level. The researchers suggested that interventions to improve sleep and reduce sleepiness during the day might help reduce the negative effect of poor asthma control on children’s health-related quality of life. [Supported by NICHD, NIAMS]

Follow-up study reveals early peanut consumption may lead to long-lasting protection against peanut allergy. A follow-up study to the Learning Early About Peanut Allergy (LEAP) study, called LEAP-On, was completed. The original LEAP study showed that regular peanut consumption begun in infancy and continued until 5 years of age led to an 81 percent reduction in development of peanut allergy in infants deemed at high risk. The results of the LEAP-On study demonstrate that this reduction of peanut allergy persists following a year of peanut avoidance by patients, suggesting long-lasting protection. [Supported by NIAID]

New criteria developed to accelerate diagnosis of rare autoimmune disorder. Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is a rare primary immunodeficiency disorder that usually develops in childhood and teenage years. Researchers have identified new criteria to accelerate diagnosis by approximately 4 years and potentially prevent life-threatening endocrine complications. [Supported by NIAID]

Rare Pediatric Diseases

Researchers identify potential cause and treatment for Smith-Lemli-Opitz Syndrome (SLOS). SLOS is a rare genetic disease that disrupts the nervous system, which can lead to microcephaly and other brain defects. Its symptoms vary, ranging from fetal abnormalities to a spectrum of physical and neurological effects, often similar to autism, in children. SLOS currently has no cure or approved treatment. The disease stems from mutations in a gene called DHCR7, which helps carry out the last step of the body’s cholesterol production. The mutations lead to cholesterol deficiency and a buildup of a compound called 7-dehydrocholesterol (7DHC), a key step in how the body produces cholesterol. Cholesterol is an essential molecule that helps form cell structure and plays a role in several biological functions, including the development and activity of neurons in the brain.

- Researchers developed a new model to study SLOS by inducing stem cells from skin samples of SLOS patients to form cells resembling neurons, testing how 7DHC interacts with cell signaling processes. They found that 7DHC caused a loss of a key signaling protein called β-catenin, which normally regulates how neurons develop. The researchers used a drug to stabilize β-catenin, showing that this drug may be a potential treatment for SLOS. [Supported by NICHD, NIGMS]

- Simvastatin, which is commonly prescribed for reducing cholesterol, may be effective for treating SLOS. In a recent study, 18 SLOS patients between the ages of 4 and 18 received treatment with either simvastatin or placebo for the first half of the study, then switched treatments for the second half. The researchers found that simvastatin significantly lowered levels of DHC in 12 out of 18 participants. The participants also had improved scores on a test measuring irritability. The
drug appeared safe for SLOS patients, with no evidence of liver or muscle toxicity. [Supported by NICHD]  

**Blocking neuronal death in Niemann-Pick Disease delays disease progression in mice.** Niemann-Pick Disease type C1 (NPC1) is a rare genetic disorder that primarily affects children and adolescents, causing a progressive decline in neurological and cognitive functions. Researchers discovered that the loss of neurons in NPC1 is caused by a process called “necroptosis,” in which cells die through inflammation processes regulated by the immune system. The scientists tested a chemical that blocks necroptosis on human cells from patients with NPC1, which prevented these cells from dying. The researchers also tested this chemical in a mouse model of NPC1. The treatment slowed the progression of NPC1 in the mice. The scientists emphasized that necroptosis is a late, if not final step, in NPC1, so blocking necroptosis will likely be only part of a combination of therapies for the disease. [Supported by NICHD]  

**Gene transfer treatment delays disease onset in a canine model of Batten Disease.** Batten disease, also called late infantile neuronal ceroid lipofuscinosis (LINCL), is a rare and fatal neurodegenerative disorder characterized by early childhood onset of motor deterioration and mental decline, seizures, and visual deficits, with death typically by age 10. The most common cause of Batten disease is due to mutations in a gene called *TPP1*, which cause deficiency of an important enzyme that helps cells to break down specific molecules. Researchers used genetic transfer techniques to place non-mutated *TPP1* genes into the cerebrospinal fluid situated in the brain ventricles, for subsequent uptake into the cells lining the brain ventricles. These cells successfully took up the gene and produced the protein, leading to protein distribution throughout the brain. The researchers tested this strategy in a canine model of the disease, and showed that the therapeutic approach delayed disease onset, extended the life span, and protected from early cognitive decline. [Supported by NINDS, NEI]  

**X-linked genetic mutation causes a form of brittle bone disease.** Osteogenesis imperfecta (OI), or brittle bone disease, is a rare genetic disorder affecting the protein collagen, which is found in bone, teeth, skin, and tendons. People with the disorder have bones that can break easily, often from a mild impact or for no apparent cause. Previously, all of the known forms of osteogenesis imperfecta were found to arise from genes on the autosomal, or non-sex, chromosomes. Scientists discovered a form of OI that results from a gene defect on the X chromosome, the first gene on a sex chromosome that could cause OI. The researchers found mutations in a gene known as *MBTPS2*. This gene contains information needed to make a protein called S2P (site-2-protease). The researchers found that mutant S2P undermines bone strength. This study shows how the genetic defect results in impaired bone formation, which could lead to treatments for this rare, frequently debilitating disease. [Supported by NICHD, NIAMS]  

**Cesarean delivery does not reduce fracture risk for babies with rare brittle bone disease.** Researchers analyzed data from 540 OI patients, showing that the subtype of OI, which correlates to OI severity, is the most important factor that determines a baby’s risk of fracture during birth. Contrary to popular belief, the method of delivery does not affect newborn fracture risk within the same subtype of OI; cesarean delivery does not protect against fractures during birth of OI babies. [Supported by NIAMS, NICHD, NIGMS]  
Glucose-6-phosphate dehydrogenase (G6PD) deficiency. A lack of the G6PD enzyme can cause newborns to develop sudden, rapidly progressing, dangerous cases of jaundice. If not treated quickly, this can result in permanent damage. Researchers developed a sensitive and accurate digital microfluidics platform for G6PD screening. This automated process could be more practical to use in resource-limited settings. [Supported by NICHD]

Pediatric diagnoses made by the Undiagnosed Diseases Network include:

- A previously unknown developmental disorder resulting in developmental delay, macrocephaly, and dysmorphic features (abnormally formed body structures). [Supported by NIH Common Fund, NHGRI]
- A collaborative effort that discovered a disorder caused by a single genetic mutation that acts as a molecular switch for sex determination, causing XX individuals to develop physically as males and XY individuals to develop as females. [Supported by NIH Common Fund, NHGRI, NICHD] https://www.ncbi.nlm.nih.gov/pubmed/27378692 [Aug 2016]

Pediatric Cancer

Sequencing all genes yields useful information for childhood cancer. Genomic sequencing of tumors is guiding diagnosis and treatment of cancer patients, but studies of children with cancer are lacking. Scientists have sought to determine how frequently a genome sequencing approach that focuses on all genes, not just those related to a patient’s cancer, yields information useful for clinical care. Combining results from cancer and normal blood cells, a team of researchers found that such an approach could potentially impact clinical cancer care in as many as 40 percent of children with cancer. In a notable number of patients, results showed mutations in genes that doctors would not have associated with the patient’s cancer type. These results suggest that a genome sequencing approach has the potential to benefit patients more broadly than focused genetic testing. [Supported by NHGRI, NCI]

Genetic predisposition to childhood cancer. Researchers conducted next-generation DNA sequencing of both the tumor and normal tissues from 1,120 pediatric cancer patients and found that 8.5 percent of patients had pathogenic or likely pathogenic mutations of genes within their normal tissue that increase their risk of developing cancer. Prior to this study, the presence of such germline mutations in pediatric cancer patients was thought to be extremely rare and restricted to children in families with strong histories of cancer. This study revealed that more than half of the children with germline mutations lacked any family history of cancer. These findings will likely change how children with pediatric cancer are monitored and evaluated, and may also change treatment approaches. [Supported by NCI]

Sunitinib malate reduces plexiform neurofibromas (pNF) in mouse model. pNFs in children and adults are symptomatic nerve and soft tissue tumors of neurofibromatosis type I (NF1), which are highly resistant to conventional chemotherapy and associated with significant morbidity and mortality. Sunitinib malate is a potent, highly selective small-molecule inhibitor with activity against multiple receptor tyrosine kinases, which have been implicated in the development of plexiform neurofibromas. In a mouse model of pNF tumors, sunitinib malate treatment reduced tumor number and size, providing insights for the design of future clinical trials. [Supported by NCI, NINDS] https://www.ncbi.nlm.nih.gov/pubmed/26375012 [Feb 2016]
**Success in slowing plexiform neurofibromas.** NF1-associated plexiform neurofibromas can cause significant morbidity and even mortality, and effective treatment remains an area of unmet need. Scientists conducted a phase II clinical trial and determined that an agent called pegylated interferon slowed the growth of plexiform neurofibromas two-fold. It also has the advantage of being able to be administered to young children who cannot swallow capsules. While these results are promising, more studies are needed to determine the optimal duration of therapy as well as adding potential long-term compliance issues. [Supported by NCI]

**Genome-wide profiles of extra-cranial malignant rhabdoid tumors (MRTs).** MRTs are rare lethal tumors of childhood that most commonly occur in the kidney and brain. Comprehensive genome analyses of pediatric extra-cranial MRT cases revealed gene expression and methylation subgroups associated with patient age, and differences in how genes are expressed in well-known developmental pathways. [Supported by NCI]

**New therapeutic target in Acute Myeloid Leukemia (AML).** Altered metabolism is a hallmark of cancer cells, and drugs that target metabolic enzymes have been effective in the treatment of a variety of cancer types. AML is the second most common type of leukemia in both adults and children, comprising approximately 25 percent of childhood leukemias. There is an urgent need for more effective therapy for AML, especially high-risk subtypes with poor survival rates. Scientists set out to identify metabolic enzymes with potential as therapeutic targets. Their data suggests that the one-carbon folate pathway could be an area of vulnerability for AML cells, and that MTHFD2, an enzyme differentially expressed in cancer compared to normal cells, could be an effective target for AML therapy. [Supported by NCI, NHLBI, NICHD]

**IDH1 variants as potential biomarkers for pediatric gliomas.** Brain tumors are the second-most common tumors in children, making up 20 percent of all pediatric cancers. More than half of pediatric brain tumors are gliomas. In recent years, the adult glioma field has seen a major breakthrough in the discovery that variant forms of the *IDH1* or *IDH2* genes are present in greater than 80 percent of certain types of adult glioma. However, until 2016, these *IDH1* and *IDH2* variants had not been implicated in gliomas in young children. Researchers have now shown *IDH1* mutations in gliomas of patients younger than ten years old for the first time. This study suggests that *IDH1* mutations could be a useful biomarker for brain tumors in pediatric populations as well as adults. [Supported by NCI, NIH OD]

**Distinguishing between pediatric and adult cystic nephromas.** Pediatric cystic nephromas (CN) are rare, benign renal neoplasms that can affect both young children and adult females. To date, there are no large studies that have identified definitive characteristics to delineate CN in these two populations. Recently, researchers reviewed the cases of 44 pediatric CN patients and identified distinctive clinical features that will allow development of better diagnostic criteria for pediatric CN. Furthermore, they found that specific genetic alterations previously identified to be associated with pediatric CN were not present in adult CN or in the related condition cystic partially differentiated nephroblastoma (CPDN). This finding that there are genetic differences between pediatric and adult CN and between CN and CPDN indicates that these are distinct diseases. The differences identified in this study will be useful for more confident diagnosis of these three conditions. [Supported by NCI]
Late mortality rate has declined over time for survivors of childhood cancer. Researchers from the Childhood Cancer Survivor Study analyzed late mortality for children with cancer. Late mortality is the total number of deaths in the late stages of an ongoing treatment or a significant time after an acute treatment. By studying 30 years of changes in treatments and 15-year mortality outcomes, researchers confirmed a reduction over time in radiation exposure and in total dose of chemotherapies that are usually administered at the most severe stages of cancer. The percentage of patients exposed to radiation therapy decreased by nearly half from the 1970s (when 77 percent of survivors had received radiotherapy) to the 1990s (when only 41 percent received radiotherapy). Although more patients received chemotherapy in recent decades, the average cumulative dose per patient decreased over time. Late mortality declined significantly over the 30 years studied. Among the five-year survivors of childhood cancer whose original diagnosis was made in the 1970s, the cumulative mortality at 15 years after diagnosis was 10.7 percent; if the original diagnosis was made in the 1990s, this risk was 5.8 percent. Deaths from late effects, secondary malignancy and pulmonary and cardiac diseases, as well as the primary malignancy, declined significantly. Although the decline in mortality could be attributed to better survivor care and screening, it is also likely that the changes in therapy over time contributed to this reduction in mortality. [Supported by NCI]

Improved treatment for children with high-risk B-cell acute lymphoblastic leukemia (B-cell ALL). In a phase III clinical trial enrolling over 3,000 children, scientists set out to determine optimum components of induction therapy and interim maintenance therapy for children with high-risk B-cell ALL. The trial showed that for children 1–9 years of age, dexamethasone treatment during induction therapy and high-dose methotrexate treatment during interim maintenance resulted in a 5-year event-free survival rate of 91.2 percent compared to 83 percent or less compared to children receiving prednisone instead of dexamethasone or receiving Capizzi methotrexate instead of high-dose methotrexate. Among all children and adolescents with high-risk B-cell ALL studied, high-dose methotrexate was superior to Capizzi methotrexate, and dexamethasone benefitted younger children but provided no benefit to children 10 years and older. [Supported by NCI]

Childhood Injuries and Maltreatment

Playing contact sports in youth may increase risk for neurodegeneration in later life. Although there are many documented cases of chronic traumatic encephalopathy (CTE) in professional athletes, the consequences of amateur athletics are less well known. A new study of donors to the Mayo Clinic Brain Bank compared the brains of men and women who had played contact and non-contact sports while in high school or college with those who had not. Pathological evidence of CTE was found in a third of the men who had played contact sports and in none of those who had not. [Supported by NINDS, NIA]

Identifying children with traumatic brain injury (TBI) at risk for ventilator-associated pneumonia (VAP). Thousands of American children are hospitalized each year for TBI. The most seriously injured of these children may be temporarily placed on a ventilator to help them breathe. Unfortunately, this life-saving device also places the child at risk for VAP, a serious infection in the lungs. Scientists at a large pediatric trauma center reviewed 119 cases of children with TBI who had been on a ventilator, and found that 42 of these children had developed VAP. The majority of VAP cases occurred before the fourth day in the hospital, and few happened after the seventh day. Children with VAP had significantly longer intensive care unit (ICU) and hospital stays, but not increased mortality. Children who had received certain treatments for elevated pressure in the brain – including barbiturate-induced coma, neuromuscular blockade, or a cooling blanket – were more likely to develop VAP. The scientists suggested that this
information could guide efforts to prevent VAP and inform early anti-VAP therapy. [Supported by NICHD]

Disparities in rehabilitation outpatient services for children with TBI. Recovery from a TBI may start in a hospital, but outpatient services like speech or physical therapy and mental health services are key to successful daily and long-term functioning. Researchers created a database of almost 300 pediatric providers and rehabilitation services in Washington State. They then contacted each provider by telephone, asking about types of services offered, acceptance of Medicaid insurance, availability of interpretation services, and other facilities. Overall, the researchers found that fewer services were available for children whose families also needed language interpretation. Less than half of all service providers accepted children with Medicaid insurance. [Supported by NICHD, NCATS]

Outcomes during inpatient rehabilitation for American Indian / Alaska Native (AI/AN) children with TBI. AI/AN children have the highest TBI-related mortality in the United States. TBI affects about 27.3 per 100,000 in the AI/AN population vs. 18.4 per 100,000 for the total population. However, little is known the AI/AN children who survive TBI. Researchers analyzed data from 114 AI/AN and 7,267 White children between 6 months to 18 years of age who received inpatient TBI rehabilitation services between 2002-2012 at facilities that utilized the Uniform Data System for Medical Rehabilitation. This system maintains data from over 800 inpatient rehabilitation facilities (approximately 70 percent of facilities) in the United States. At discharge, patients were assessed using developmental functional quotients (DFQs), which measured their overall dependence or independence in terms of mobility and cognitive ability. A higher DFQ indicates that a child is functioning closer to the level expected at that particular age. Overall, these functional outcomes were not associated with race, though among a small subgroup with loss of consciousness exceeding 24 hours, AI/AN race was associated with a lower DFQ for movement. Interestingly, an AI/AN child discharged from a rehabilitation facility in 2012 scored much higher on the cognitive test compared to an AI/AN child discharged in 2002, which the researchers attribute to children better understanding mobile technology to reach their families, which may improve some of the skills tested. This difference was not seen in White children. These findings show that, though AI/AN race was not associated with functional outcomes after inpatient rehabilitation for children with TBI, providers should not assume that AI/AN children with more severe injuries will have the same rehabilitation experience as the general population. Further research is needed to examine the effects of cultural sensitivity and patient outcomes for AI/AN children. [Supported by NICHD]

New guidelines to help doctors screen for young victims of abusive head trauma. Brain injury stemming from abuse, called abusive head trauma, is the leading cause of death among abused young children, yet doctors often miss the diagnosis. A skeletal survey – that is, a series of X-rays that check for fractures – can be a crucial tool for finding abuse that a doctor may not see during a physical exam. Doctors are sometimes uncertain about when to perform a skeletal survey. Researchers set out to develop a set of guidelines that would help doctors decide when to perform a skeletal survey on children under 2 years old who have a certain type of head trauma. The team used a combination of literature reviews and input from a panel of 12 pediatric medical experts to write the guidelines. The researchers believe that implementing guidelines like these will improve detection of abusive head trauma. [Supported by NICHD]

Understanding the role of genes in childhood abuse and adult mental health. Scientists have begun to study the role of oxytocin, a hormone found in the brain that is involved in social behaviors and the development of interpersonal bonds, in the context of childhood experiences. By studying small changes in the gene that is involved in oxytocin uptake, OXTR, scientists can assess whether abuse in childhood
affects genetic pathways that could influence behavior later in life. Researchers studied 393 African American adults with a history of person-on-person violence. Most of the participants had experienced one major trauma during their lifetime. The researchers detected epigenetic changes at sites near OXTR in 68 percent of the genetic signatures they tested. A history of child abuse appeared to correlate with sites of epigenetic changes near specific genetic variations. The epigenetic changes at these sites appeared in people who had experienced childhood abuse and adult depression or anxiety, but the changes did not fully explain the link between the two issues. [Supported by NICHD, NIMH, NIDA, NIGMS]

Children with disabilities more likely to be maltreated and placed in foster care. Children with disabilities are at increased risk for mistreatment, and neglect accounts for the majority of such cases. However, child protective services often cannot substantiate cases of neglect when they are first reported. Because of the lack of evidence, the children remain in their homes and are at risk for further mistreatment. A group of researchers investigated how much time typically passes between the first, unsubstantiated report of mistreatment and a new report of mistreatment of the same child. The researchers looked at the records of 489,176 children with unsubstantiated reports of neglect from 33 states, Puerto Rico, and Washington, D.C., and followed them for 4 years. Of these children, 12,610 had disabilities. The researchers found that children with disabilities were more likely to be referred to child protective services again and to be placed into foster care. The time between incidents was also shorter for children with disabilities. Overall, children with disabilities were 1.4 times as likely to be re-referred to child protective services, 1.8 times as likely to have substantiated maltreatment, and 2.7 times as likely to be put into foster care, compared with children without disabilities. [Supported by NICHD]

