

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**National Institutes of Health**

**Report to Congress:**

**The Fiscal Year 2015 Pediatric Research Initiative**

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## **PEDIATRIC RESEARCH AT THE NATIONAL INSTITUTES OF HEALTH**

National Institutes of Health (NIH) research advances have transformed the diagnosis, treatment, and prevention of disease. Children have benefitted greatly from revolutionary progress in biomedical research. Infant death rates have dropped precipitously in the United States over the past 50 years. Survival rates for respiratory distress syndrome have gone from 5 percent in the 1960s to 95 percent today. The rates of Sudden Infant Death Syndrome (SIDS) have declined considerably, with the mortality rate in 2014 being one-third the rate of 1990. Transmission of HIV from infected mother to fetus and infant has fallen to less than 1 percent. *Haemophilus influenzae* type B (Hib), once the leading cause of acquired intellectual and developmental disabilities, has been nearly eliminated after the introduction of a vaccine partially funded by NIH. Scientists' understanding of how children grow and develop has improved immensely and informed early intervention efforts that have dramatically improved the lives of millions of children worldwide.

Pediatric research continues to be an NIH priority. The NIH's strong basic research portfolio provides the foundation for pediatric research in a variety of scientific areas, including neurodevelopment, cardiology, cancer, and behavioral and social sciences. In fiscal year (FY) 2015, the NIH funded research grants and projects directed specifically at pediatric research for a total of \$3,632,480,488, 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 and Centers (ICs), taking a leadership role in many pediatric research efforts that involve trans-NIH collaborations. However, all of the ICs 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 2015.

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

- (1) “to increase support for pediatric biomedical research within the National Institutes of Health to realize the expanding opportunities for advancement in scientific investigations and care for children;
- (2) to enhance collaborative efforts among the Institutes to conduct and support multidisciplinary research in the areas that the Director deems most promising; and
- (3) in coordination with the Food and Drug Administration, to increase the development of adequate pediatric clinical trials and pediatric use information to promote the safer and more effective use of prescription drugs in the pediatric population.”

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

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

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

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

## **SELECTED SCIENTIFIC RESEARCH ADVANCES IN PEDIATRICS**

Selected recent advances in pediatric research are described below. Each of these advances has resulted from NIH-supported studies. Although these advances are by no means a comprehensive compilation, they represent the wide range of the NIH's scientific portfolio in pediatrics. Advances in child and adolescent development, rare diseases, treatment of serious pediatric illnesses, prevention, and global health research are emphasized. Many of these advances resulted from programs that are supported by multiple NIH ICs.

### **Child Development and Aging**

***Infants Can Learn Sign Language from Videos:*** NICHD-funded researchers have found that children as young as 15-months-old can learn how to express themselves by watching videos, using "baby signs" adapted from American Sign Language teaching videos (e.g., patting their heads to mean "hat"). High-quality television programming has been shown to be an effective source of learning in preschool and school-age children, but prior evidence supporting infants learning from purportedly educational videos has been doubtful. For three weeks, infants were exposed to the baby signs via one of three different short home sessions: one group by video with parental interactions, one group by video without parental interactions, and one group looking at signs in a picture book with parental interactions. All of the infants learned the signs, including the ones who had watched the video without parental interactions. After a fourth week, without any exposure to the signs, the infants still remembered what they had learned. ([PMID 25622926](#)) [May 2015]

***Development of White Matter May Predict Reading Ability:*** Although some children have difficulty learning to read, we have limited understanding of what causes reading problems such as dyslexia. NICHD-funded scientists examined whether changes in white matter are associated with later reading ability, above and beyond what can be explained by other factors related to learning to read. White matter is the part of the brain that is important for thinking, learning and communication across different brain regions. Using magnetic resonance imaging (MRIs), researchers examined the brains of 38 children when they were in kindergarten, and then again three years later. At both time points the children were also

given a series of reading and vocabulary tests that are generally predictive of reading ability later in life. Results showed that the changes in children's white matter were uniquely associated with reading performance. Understanding brain development of individual children may one day have a role in identifying children at risk for reading difficulties. ([PMID 25212581](#)) [Oct 2014]