Pediatric Critical Care and Emergency Care

Protocol treatment is associated with better outcomes for children with severe sepsis. Sepsis is an intense, generalized immune system response to infection. If not brought quickly under control, sepsis can cause irreversible organ failure and death. Researchers reviewed what happened when children with severe sepsis came to the emergency department of a children’s hospital. Young patients treated according to a specific treatment protocol were significantly more likely to be free of organ dysfunction after two days of hospitalization and have shorter hospital stays, compared with children receiving non-protocol “usual care.” The hospital’s treatment teams had been trained to recognize early signs of severe sepsis and septic shock in children. They were also sent monthly reminders to use the protocol. The researchers suggested that the team’s shared acknowledgment and confidence that they were providing care within the protocol could have contributed to the results. The researchers also acknowledged that different protocols may be needed in different hospitals of the country and of the world, but that a “hospital-specific” sepsis protocol may be helpful in various other settings. [Supported by NICHD, NHLBI, NIGMS]
**Epidemiology of preventable safety events in pre-hospital emergency medical service (EMS) for children.** Researchers recently completed a national survey of more than 750 EMS providers to identify factors related to safety events and errors. The researchers identified airway management skills, personal anxiety, limited pediatric care skill and experience, and family members leading to delays or interference with care as key factors that may contribute to pediatric safety events. In addition, while surveyed EMS providers identified medication errors and team member communication as issues, these factors ranked lower than what has been seen in similar studies for in-hospital settings. These findings suggest that changes in training of EMS providers may be helpful to prevent medical errors in providing emergency care for children in out-of-hospital settings. [Supported by NICHD]


**Quality of care varies across different levels of neonatal intensive care units (NICUs).** In 2014, over 55,000 infants in the United States were born weighing less than 1500 grams (less than 3.3 pounds), which is considered to be very low birth weight (VLBW). NICUs deliver specialized care to these babies, generally decreasing infant mortality. Researchers analyzed the quality of care for over 21,000 VLBW infants born during a five-year period in over 130 NICUs in California. The NICUs were categorized based on their level of care: Level I facilities provide basic care to premature babies at low risk, while Level IV facilities are capable of caring for the most complex and critically ill newborns, including surgery. The researchers found that the quality of care varied widely across all levels of NICUs. There was no consistent relationship between the level of the NICU and the quality of care rendered. [Supported by NICHD, NIDDK]


**Disparities in pain treatment for children with appendicitis.** Scientists reviewed a national database of medical records for nearly 1 million emergency department visits by children who were diagnosed with appendicitis. Nearly all these children were admitted to the hospital from the emergency department. The researchers found that appendicitis pain appeared to be undertreated, with only 57 percent of children receiving any pain medication. Black children were less likely to receive any pain medication for moderate pain, and less likely to receive opioids for severe pain. [Supported by NICHD]


**Teen sexual assault victims may not receive recommended measures in pediatric emergency departments.** Adolescents are especially vulnerable to sexual assault. Recent, nationally representative data indicate that 10.5 percent of female high school students and 4.5 percent of male high school students reported being sexually assaulted. Researchers assessed how 38 pediatric hospital emergency departments administered testing and preventive treatments for adolescent victims of sexual violence. The scientists analyzed data on more than 12,000 cases of 12- to 18-year-old sexual assault victims. Fewer than half (44 percent) of the adolescents received recommended tests (certain sexually transmitted infections (STIs), pregnancy), and fewer still (35 percent) received recommended preventive measures, including STI prevention and emergency contraception. [Supported by NICHD]

Emergency department provider bias may impact care for American Indian children. Researchers partnered with Tribes and hospital emergency departments throughout the Upper Midwest to examine patterns of emergency department use and care for AI children. A survey of care providers at five hospitals measured implicit and explicit bias towards children and caregivers in the emergency department. This research found that 84 percent of clinicians had an implicit preference for White adults or children. In addition, the greater the number of AI children seen in the emergency department, the more clinicians saw AI children as challenging and caregivers as less compliant. Further research is needed to determine how emergency department clinician biases influence health care or outcomes disparities and what types of interventions can be created to reduce disparities. [Supported by NIMHD] https://www.ncbi.nlm.nih.gov/pubmed/26974675 [June 2016]

Children who survive cardiac arrest lose some mental function. The number of children under 18 who experience sudden cardiac arrest is unknown, but estimates range between about 1,000 and nearly 10,000 per year. Children who survive out-of-hospital sudden cardiac arrest but arrive at the hospital in a coma often lose some mental function. Doctors have started using a new way to treat these children: chilling their bodies to below normal body temperature, possibly helping to preserve function until the doctors can bring the children back to consciousness. A recent study tested whether this treatment, called therapeutic hypothermia, led to better results than standard treatment. Researchers compared children’s function a year after they experienced sudden cardiac arrest, based on the type of treatment they received. Out of 295 children enrolled in the study, 96 survived 1 year after their cardiac arrest, and the researchers tested 85 of them. Overall, the researchers found that all these children lost significant social, behavioral, physical, and mental function. Only about half still functioned at a near-normal level (a score of 70 or higher on a scale in which 100 is average), and many had severe impairment. Children 6 years or older showed the most loss. The researchers concluded that all these children lost function, regardless of the type of treatment they received (therapeutic hypothermia or not) or any other factor. [Supported by NHLBI, NICHD, NCATS] https://www.ncbi.nlm.nih.gov/pubmed/26940987 [Apr 2016]

Clinical Care, Outreach, and Services

Health challenges for rural children. Children who live in rural areas are more likely to live in poverty, have unmet medical needs, and rely on Medicaid for their health care. However, children’s hospitals that provide specialized care are primarily located in urban areas. Researchers compared the patient characteristics and hospital utilization of rural children and non-rural children, reviewing 672,190 admissions at 41 children’s hospitals in 24 states. Rural children accounted for 12 percent of the total hospital admissions. After analyzing the hospital records, the researchers found many differences between rural children and non-rural children. Rural children were more likely to have complex chronic conditions. Rural children accounted for higher inpatient costs and had a slightly increased likelihood of being readmitted to a hospital in 30 days. [Supported by NICHD] https://www.ncbi.nlm.nih.gov/pubmed/27244794 [May 2016]

Hospital quality impacts racial/ethnic disparities in severe maternal morbidity. Black women are more than twice as likely as White women to experience severe maternal morbidity during the delivery of their children. Researchers found that the hospital setting may play a critical role in these disparities. Black women who delivered at hospitals with the highest numbers of Black patients were at the highest risk for poor outcomes. Focusing care quality interventions on hospitals serving high rates of expectant Black mothers could result in considerable improvements in care for all women accessing care at these facilities. [Supported by NIMHD, NICHD] https://www.ncbi.nlm.nih.gov/pubmed/26283457 [Jan 2016]
Caregiver responses to early cleft palate care. The treatment for cleft lip and palate (CLP) is long and arduous, starting in infancy and often lasting into young adulthood. Having a child with a chronic condition like CLP is stressful for parents yet, some evidence suggests that having a child with a chronic condition can also foster resilience and positive adjustment in parents. Researchers examined caregiver responses to early CLP care for their infants. Caregivers were selected from one of two treatment groups: traditional care only and nasoalveolar molding (NAM) plus traditional care. While the first year of care was demanding for both groups, NAM onset and the child’s surgery were especially stressful times. Caregivers used optimism, problem-solving behavior, and social support to cope with this stress. Caregivers of NAM-treated infants experienced more positive psychosocial outcomes than caregivers whose infants had traditional care only. This research demonstrates the importance of considering caregivers in CLP treatments and offers new approaches to support caregivers and therefore improve the lives of children with CLP. [Supported by NIDCR]

Education program improved asthma self-management for rural children and their parents. Compared to a control group who were provided weekly general information, rural participants in an asthma education program delivered either through a weekly asthma class or an asthma day camp improved children's and their parent's asthma self-management. Fewer hospitalizations, fewer ER and office visits, and significant reductions in asthma severity were reported. This study provides an example of strategies for improving asthma self-management for children who live in rural areas. [Supported by NINR]

Improving the quality of well-child care for low-income families. Visits to the pediatrician for well-child check-ups are intended to give families the opportunity to identify and address important health, social, development, and behavioral issues. However, often there is not enough time to discuss many issues. Researchers conducted a study to assess the effects of a new well-child care intervention program, “PARENT-focused Redesign for Encounters, Newborns to Toddlers (PARENT)”, on the quality of well-child care visits among low-income families. The PARENT intervention included: (1) a parent coach serving as a health educator and the primary provider of routine preventive care services, screening, and guidance, (2) a web-based tool parents could use to select issues for upcoming visits, (3) a text messaging service with age-specific health messages to families, and (4) a brief problem-based visit with a pediatric clinician that included a physical exam. The study involved 251 families, with children 12 months or younger, from two independent pediatric practices located in a low-income area for one year, with one practice receiving the PARENT program and the other administering the usual well-child visits. At the end of the study, compared to families with the usual well-child care visits, the families in the PARENT intervention rated their care significantly higher in all preventive care services. There were 52 percent fewer emergency department visits in the intervention group, although there were no significant differences between the two groups in the number of sick visits or use of urgent care. [Supported by NICHD]

Revised WIC food package improved children’s diet quality. The Special Supplemental Nutrition Program for Women, Infants, and Children (called WIC) provides healthy food to low-income pregnant women, infants, and children up to the age of 5 years. The WIC program package was revised in 2009 to include more fruits, vegetables, whole grains, and lower-fat milk. Researchers used data from the National Health and Nutrition Examination Survey to analyze the diets of children (ages 2-4 years) from low-income households, before and after the 2009 change in the WIC food package. The researchers calculated the Healthy Eating Index (HEI), a score with 100 possible points measuring adherence to dietary guidelines, from information provided by caregivers on what the children ate over the previous 24-hour period. The study results showed that the HEI scores for the children participating in the WIC program increased after the 2009 changes. Nonparticipants showed smaller gains. Roughly half of the
children in WIC households were eating vegetables and beans, compared to only 1 in 5 non-WIC children. The switch from whole milk to low-fat milk did not result in decreased milk consumption. [Supported by NICHD] https://www.ncbi.nlm.nih.gov/pubmed/27244804 [May 2016]

**Intimate partner violence in rural low-income families.** Researchers recently reported a high prevalence of intimate partner violence over a five-year period among a representative sample of families living in rural, low-income communities in eastern North Carolina and central Pennsylvania. Researchers surveyed and visited families that recently had a new baby, beginning when the child was six months old and continuing periodically through the child’s fifth year. Depending on the timing of these visits, between 20-41 percent of couples reported intimate partner violence – quite a bit higher than national rates. Violence was most prevalent around the time of the birth of the child, decreasing significantly over the following five years. These findings suggested that perinatal and newborn health care visits are opportunities to conduct screening for intimate partner violence and to offer resources for individuals experiencing or at risk for violence. [Supported by NICHD] https://www.ncbi.nlm.nih.gov/pubmed/26709334 [Jan 2016]

**Technology and Tools**

**Developing a newborn screening tool to detect Niemann-Pick Disease.** Niemann-Pick disease type C (NPC) is a rare but fatal disorder that is caused by defects in how the body stores cholesterol. Because NPC symptoms vary widely, the disease often goes undetected, causing the brain and body to degenerate beyond the point of treatment. Current methods to screen for the disease are invasive or take a long time to process. Researchers analyzed dried blood spot samples from over 4900 normal newborns, 134 carriers of a defective NPC gene who will not develop the disease, and 44 NPC patients. In particular, the researchers analyzed each subject’s bile acids, which are found in bile, a substance produced by the liver. The researchers found that one bile acid (bile acid B) is increased 101-fold in patients with NPC. They also developed a two-step method that can quickly detect bile acid B in dried blood spots. This method could help detect Niemann-Pick disease in patients soon after they are born, allowing doctors to treat NPC patients as soon as possible and increasing these children’s ability to survive. [Supported by NICHD, NIDDK, NINDS, NHLBI] https://www.ncbi.nlm.nih.gov/pubmed/27147587 [May 2016]

**Potential new strategy for detecting bacterial infections in newborns.** Determining whether young infants have a fever caused by bacteria typically requires isolating live bacteria from blood, urine, or spinal fluid and growing the bacteria in a laboratory culture, often over the course of a few days. This method may also involve complicated medical procedures, such as a lumbar puncture (spinal tap). Waiting for test results may result in lengthy hospital stay. Developing fast and noninvasive diagnostic tools may provide better outcomes and lower treatment costs for young infants with fevers of unknown cause. With advances in genetic sequencing technology, researchers have explored diagnosing infections by assessing the body’s immune response. When the immune system wards off an infection, immune cells activate certain genes, depending on whether the infection results from bacteria or viruses. Collectively, these distinct genes form what is called a “biosignature.” Previous studies have suggested that analyzing immune cell biosignatures can distinguish between bacterial and viral infections; however, scientists were uncertain if this would work in young infants because their immune systems are not fully developed. Scientists tested samples from 279 infants with fevers, as well as 19 healthy infants without fevers. Some of the fevers were caused by bacterial infections, but some were not. The research team identified a biosignature of 66 genes, measured in a small blood sample, from which they could distinguish between newborns with or without bacterial infections. These serious bacterial infections included urinary tract infections, brain or spinal fluid infections (bacterial meningitis) and blood infections (bacteremia), all of
which are typically diagnosed by growing bacteria from samples of body fluids. These preliminary findings indicate that biosignatures could ultimately lead to a fast and noninvasive test for diagnosing bacterial infections in infants with fevers. [Supported by NICHD]

Assessing cognitive changes in people with intellectual disabilities. For years, many scientists believed that intellectual disabilities were permanent, and that it was not feasible to significantly improve cognitive function in people with intellectual disabilities. Recently, research in animals has suggested that it may be possible to develop medications that could improve brain function and learning in people with some types of intellectual disabilities, and some behavioral interventions have also shown promise in human studies. To test such treatments, scientists will need to establish reliable ways to measure cognitive changes in people with disabilities. Researchers conducted a pilot study using an NIH-developed battery of cognitive tests that were originally tested in the general population. The tests measured important functions like working memory, processing speed, and vocabulary. The researchers then gave these same tests to people of varying ages with fragile X syndrome, Down syndrome, autism, and other causes of intellectual disability. They discovered that the tests could feasibly be used to assess cognitive functioning in individuals with intellectual disabilities. [Supported by NICHD, NCATS]

Knockout Mouse Phenotyping Program (KOMP2). Scientists have been using mouse models to study “essential genes,” or genes that are necessary for survival. Researchers recently found that about a third of all protein-coding genes are essential for life, helping to fill a major gap in the understanding of the genome. The finding suggests those genes may also be essential to human life and health, and could be good places to look for answers to miscarriages, stillbirths, or unexplained genetic conditions in people, and particularly pediatric diseases. [Supported by NIH Common Fund, NHGRI, NCI] https://www.ncbi.nlm.nih.gov/pubmed/27626380 [Sep 2016]

New MRI coils aim to improve patient comfort and decrease scan time. Researchers have developed 3D printed MRI coils that can be bent and easily wrapped around an infant. The close proximity of the coils allows high quality images to be obtained with much shorter MRI scan times. This is particularly important for pediatric patients and infants that are unable to hold still for long scan times. [Supported by NIBIB]

Bioengineering students design smart pill to help diagnose tuberculosis in children. In 2016, a student research team developed a technology to diagnose tuberculosis in children, a challenge of this worldwide infectious disease. The team created a “smart pill” that is swallowed to passively collect a gastric acid sample from pediatric patients, who are often unable to cough forcefully enough to produce a sputum sample for testing. Current diagnostic practices are invasive, require stable electricity, and must be overseen by a trained clinician. After the smart pill is swallowed it stays intact as it moves through the digestive system. The sample, which contains traces of the swallowed sputum, is then analyzed for tuberculosis. The pill is low-cost, far less painful for the children, and can be used in areas where experts are not available. [Supported by NIBIB]
Global Pediatric Health

New treatment combination decreases severity of drug-resistant malaria in pregnancy. In sub-Saharan Africa, malaria during pregnancy is responsible for up to 20 percent of low birthweight deliveries and more than 100,000 infant deaths each year. In many parts of Africa, the parasite that causes malaria has grown resistant to standard treatment. Now, however, a rigorous clinical trial has shown that a different, two-drug regimen is a reliable alternative. The study included 300 pregnant women from Tororo, Uganda, ranging from 12 to 20 weeks pregnant. The women were assigned at random to one of three groups for preventive treatment: (1) an intervention group that received the new treatment at three times during pregnancy; (2) an intervention group that received the same drug combination, but once each month; and (3) a comparison group that received the standard treatment at three times during pregnancy. The researchers evaluated the women for malarial infection in the placenta. From the group who received standard treatment, 50 percent of the women had placental malaria, compared with 34.1 percent from the first group who received three doses of the new treatment, and only 27.1 percent from the second group who received monthly doses of the new treatment. Women who received a monthly dosing had lower risk of any adverse birth outcomes, such as spontaneous abortion, stillbirth, low birthweight, preterm delivery, or birth defects. The researchers concluded that monthly dosing with the new treatment provided the best protection against malaria. Additional studies will determine if the drug combination could provide an effective alternative treatment in other parts of Uganda and elsewhere in Africa. [Supported by NICHD]


Malaria reduces cognitive development in children. In an area of Uganda with high rates of malaria infection, researchers placed children from infancy to age 2 years into four groups; one group received no preventive medicine, and the other three groups received different types of preventive malaria treatment. None of the children had HIV, but about one-third had been exposed to the virus before or after birth. The researchers tested the children’s mental and motor development at ages 2 and 3. They compared the test results and the number of times each child had been ill with malaria or malaria with anemia (anemia often accompanies malarial infection). The researchers found a strong relationship between the number of malaria bouts and the children’s mental and motor development scores at ages 2 and 3 years. Children who had been exposed to HIV at birth were also more likely to have lower mental development scores at age 3. [Supported by NICHD]


HIV Therapy for breastfeeding mothers can virtually eliminate transmission to babies. Recent findings from the Promoting Maternal and Infant Survival Everywhere (PROMISE) study, a large clinical trial conducted in South Africa, showed that HIV-infected mothers with healthy immune systems who took a three-drug antiretroviral regimen during breastfeeding essentially eliminated any HIV transmission via breast milk to their infants. PROMISE investigators found that both three-drug maternal antiretroviral therapy and daily infant nevirapine were safe and effective at preventing HIV transmission at birth and during breastfeeding. Overall, infant mortality in the study was extremely low, with nearly all babies surviving their first year of life. [Supported by NIAID, NICHD]


Childhood pneumonia in a well-vaccinated South African birth cohort. Pneumonia is a leading cause of death in the neonatal period, and accounts for almost 20 percent of deaths in children before age 5 years. Reductions in this rate have been observed in higher-income nations and Latin America as a result of vaccinations against certain bacteria known to cause severe pneumonia. Despite adoption of the vaccines, South Africa has not seen significant changes in pneumonia-related mortality in children. To find the
main causes of pneumonia in South African infants and children, researchers studied bacteria in children with pneumonia and healthy controls. The results indicated that current vaccines are not effective in South African children; therefore, new vaccines and/or additional strategies (such as vaccination of pregnant women) are needed for greater prevention of childhood pneumonia in South Africa. [Supported by NHGRI]

**Bacteria in the gut can help young children avoid undernutrition.** Through analysis of breast milk samples from Malawian mothers with healthy or undernourished infants, scientists discovered that the breast milk of mothers with severely stunted infants had lower levels of sugars called sialylated oligosaccharides, which are digested not by humans but by their gut bacteria. In germ-free mouse and piglet models transplanted with gut microbes from one of the stunted infants and fed a typical Malawian diet with or without supplemental sialylated oligosaccharides, the scientists showed that mice who received the supplemental sugars had improved muscle mass and metabolism. This research points toward potential solutions for childhood malnutrition in the form of new microbial or nutrient-based interventions that might complement existing dietary approaches. [Supported by NIDDK, NIAMS] https://www.ncbi.nlm.nih.gov/pubmed/26898329 [Feb 2016]

**Identifying a safe level to treat low blood sugar in newborns.** Glucose levels that are too low – or too high – may lead to brain injury in newborns and possibly result in severe intellectual and developmental disabilities. Until now, the threshold for blood sugar had only been an estimate, never having been verified by a research study in people. However, a new study has now confirmed that infants treated for hypoglycemia at the recommended threshold level were no more likely to experience neurological problems by two years of age than those in a comparable group who did not need treatment. Researchers studied a total of 404 newborns at the Waikato Hospital in Hamilton, New Zealand. All were born at risk of hypoglycemia, and researchers tested the infants’ blood glucose periodically for up to 48 hours. Of these infants, 216 had low blood glucose levels. These infants were treated with additional feedings of oral or intravenous glucose. When all the children reached two years of age, they were tested to measure their developmental progress, cognitive and language skills, vision, hearing, physical coordination and executive functioning (ability to concentrate and carry out tasks appropriate for their age.) The scientists did not find any deficits in any of these areas (referred to collectively as “neurosensory impairments”) between the two groups (children who needed treatment and children who did not). These reassuring findings reinforce current treatment guidelines for hypoglycemia in newborns. [Supported by NICHD]

**Iron supplements in infancy may help motor development.** Lack of adequate iron during pregnancy and infancy is common, and infants with inadequate iron levels are at risk for poor motor (movement) skills. Building on a prior study of iron supplementation for pregnant women in rural China, researchers continued a carefully controlled trial to study the effects of providing iron supplements for the infants of these women from age six weeks through nine months. The results indicated that iron supplementation in infancy, whether or not a child’s mother had received iron supplements during pregnancy, may improve infants’ gross motor test scores. However, the results did not show that supplements both during pregnancy and infancy would confer any greater benefits in early motor development. [Supported by NICHD]
SELECTED NEW AND EXPANDED RESEARCH EFFORTS FOR FY 2016 IN PEDIATRICS

Selected New Pediatric Research Efforts for FY 2016

NIH ICOS launched a range of new research programs and efforts related to pediatrics in FY 2016. Selected highlights of new initiatives are given below. Several programs are focused on understanding risk factors for complex conditions in children. The majority of the programs are concerned with developing and delivering evidence-based treatments.

Environmental influences on Child Health Outcomes (ECHO). In September 2016, the NIH announced over $157 million in awards to establish 35 Pediatric Cohort projects, a Coordinating Center, a Data Analysis Center, a Patient/Person Reported Outcomes Core, six Children’s Health Exposure Analysis Resource projects, 17 IDeA States Pediatric Clinical Trials Network (ISPCTN) research sites, and the ISPCTN Data Coordination and Operating Center. In addition, the NIH awarded $7 million to maintain the National Children’s Study data and biorepositories. The 35 ECHO Pediatric Cohort awards consist of many individual cohorts of mothers and children with a broad range of early life environmental exposures, including physical, chemical, biological, behavioral, social factors. ECHO focuses on four key high-impact pediatric outcomes: (1) Upper and lower airway, (2) Obesity, (3) Pre-, peri-, and postnatal outcomes, and (4) Neurodevelopment. By harmonizing the information gathered from existing cohort studies of mothers and children, complemented by new data that the cohorts will obtain from participants, ECHO will create a large ECHO-wide cohort – collectively > 50,000 children – that will greatly increase scientists’ ability to answer critical public health questions about the impact of early life exposures on children’s health. [Supported by NIH Common Fund]
https://www.nih.gov/echo

Clinical Sites for the IDeA States Pediatric Clinical Trials Network. The goal of the IDeA States Pediatric Clinical Trials Network is to provide medically underserved and rural populations with access to state-of-the-art clinical trials, apply findings from relevant pediatric cohort studies to children in IDeA state locations, and build pediatric research capacity at a national level. [Supported by NIH OD, NIGMS]

Molecular Transducers of Physical Activity in Humans aims to uncover the molecular changes that occur in response to exercise. This program is expected to transform clinical medicine’s use of physical activity as a treatment and preventive strategy. Although researchers have demonstrated that physical activity is good for us in many ways, they know little about the molecules that cause these improvements. Scientists and clinicians increasingly recognize that physical activity is an essential component of health, growth, and development, and there are critical periods when exercise can lead to long-term improvements in health. By combining data on these long-term improvements with the molecular changes that occur when children and adolescents exercise, the research conducted will show whether the molecular transducers of health benefits differ in children and in adults and during different stages of development. [Supported by NIH Common Fund]
https://commonfund.nih.gov/MolecularTransducers

Detecting and Preventing Suicide Behavior, Ideation and Self-Harm in Youth in Contact with the Juvenile Justice System. Suicidal ideation and behavior are highly prevalent among youth in contact with the juvenile justice system, who are estimated to have a three times greater risk for dying by suicide than youth in the general population. This program supports research that develops and tests broadly
implementable service system interventions to rapidly identify and effectively respond, so as to reduce suicidal behavior, suicidal ideation, and non-suicidal self-harm (NSSI) in justice-involved youth. [Supported by NIMH]

**Rapid Assessment of Zika Virus (ZIKV) Complications.** This funding opportunity announcement was initiated in February 2016 for expedited review and funding to counteract the Zika public health emergency. ZIKV is a single-stranded RNA virus of the Flaviviridae family. It is transmitted to humans primarily through the bites of infected *Aedes* mosquitoes, though both perinatal/in utero and sexual transmission have been reported. Initially discovered in 1947, it has been reported in the Americas since 2014, with a major outbreak in Brazil starting in 2015. Symptomatic disease is seen in about 20 percent of infected people and is usually self-limited. However, an association between ZIKV infection in pregnant women and severe microcephaly in their babies has been very concerning and prompted the World Health Organization to declare this potential complication a public health emergency. [Supported by NICHD, ORIP, NIAID, NICD, NIMH, NINDS, NEI, NIBIB, NHLBI]

**Zika in Infants and Pregnancy (ZIP) Cohort Study.** In June 2016, the NIH and Fundacao Oswaldo Cruz-Fiocruz (Fiocruz), a national scientific research organization linked to the Brazilian Ministry of Health, began a multi-country study to evaluate the magnitude of health risks that Zika virus infection poses to pregnant women and their developing fetuses and infants. The ZIP study aims to enroll as many as 10,000 pregnant women ages 15 years and older at up to 15 sites. The participants will be in their first or early second trimester of pregnancy and will be followed throughout their pregnancies to determine if they become infected with Zika virus and if so, what outcomes result for both mother and child. The participants’ infants will be carefully followed for at least one year after birth. [Supported by NICHD, NIAID, NEI, Fiocruz]

**Safety and Outcome Measures of Pain Medications Used in Children and Pregnant Women.** Severe and persistent pain which is not effectively treated during pregnancy can result in depression, anxiety, and high blood pressure which may lead to complications in pregnancy. Both over-the-counter (OTC) and prescription pain medicines are used to treat acute and chronic pain during pregnancy, labor delivery and postpartum. However, there are potential risks of using OTC and prescription medications during pregnancy. The purpose of this program is to (1) promote preclinical, translational, clinical and epidemiological research in pain medications use in children or in pregnant women to fill knowledge gaps in safe use of the pain medications in these special populations; and (2) develop effective instruments or approaches to assess and evaluate maternal and child outcomes of pain medication treatments. There is a need for data on pain medications used in children and pregnant women to be shared and made available to the scientific community for future studies and to encourage replication of findings and meeting the goal of further advancing research in this area. [Supported by NICHD]
**Understanding HIV Persistence in Infants.** The goal of this research is to advance knowledge of the pathogenesis of perinatal HIV-1 infection by exploring the unique aspects of the infant’s developing immune system and its interaction with the virus, including establishment of HIV-specific immune responses and viral reservoirs. [Supported by NIAID, NICHD, NIMH]


**Dual-Affinity Re-Targeting Proteins for Cure of Newborn Infant HIV-1 Infection.** The proposed research will examine the efficacy of novel antibody-based immunotherapeutic proteins for elimination of infant cells infected with HIV-1 viruses involved in mother-to-child transmission. The research will provide a foundation for the development of passive immunization strategies designed to cure infant HIV-infection. [Supported by NIAID]

AI127022: https://projectreporter.nih.gov/project_info_description.cfm?aid=9203119

**Immunity and HIV Persistence in Perinatal HIV Infection.** The proposed research seeks to understand how an infant’s immune system works in concert with early HIV treatment to combat HIV persistence. Its goal is to achieve the next step toward a cure for HIV and enable a state of prolonged remission without the need for drugs for controlling HIV. [Supported by NIAID]

AI127347: https://projectreporter.nih.gov/project_info_description.cfm?aid=9211649

**Perinatal Stroke,** which affects more than 1 in 3,000 live births, has few specific treatments, prevention strategies, and rehabilitative approaches. This program supports basic or translational research relating to perinatal stroke, hopefully leading to therapeutic targets in perinatal stroke and understanding underlying causes. [Supported by NHLBI, NINDS]


**Asthma Care Implementation Programs.** The Coordinated Federal Action Plan to address asthma disparities concluded that comprehensive implementation programs, involving several coordinated interventions, would be the best way to address the many factors that drive asthma disparities. Scientists are developing interventions targeting four different areas that influence the health of children with asthma: medical care, family, the home, and the community. [Supported by NHLBI]


**Improving Diabetes Management in Pre-teens, Adolescents and/or Young Adults with Type 1 Diabetes.** Diabetes management requires complex balancing of medication dosing, diet, and physical activity in order to achieve good glucose control while avoiding hypoglycemia. Treatment regimens for tight glucose control can be especially challenging for very young children and their families. For example, smaller insulin doses can be more challenging to calculate and young children are more susceptible to hypoglycemia, particularly at night. There are also challenges specific to development, such as a young child's more limited ability to detect and communicate changes in their physical status, unpredictable/picky eating, and variable activity and sleep patterns. The goal of this program is to support research to develop, refine, and pilot test innovative strategies to improve management of type 1 diabetes in young children (under 5 years old) and/or school-aged children (ages 5 to 9 years old).

Establishing Basic Science-Clinical Collaborations to Understand Structural Birth Defects. This program seeks to establish basic science-clinical collaborations by providing small grants to teams of basic scientists, physician scientists, and/or clinicians. The goal is to facilitate the gathering of preliminary data to support future, larger research grant applications that will combine expertise and integrate basic, translational, and/or clinical approaches to understanding the developmental biology, genetics, and/or environmental basis of structural birth defects.

[Supported by NICHD, ORIP, NIAAA, NIDA, NIDCR, NIEHS, NINDS]

Center of Research Translation in Muscular Dystrophy Therapeutic Development. The muscular dystrophies are a group of genetic diseases that cause progressive muscle weakness and degeneration. This program seeks to accelerate the translation of genetic therapies to potentially treat some of the most common forms of muscular dystrophy, including Duchenne muscular dystrophy and facioscapulohumeral muscular dystrophy. [Supported by NIAMS]
https://www.niams.nih.gov/News_And_Events/Announcements/2016/CORT_awardees_2016.asp
[NIAMS News Release, Oct 2016]
AR070604: https://projectreporter.nih.gov/project_info_description.cfm?aid=9194559

Strategic Plan for Cerebral Palsy. Two scientific workshops were convened to identify gaps in research and identify priorities for cerebral palsy in November 2014 (“The State of the Science and Treatment Decisions in Cerebral Palsy”) and March 2016 (“Basic and Translational Research in Cerebral Palsy”). These workshops brought together scientists, clinicians, advocates, and other stakeholders to discuss topics such as the current gaps in the evidence base for therapeutics and interventions, and the role of non-human basic research in understanding the biology of CP and the development of new therapies. Key recommendations from both workshops were incorporated into a 5-year strategic plan. [Supported by NINDS, NICHD]
https://www.ninds.nih.gov/News-Events/Directors-Messages/All-Directors-Messages/Comment-NINDSNICHD-Plan-Cerebral-Palsy

Phase II clinical trial in Fragile X to promote neuroplasticity. NINDS (with support from NICHD and NIDCD) recently funded a large, Phase II clinical trial (NS096767; clinicaltrials.gov: NCT02920892) that will be run through NeuroNEXT, a clinical trials network. A large body of preclinical evidence suggests that blockers of the metabotropic glutamate receptor (mGluR) could be an effective therapy in treating Fragile X Syndrome. Unlike in previous, unsuccessful clinical trials using this drug, this trial will test whether a blocker of mGluR5 (AFQ056, developed by Novartis) can boost language learning in very young children with Fragile X Syndrome who will also undergo an intensive language intervention in combination with the drug. This study is significant because it will provide a definitive test of the mGluR theory in humans, and if it is successful, the findings will lead to a paradigm shift for trial design in the neurodevelopmental disorders field. Enrollment will start in Spring 2017. [Supported by NINDS, NICHD, NIDCD]
https://clinicaltrials.gov/ct2/show/NCT02920892

Preventing Epilepsy using Vigabatrin in Infants with Tuberous Sclerosis Complex. Previous research showed that an EEG abnormality during infancy is a reliable biomarker to identify TSC patients who will develop infantile spasms/epilepsy in the near future. As a result of these findings, scientists are now conducting a double-blind placebo-controlled clinical trial (“Preventing epilepsy using vigabatrin in infants with TSC”; PREVeNT) that will utilize EEG to identify TSC infants at risk for epilepsy and study the effectiveness of early intervention with vigabatrin, an anticonvulsant medication, on preventing seizures and improving neurocognitive outcomes in infants with TSC. [Supported by NINDS]
NS092595: https://projectreporter.nih.gov/project_info_description.cfm?aid=9103780
Enhancing Functioning in Individuals with Social Impairments. This initiative will support early-stage development and initial testing of novel technologies for use as interventions targeting social functioning, as well as ground-breaking technologies that could be used to augment existing, established interventions that are focused on the social domain. Projects funded under this initiative will create “social prosthetics”: scalable technology or devices that can enhance functioning to meet the needs of children and adults with social impairments, with the ultimate purpose of having a clinically meaningful effect on their quality of life. [Supported by NIMH]

Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults with Mental Illness (ALACRITY) Research Centers. The ALACRITY Centers support transdisciplinary teams of clinical and mental health services researchers, behavioral scientists, social scientists, health information and communications technologists, health systems engineers, decision scientists, and mental health stakeholders (e.g., service users, family members, clinicians, payers) engaging in high-impact studies that will significantly advance clinical practice and generate knowledge that will fuel transformation of mental health care in the United States. The ALACRITY Centers program is intended to support research that demonstrates an extraordinary level of synergy across disciplines and has a high potential for increasing the public health impact of existing and emerging mental health interventions and service delivery strategies. The ALACRITY Centers program is also expected to provide opportunities for graduate students, postdoctoral researchers, and new researchers to participate in transdisciplinary, T2 translational mental health research. [Supported by NIMH]

Rheumatic Diseases Research Resource-based Centers. These Centers will provide critical research infrastructure, shared facilities, services, and/or resources to groups of scientists conducting research on rheumatic diseases, in areas such as inflammatory arthritis, pediatric rheumatic diseases, and precision medicine. [Supported by NIAMS]
AR070253: https://projectreporter.nih.gov/project_info_description.cfm?aid=9162777
AR070549: https://projectreporter.nih.gov/project_info_description.cfm?aid=9171177
AR070155: https://projectreporter.nih.gov/project_info_description.cfm?aid=9162257

Center for Lupus Research (CLR). In the autoimmune disease systemic lupus erythematosus, or lupus, many organs and organ systems including the skin, joints, heart, lungs, kidneys, and brain, can be affected. Building on pioneering work to correlate lupus disease activity with certain gene expression profiles, the researchers aim to understand how the changes in gene expression contribute to lupus disease pathogenesis. The CLR will develop tools to monitor these pathways in patients, potentially leading to new interventional strategies and personalized treatments. [Supported by NIAMS]
AR070594: https://projectreporter.nih.gov/project_info_description.cfm?aid=9194907

Urinary Stone Disease Research Network (USDRN). The Urinary Stone Disease Research Network (USDRN) was established to a) design and conduct a randomized clinical trial to investigate the impact of increased fluid intake and increased urine output on the rate of recurrence of urinary stones in adults and children, b) conduct clinical research to understand and mitigate ureteral stent-related pain and symptoms, and c) provide data and collect biological samples from the studies to create a resource for future researchers. [Supported by NIDDK]
**Pediatric Diagnostic Biomarkers for Active Pulmonary Tuberculosis (TB) Disease.** TB can be difficult to detect in young children. Additionally, children present with a wide spectrum of disease manifestations, severity, and with non-specific clinical symptoms that mimic other childhood respiratory diseases. The purpose of this program is to support projects to identify and/or validate biomarkers or biomarker combinations leading to improved diagnosis of active pulmonary TB in children, including HIV-infected children. [Supported by NIAID]

**Engaging Youth and Young Adults from Health Disparity Populations in the HIV Treatment Cascade.** This initiative will support research projects that implement and test comprehensive service approaches to engage and retain youth and young adults (age 12-25 years) from health disparity populations in the HIV Treatment Cascade, which includes diagnosis, linkage to care, engagement in care, retention in care, initiation of antiretroviral therapy (ART), and achievement of viral suppression. [Supported by NIMHD]

**Risk of Adolescence and Injury in HIV Susceptibility (RAIS).** Of the 2.3 million new HIV infections globally per year, 30-40 percent occur in adolescents and young adults (15-24 years of age), with higher incidence in endemic areas. Although significant information is available on the socio-behavioral factors that lead to increased vulnerability of adolescents to HIV infection, knowledge about the contribution of mucosal adolescent biology is very limited. This program aims to stimulate biomedical research to identify how mucosal environment changes during normal anogenital maturation (adolescence), and/or injury across all ages, affects HIV susceptibility. The long-term goal of this program is to generate knowledge that will aid in the development of prevention modalities that are safe and effective in adolescents and in persons with mucosal injury. [Supported by NIAID, ORWH, NICHD]

**Seek, Test, Treat and Retain for Youth and Young Adults Living with or at High Risk for Acquiring HIV.** The purpose of this program is to examine seek, test, treat and retain approaches among youth and young adults (ages 13-25) who are at high risk for HIV acquisition or have already acquired HIV. Youth are the target of this program because they demonstrate lower levels of screening and engagement across the HIV continuum of care and HIV+ youth are less likely to achieve viral suppression than those at older ages. [Supported by NIDA]

**Targeted Clinical Research to Address Select Viral Infections.** This initiative aims to foster the development of effective therapies or therapeutic strategies for rare and/or emerging viral diseases of medical importance in targeted patient populations. New additions include studies to:

- Prospectively examine adenovirus infection and other important infections in a population of pediatric allogeneic hematopoietic stem cell transplant recipients. [Supported by NIAID, HHSN272201600014C]
- Assess the burden of neonatal HSV infections, via 1) abstraction of data from large United States national databases on HSV incidence, mortality, disease manifestations, treatments, outcomes and societal costs; 2) a retrospective assessment of the prevalence neonatal HSV disease in Peru; and 3) a prospective assessment of incidence and frequency of neonatal HSV infections in Peru. [Supported by NIAID, HHSN272201600018C]
- Develop and implement a multi-center clinical study on congenital cytomegalovirus infection (CMV) in infant pediatric patients. The study combines a large screening/enrollment effort and enrollment of a subset of patients with confirmed CMV infection into an interventional arm of the study using valganciclovir as the treatment. [Supported by NIAID, HHSN272201600017C]
**The Beau Biden Cancer Moonshot** to accelerate cancer research aims to make more therapies available to more patients, while also improving our ability to prevent cancer and detect it at an early stage, with an ambitious goal of making a decade’s worth of progress in cancer prevention, diagnosis, and treatment in just five years. A Blue Ribbon Panel of experts identified childhood cancer as one of the seven core areas within this initiative, two elements of childhood cancer were specifically highlighted – fusion oncoproteins and immunotherapy. New research efforts will study the unique molecular changes that drive many childhood cancers (fusion oncoproteins), specifically those that arise from fusions in transcription factors and other cellular targets that are often considered “undruggable”. The immunotherapy element will focus on translational science to ensure that pediatric cancer patients benefit from the advances in immunotherapy seen in adults. [Supported by NCI]