***Changes in Different Types of Cognitive Skills Through the Lifespan:*** Previous research suggested that people who are middle-aged and older typically score higher on vocabulary tests, crossword puzzles and other measures that include both memory and intelligence together, while short-term memory and puzzle solving abilities tended to peak at younger ages. To understand better how different sets of skills change throughout the life span, NICHD-supported researchers analyzed a large number of scores on different types of cognitive tests taken by people of a variety of ages. These tests measured skills like memory for abstract symbols and strings of digits, problem solving, and ability to read emotions from strangers' eyes. The researchers looked at the effect of age on each type of test. They found that different abilities peaked at different ages, suggesting that there is probably not a single age where most abilities reach their peak. Processing speed — the quickness with which someone can manipulate digits, words or images — generally peaked in the late teens, and memory for some things, like names, was strongest among people in their early 20s. Other memory-based skills, including the ability to recall faces and do some mental manipulation of numbers, peaked about age 30. In the results from another test, which involved reading strangers' moods from the expression in their eyes, people in their 40s or 50s consistently did the best, and that skill declined very slowly later in life. ([PMID 25770099](#)) [Apr 2015]

***Levels of Cognition in Early Life Could Influence Biological Age:*** Supported by the NIA, the Dunedin Longitudinal Study has followed over 1000 individuals from birth to midlife since 1972. Researchers found strong associations between early life assessments of cognitive function and biological age at midlife assessed along several dimensions. Study members with higher levels of early life cognition had younger-looking faces, scored younger on a set of biomarkers, had “younger” cardiovascular systems, and, to a lesser extent, longer telomeres, suggesting that poor cognitive function early in life may accelerate the aging process. ([PMID 26014827](#)) The Dunedin Longitudinal Study was also the fourth top science story in 2015, according to *Science News*, for the Quantification of Biological Aging in Young Adults. ([PMID 26150497](#)) Findings also reveal that perinatal complications are related to shorter leukocyte telomere length in midlife. This finding provides support for early-life developmental programming by linking newborns' perinatal complications to accelerated aging at midlife. ([PMID 25349321](#)) [Nov 2014 to Jul 2015]

### ***Environmental, Family, and Community Influences***

***Low-Level Prenatal Lead Exposure:*** In this study, using sensitive measures of neural functioning, researchers funded by NIEHS and NICHD found that lead levels in cord blood higher than 2.00 µg/dL were associated with adverse effects on the development of auditory recognition memory at 2 months. Virtually all children in this study had cord blood lead levels below 5.00 µg/dL, the new CDC reference level. The results suggest that there are adverse effects of prenatal lead exposure below this level. ([PMID 25350757](#)) [Oct 2014]

***Exposure to Flame Retardants:*** NIEHS-funded scientists continue to examine levels of flame retardant exposure in people and identify distinct populations who have higher exposures due to their occupations (flight attendants [PMID 23413926](#), nail salon workers [PMID 26485058](#)) or life stage (children [PMID 22763040](#)). Recent work has indicated Firemaster 550, a flame retardant used in a wide variety of consumer products, is an endocrine disruptor in rats and components of the mixture were found in both exposed mothers and their offspring. ([PMID 23139171](#)) NIEHS-funded research continues to explore the link between flame retardant exposure and effects on thyroid hormone ([PMID 26004626](#), [PMID](#)

[26433919](#)) and childhood neurodevelopmental defects ([PMID 26271888](#)). Recent work indicates that higher levels of certain maternal lead compounds are linked to decreased newborn cord blood methylation of TNF $\alpha$ , a proinflammatory gene involved in immunological response, and increased levels of TNF $\alpha$  protein expression. These results indicate that exposure to this flame retardant may reprogram a newborn's immunological response ([PMID 26406892](#)). [Feb 2013, Jan 2016, Jul 2012, Feb 2013, Jun 2015, Nov 2015, Nov 2015]