[https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative](https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative) [NCI Cancer Moonshot]
[https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/blue-ribbon-panel](https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/blue-ribbon-panel) [Cancer Moonshot BRP Report]


**Pediatric Provocative Questions.** This initiative is supporting research projects designed to use sound and innovative strategies to solve specific problems and paradoxes in childhood cancer research identified by the National Cancer Institute (NCI) as the NCI’s Pediatric Provocative Questions (Pediatric PQs). The initiative is meant to challenge cancer researchers to think about and elucidate specific problems in key areas of pediatric cancer research that are deemed important but have not received sufficient attention. The initiative includes nine Pediatric PQs that represent diverse fields relevant to childhood cancer research ranging from basic research on mechanisms of cancer development to research addressing important issues for survivors of childhood cancer. [Supported by NCI]


**Gene Fusions in Pediatric Sarcomas Initiative.** Pediatric sarcomas are a diverse group of bone and soft tissue cancers that account for about thirteen percent of cancers in young people under the age of twenty. Several types of pediatric sarcomas are characterized by tumor-associated chromosomal abnormalities caused by rearranging parts of different chromosomes, which result in expression of fusion proteins critical for cancer development. Detecting these fusion proteins is a way to diagnose these cancers; therefore, researchers set out to determine the molecular and biochemical mechanisms by which these proteins cause transformation of a normal cell into a tumor cell. Aligned with the Cancer Moonshot BRP recommendations, the goals of this program are to develop faithful models of these pediatric cancers, identify their key dependencies, and use this information to develop novel therapeutic approaches that target these mechanisms. [Supported by NCI]


**Phase I Clinical Trial to Evaluate Toxicity of a Novel Agent in Children with Cancer of the Central Nervous System (CNS).** Primary malignant cancers of the CNS account for less than 2 percent of all malignancies, yet brain tumors are the second most common cause of cancer-related deaths in children. Surgical removal of some childhood CNS malignancies, such as intrinsic diffuse pontine gliomas, is not an option because of the location of the tumor in the brain. Therefore, effective treatments that can enter the brain are needed. The primary goal of this Phase I trial will be to evaluate the safety and use of an anticancer therapy (DM-CHOC-PEN) for children with advanced cancer involving the CNS. This drug can cross the network of blood vessels and cells (i.e., the blood-brain barrier) that protect the normal brain from harmful substances. The drug can accumulate in CNS tumor tissue in humans, and has produced objective responses, with non-harmful side effects, that have improved quality of life and overall survival
in adult clinical trials. This Phase I trial is designed to document toxicities, define an acceptable maximum tolerated dose, and identify anticancer activity for the new therapy. [Supported by NCI] https://clinicaltrials.gov/ct2/show/study/NCT02889445
CA203351: https://projectreporter.nih.gov/project_info_description.cfm?aid=9047161

Research to Advance the Understanding and Management of the Multiple Organ Dysfunction Syndrome in Children. Multiple organ dysfunction syndrome (MODS) is a clinical condition commonly encountered in the pediatric intensive care unit that is associated with significant morbidity and mortality. It is characterized by the failure or dysfunction of a consistent group of body organs or organ systems. It is triggered by a wide range of disease processes and clinical insults, most notably sepsis and trauma, and is frequently associated with uncontrolled inflammation. Although quite varied, some published reports suggest an incidence as high as 57 percent among patients admitted to the pediatric intensive care unit (PICU). Despite the high prevalence and these unfavorable outcomes, this condition remains poorly understood. NICHD recently sponsored a workshop of multidisciplinary experts in the field of Pediatric MODS to describe the state of the science and to identify key areas for research. Stemming from that workshop, this initiative aims to promote broad research areas for MODS, including epidemiology and outcomes; detection and monitoring of MODS; pathophysiology; specific triggering etiologies; and promising therapies. [Supported by NICHD]

Global Noncommunicable Diseases and Injury Across the Lifespan: Exploratory Research. This program supports planning, design and initial pilots for locally relevant and catalytic research on non-communicable diseases or injury in low and middle-income countries. [Supported by FIC, NCCIH, NCI, NEI, NIDA, NINR, NIMHD, ODS, ORWH, NIA, OBSSR, NICHD]

Selected Expanded Pediatric Research Efforts for FY 2016

In addition to launching new research programs, NIH ICOS 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.

Lifespan Human Connectome Project: Development (RFA-MH-16-150) and Baby Connectome (RFA-MH-16-160). The NIH Human Connectome Project (HCP), funded since 2010 by the NIH Blueprint for Neuroscience Research, is a large-scale effort to develop a comprehensive reference atlas of neuronal connectivity – that is, a connectome. The original HCP mapped brain connectivity in 1,200 healthy adults and is making this data freely available to the scientific community. The HCP aims to increase understanding of what makes us uniquely human, and also sets the stage for studies of abnormal brain circuits that appear in many mental illnesses. In 2016, NIH funded two extensions to the HCP to support the study of infants and youth, in order to capture the structural and functional changes that occur in the brain during typical development (MH110274, MH109589). The collaborative projects funded through these two initiatives will enable scientists to map out the connectivity of the human brain from birth to age 21, with methods that will maximize compatibility with the young adult connectome.
[Supported by NIH Blueprint for Neuroscience Research, NIMH, NEI, NIA, NIAAA, NIBIB, NICHD, NIDCD, NIDCR, NIDA, NIEHS, NINDS, NINR, NCCIH]
**Children’s Environmental Health and Disease Prevention Research Centers.** These jointly funded NIEHS/EPA centers study individual, regional, national, and global environmental exposures and their effects on children’s health. The centers connect basic scientists, behavioral scientists, social scientists, pediatricians and other clinicians, and public health professionals, all working together to improve the health and environments of children. The centers apply community-based, participatory research techniques in which community organization partners play a vital role in informing, implementing, and sharing what the findings mean. Additionally, each center has a designated physician scientist to ensure research is translated into practical information for health care providers. Five new centers were funded in 2016, and will focus on topics including the impact of the microbiome on prenatal and infant health, impact of maternal exposures to environmental chemicals on early child development and health, the relationship between childhood leukemia and the environment, effects of exposure to polycyclic aromatic hydrocarbons and outcomes like obesity and behavior problems, and links between childhood obesity and asthma. [Supported by NIEHS, EPA]

**The Environmental Determinants of Diabetes in the Young (TEDDY).** TEDDY was established to determine the infectious agents, dietary factors, or other environmental conditions that trigger type 1 diabetes (T1D) in high-risk individuals. This study is following over 6,000 newborns until age 15. TEDDY has collected 3.2 million samples to date to investigate etiology and pathogenesis of islet immunity and T1D. In FY 2016, TEDDY was expanded to use new blood cell sample analysis technologies to investigate how epigenetic modifications and infectious agent exposures affect islet autoimmunity and T1D. [Supported by NIDDK, NIAID, Special Statutory Funding Program for Type 1 Diabetes Research]

**Pediatric Optic Neuritis Prospective Outcomes Study.** Optic neuritis (ON) is an inflammatory disease of the optic nerve, the bundle of nerve fibers that transmits visual signals from the eye to the brain. Commonly occurring in adults and children with multiple sclerosis, ON can cause vision loss, or reduce ability to see colors, and pain associated with eye movements. The causes, natural history, prognosis, and response to therapy of pediatric optic neuritis are not well understood, based mainly on case reports. A clinical trial in adults with ON showed that corticosteroid drug therapy improved vision in the short-term, but did not affect long-term prognosis, and risks were dependent on the method of administration. In children, the manifestation of ON is different from adults, and risk profile will vary with chronic administration of therapy. The pediatric ON treatment trial will evaluate various therapies and methods of administration to provide an evidence base for treatment in children. An initial pilot study is focusing on recruiting patients for a prospective study on pediatric ON to understand prognosis, treatment trends, and assessing disease progression with advanced imaging tools. [Supported by NEI]

**Reducing Cardiometabolic Risk in Youth with Serious Emotional Disturbance or Severe Mental Illness.** While newer antipsychotics are more tolerable than older drugs, they carry high risk for adverse metabolic effects (e.g., obesity, diabetes, and hyperlipidemias). In 2015, a funding opportunity announcement was issued to encourage research on effective screening and risk management of youth for whom newer antipsychotics are the best option. In 2016, three complementary grants were awarded to test...
alternative models for reducing weight gain and cardiometabolic risk among medicated youth. (MH110945, MH110968, MH110965) [Supported by NIMH]
MH110945: https://projectreporter.nih.gov/project_info_description.cfm?aid=9176370&icde=32215279
MH110968: https://projectreporter.nih.gov/project_info_description.cfm?aid=9177934&icde=32215294

**Sickle Cell Disease Implementation Consortium.** A new implementation science initiative will support clinical sites that assess the degree to which multi-modal, multi-sector interventions improve the rate at which patients with sickle cell disease (SCD) receive appropriate care. Under the currently prevailing system of non-integrated care, many adolescent and adult patients with SCD fail to receive evidence-based interventions. [Supported by NHLBI]

**Oral Health Disparities Consortium.** To reduce or eliminate oral health disparities, multidisciplinary research teams will study the impact of holistic, population health, and other approaches to take decisive action against oral health disparities in children at multiple levels of influence, including families, neighborhoods, and health care systems. [Supported by NIDCR]

**The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network** supports interventional trials to establish correct drug dosing with appropriate formulations of ART for HIV-infected children, correct dosing and formulations for HIV-infected children with TB, and methods to further reduce perinatal HIV transmission. The mission of the IMPAACT Network, which is worldwide in scope, is to significantly decrease incident HIV and HIV-associated infections including mother-to-child transmission (MTCT) and to decrease mortality and morbidity due to HIV and HIV-associated coinfections and comorbidities among infants, children, adolescents and pregnant/postpartum women. [Supported by NIAID, NICHD, NIMH] (NCT0106115, NCT01253538)
https://clinicaltrials.gov/ct2/show/NCT01061151
https://clinicaltrials.gov/ct2/show/NCT01253538

- **Clinical Trials to develop a Pediatric Respiratory Syncytial Virus (RSV) Vaccine.** A new trial in the IMPAACT Network in FY 2016 will evaluate pediatric live-attenuated RSV vaccine candidates.
  AI068632: https://projectreporter.nih.gov/project_info_description.cfm?aid=8975586

- **Evaluation of HIV Antiretroviral Drugs in Severely Malnourished Children.** Severe malnutrition is one of the most common presentations of HIV infection in South Africa. The damaging effects of malnutrition in the gut may lead to inadequate HIV antiretroviral drug absorption. In this Phase IV study, researchers are evaluating the steady state pharmacokinetics of several HIV ART drugs (zidovudine, lamivudine and lopinavir/ritonavir) in severely malnourished HIV-1 infected children. [Supported by NIAID] (AI068632)
  AI068632: https://projectreporter.nih.gov/project_info_description.cfm?aid=8975586
  IMPAACT P1092: http://impaactnetwork.org/studies/P1092.asp

**Advancing Understanding, Prevention, and Management of Infections Transmitted from Women to their Infants.** The purpose of this program is to improve the understanding, prevention and clinical outcomes of non-HIV infections transmitted from women to their offspring during pregnancy, labor and delivery, and breastfeeding. This research will increase scientific understanding of and treatments for high-priority perinatal infections, which include, but are not limited to, cytomegalovirus, herpes simplex
viruses, toxoplasmosis, viral hepatitis, Human T-cell lymphotropic viruses (HTLV-1/2), Trypanosoma cruzi (Chagas disease), enteroviruses, and parvovirus B19. [Supported by NICHD]

The Pediatric Oncology Consortium. A new Phase I study conducted by the Pediatric Brain Tumor Consortium will assess the side effects and best dose of panobinostat in treating younger patients with diffuse intrinsic pontine glioma that is growing, spreading, or getting worse (progressive). Panobinostat may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth. [Supported by NCI]
https://clinicaltrials.gov/ct2/show/NCT02717455

Clinical Trials Program for Children with Cancer. Through its cooperative groups, NCI is supporting nationwide clinical trials introducing new immunotherapy agents and other types of therapy into evaluation for children with cancer on an ongoing basis. During FY 2016, clinical trials evaluating a number of novel agents and new treatment approaches were initiated or expanded in scope. [Supported by NCI]

ICU-Resuscitation Project (ICU-RESUS). Scientists are conducting a new clinical trial to test a new approach to improving CPR quality and outcomes in children who have a cardiac arrest in the ICU. The new strategy includes 1) CPR training at the point-of-care (in the ICU rather than a classroom away from patients); and 2) interdisciplinary structured reviews of each cardiac arrest that emphasize patient-centric physiology. [Supported by NHLBI, NICHD]
https://clinicaltrials.gov/ct2/show/NCT02837497

Pediatric Palliative Care Provider Perspectives. As part of the Pediatric Palliative care initiative, Palliative Care: Conversations Matter®, NINR has expanded its website with information on improving palliative care for children taken from interviews with palliative care providers. The website provides perspectives on pediatric palliative care from a variety of individuals that work as part of a team to provide help and care for patients and their families in the context of pediatric palliative care. Pediatric palliative care team members share their experiences through a series of interviews. [Supported by NINR]
https://www.ninr.nih.gov/newsandinformation/conversationsmatter/pcproviders

Funding Opportunities in FY 2016 for Pediatric Research

In FY 2016, the NIH issued 247 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 ICOs have taken steps to address in pediatric research. In FY 2016, the NIH issued FOAs in research to advance safety and outcome measures of pain medications in children and pregnant women, community-based participatory research, bioengineering technologies, pediatric health disparities, environmental influences on child health, autism research, Zika virus research, diabetes, nutrition, obesity, underage drinking, substance abuse, 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 2016, NIH funded an estimated 96 pediatric centers programs that supported pediatric research, with an additional 136 programs funded under cooperative agreement mechanisms that are often similar in structure to centers. Many, but not all, pediatric research programs were focused exclusively on child health. For example, the NIH launched a seven-year initiative called the Environmental Influences on Child Health Outcomes Program, designed to support multiple longitudinal studies using existing study populations to investigate environmental exposures. The center/network programs supporting pediatric research at the NIH include some that are targeted to a specific disease or condition, such as the Autism Centers of Excellence. Others, like the pediatric component of the Clinical and Translational Science Awards, are not specific to any one condition. Other pediatric research programs are funded using non-center research mechanisms, such as R01 research grants. This report highlights selected key ongoing NIH programs in pediatric research, funded through a variety of research grant and contract mechanisms and interagency agreements.

Child Development

**Adolescent Brain Cognitive Development Study (ABCD).** NIH launched the Adolescent Brain Cognitive Development (ABCD) Study in September 2015 to gain better understanding of brain, cognitive, social, and emotional trajectories from childhood through adolescence. In September 2016, the ABCD Study began recruiting children ages 9-10, before they initiate substance use, targeting a total enrollment of ~10,000 participants by the end of 2018. Researchers will follow these children over the next decade, using non-invasive neuroimaging and cognitive, academic, social, emotional, and biological assessments to determine how childhood experiences (e.g., sleep; screen time; sports and arts involvement; alcohol, tobacco, and other substance use) interact with each other and with children’s changing biology to affect brain development and other outcomes (e.g., physical and mental health, academic achievement). The study allows researchers to examine how pre-existing differences in brain structure and function may contribute to substance misuse. Anonymized data will be released annually to the research community in an open science model to allow scientists world-wide to conduct analyses and pool resources to answer a variety of scientific questions that will guide education, substance use prevention, and other health promotion policies to ensure the wellbeing and success of the Nation’s children. [Initiated by the Collaborative Research on Addiction at NIH (CRAN, consisting of NIDA, NIAAA, NCI), which will lead this effort in partnership with NICHD, NIMH, NIMHD, NINDS, and OBSSR]

[https://abcdstudy.org/](https://abcdstudy.org/)

**Upstate KIDS Study and Follow-Up Study.** The Upstate KIDS study was designed to determine if fecundity and various infertility treatments adversely affect the growth, motor, and social development of children from birth through three years of age. Researchers tracked infants conceived with and without infertility treatment who resided in the 57 counties comprising Upstate New York State (exclusive of the five boroughs of New York City) using the “infertility check box” on the birth certificate for cohort selection. Parents and their infants were recruited at approximately 4-8 months of infant age, with 1,297 infants with reported infertility treatment and over 3,692 “unexposed” infants without reported infertility treatment. Recent studies have drawn attention to the concern that children conceived by infertility treatment may have higher cardio-metabolic risk than spontaneously conceived children. Through a follow-up study, the cohort will be followed to 8 years of age, focusing on childhood cardio-metabolic outcomes (i.e., obesity, high blood pressure, metabolism) and assessing epigenetic differences as measured by DNA methylation using collected biospecimens among approximately 900 children. [Supported by NICHD]

[https://www.nichd.nih.gov/about/org/diphr/eb/research/pages/infant-development.aspx](https://www.nichd.nih.gov/about/org/diphr/eb/research/pages/infant-development.aspx)
**Population Survey Data.** Population surveys provide critical information for identifying risk factors and health disparities across a wide variety of conditions. Among the population studies that continue to contribute to the scientific literature on pediatric research are the Fragile Families survey (HD036916), the National Longitudinal Survey of Youth (AHD14002001), the National Survey of Family Growth (AHD12020001), and the National Longitudinal Study of Adolescent to Adult Health (HD031921). Another example, the NEXT Generation Study, is a seven-year longitudinal assessment of a representative sample of United States adolescent and young adults starting at grade 10, which identifies adolescent health status, social/environmental factors, and risk behaviors from mid-adolescence through post high school years. [Supported by NICHD; Add Health also supported by NIA, NIDA, NIDCD; NEXT study also supported by NIAAA, NHLBI, NIDA, HRSA]

Fragile Families: https://projectreporter.nih.gov/project_info_description.cfm?aid=8883631
NLSY: https://projectreporter.nih.gov/project_info_description.cfm?aid=8890973
NSFG: https://projectreporter.nih.gov/project_info_description.cfm?aid=8739261
Add Health: https://projectreporter.nih.gov/project_info_description.cfm?aid=8891938
NEXT Generation Study: https://www.nichd.nih.gov/about/org/diphr/hbb/research/pages/next.aspx

**Biophysical and Biomechanical Aspects of Embryonic Development.** To better understand the role of the physical and mechanical forces exerted during development, this initiative focuses on promoting studies aimed at understanding the in vivo aspects of biomechanics of morphogenesis, the biological process that causes an organism to develop its shape. The genetic and chemical environment of cells and tissues result in changes in physical forces, which regulate gene function and how cells specialize into different types of tissues. Advancing our knowledge of the physical aspects of development will provide a broader view on how the genome of multicellular organisms functions in association with physical forces to specify final shape and architecture of an organ and/or an entire organism. [Supported by NICHD]


**Behavioral Determinants and Developmental Imaging.** Researchers seek to understand determinants of behavior and behavioral changes occurring during development, studying nonhuman primates, as well as normative and clinical populations. Novel in vivo structural and functional imaging methods will be developed and applied to provide correlative information to assist in addressing these processes and potentially provide translational methods for assessing salient changes in the developing brain. [Supported by NICHD]

https://www.nichd.nih.gov/about/org/dir/affinity/BDDI/Pages/default.aspx

The **Learning Disabilities Research Centers (LDRC) Consortium** is 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.

NICHD LDRC Consortium: https://www.nichd.nih.gov/research/supported/Pages/ldrc.aspx
NICHD Learning Disabilities Innovation Hubs: https://www.nichd.nih.gov/research/supported/Pages/ldhubs.aspx
Environmental and Social Influences

Children’s Health Exposure Analysis Resource (CHEAR). This initiative has created a resource to provide the NIH-funded research community with access to laboratory and statistical analyses that will allow for the addition or expansion of environmental exposures as a component of ongoing epidemiological and clinical research, thereby creating a public resource of children’s exposures across the country. Exposures measured encompass the breadth of the exposome, the totality of biological, psychosocial, chemical, and physical factors to which humans are exposed. [Supported by NIEHS] https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-15-011.html https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-15-009.html https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-15-010.html

WHO-NIEHS Collaborating Centre for Environmental Health Sciences. Children have a special vulnerability to physical, chemical, and biological environmental threats. According to the World Health Organization (WHO), environmental factors account for one-third of the global disease burden in children. NIEHS provides support for the WHO Collaborating Centres for Children's Environmental Health Network, 10 research institutes around the world, each of which acts as a hub to strengthen national or regional capacity to advance children's environmental health. [Supported by NIEHS] https://www.niehs.nih.gov/research/programs/geh/partnerships/index.cfm

Centers of Excellence on Environmental Health Disparities. Five Centers combine basic and translational research and community involvement to improve understanding of environmental health disparities as well as identify mitigation and prevention strategies to decrease the public health burden. [Supported by NIEHS, NIMHD, EPA] https://www.nimhd.nih.gov/programs/extramural/coe/environmental.html

Centers for Children’s Environmental Health and Disease Prevention Research. Since 1998, the Children’s Environmental Health and Disease Prevention Research Centers have studied individual, regional, national, and global environmental exposures and the effects on children’s health. The centers connect basic scientists, behavioral scientists, social scientists, pediatricians and other clinicians, and public health professionals, all working together to improve the health and environments of children. [Supported by NIEHS, EPA] https://www.niehs.nih.gov/research/supported/centers/prevention/

Assessing Sex and Gender Differences in Painful Digestive Disorders. In both animal and human studies, scientists are examining sex and gender differences in the interaction of gut and brain pathways in the development of irritable bowel syndrome (IBS) and other abdominal pain disorders. [Supported by NIDDK, ORWH] http://uclacns.org/center-for-neurovisceral-sciences-and-womens-health/

Environmental Exposures and Health: Exploration of Non-Traditional Settings. The purpose of this program is to encourage interdisciplinary research aimed at promoting health, preventing and limiting symptoms and disease, and reducing health disparities across the lifespan for those living or spending time in non-traditional settings (i.e., community centers; pre-school and non-traditional school environments (e.g., churches, daycare, home-based schools, dormitories, alternative schools, and playgrounds); child and older adult foster care facilities; older adult day care facilities; half-way homes; and assisted living and long-term care facilities). [Supported by NINR, NIEHS] https://grants.nih.gov/grants/guide/pa-files/PA-16-263.html https://grants.nih.gov/grants/guide/pa-files/PA-16-273.html
Pregnancy and Newborns

Chronic Hypertension and Pregnancy (CHAP) Study. This large multi-center randomized trial is evaluating various drug treatment strategies for mild chronic hypertension in pregnant women in terms of effectiveness, safety, and optimal gestational age for delivery. While there are established best practices for treating chronic hypertension in the general population, there is no equivalent standard for pregnant women due to concerns that treating the mother may adversely affect the fetus. The CHAP trial aims to shed light on the benefits vs. risks of treatment, with the potential to change practice. [Supported by NHLBI]
https://clinicaltrials.gov/ct2/show/NCT02299414
HL120338: https://projectreporter.nih.gov/project_info_description.cfm?aid=9093832&icde=33735873

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 provides the expert infrastructure needed to test therapeutic drugs during pregnancy, allowing researchers to conduct safe, technically sophisticated, and complex studies that will help clinicians protect women’s health, improve birth outcomes, and reduce infant mortality. [Supported by NICHD]
https://www.nichd.nih.gov/research/supported/Pages/opru_network.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. Current projects include an observational study of hepatitis C in pregnancy and a clinical trial to determine whether administering hyperimmune globulin for congenital cytomegalovirus (CMV) can reduce mother-to-child transmission of CMV infection. [Supported by NICHD]
https://www.nichd.nih.gov/research/supported/Pages/mfmu.aspx

Transmission of viruses between mothers and infants. Several studies explored how to characterize and prevent the transmission of viruses between mothers and infants, including:

- Maternal and Infant Immunization to Eliminate Breast Milk Transmission of HIV-1 in the nonhuman primate model.
  A117915: https://projectreporter.nih.gov/project_info_description.cfm?aid=9038232
- Functional Cure and Virus Eradication in Macaque Infants and Neonates. This study is testing a strategy that combines ART with immunization using a live but weakened rubella virus-based vaccine vector that targets several HIV proteins. Scientists will determine if this treatment can not only completely suppress HIV replication in babies infected at birth, but also induce such strong immune response that HIV will not reemerge when ART is stopped.
  A1118586: https://projectreporter.nih.gov/project_info_description.cfm?aid=9139875
- Evaluation of Early Suppressive Combination ART (cART) on Sustained Remission in Perinatally HIV-Infected Infants. Two studies are being supported to assess how cART treatment affects the growth and replication of HIV, and immune response, in infants.
  IMPAACT P1115: https://clinicaltrials.gov/ct2/show/NCT02140255
  A1068632: https://projectreporter.nih.gov/reporterapi.cfm?PROJECTNUM=UM1AI068632&Fy=all
Infant Immune System: Implications for Vaccines and Response to Infections. This program supports research to advance understanding of immune system development and defense mechanisms in neonates and infants. Results from these studies are defining infant-specific immune processes that may be targeted to improve vaccine efficacy in this vulnerable population. [Supported by NIAID, NICHD, NIEHS, ORWH]

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. [Supported by NICHD, with co-funding from other ICs for specific projects]
https://www.nichd.nih.gov/research/supported/Pages/nrn.aspx

Natural History of Disorders Identifiable by Screening of Newborns. The NIH supported a new initiative in 2016 to encourage research on the natural history of disorders, such as metabolic disorders, that already or could potentially benefit from early identification through newborn screening. [Supported by NIDDK, NICHD]

Preterm Epo Neuroprotection Trial (PENUT Trial). Extremely Low Gestational Age Neonates (ELGANs) born prior to 28 weeks of gestation are at high risk for death or moderate to severe neurodevelopmental impairment, including cerebral palsy. The PENUT Trial seeks to determine whether neonatal treatment with recombinant erythropoietin (Epo) will decrease early mortality and neurodevelopmental disability in ELGANs, as measured at two years of age. 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. (NCT01378273) (NS077953) [Supported by NINDS, NIDDK]
NCT01378273: https://clinicaltrials.gov/ct2/show/NCT01378273
NS077953: https://projectreporter.nih.gov/project_info_description.cfm?aid=8841021

The Hunter Kelly Newborn Screening Research Program funds an array of newborn screening related research that focuses on:
- Developing systematic methods to identify additional conditions appropriate for newborn screening;
- Developing and testing innovative interventions and treatments to improve outcomes;
- Educating the provider workforce;
- Developing and implementing appropriate information and communication systems for parents and providers; and
- Sponsoring ongoing programs of research and research training in newborn screening.
[Supported by NICHD]
The Newborn Screening Translational Research Network (NBSTRN) seeks to improve the health outcomes of newborns with genetic or congenital disorders through an infrastructure that provides the research community with access to resources for newborn screening. NBSTRN has developed three tools to facilitate newborn screening research:

- Virtual Repository of Dried Blood Spots (VRDBS). A web-based tool that enables state program personnel to control and manage access to specimens for newborn screening related research. [Supported by NICHD]
  
  https://nbstrn.org/research-tools/virtual-repository-of-dried-blood-spots

- Longitudinal Pediatric Disease Resource (LPDR). A secure informatics system designed to enable enhanced data collection, sharing, management and analysis for conditions identified as part of newborn screening or for conditions that may benefit from newborn screening. [Supported by NICHD]
  
  https://nbstrn.org/research-tools/longitudinal-pediatric-data-resource

- Laboratory Performance Database (R4S). This web-based application for the collection and reporting of analytical results has been developed and widely adopted into the routine practice of newborn screening laboratories worldwide.
  
  https://nbstrn.org/research-tools/lab-performance-database

[Supported by NICHD]

Newborn Screening Coding and Terminology Guide. This online guide uses nationally-accepted vocabulary and electronic messaging standards to enable laboratories, clinicians, public health officials, and researchers to exchange and aggregate newborn screening results from all of the states as a key Big Data resource. [Supported by NLM]

https://newbornscreeningcodes.nlm.nih.gov/nb/sc/constructingNBSHL7messages

Nutrition and Obesity in Pregnancy and Childhood

The Hyperglycemia and Adverse Pregnancy Outcome Follow-Up Study (HAPO-FUS) 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. [Supported by NIDDK, NICHD]

https://www.niddkrepository.org/studies/hapo-fus/

Understanding Factors in Infancy and Early Childhood (Birth to 24 months) That Influence Obesity Development. This research initiative seeks to characterize or identify factors in early childhood (birth to 24 months) that may increase or mitigate risk for obesity and/or excessive weight gain and/or to fill methodological research gaps relevant to the understanding of risk for development of obesity in children. Studies may also assess factors relevant to families and/or caregivers of children from birth to 24 months.

[Supported by NIDDK, NICHD, NIMHD, OBSSR, NHLBI]


Primary care pediatrics Learning, Activity and Nutrition (PLAN). Researchers are conducting a multi-site clinical trial testing the effectiveness of a family-based weight loss intervention compared to standard usual care for overweight or obese children aged 6 to 12. [Supported by NHLBI]

HL131552: https://projectreporter.nih.gov/project_info_description.cfm?aid=9080448
**Dietary Supplement Databases.** The Office of Dietary Supplements (ODS) has an active program to build and maintain databases of information about dietary supplement products and their ingredients sold in the United States that are useful to the scientific research community and not available elsewhere including:

- **Dietary Supplement Label Database (DSLD).** Launched in June 2013, the DSLD is a searchable database of information taken from the labels of dietary supplement products. It is a joint project of ODS and the National Library of Medicine (NLM) in collaboration with USDA, DCD, FDA, and DoD. About 1,000 new product labels are entered into the DSLD each month so that in time almost all of the dietary supplement products in the market will be included. There are currently more than 50,000 labels in the database. [https://ods.od.nih.gov/Research/Dietary_Supplement_Label_Database.aspx](https://ods.od.nih.gov/Research/Dietary_Supplement_Label_Database.aspx)

- **Dietary Supplement Ingredient Database (DSID).** The DSID provides analytically derived estimated levels of ingredients in dietary supplement products. Developed by the Nutrient Data Laboratory at USDA in collaboration with, and with funding from, ODS. The DSID currently includes multivitamin/multimineral dietary supplements for adults and children and vitamin B-6 and thiamine supplements. [https://dietarysupplementdatabase.usda.nih.gov/](https://dietarysupplementdatabase.usda.nih.gov/)

  [Supported by ODS]

**The Healthy Communities Study** is an important five-year study that looks at how characteristics of programs and policies in communities across the United States are related to children's eating, physical activity behaviors, and their health. This large study includes over 120 communities and about 5,000 families. The HCS collects information from families on their children's eating habits and physical activities; from health care providers on children's health histories; from schools on their food and physical activity environments; and, from community leaders on local programs and policies. Findings from this study will help inform community leaders about what aspects of programs and policies may help children's health. [Supported by NHLBI, NCI, NICHD, NIDDK, OBSSR, CDC] [https://www.nhlbi.nih.gov/research/resources/hcs/](https://www.nhlbi.nih.gov/research/resources/hcs/)

**Diabetes**

**Advanced Clinical Trials to Test Artificial Pancreas Device Systems in Type 1 Diabetes.** Advanced clinical trials are testing the outpatient clinical safety and efficacy of artificial pancreas device systems in type 1 diabetes with the objective of improving glycemic control and reducing acute and chronic complications of the disease. These trials should generate data able to satisfy safety and efficacy requirements by regulatory agencies regarding the clinical testing of artificial pancreas device systems. [Led by NIDDK; supported by the Special Statutory Funding Program for Type 1 Diabetes Research] [https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-16-008.html](https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-16-008.html)

**Type 1 Diabetes TrialNet.** TrialNet is an international network of researchers who are exploring ways to prevent, delay, and reverse the progression of type 1 diabetes. TrialNet screens large numbers of people and conducts clinical trials of agents to prevent type 1 diabetes in at-risk people and to slow disease progression in people who are newly diagnosed. [Led by NIDDK; supported by the Special Statutory Funding Program for Type 1 Diabetes Research and regular NIDDK appropriated funds] [https://www.trialnet.org/](https://www.trialnet.org/)

**SEARCH for Diabetes in Youth Cohort Study.** SEARCH provides population-based data on the incidence and prevalence of diabetes and its complications in United States youth. [Led by the CDC and NIDDK; supported by the Special Statutory Funding Program for Type 1 Diabetes Research] [https://www.searchfordiabetes.org/dspHome.cfm](https://www.searchfordiabetes.org/dspHome.cfm)
Consortium for the Study of Chronic Pancreatitis Diabetes and Pancreatic Cancer (CPDPC). The NIDDK, with support from NCI, continues to support this consortium to pursue clinical research on pancreatic diseases, including chronic pancreatitis, acute recurring pancreatitis, pancreatic cancer, and the type 3c diabetes that may result from these diseases. The consortium is enabling researchers to make strides towards the goals of earlier diagnosis, targeted treatment, and prevention of pancreatic disease in a diverse population of patients. As a component of the CPDPC, researchers in the INSPPIRE (International Study Group of Pediatric Pancreatitis: In Search for a Cure) consortium recently found that genetics, birth defects, and ethnicity may play important roles in the occurrence of pancreatitis in children. [Supported by NIDDK, NCI]

Structural Anomalies and Birth Defects

Birth Defects Initiative and Working Group. 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. [Supported by NICHD, NIAAA, NIDCR, NIDDK, NIEHS, NINDS]
https://www.nichd.nih.gov/research/supported/Pages/bdiwg.aspx

Genetic Susceptibility & Variability of Human Structural Birth Defects. This program supports research using animal models in conjunction with translational/clinical approaches to identify the specific genetic, epigenetic, environmental, or gene/environment interactions associated with structural birth defects in human populations. [Supported by NICHD, NIDCR, NIEHS]

Intellectual and Developmental Disabilities

Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Centers (EKSIDDRCs). The program, established one year after the NICHD’s founding, supports researchers whose goals are to advance understanding of a variety of conditions and topics related to Intellectual and Developmental Disabilities (IDD). Fifteen research centers, located at universities and children’s hospitals throughout the country, conduct projects including evaluation of animal and humans with IDD-related disorders, multimodal treatment studies in fragile X syndrome, and studies of complementary treatments for a rodent model of hypoxic encephalopathy. [Supported by NICHD]
https://www.nichd.nih.gov/research/supported/Pages/eksiddrc.aspx

Outcome Measures for Use in Treatment Trials of Individuals with Intellectual and Developmental Disabilities. For years, scientists have sought to alleviate the debilitating cognitive, behavioral, and comorbid medical symptoms associated with IDD. In recent years, progress in basic research has resulted in identification of underlying mechanisms in several neurodevelopmental disorders that have led to trials for therapeutics. While this progress is highly encouraging, it has become evident that there is a gap in the ability to effectively translate mechanistic discoveries into targeted therapies for humans. One major obstacle to the demonstration of efficacy in human trials in individuals with IDD has been the lack of generally accepted endpoints to assess improvement in function. Individuals with IDD are heterogeneous,
both across and within disease groups, with a broad range of cognitive abilities and challenging behaviors that can vary across the lifespan, making assessment difficult. This initiative supports development of informative outcome measures for use in clinical trials for individuals with intellectual and developmental disabilities (IDD), focusing ongoing clinical and translational research on a neglected area essential for therapy and pharmacological treatment development. [Supported by NICHD]


**The Down Syndrome Consortium** is a public-private collaboration that launched a Down syndrome registry, DS-Connect©, which safely and confidentially facilitates contacts and information among people with Down syndrome and their family members, researchers, parents, and support groups. [Supported by NICHD, NCI, NHLBI, NIMH, NINDS, NIA, NIMHD]

Down Syndrome Consortium: https://downsyndrome.nih.gov/Pages/default.aspx

DS-Connect: https://dsconnect.nih.gov/

**The Fragile X Syndrome Research Center (FXSRC) Program** supports research to improve the diagnosis and treatment of Fragile X syndrome (FXS) and its related conditions. The FXSRCs are geared toward stimulating multidisciplinary, multi-institutional research with the common goal of facilitating the translation of basic research findings from bench to bedside and bedside to community. [Supported by NICHD, NINDS, NIMH]

https://www.nichd.nih.gov/research/supported/Pages/ccrfx.aspx

**Autism Centers of Excellence (ACEs).** The ACE Program is a trans-NIH initiative that supports large-scale multidisciplinary studies on autism spectrum disorders (ASDs), with the goal of determining the disorders' causes and the best treatments for them. The program includes ACE research centers, which foster collaboration between teams of specialists who share the same facility to address a particular research problem in depth, and ACE research networks, which consist of researchers at many facilities in locations throughout the country, all of whom work together on a single research question. The ACE program currently comprises three research centers and eight research networks around the United States. [Supported by NICHD, NIMH, NIDCD, NINDS, NIEHS]

https://www.nichd.nih.gov/research/supported/Pages/ace.aspx


**The Autism Biomarkers Consortium for Clinical Trials (ABC-CT).** Researchers are evaluating EEG and eye-tracking measures as potential biomarkers of social functioning to use for stratification (defining subtypes with a common biological feature) and/or markers of treatment response in future clinical trials. [Supported by NIMH, NINDS, NICHD]

www.asdbiomarkers.org

NIMH Repository and Genomics Resource: https://www.nimhgenetics.org/

**The National Database for Autism Research (NDAR)** is an NIH-funded research data repository that aims to accelerate progress in autism spectrum disorders (ASD) research through data sharing, data harmonization, and the reporting of research results. NDAR also serves as a scientific community platform and portal to multiple other research repositories, allowing for aggregation and secondary analysis of data. Data from over 100,000 consenting de-identified research participants are available for secondary analysis by other qualified researchers through NDAR. All data within NDAR are harmonized (e.g., the same names for each piece of data collected are used) and validated (e.g., reported values are consistent with other projects) to a community-established common data definition. More than 80 percent of newly-awarded NIH human-subject grants related to ASD are or will be contributing data to NDAR. [Feb 2016]


https://ndar.nih.gov/
Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (MDCRCs) 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. 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. [Supported by NICHD, NINDS, NIAMS, NHLBI]  
https://www.nichd.nih.gov/research/supported/Pages/mdcrc.aspx

Neurological Disorders and Mental Health

The Approaches and Decisions in Acute Pediatric TBI Trial (ADAPT) is a five-year observational study to evaluate key aspects of pediatric traumatic brain injury (TBI) care for which evidence is lacking and practices vary across centers. [Supported by NINDS]
http://www.adapttrial.org/

The NIMH Intramural Research Program is conducting studies that:

- Investigate multiple rare genetic disorders caused by abnormal numbers of sex chromosomes. The purpose is to create models for understanding how genetic and brain changes lead to common neurodevelopment disorders (NDDs) such as autism spectrum disorder, attention-deficit/hyperactivity disorder, and intellectual disability. https://www.ncbi.nlm.nih.gov/pubmed/26745832