***MRI Reveals How Early Life Air Pollution Exposure Affects the Brain:*** Supported by NIEHS and NIMH, one of the largest pediatric MRI studies to date showed a relationship between increased prenatal exposure to polycyclic aromatic hydrocarbons (PAH) and later childhood reductions in the white matter surface of the left hemisphere of the brain. This finding is concerning because lower white matter is associated with both slower processing of information and behavioral problems such as ADHD and aggression. For postnatal PAH exposure measured at age five, researchers found additional disturbances in development of white matter in the dorsal prefrontal region of the brain, which is associated with concentration, reasoning, judgment, and problem-solving ability. The effects of postnatal exposure were spatially distinct and statistically independent from the effects of prenatal PAH exposure. ([PMID 25807066](#)) [Jun 2015]

***Decreased Air Pollution Levels over the Past Several Decades in Southern California was Associated with Improvements in Respiratory Health among Children:*** NIEHS-supported scientists measured lung function annually in 2,120 children from three separate cohorts corresponding to three separate time periods. The researchers found that improvements in air quality had an association with significant improvements in lung-function development in both boys and girls, and in children with and without asthma. ([PMID 25738666](#)) [Mar 2015]

***Phthalates Heighten Risk for Childhood Asthma:*** NIEHS-supported researchers were the first to demonstrate an association between childhood asthma and prenatal exposure to two phthalates used in a diverse array of household products. Children born to mothers exposed during pregnancy to higher levels of the chemicals, butylbenzyl phthalate (BBzP) and di-n-butyl phthalate (DnBP) had a 72 percent and 78 percent increase in risk of developing asthma between age 5 and 11, respectively, compared with children of mothers with lower levels of exposure. ([PMID 25230320](#)) [Oct 2014]

***Characterizing Transgenerational Genetic Effects of Dioxin Using Zebrafish:*** Fetal exposure to the chemical dioxin is associated with diseases of almost every organ system. Researchers funded by the NIH DPCPSI's Office of Research Infrastructure Programs (ORIP) and NIEHS used zebrafish as a model to assess the transgenerational effects of toxic chemicals and their role in the fetal basis of adult disease. A single, sublethal exposure to dioxin in juvenile zebrafish can result in skeletal, nervous system, reproductive, and behavioral abnormalities in adult animals. Similar abnormalities were observed in the next two generations of progeny, even in the absence of any direct exposure to the toxin. ([PMID 25194296](#)) [Dec 2014]

***Breastfeeding beyond Two Months May Help Protect Children from Obesity Later in Life:*** Breastfeeding has been shown to have many benefits for mothers and children, but scientists are not sure how breastfeeding can impact child obesity. To explore this question, researchers collected information on 595 children for two years. The NICHD-supported researchers asked mothers to fill out questionnaires and give access to their children's medical records, so they could assess breastfeeding, other health behaviors, and child growth. The results showed that infants who were breastfed for less than two months gained weight more rapidly than infants who were breastfed for longer periods of time. This was especially true for children who already had other risk factors for obesity. Providing breastfeeding support may help protect against obesity later in life. ([PMID 25554813](#)) [Jan 2015]

***Stable Relationships Can Ease Symptoms of Depression in Adults Abused as Children:*** The effects of child abuse last long after a child has grown up. Few mental health treatment programs are designed specifically for adults who were abused as children, in part because doctors do not know how best to help them. Previous research has shown that stable, positive relationships may help reduce the symptoms of depression for adults who were abused as children. To better understand these effects, researchers supported by NICHD analyzed data from two studies: one that looked at seventh- and eighth-graders and another that studied the same participants 11 years later. The researchers also used data from Child Protective Services to determine how many of the study participants were abused as children. The researchers found that adults who had been abused as children were indeed more likely to report symptoms of depression, but being in stable romantic relationships mitigated those symptoms. The data showed that successful, positive relationships reduced depression symptoms more in adults who had been abused as children than in those who had not. ([PMID 25912653](#)) [Aug 2015]

***Improving Work Conditions Can Increase Parents' Time with their Children:*** Working parents, juggling responsibilities at home and the office, often feel stressed over conflicting demands on their time. NICHD-supported researchers assessed whether parents participating in a workplace intervention to increase employees' flexibility reported more daily time with their children compared with parents not participating. A sample of employees, with children ages 9 to 17, responded to daily telephone surveys at the beginning of the study and again 12 months later. During these calls, parents reported how much time they spent with their child that day. Parents participating in the intervention reported spending more per day with their children. However, mothers' time with children increased more than fathers' time. Moreover, parents were more likely to spend more time with daughters compared with sons. ([PMID 25869371](#)) [May 2015]