- Understand the brain mechanisms mediating chronic, severe irritability in youth to develop new treatments. Antipsychotic medication is frequently used to control irritability, despite significant side-effects and lack of a good evidence base. Scientists are working to understand brain mechanisms mediating irritability and to use those insights to develop new treatments. https://www.ncbi.nlm.nih.gov/pubmed/26745832
[Supported by NIMH]

Substance Use

College Alcohol Intervention Matrix (CollegeAIM). In September 2015, NIAAA released the College Alcohol Intervention Matrix (CollegeAIM) guide and website, a research-based, interactive, user-friendly decision tool to help colleges and universities select appropriate strategies to meet their alcohol intervention goals. Developed with leading college alcohol researchers, CollegeAIM allows users to compare individual and environmental strategies to other alternatives based on factors such as cost and effectiveness, and find new evidence-based interventions that fit the unique needs of their campus community. NIAAA embarked on a multifaceted effort throughout FY 2016 to promote and disseminate CollegeAIM, including presentations at national higher education conferences, and regional workshops demonstrating use of CollegeAIM. [Supported by NIAAA]  
https://www.collegedrinkingprevention.gov/CollegeAIM/

National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) is an accelerated longitudinal study of more than 800 youth ages 12-21 that is aimed at assessing the short- and long-term effects of alcohol exposure on the developing adolescent brain, and identifying brain characteristics that may increase risk for alcohol use disorder. [Supported by NIAAA]  
http://www.ncanda.org/
Neurobiology of Adolescent Drinking in Adulthood (NADIA). The NADIA consortium supports animal studies to define the underlying neurobiological mechanisms of adolescent alcohol exposure on adult brain function and behavior. The NADIA consortium was renewed in 2015. [Supported by NIAAA]

Drug Abuse Prevention Intervention Research. Researchers are using rigorous scientific methods to test theoretically derived hypotheses to increase understanding of the science of drug use prevention within diverse populations and settings and across the lifespan. Scientists are assessing cognitive, behavioral, and social processes as they relate to: 1) development of novel prevention approaches; 2) efficacy and effectiveness of prevention interventions or programs; 3) processes that optimize the selection, integration, implementation and sustainability of science-based prevention, including systems-level and health economic factors; and 4) methodologies appropriate for studying complex aspects of prevention science. [Supported by NIDA]

The Population Assessment of Tobacco and Health (PATH) Study is a large-scale NIH/FDA collaboration on a national longitudinal cohort study that is following 46,000 United States adults and youth to examine patterns in tobacco product use, behaviors, attitudes, beliefs, exposures, and health in order to enhance the evidence base that informs FDA's regulatory decision-making. [Supported by NIDA, FDA]
https://pathstudyinfo.nih.gov/UI/HomeMobile.aspx

Bone and Muscle Health

The Bone Mineral Density in Childhood Study (BMDCS) is a multi-center, longitudinal study of bone accrual in healthy children and adolescents that was performed at five clinical centers in the United States. The study provides the longitudinal measurement of bone mass, linear growth, sexual and skeletal maturation, dietary intake, physical activity, and health history. This study offered an unprecedented opportunity to identify predictors of the timing and magnitude of peak bone mass, a major determinant of osteoporosis in later adulthood. [Supported by NICHD]
https://www.nichd.nih.gov/research/supported/Pages/bmdcs.aspx

Childhood Disease, Allergies, and Immunity

Otitis Media. Otitis media (OM), or middle ear infection, is one of the most common reasons for an infant to visit a doctor: Seventy-five 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. Scientists are examining 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. Researchers are also investigating the delivery of drugs to the middle ear and conducting studies that seek to develop vaccines against OM. [Supported by NIDCD]
**Early Hearing Detection and Intervention (EHDI) Federal Partners.** In October 2016, representatives from the NIH (NIDCD), CDC, and HRSA met to share how each agency implements its EHDI program, to identify existing gaps within the EHDI system, common EHDI goals across all three agencies, and opportunities for further collaboration. The three Federal partners will continue meeting regularly and are planning to include additional Federal stakeholders at future meetings. [Supported by NIDCD, CDC, HRSA]

CDC EHDI State Programs: [https://www.cdc.gov/ncbddd/hearingloss/ehdi-programs.html](https://www.cdc.gov/ncbddd/hearingloss/ehdi-programs.html)

The **Bench to Bassinet program** is a pediatric cardiovascular translational research program that encompasses:

- The **Cardiovascular Development Consortium** generates and disseminates comprehensive data about the molecular networks and pathways that regulate cardiovascular development using model organism systems and high-throughput technologies. [Supported by NHLBI] [https://benchtobassinet.com/about/aboutcvdc.aspx](https://benchtobassinet.com/about/aboutcvdc.aspx)

- The **Pediatric Cardiac Genomics Consortium (PCGC)** identifies genetic causes of congenital heart disease (CHD) and works to relate genetic variants to clinical outcomes. The PCGC has recruited over 9000 subjects with CHD and their relatives. [Supported by NHLBI, NICHID] [https://benchtobassinet.com/Centers/PCGCCenters.aspx](https://benchtobassinet.com/Centers/PCGCCenters.aspx)

- The **Pediatric Heart Network (PHN)** conducts clinical research on CHD and other cardiovascular disorders. The PHN has nine main clinical sites, a data coordinating center and many auxiliary sites. The PHN has enrolled approximately 3700 patients into observational studies. [Supported by NHLBI]

[https://benchtobassinet.com/Centers/PHNCenters.aspx](https://benchtobassinet.com/Centers/PHNCenters.aspx)

**Childhood Liver Disease Research Network (ChiLDReN).** The Network is designed to improve understanding of pediatric liver diseases, including 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. [Supported by NIDDK]

[https://childrennetwork.org/](https://childrennetwork.org/)

**Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN).** This Network focuses on the etiology, contributing factors, natural history, complications, and therapy of this form of nonalcoholic fatty liver disease through studies in children and adults. In a previous study by Network researchers, a specific form of vitamin E was found to improve NASH in some children (PMID 21521847). A more recent study testing the drug cysteamine bitartrate found that, while it did not reduce nonalcoholic fatty liver disease in children, it did improve liver enzymes and inflammation within the liver (PMID 27569726). [Supported by NIDDK]


[https://jhuccs1.us/nash/](https://jhuccs1.us/nash/)

**Hepatitis B Research Network.** The Network, including its seven pediatric study sites, is promoting translational research on hepatitis B focusing upon elucidating the pathogenesis and natural history and development means of treatment and control. The study continued to receive support in 2016, through ongoing projects at several clinical centers as well as a new initiative to fund one of its clinical centers for up to 3 years. [Supported by NIDDK]


[https://www.hepbnet.org/](https://www.hepbnet.org/)
**Chronic Kidney Disease in Children (CKiD)** 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 has been funded to investigate genetic factors associated with progression of kidney disease in the study population. CKiD recently has been renewed through 2018, and expanded to allow for the recruitment of additional patients. [Supported by NIDDK, NICHD, NHLBI]. Data from CKiD can be found in the CKD Surveillance System (https://nccd.cdc.gov/ckd/data.aspx). [Supported by CDC] [https://statepi.jhsph.edu/ckid/](https://statepi.jhsph.edu/ckid/)

**Cure Glomerulonephropathy (CureGN).** The multicenter five-year cohort study seeks to enroll 2,400 children and adults with the following glomerular diseases: minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), and IgA nephropathy (IgAN). Participants will be followed longitudinally to better understand the causes of disease, response to therapy, and disease progression, with the ultimate objective to cure glomerulonephropathy. [Supported by NIDDK] [https://curegn.org/](https://curegn.org/)

**Environmental and Genetic Risk Factors for Juvenile Dermatomyositis and Other Pediatric Systemic Rheumatic Diseases.** NIEHS researchers have identified environmental risk and severity factors for juvenile dermatomyositis and other pediatric systemic rheumatic diseases, including juvenile idiopathic arthritis and juvenile systemic lupus erythematosus. NIEHS intramural researchers are planning studies to analyze environmental exposure questionnaire data from the Twin Sibling and MYORISK studies to further examine ultraviolet light, infections, vaccines, maternal pregnancy issues, and psychosocial stressors as potential environmental risk factors. They will also attempt to examine the role of these exposures in outcomes in children with myositis. [Supported by NIEHS] Twin Sibling Study: [https://www.niehs.nih.gov/research/clinical/studies/twin-sibs/index.cfm](https://www.niehs.nih.gov/research/clinical/studies/twin-sibs/index.cfm) MYORISK Study: [https://www.niehs.nih.gov/research/clinical/studies/myorisk/index.cfm](https://www.niehs.nih.gov/research/clinical/studies/myorisk/index.cfm)

**Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN).** The ATN is the only national, multicenter research network devoted to the health and well-being of HIV-infected and at-risk adolescents and young adults. The ATN has extensive experience in recruiting and retaining understudied youth populations in the United States. Over the past 10 years (2003-2013), they have had over 26,000 enrollments among 88 ATN studies, with enrollment and retention rates among completed studies over 90 percent. The primary mission of the ATN is to conduct both independent and collaborative research that explores promising behavioral, microbial, prophylactic, therapeutic, and vaccine modalities in HIV-infected and at-risk adolescents, ages 12 years through 24 years. ATN activities encompass the full spectrum of research needs for youth, from primary prevention – including HIV preventive vaccine, microbicide, and pre-exposure prophylaxis trials – for HIV at-risk youth in the community to secondary and tertiary prevention with clinical management of HIV infection among youth along the entire HIV care continuum. Secondary and tertiary prevention research investigates novel treatment strategies and regimens, drug adherence, risk reduction interventions, and linkage and engagement to care strategies that can lead to optimal antiretroviral therapy initiation and virologic suppression outcomes. [Supported by NICHD, NIDA, NIMH, NIMHD, NIAID, NIH OD] [https://www.nichd.nih.gov/research/supported/Pages/atn.aspx](https://www.nichd.nih.gov/research/supported/Pages/atn.aspx)

**Pediatric HIV/AIDS Cohort Study (PHACS).** PHACS began in 2005 to address two critical pediatric HIV research questions: What is the long-term safety of fetal and infant exposure to antiretroviral therapy (ART)? What are the effects of perinatally acquired HIV infection in adolescents? The overall goals of this Network are to: understand how HIV and its treatment affect growth and development, sexual
maturation, organ function, and socialization of perinatally HIV-infected pre-adolescents, adolescents, and young adults; acquire more definitive information on the long-term safety of ART when used during pregnancy and in newborns; ensure a mechanism is in place to estimate the upper bounds of risk for children who were exposed to ART during maternal treatment to prevent perinatal HIV transmission; and continue the follow-up study of these populations. [Supported by NICHD, NIAAA, NIAID, NIDCD, NIDCR, NIDA, NIMH, NINDS]

https://www.nichd.nih.gov/research/supported/Pages/phacs.aspx

The Human Immunology Project Consortium uses systems biology approaches to identify possible biomarkers of immune protection against natural infections, as well as vaccine efficacy in adult and pediatric populations, including analysis of childhood immune responses to dengue virus infection and the chicken pox vaccine (Varivax). [Supported by NIAID]

http://www.immuneprofiling.org/hipc/page/show

The Vaccine and Treatment Evaluation Units (VTEUs) evaluate vaccines and therapies against infectious diseases. Current VTEU studies include a clinical trial to evaluate whether five days of antibiotics instead of ten is effective at treating community-acquired pneumonia in children. [Supported by NIAID]


Clinical research on immune-mediated diseases in pediatric cohorts include:

- **The Consortium for Food Allergy Research** develops treatment and prevention strategies to combat food allergies. [Supported by NIAID]
- **The Clinical Trials in Organ Transplantation in Children** initiative aims to reduce immune-mediated morbidity and mortality and long-term graft dysfunction and/or loss unique to pediatric transplant recipients. [Supported by NIAID]
- **The Immune Tolerance Network** develops treatment and prevention strategies by inducing tolerance for respiratory and food allergies, asthma, autoimmune diseases, and organ transplantation. [Supported by NIAID]
- **The Primary Immune Deficiency (PID) Clinic** is the focal point for studies of the genetics, pathophysiology, and treatment of PID diseases (PIDD). The PID Clinic accepts patients from two years old and onward who have a known or suspected PIDD. People who have a PIDD, but who have not previously been diagnosed, usually suffer from recurrent, unusual, or difficult-to-treat infections. [Supported by NIAID]
- **The NIAID Intramural Research Program** focuses on the development of vaccines for childhood diseases, including rotaviruses, herpesviruses, malaria, and major pediatric respiratory pathogens for which no vaccines currently exist, such as RSV. [Supported by NIAID]
- **The Inner-City Asthma Consortium** uses immune-based-therapies to reduce asthma severity and prevent disease. [Supported by NIAID]

**Trans-Omics for Precision Medicine.** The Trans-Omics for Precision Medicine (TOPMed) Program is funding large-scale whole-genome sequencing of more than 20,000 childhood asthma DNA samples from mostly minority populations to investigate racial and ethnic disparities in asthma. [Supported by NHLBI]

**Rare Pediatric Diseases**

*The Rare Diseases Clinical Research Network (RDCRN)* conducts collaborative clinical research in rare diseases, including longitudinal studies of individuals with rare diseases, clinical studies, and/or clinical trials. The RDCRN also aims to provide up-to-date information for patients and to assist in connecting patients with advocacy groups, expert doctors, and clinical research opportunities. 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 Rett syndrome. [Led by NCATS; Supported by NICHD, NCI, NHLBI, NIAID, NIAMS, NIDCR, NIDDK, NIMH, NINDS, OD]

https://ncats.nih.gov/rdcrn

Some examples of consortia include:

- **Developmental Synaptopathies Consortium** includes teams of researchers conducting mechanistic studies of genetic conditions related to autism spectrum disorders (ASD) and intellectual disability, to uncover shared molecular pathways and potential new therapeutic targets. Many genes have been implicated in a spectrum of rare disorders associated with autism, and they appear to converge on a few common pathways. Deeper understanding of the shared pathophysiology may elucidate mechanisms of other causes of ASD, and pave the way for shared treatment possibilities. This consortium has projects related to three well-established genetic syndromes that are associated with high penetrance for ASD: TSC1/2, PTEN and SHANK3 mutations. [Supported by NINDS, NICHD, NIMH, NCATS] http://www.rarediseasesnetwork.org/cms/dsc

- **Rett and MECP2-Related Disorders Consortium (H3).** This Consortium studies three distinct disorders: Rett syndrome (RTT), MECP2 duplication disorder, and RTT-related disorders that are caused by *CDKL5* and *FOXL1* mutations and have similar phenotypes to RTT. [Supported by NICHD, NINDS] https://www.rarediseasesnetwork.org/cms/rett

- **Sterol & Isoprenoid Research (STAIR) Symposium.** The STAIR Consortium studies disorders related to cholesterol and other sterol and isoprenoid metabolism, such as Smith-Lemli-Opitz syndrome (SLOS), Niemann-Pick disease type C (NPC), Sjögren-Larsson syndrome (SLS), mevalonate kinase deficiency (MKD), sitosterolemia, and cerebrotendinous xanthomatosis. [Supported by NICHD, NCATS] http://www.rarediseasesnetwork.org/cms/STAIR

- **Urea Cycle Disorders Consortium.** This Consortium examines disorders that affect the body’s urea cycle, which regulates the metabolic process of converting wastes from the breakdown of food into urea that is excreted in urine. In urea cycle disorders, these wastes build up in the blood and cause neurological and other developmental problems. [Supported by NICHD, NCATS] https://www.rarediseasesnetwork.org/cms/UCDC

- **The Brittle Bone Disorders (BBD) Consortium.** The Consortium’s goals include enhanced understanding of genetic forms of osteogenesis imperfecta, expanded treatment options and develop quality of care measures, and training of the next generation of physicians and scientists in genetic bone diseases. [Supported by NIAMS, NIDCR, NIDCD, NCATS] https://www.rarediseasesnetwork.org/cms/BBD

*The Therapeutics for Rare and Neglected Diseases (TRND) program* establishes collaborative research partnerships with public and private entities, which leverage the unique strengths and capabilities of each party to develop new technologies and models that improve the efficiency of therapeutic development. TRND staff from NCATS provides drug development expertise and resources, working with research partners to move potential therapeutics through pre-clinical testing. [Supported by NCATS]

https://ncats.nih.gov/trnd
The Undiagnosed Diseases Network (UDN) is designed to accelerate discovery and innovation in the way we diagnose and treat patients with previously undiagnosed diseases. The specific goals of the network are to: (1) improve the level of diagnosis and care for patients with undiagnosed diseases through the development of common protocols designed by a large community of researchers; (2) facilitate research into the etiology of undiagnosed diseases, by collecting and sharing standardized, high-quality clinical and laboratory data including genotyping, phenotyping, and documentation of environmental exposures; and (3) create an integrated and collaborative community across multiple clinical sites and among laboratory and clinical researchers prepared to investigate the pathophysiology of these new and rare diseases. A significant proportion (~40 percent) of participants enrolled in the UDN are children; consequently, UDN has made and will continue to make discoveries in the diagnosis and treatment of rare diseases that affect pediatric populations. [Supported by NIH Common Fund]
https://commonfund.nih.gov/Diseases/index

Pediatric Cancer

The Childhood Cancer Survivor Study began in 1994 to examine the long-term effects of cancer and cancer therapy in childhood cancer survivors. To date it includes approximately 35,000 survivors of childhood cancer diagnosed between 1970 and 1999 and their unaffected siblings. Data from the study are used to analyze the long-term toxicities associated with cancer treatments and to identify which treatments are least likely to lead to negative health outcomes in survivors. In addition, the CCSS also conducts intervention studies in survivors to examine the best ways to screen for and prevent subsequent cancers and to improve health outcomes, including early identification of cardiac toxicity. [Supported by NCI]
NCI Overview of the CCSS: https://www.cancer.gov/types/childhood-cancers/ccss
Official CCSS Website: https://ccss.stjude.org/
St. Jude Lifetime Cohort Study Website: https://www.stjude.org/research/clinical-trials/sjlife-long-term-effects.html

NCI supports a comprehensive research program for children with cancer, ranging from basic molecular projects, through preclinical testing and clinical trials, to epidemiological studies to identify potential factors associated with childhood cancer development. An ultimate goal of this research is the identification of more effective and less toxic treatments so that all children diagnosed with cancer will survive their cancer and will grow to become healthy adults. Ongoing research initiatives include:

- **The Pediatric Brain Tumor Consortium (PBTC),** a multidisciplinary cooperative research organization devoted to the identification of superior treatment strategies for children with primary brain tumors. https://www.pbtc.org/
- **The Pediatric Preclinical Testing Consortium (PPTC),** which identifies new, more effective agents for treating childhood cancers. http://www.ncipptc.org/
- **The Pediatric Oncology Branch (POB)** conducts high-risk high-impact basic, translational and clinical studies. https://ccr.cancer.gov/Pediatric-Oncology-Branch
- **The TARGET Initiative,** a public-private partnership harnessing genomics technology to identify molecular changes that drive childhood cancers. https://ogc.cancer.gov/programs/target
- A comprehensive program of **Clinical Studies of Familial Cancer Syndromes,** several of which include children. https://dceg.cancer.gov/research/what-we-study/hereditary-cancer-syndromes
- **The Children's Oncology Group (COG),** 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. NCI is supporting many clinical trials of high-priority novel agents through the NCI clinical trials programs, including trials of targeted therapies and immunotherapies. The types of cancers addressed include relapsed/refractory solid tumors and lymphomas, newly diagnosed high-risk Hodgkin
lymphoma, certain relapsed leukemias, osteosarcoma, and Ewing sarcoma, and certain pediatric brain tumors. [https://childrensoncologygroup.org/]

- **The COG Phase I and Pilot Consortium** is separately funded by NCI to conduct early-phase trials and pilot studies so new anticancer agents can be rapidly and efficiently introduced into pediatric cancer care. These efforts are supported in addition to COG’s conduct of traditional late-phase clinical trials. [https://www.childrensoncologygroup.org/index.php/phase-1-home]

- **NCI Experimental Therapeutics Program (NExT).** NCI has prioritized the development of new treatments for pediatric cancer in the NExT Program. This program focuses on advancing breakthrough discoveries in basic and clinical research into new therapies, and each agent accepted into the NExT Program is considered for its relevance to pediatric cancers. [https://next.cancer.gov/]

- **Li-Fraumeni Syndrome Study.** Li-Fraumeni Syndrome (LFS) is a rare, inherited disorder which leads to a higher risk of developing certain cancers. These cancers tend to occur at younger ages in patients with LFS than in the general population. The types of tumors most frequently seen in LFS include bone and soft tissue cancers (called "sarcomas"), breast cancer, brain tumors, and cancer of the adrenal gland. The diagnosis of LFS is based on an individual’s personal and family history of cancers. Heritable disease-causing changes in a gene called TP53 is currently the only known cause of LFS and is identified in about 70 percent of families with a clinical diagnosis of LFS. [https://lfs.cancer.gov/]

- **Inherited Bone Marrow Failure Syndromes (IBMFS) Study.** The inherited bone marrow failure syndromes (IBMFS) are a group of rare genetic blood disorders in which there is usually some form of aplastic anemia (failure of the bone marrow to produce blood), associated with a family history of the same disorder. Some of these conditions have typical changes in physical appearance or in laboratory findings which suggest a specific diagnosis. Patients with these syndromes have a very high risk of development of cancer (either leukemia or certain solid tumors). Investigators in the NCI Division of Epidemiology and Genetics have been leading an ongoing clinical study in order to better understand how cancers develop in persons with IBMFS, with the aim of improving the healthcare that can be offered to persons with these disorders. [https://marrowfailure.cancer.gov/index.html]

- **Pleuropulmonary Blastoma DICER1 Syndrome Study.** Pleuropulmonary blastoma (PPB) is a rare tumor of the lung. Research has shown that PPB may be part of an inherited cancer predisposition syndrome caused by changes in a gene known as DICER1. The PPB Cancer Study is an observational study of children with PPB and their families. [https://ppb.cancer.gov/]

- **Retinoblastoma Survivors Follow-up Study.** Investigators in the NCI Division of Epidemiology and Genetics are studying retinoblastoma (Rb), a cancer that forms in the tissues of the retina (the light-sensitive layers of nerve tissue at the back of the eye). Rb usually occurs in children younger than five years, and may be hereditary or nonhereditary. Despite excellent survival rates among children treated for Rb, survivors with a germline mutation in their Rb1 gene (hereditary Rb) are prone to subsequent cancers including sarcomas, melanoma, and cancers of the brain and nasal cavity. [https://dceg.cancer.gov/research/cancer-types/retinoblastoma]

[Supported by NCI]

**Specialized Programs of Research Excellence (SPOREs)** promote collaborative, interdisciplinary translational cancer research. The SPORE program supports several research groups focused on pediatric cancer projects that include various basic and clinical studies in astrocytomas, gliomas, neuroendocrine tumors, and sarcomas. [Supported by NCI]

[https://trp.cancer.gov/spores/bylocation.htm]
Developmental Endocrine Oncology and Genetics. Intramural researchers are conducting investigations on endocrine complications faced by pediatric cancer survivors. Additional studies to improve clinical care for pediatric patients with many types of endocrine cancers including pheochromocytoma, Cushing disease, and thyroid cancer. [Supported by NICHD]
https://www.nichd.nih.gov/about/org/dir/affinity/DEOG/Pages/default.aspx

Childhood Injuries and Maltreatment

National Center for Medical Rehabilitation Research (NCMRR). Through basic, translational, and clinical research, the NCMRR aims to foster development of scientific knowledge needed to enhance the health, productivity, independence, and quality-of-life of people with physical disabilities. The NCMRR supports research on the following topics: pathophysiology and management of chronically injured nervous and musculoskeletal systems (including stroke, traumatic brain injury, spinal cord injury, and orthopedic conditions); repair and recovery of motor and cognitive function; functional plasticity, adaptation, and windows of opportunity for rehabilitative interventions; rehabilitative strategies involving pharmaceutical, stimulation, and neuroengineering approaches, exercise, motor training, and behavioral modifications; pediatric rehabilitation; secondary conditions associated with chronic disabilities; improved diagnosis, assessment, and outcome measures; and development of orthotics, prosthetics, and other assistive technologies and devices. NCMRR also supports research on therapies and rehabilitative approaches for cerebral palsy. [Supported by NICHD]
https://www.nichd.nih.gov/about/org/ncmrr/Pages/overview.aspx

The Medical Rehabilitation Research Infrastructure Network. This network, funded through the National Center for Medical Rehabilitation Research with additional support from the National Institute of Neurological Disorders and Stroke and the National Institute of Biomedical Imaging and Bioengineering, builds research infrastructure in medical rehabilitation by providing researchers with access to expertise, courses and workshops, technologies, and collaborative opportunities from allied disciplines, such as neuroscience, engineering, applied behavior, and the social sciences. [Supported by NICHD, NINDS, NIBIB]
https://www.nichd.nih.gov/research/supported/Pages/mrrin.aspx

CAPSTONE Centers for Multidisciplinary Research in Child Abuse and Neglect address child maltreatment as a significant public health concern. This program will allow researchers to: assess the efficacy and effectiveness trials of child abuse and neglect interventions; examine the long-term impact of specific and understudied types of maltreatment; study the neurobiology of abuse and neglect and implications for health outcomes; and develop screening tools and assessment measures for early identification and treatment of specific types of abuse and neglect. [Supported by NICHD]

Pediatric Critical Care and Emergency Care

Collaborative Pediatric Critical Care Research Network (CPCCRN). Focusing on critically ill infants and children, this national resource 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. Research topic areas include: bereavement and grief, functional outcomes, intensive care clinical processes and protocols, and infection and sepsis. [Supported by NICHD]
https://www.nichd.nih.gov/research/supported/Pages/cpccrn.aspx
Clinical Care, Outreach, and Services

**NIH Pediatric Rheumatology Clinic.** The NIH Pediatric Rheumatology Clinic 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 to gain a better understanding of why some children develop them. The Clinic consists of two major parts: a clinic and a health information resource center. In the clinic, medical staff diagnose and treat children with arthritis, periodic fever syndromes, lupus, and other rheumatic diseases who are enrolled in clinical trials. The health information resource center provides written and oral information on signs and symptoms of arthritis and rheumatic diseases as well as tips for maintaining wellness and managing disease. [Supported by NIAMS]
https://www.niams.nih.gov/Health_Info/Pediatric_Diseases/default.asp

The **National Child & Maternal Health Education Program (NCMHEP)**, involving over 30 federal and non-federal organizations, is designed to identify key challenges in child and maternal health, review relevant research and initiate educational activities that advance the knowledge base of the field, and improve the health of women and children. [Supported by NICHD, ORWH, CDC, IHS, HRSA, HHS OMH, HHS OWH, 28 member organizations]
https://www.nichd.nih.gov/ncmhep/Pages/index.aspx

**Safe to Sleep** is a public health campaign program to reduce the risk of SUID (sudden unexpected infant death). Many SUID cases are due to accidental suffocation, such as when an infant becomes trapped between a mattress and a wall, or when bedding material presses on or wraps around an infant's neck. In addition to placing infants on their backs to sleep, the Safe to Sleep Campaign emphasizes other ways to reduce the risk of sudden infant death. This includes placing infants in their own safe sleep environment and not on an adult bed, without any soft bedding such as blankets or quilts. Safe to Sleep also emphasizes breast feeding infants when possible, which has been associated with reduced SIDS risk, and eliminating other risks to infant health that have been identified through research. These other risk factors include overheating, exposure to tobacco smoke, and a mother's use of alcohol and illicit drugs. [Supported by NICHD]
https://www.nichd.nih.gov/sts/Pages/default.aspx

Technology and Tools

**Pediatric Research using Integrated Sensor Monitoring Systems (PRISMS).** As the most common pediatric chronic disease, asthma affects more than six million children in the United States. To address this complex disease that involves the interaction of environmental, physiological, and behavioral factors, the PRISMS program is designed to develop sensor-based, integrated health monitoring systems for measuring environmental, physiological, and behavioral factors in children. Collaborative teams of researchers are developing noninvasive health monitoring systems for pediatric asthma research and for other chronic diseases in the future. One arm of this collaboration is developing both wearable and non-wearable sensors to monitor environmental exposure, physiological signals (such as children’s activity), and behavior in children’s natural environments. To date, progress is being made in creating a variety of sensors for use by individuals or in households that could measure air pollution levels, physical activity, breathing patterns, inhaler use, or heart rate. Another arm of this research project is designing “plug and play” wireless or hardwire platforms to collect, protect, and analyze data gathered from the sensors. A third group will coordinate and house data from the PRISMS program and integrate other relevant data sources such as geographical location, air quality data, and traffic patterns. [Supported by NIBIB] https://www.nibib.nih.gov/research-funding/prisms
**Gabriella Miller Kids First Pediatric Research Program.** The Common Fund’s Gabriella Miller Kids First Pediatric Research Program (Kids First) is developing a large-scale data resource for the pediatric research community. The resource will allow researchers everywhere access to vast amounts of childhood cancer and structural birth defects genetics and clinical data that will greatly accelerate their research. The resource will also allow researchers to examine childhood cancer and structural birth defects together to uncover new connections between them that might not have been uncovered had one or the other been examined independently. This is anticipated to accelerate scientific progress in pediatric research that will improve the lives of the children and families impacted by childhood cancer and structural birth defects. In FYs 2015 and 2016, the Kids First program supported DNA sequencing centers to provide whole genome sequencing support for seven and eight cohorts of children, respectively, with childhood cancer or structural birth defects. [Supported by NIH Common Fund]

Kids First website: https://commonfund.nih.gov/KidsFirst
Kids First funded research: https://commonfund.nih.gov/kidsfirst/fundedresearch

**The Pediatric Trials Network (PTN)** provides evidence for optimal dosing of commonly used medications in infants and children. Current studies include research on the pharmacokinetic and pharmacodynamics properties of antipsychotic drugs in children and adolescents, a study on the effectiveness of sildenafil to decrease the risk of pulmonary arterial hypertension in preterm infants, and research on the pharmacokinetics of methadone to treat opioid withdrawal in children. [Supported by NICHD, BPCA]

https://pediatrictrials.org/

**Pediatric Patient-Reported Outcomes in Chronic Diseases (PEPR) Consortium** aims to test several pediatric patient-reported outcome tools that measure aspects of physical, mental, and social well-being such as pain, anxiety, and peer relationships. [Supported by NIAMS]

https://www.niams.nih.gov/funding/Funded_Research/PEPR/

**The Electronic Medical Records & Genomics Network (eMERGE) pediatric sites.** The Electronic Medical Records & Genomics Network (eMERGE) consists of nine study sites, two central sequencing and genotyping centers, and a coordinating center located across the country. Broadly, eMERGE seeks to link existing biorepository samples to electronic medical records (EMRs) for genomic discovery and genomic medicine research. The specific aims of eMERGE phase III are to (1) sequence and assess the phenotypic implication of rare variants in approximately 100 clinically relevant genes presumed to affect gene function in about 25,000 individuals; (2) integrate genetic variants into EMRs for improvement of genetic risk assessment, prevention, diagnosis, treatment and/or accessibility of genomic medicine; (3) create community resources such as phenotyping/genotyping tools; and (4) conduct research on best practices for informed consent, protection of human subjects for data sharing, and return of genomic results. This consortium is also exploring issues related to informed consent and return of results for children participating in genomic medicine studies. [Supported by NHGRI, NICHD]

https://emerge.mc.vanderbilt.edu/publications/

**The Clinical Genome Resource (ClinGen): Pediatric Neurology Working Group.** The Clinical Genome Resource (ClinGen) aims to build an authoritative central resource that defines the clinical relevance of genes and variants for use in precision medicine and research. To do so, ClinGen scientists are developing standard approaches for sharing genomic and phenotypic data provided by clinicians, researchers, and patients through centralized databases, such as ClinVar, and are working to standardize the clinical annotation and interpretation of genomic variants. Working groups are implementing evidence-based expert consensus methods to curate the clinical validity and medical actionability of genes and variants. The Pediatric Neurology ClinGen working group is specifically identifying and curating genes and
variants related to pediatric neurological conditions. Their work will enhance the medical treatment of
these conditions. [Supported by NHGRI, NICHD]
ClinGen website: https://www.clinicalgenome.org/

**Genome Sequencing to Identify the Genomic Bases of Mendelian and Common Diseases.** The Centers
for Mendelian Genomics (CMG) was designed to advance the discovery of genes and variants related to
Mendelian disorders. The complications of Mendelian genetic disorders often present themselves in early
years of life. Since their inception, the CMG have identified several hundreds of casual genes for
Mendelian and monogenic diseases. Building on the success of the CMG, in 2016 a new group of
sequencing centers has begun to focus on common disease genomics. Among other conditions, the new
Centers for Common Disease Genomics (CCDG) will investigate the genomics of autism and Type 1 diabetes. [Supported by NHGRI, NHLBI, NEI]
CMG: http://mendelian.org/
CCDG: http://ccdg.rutgers.edu/

**Clinical Sequencing Exploratory Research Program (CSER).** The Clinical Sequencing Exploratory
Research (CSER) consortium was established in 2010 and is working to address critical questions about
the application of genomic sequencing to the clinical care of individual patients. This includes generation
of genomic sequence data, interpretation and translation of the data for the physician, communication to
the patient, and an examination of the ethical, legal, and psychosocial implications of bringing broad
genomic data into the clinic. Several CSER study sites are focused on pediatric conditions such as
pediatric cancer and intellectual disability and developmental delay. One site is also exploring the use of
genome sequencing in pre-conception carrier testing. An example of a finding that emerged from CSER
was that the group found that a genome sequencing approach could potentially impact clinical cancer care
in as many as 40 percent of children. The first phase of CSER is ending, and in 2017 CSER will enter its
second iteration. [Supported by NHGRI, NCI, NIMHD]
https://www.genome.gov/cser/

**The Sudden Death in the Young (SDY) Case Registry** is a collaborative effort to 1) describe the
incidence of SDY in the United States using population-based surveillance, 2) compile data from SDY
cases to create a resource of information and DNA samples for research, 3) encourage standardized
approaches to investigation, autopsy, and categorization of SDY cases, 4) develop partnerships between
local, state, and federal stakeholders toward a common goal of understanding and preventing SDY, and 5)
support families who have lost loved ones to SDY by providing resources on bereavement and medical
evaluation. In April 2016, three research groups began to collaborate in using the registry to explore the
genetic etiology of sudden cardiac death in the young and to explore how families are evaluated after
suffering an SDY event. [Supported by NHLBI, NINDS, CDC]
https://content.govdelivery.com/accounts/USCDC/bulletins/d97a24

**The Genetic and Rare Diseases Information Center** provides comprehensive information on rare and
genetic diseases to patients, researchers, and the public. Information includes ongoing research, disease
symptoms, and treatment options. GARD information specialists are available by phone to discuss
questions in English and Spanish. [Supported by NCATS, NHGRI]
https://rarediseases.info.nih.gov/
"FaceBase: Accelerating Research on Craniofacial Development." The FaceBase consortium continues to produce and release large datasets for use by the craniofacial development and dysmorphology research community. First established in FY 2009 and continued through the funding of 10 new projects in FY 2014, the consortium makes these datasets, as well as any associated visualization tools, available through a website developed and managed by a central data management and coordination hub. The consortium’s bioinformatics efforts are directed towards maximizing the integration and utility of these datasets while protecting the privacy of human research participants. In line with the NIH’s efforts through its Big Data to Knowledge initiative (BD2K), the consortium is working to organize and structure its datasets using publicly available standard naming methods and existing data models employed by the wider bioinformatics research community. To facilitate harmonization of FaceBase data with bioinformatics community data standards, BD2K is supporting a collaboration between FaceBase and the NIH-funded Monarch Initiative. These efforts are expected to facilitate research in laboratories outside of the consortium and provide the building blocks for novel bioinformatics and systems biology analyses of craniofacial development. NIDCR further supports use of the FaceBase datasets through a funding opportunity announcement (PAR-16-362) promoting secondary analysis of FaceBase data. [Supported by NIDCR, NLM]

FaceBase: [https://www.facebase.org/](https://www.facebase.org/)
BD2K: [https://commonfund.nih.gov/bd2k/index](https://commonfund.nih.gov/bd2k/index)
Monarch Initiative: [https://monarchinitiative.org/](https://monarchinitiative.org/)

"The Human Oral Microbiome Database," an online database, allows the research community to investigate genomic data and taxonomic naming schemes, utilize analysis tools, and obtain reference bacterial strains to better understand associations between the oral microbiome and oral and systemic disease. [Supported by NIDCR]

http://www.homd.org/

"The Pumps for Kids, Infants, and Neonates (PumpKIN) program" was designed to meet a long-standing need for circulatory support devices specifically for young children with severe heart failure. The device development phase of the program successfully resulted in a miniaturized implantable device, the Jarvik 2015 VAD, for children weighing 8-20 kg. The PumpKIN clinical trial, which will commence in 2017, is designed to evaluate the device’s safety and benefit in these very ill children. [Supported by NHLBI]


"Neurodevelopmental Assessment of Infants and Children in Resource-Limited Settings." This program aims to stimulate small business applications to develop tools and/or materials to assess cognitive functioning of infants and children in resource-limited settings. [Supported by NICHD, NIMH]


"National Primate Research Centers (NPRCs)." The seven NPRCs provide facilities and expertise for comprehensive investigations related to fetal, neonatal and childhood health. NPRC facilities include nurseries and intensive care units for newborn and young animals, as well as large outdoor corrals in which large peer-groups of young animals are reared in natural settings. These animal models have provided insights on the effects of congenital cytomegalovirus and moderate maternal nutrient restriction on fetal development. [Supported by ORIP]

https://nprcresearch.org/prime/
Global Pediatric Health

Domestic & International Pediatric & Maternal HIV Clinical Studies Network. Currently composed of 15 domestic sites in 11 states and territories and 14 international sites in Argentina, Brazil, Kenya, Tanzania, and Thailand, plus a Data Coordinating Center (DCC), this network conducts trials related to preventing and treating HIV infection and its complications in newborns, infants, children, adolescents, and pregnant women. Recently, network researchers have broadened their focus to include TB, malaria, hepatitis, and investigation of vaccines to prevent HIV-related or other high-priority infectious diseases in children, adolescents, and pregnant women, in addition to treatment of HIV infection. [Supported by NICHD]
https://www.nichd.nih.gov/research/supported/Pages/pphsn.aspx

Global Network for Women’s and Children’s Health Research. The Global Network supports and conducts clinical trials in resource-limited countries by pairing foreign and United States researchers, 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, which 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. [Supported by NICHD]
https://www.nichd.nih.gov/research/supported/Pages/globalnetwork.aspx

Pediatric Research at the NIH Clinical Center

The NIH Clinical Center is the clinical research facility of the NIH. It provides patient care, services, training, and the environment in which NIH clinician scientists creatively translate emerging knowledge into better understanding, detection, treatment and prevention of human diseases. In FY 2016, fourteen Institutes admitted 3,316 pediatric patients to the Clinical Center to 283 protocols that included children who were seen on 13,358 out-patient days and 491 inpatient admissions for 4,632 pediatric in-patient days. The proportion of Clinical Center activity that involved children was 11 percent of all Clinical Center inpatient activity and 13 percent of all Clinical Center outpatient visits. Overall, the proportion of Clinical Center patients under age 18 years increased from 12 to 13 percent. Other significant increases include a 12 percent increase in outpatient visit-days, a 4 percent increase in individual patients seen, and a 7 percent increase in protocols that saw children.

Natural history studies, often in patients with rare diseases, make up about half of the pediatric clinical research conducted at the Clinical Center. Understanding the basis for rare diseases often leads to new approaches to common problems. Most of the other clinical research studies are the early Phase 1 and 2 trials that are the first studies of new treatments and therapies, with 1,643 clinical research studies, 35 percent in children.

A comprehensive pediatric program is part of the state-of-the-art Clinical Research Center that opened April 2, 2005 at the NIH. The Clinical Research Center has one unified pediatric multi-Institute unit with 22 beds and 14-day hospital stations, one 6-bed pediatric behavioral health inpatient unit plus room for 2 day patients, and a multi-Institute pediatric outpatient clinic with 21 patient care rooms. The size of the pediatric area was determined based on protocol activity, and trends toward implementing new protocols in an ambulatory setting.
To accommodate the growing number of pediatric intramural research subjects, The Children’s Inn at the NIH completed its first expansion in FY 2004. Now almost doubled in size, the family-centered residence can care for 65 families every night. In FY 2016, 1,572 families stayed 15,479 nights at The Inn and The Woodmont House, a transitional home that was opened in FY 2011 to accommodate up to 7 families requiring longer stays. This represents an 8.1 percent increase in nights accommodated. In FY 2014, the Children’s Inn opened 4 isolation rooms. The isolation rooms can accommodate residents on contact isolation for certain infections. In FY 2016, The Inn had 15 residents stay for 547 nights in these isolation rooms. Since its opening in 1990, more than 12,000 families have stayed at The Inn and The Woodmont House. Children and families have come from all 50 states and 94 countries.

Other Cross-Cutting Areas of Pediatric Research

**Pediatric Pharmacology and the Best Pharmaceuticals for Children Act.** Federal legislation and FDA regulations require that new drugs be found safe and effective for their intended use(s) before the drugs are approved for marketing. 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 not approved for use in children and therefore are used without adequate understanding of appropriate dose, safety, or efficacy.

The Best Pharmaceuticals for Children Act (BPCA) established a process for the NIH, the FDA, and pediatric experts to identify drugs that are used in pediatric care and for which studies would have public health benefit. If industry does not fund studies on drugs prioritized under BPCA, the NICHD and other NIH ICs support research to address the need. [https://bpca.nichd.nih.gov/](https://bpca.nichd.nih.gov/)

**Specialized Centers in Research in Pediatric Developmental Pharmacology (RPDP).** The RPDP 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. [https://www.nichd.nih.gov/research/supported/Pages/srpd.aspx](https://www.nichd.nih.gov/research/supported/Pages/srpd.aspx) [https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-16-014.html](https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-16-014.html)
**Clinical and Translational Science Award (CTSA) Program.** The 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 researcher 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 researchers who are also pediatricians, and more than 50 of the centers included children’s hospitals conducting pediatric research as partners in their CTSA applications. 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. [Supported by NCATS]

https://ncats.nih.gov/ctsa

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

**Child Neurologist Career Development Program (CNCDP).** The CNCDP facilitates and supports the research career development of child neurologists, at educational institutions or professional organizations, who have made a commitment to independent research careers. The CNCDP will generally provide individuals with the knowledge, tools and research experience that will enable them to develop a significant research project funded by an individual career development award or research grant. [Supported by NINDS]


**The Child Health Research Career Development Award (CHRCDA) 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, 780 pediatric researchers working in 15 different subspeciality areas of pediatrics in 38 pediatric departments throughout the United States have benefitted from this program. [Supported by NICHD]

https://www.nichd.nih.gov/research/supported/Pages/chrcda.aspx

**The Pediatric Scientist Development Program (PSDP)** provides 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. [Supported by NICHD]

https://www.cincinnatichildrens.org/education/research/psdp

**The 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. [Supported by NICHD]

http://www.pccsdp.org/
**Fogarty Global Injury and Trauma Research Training Program (RFA-TW-16-001).** This program aims to strengthen injury and trauma research capacity at academic institutions in low- and middle-income countries (LMICs) through support for research training programs. [Supported by FIC, NIH OD ORWH, NICHD]


**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.

https://www.lrp.nih.gov/eligibility-programs
APPENDIX

Table 1: All NIH Pediatric Research, FY 2016
Table 2: Pediatric Research Initiative, FY 2016
Table 3: NIH Funding Opportunity Announcements That Solicited Applications for Pediatric Research, FY 2016
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 2016

The totals below were derived from the 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 FY 2016 NIH-funded grants and projects in pediatric research is available at [https://report.nih.gov/categorical_spending_project_listing.aspx?FY=2016&ARRA=N&DCat=Pediatri c](https://report.nih.gov/categorical_spending_project_listing.aspx?FY=2016&ARRA=N&DCat=Pediatri c). The term “Common Fund” refers to research funded through the Office of Strategic Coordination, OD, NIH, to address key scientific issues that no one ICO is positioned to address alone.

<table>
<thead>
<tr>
<th>NIH ICO</th>
<th>Fiscal Year 2016</th>
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<tr>
<td>FIC</td>
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<td>NCATS</td>
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<td>Common Fund</td>
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<td>Type 1 Diabetes</td>
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Table 2: Pediatric Research Initiative, FY 2016

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 ICOs had set aside specified amounts of available funds. “Significant expansions” may include substantial increases in funding to expand an existing ICO 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 ICO for research that meets this definition. A list of FY 2016 NIH-funded grants and projects for the PRI is available at: https://report.nih.gov/categorical_spending_project_listing.aspx?FY=2016&ARRA=N&DCat=Pediatric%20Research%20Initiative

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<td>NLM</td>
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<td>OD</td>
<td>$77,262,428</td>
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<td>Type 1 Diabetes</td>
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<td><strong>Grand Total</strong></td>
<td><strong>$388,938,833</strong></td>
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Table 3: NIH Funding Opportunity Announcements That Solicited Applications for Pediatric Research, FY 2016

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<th>Announcement Number</th>
<th>Issuing Organization</th>
<th>Activity Code</th>
<th>Title</th>
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<tr>
<td>PA-16-022</td>
<td>NINR</td>
<td>R15</td>
<td>Innovative Questions in Symptom Science and Genomics (R15)</td>
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<td>PA-16-023</td>
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<td>Innovative Questions in Symptom Science and Genomics (R21)</td>
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<td>PA-16-024</td>
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<td>R01</td>
<td>Innovative Questions in Symptom Science and Genomics (R01)</td>
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<td>PA-16-031</td>
<td>NICHD</td>
<td>R21</td>
<td>Advancing Understanding, Prevention and Management of Infections Transmitted from Women to their Infants (R21)</td>
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<td>PA-16-032</td>
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<td>R01</td>
<td>Advancing Understanding, Prevention, and Management of Infections Transmitted from Women to their Infants (R01)</td>
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<td>PA-16-046</td>
<td>NIEHS</td>
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<td>Limited Competition: Exposure Analysis Services for the Environmental Influences on Children's Health Outcomes (ECHO) Program (Admin Supp)</td>
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<td>PA-16-086</td>
<td>NCI</td>
<td>–</td>
<td>Supplements to Promote Clinical Research Studies on Pediatric Burkitt Lymphoma in Low- and Middle-Income Countries (Admin Supp)</td>
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<td>PA-16-087</td>
<td>NICHD</td>
<td>R21</td>
<td>Oocyte Mitochondrial Function in Relation to Fertility, Aging, and Mitochondrial Diseases (R21)</td>
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<td>PA-16-088</td>
<td>NICHD</td>
<td>R01</td>
<td>Oocyte Mitochondrial Function in Relation to Fertility, Aging, and Mitochondrial Diseases (R01)</td>
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<td>PA-16-101</td>
<td>NICHD</td>
<td>R03</td>
<td>Multidisciplinary Research in Vulvodynia (R03)</td>
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<tr>
<td>PA-16-102</td>
<td>NICHD</td>
<td>R01</td>
<td>Multidisciplinary Research in Vulvodynia (R01)</td>
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<td>PA-16-144</td>
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<td>R01</td>
<td>Role of Astrocytes and Astrocytic Networks in Drug Abuse (R01)</td>
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<td>PA-16-145</td>
<td>NIDA</td>
<td>R21</td>
<td>Role of Astrocytes and Astrocytic Networks in Drug Abuse (R21)</td>
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<td>PA-16-146</td>
<td>OBSSR</td>
<td>R01</td>
<td>Population Health Interventions: Integrating Individual and Group Level Evidence (R01)</td>
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<td>PA-16-147</td>
<td>OBSSR</td>
<td>R21</td>
<td>Population Health Interventions: Integrating Individual and Group Level Evidence (R21)</td>
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<td>PA-16-159</td>
<td>NIDDK</td>
<td>R01</td>
<td>Advances in Polycystic Kidney Disease (R01)</td>
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<td>PA-16-165</td>
<td>NIDDK</td>
<td>R01</td>
<td>Obesity Policy Evaluation Research (R01)</td>
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<td>NIDDK</td>
<td>R01</td>
<td>Diet and Physical Activity Assessment Methodology (R01)</td>
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<td>PA-16-169</td>
<td>NIDDK</td>
<td>R01</td>
<td>Understanding Factors in Infancy and Early Childhood (Birth to 24 months) That Influence Obesity Development (R01)</td>
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<td>PA-16-173</td>
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<td>Limited Competition: Tissue Chips for Rare Diseases (Admin Supp)</td>
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<td>PA-16-175</td>
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<td>R21</td>
<td>Exploratory Grants in Cancer Epidemiology and Genomics Research (R21)</td>
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<td>PA-16-183</td>
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<td>Limited Competition: Rare Diseases Clinical Research Network (RDCRN) Project Supplements for Clinical Trials to Repurpose Drugs in Collaboration with E-Rare Awardees (Admin Supp)</td>
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<td>Mechanisms, Models, Measurement, and Management in Pain Research (R21)</td>
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<td>PA-16-232</td>
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<td>Prescription Drug Abuse (R21)</td>
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<td>Prescription Drug Abuse (R01)</td>
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<td>NCI</td>
<td>R01</td>
<td>Gene Fusions in Pediatric Sarcomas (R01)</td>
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<td>NCI</td>
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<td>PA-16-258</td>
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<td>Mechanisms of Cancer and Treatment-related Symptoms and Toxicities (R21)</td>
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<td>PA-16-263</td>
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<td>Environmental Exposures and Health: Exploration of Non-Traditional Settings (R01)</td>
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<td>Safety and Outcome Measures of Pain Medications Used in Children and Pregnant Women (R01)</td>
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<td>PA-16-312</td>
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<td>Small Grants on Primary Immunodeficiency Diseases (R03)</td>
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<td>Exploratory/Developmental Investigations on Primary Immunodeficiency Diseases (R21)</td>
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<td>Limited Competition: Clinical Research Investigator Supplement (CRIS) for the Maternal Fetal Medicine Units (MFMU) Network and the Neonatal Research Network (NRN) (Admin Supp)</td>
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<td>DA-17-015</td>
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<td>NIDA Translational Avant-Garde Award for Development of Medication to Treat Substance Use Disorders (UG3/UH3)</td>
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<td>DK-15-019</td>
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<td>DP3</td>
<td>Research Using Biosamples and Subjects from Type 1 Diabetes Clinical Studies Complications (DP3)</td>
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<td>DK-15-026</td>
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<td>Diabetes Research Centers (P30)</td>
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<td>DK-15-506</td>
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<td>UC4</td>
<td>Limited Competition: Understanding How Epigenetics and Infections Impact Autoimmunity and Diabetes in The Environmental Determinants of Diabetes In The Young Study (TEDDY) (UC4)</td>
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<td>DK-16-001</td>
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<td>Improving Diabetes Management in Pre-teens, Adolescents and/or Young Adults with Type 1 Diabetes (DP3)</td>
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<tr>
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<td>DP3</td>
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<td>R43/R44</td>
<td>Development of New Technologies and Bioengineering Solutions for the Advancement of Cell Replacement Therapies for Type 1 Diabetes (R43/R44)</td>
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<td>DK-16-005</td>
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<td>Identification of Mechanisms Mediating the Effects of Sleep on Diabetes-Related Metabolism in Humans (R01)</td>
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<td>Standardization of C-peptide and HbA1c Measurements Program (UC4)</td>
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<td>Limited Competition for the Continuation of Epidemiology of Diabetes Interventions and Complications (EDIC) Study Clinical Research Center (Collaborative U01)</td>
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<td>Limited Competition for Data Coordinating Center (DCC) for NIDDK Inflammatory Bowel Disease Genetics Consortium (IBDGC) (U24)</td>
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<td>Neuroimaging Informatics Tools and Resources Clearinghouse (U24)</td>
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<td>Big Data to Knowledge (BD2K) Community-based Data and Metadata Standards Efforts (R24)</td>
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<td>Intellectual and Developmental Disabilities Research Centers 2016 (U54)</td>
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<td>Specialized Centers in Research in Pediatric Developmental Pharmacology (U54)</td>
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<td>RFA-HD-17-002</td>
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<td>R21/R33</td>
<td>Use of 3D Printing for Creation of Implantable Devices (R21/R33)</td>
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<td>Learning Disabilities Innovation Hubs (P20)</td>
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<td>Assessing Human Placental Development and Function Using Existing Data (R01)</td>
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<td>RFA-HD-17-005</td>
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<td>Global Network for Women’s and Children’s Health Research Data Coordinating Center (U24)</td>
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<td>Understanding STI Co-Infection In At Risk and HIV Infected Adolescents and Young Adults (R01)</td>
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<td>Animal-Assisted Interventions for Special Populations (R03)</td>
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<td>Animal-Assisted Interventions for Special Populations (R21)</td>
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<td>Developmental Mechanisms of Human Structural Birth Defects (P01)</td>
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<td>Clinical Sequencing Evidence-Generating Research (CSER2) - Clinical Sites (U01)</td>
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<td>UM1</td>
<td>Household Air Pollution (HAP) Health Outcomes Trial (UM1)</td>
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<td>U01</td>
<td>Prematurity-Related Ventilatory Control (Pre-Vent): Role in Respiratory Outcomes Clinical Research Centers (CRC) (U01)</td>
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<td>RFA-HL-16-016</td>
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<td>Pediatric Heart Network Clinical Research Centers (UG1)</td>
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<td>Clinical Centers for the NHLBI's Precision Interventions for Severe and/or Exacerbation Prone Asthma (PrecISE) Network (UG1)</td>
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<td>RFA-HL-17-012</td>
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<td>Small Market Awards: SBIR Phase IIB Competing Renewals for Heart, Lung, Blood, and Sleep Technologies with Small Commercial Markets (R44)</td>
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<td>Bold New Bioengineering Methods and Approaches for Heart, Lung, Blood and Sleep Disorders and Diseases (R21)</td>
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<td>The Role of Dysbiosis in Cardiovascular, Pulmonary and Hematological Complications During HIV Infection (R01)</td>
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<td>Cardiovascular and Pulmonary Research on E-Cigarettes (R01)</td>
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<td>RFA-HL-17-022</td>
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<td>Maximizing the Scientific Value of the NHLBI Biorepository: Scientific Opportunities for Exploratory Research (R21)</td>
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<td>Perinatal Stroke (R01)</td>
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<td>Engaging Youth and Young Adults from Health Disparity Populations in the HIV Treatment Cascade (R01)</td>
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<td>BRAIN Initiative: Development and Validation of Novel Tools to Analyze Cell-Specific and Circuit-Specific Processes in the Brain (R01)</td>
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<td>Adaptation/Optimization of Technology (ADOPTech) to Support Social Functioning (R21)</td>
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<td>Services Research for Autism Spectrum Disorder across the Lifespan II (ServASD II): Pilot Research on Services for Transition-Age Youth (R34)</td>
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<td>Collaborative Hubs to Reduce the Burden of Suicide among American Indian and Alaska Native Youth (U19)</td>
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<td>Understanding and Addressing the Multi-level Influences on Uptake and Adherence to HIV Prevention Strategies Among Adolescent Girls and Young Women in Sub-Saharan Africa (R01)</td>
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<td>Data Coordinating and Operations Center for the IDeA States Pediatric Clinical Trials Network (U24)</td>
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<td>Environmental Influences on Child Health Outcomes: Patient Reported Outcomes Research Resource Center Core (ECHO PRO Core) (U24)</td>
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<td>Molecular Transducers of Physical Activity Genomics, Epigenomics and Transcriptomics Chemical Analysis Sites (U24)</td>
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<td>D43</td>
<td>Fogarty Global Injury and Trauma Research Training Program (D43)</td>
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<td>FIC</td>
<td>R01</td>
<td>International Tobacco, and Health Research and Capacity Building Program (R01)</td>
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### Table 4: Acronyms for NIH Institutes, Centers, and Offices and Other Federal Agencies Referred to in This Report

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<th>Acronym</th>
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<td>CC</td>
<td>Clinical Center</td>
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<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
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<tr>
<td>CF</td>
<td>Common Fund, Office of Strategic Coordination, DPCPSI, OD</td>
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<tr>
<td>DPCPSI</td>
<td>Division of Program Coordination, Planning, and Strategic Initiatives, OD</td>
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<tr>
<td>EPA</td>
<td>Environmental Protection Agency</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FIC</td>
<td>John E. Fogarty International Center</td>
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<td>HHS</td>
<td>Department of Health and Human Services</td>
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<tr>
<td>ICOs</td>
<td>NIH Institutes, Centers, and Offices</td>
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<tr>
<td>NCATS</td>
<td>National Center for Advancing Translational Sciences</td>
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<tr>
<td>NCCIH</td>
<td>National Center for Complementary and Integrative Health</td>
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<td>NCI</td>
<td>National Cancer Institute</td>
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<tr>
<td>NEI</td>
<td>National Eye Institute</td>
</tr>
<tr>
<td>NHLBI</td>
<td>National Heart, Lung, and Blood Institute</td>
</tr>
<tr>
<td>NHGRI</td>
<td>National Human Genome Research Institute</td>
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<td>NIA</td>
<td>National Institute on Aging</td>
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<td>NIAAA</td>
<td>National Institute on Alcohol Abuse and Alcoholism</td>
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<tr>
<td>NIAID</td>
<td>National Institute of Allergy and Infectious Diseases</td>
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<tr>
<td>NIAMS</td>
<td>National Institute of Arthritis and Musculoskeletal and Skin Diseases</td>
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<tr>
<td>NIBIB</td>
<td>National Institute of Biomedical Imaging and Bioengineering</td>
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<td>NICHD</td>
<td><em>Eunice Kennedy Shriver</em> National Institute of Child Health and Human Development</td>
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<td>NIDA</td>
<td>National Institute on Drug Abuse</td>
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<td>NIDCD</td>
<td>National Institute on Deafness and Other Communication Disorders</td>
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<tr>
<td>NIDCR</td>
<td>National Institute of Dental and Craniofacial Research</td>
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<td>NIDDK</td>
<td>National Institute of Diabetes and Digestive and Kidney Diseases</td>
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<td>National Institutes of Health</td>
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<td>National Institute of Mental Health</td>
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<td>NIMHD</td>
<td>National Institute on Minority Health and Health Disparities</td>
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<td>NINDS</td>
<td>National Institute of Neurological Disorders and Stroke</td>
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<td>NINR</td>
<td>National Institute of Nursing Research</td>
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<td>ORWH</td>
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<tr>
<td>OBSSR</td>
<td>Office of Behavioral and Social Sciences Research, DPCPSI, OD</td>
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<td>ODP</td>
<td>Office of Disease Prevention, DPCPSI, OD</td>
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