***Low-Income, Non-Resident Fathers Provide Gifts, Goods and Services:*** Fewer than half of children eligible for formal child support payments receive the full amount, and many receive no payment at all. However, parents may contribute to a child by providing "in-kind" support, including goods (such as diapers and formula), services (payments made directly to a child-care provider, for example), or gifts. In three cities – Austin, Texas; Philadelphia, Pennsylvania; and Charleston, South Carolina – NICHD-supported researchers interviewed low-income fathers who did not live with their children. Of all the support these fathers contributed towards their children, about one-quarter was given in an "in-kind" form. The reported value of the in-kind support was higher for children who were younger and had more hours of visitation with their fathers. Similarly, fathers with greater education and no current substance abuse problems reported higher values of in-kind support. However, fathers who lacked stable employment or were black reported giving a greater percentage of their contribution in-kind. Most of the value of in-kind support came from items that were visible and could be offered directly to the child, such as food treats, clothing, shoes, and toys. The results of the interviews with the fathers showed that the fathers preferred to provide in-kind support because it helped them form a bond with their children. ([PMID 26052162](#)) [Jun 2015]

***Fewer U.S. Men Fathered Children Outside of Marriage in 2000-2010, Compared with Previous Decades:*** NICHD-funded researchers examined fatherhood trends of nonmarital first births over the last 30 years. They used data from the National Survey of Family Growth, which is a nationally representative survey of the U.S. household population. The results showed that fewer unmarried American men became first-time fathers in 2000-2010, compared with previous decades. The declining trend largely reflected changing patterns among black fathers; there was no significant change among unmarried white or Hispanic fathers. The national survey results also showed a larger proportion of unmarried first-time fathers living with the mother and child than in the past. ([PMID 26046827](#)) [Jun 2015]

***More Reading at Home Increases Children's Brain Activity While Listening to a Story:*** Many studies have found that adults reading to children will improve the children's language skills later in life, but no



one knows exactly how early reading influences brain development. During a longitudinal MRI study of normal brain development, scientists supported by NICHD studied the functional brain activity of 19 children between three- to five-years-old, as they listened to stories. Compared to children who had not been previously exposed to reading, children who had previously been exposed to lots of reading had more activity in the left side of the brain in a region associated with understanding and language, which is later involved in reading. ([PMID 26260716](#)) [Sep 2015]

***Behaviors in Early Adolescence Predict Troubles in Young Adults:*** Young adolescents seeking popularity with their peers may engage in certain behaviors, such as minor delinquency (shoplifting, vandalism), selection of friends on the basis of appearance, and precocious romantic relationships. Young teens' early attempts to act older than their age may seem normal or even harmless. However, NICHD-funded researchers followed young people from ages 13 to 23 and found that when these behaviors occur early in adolescence, teens are more likely to experience non-trivial difficulties in young adulthood. For example, adults who had exhibited these behaviors in the early teen years were more likely to have problems with close relationships and substance abuse, as well as elevated levels of criminal behavior. The researchers concluded that the time frame when seemingly minor behaviors occur is more predictive of adult problems than the specific types of behaviors. ([PMID 24919537](#)) [Sep/Oct 2014]

***Kids Expecting Aggression from Others Become Aggressive Themselves:*** In a four-year study of children from diverse groups in nine countries worldwide, NICHD intramural researchers asked mothers and children to independently rate the children's degree of aggressive behavior. The researchers then presented their young subjects with stories about situations that might involve someone acting hostilely toward them: someone bumping them from behind and causing them to step into a puddle of water, for example. The children were asked whether the other person was hostile or harmless in intent, and how they would react. The scientists found differences between groups in the degree to which children displayed "hostile attributional bias" – that is, a tendency to interpret ambiguous behavior as hostile. Children with higher hostile attributional bias scores had higher ratings of chronic aggressive behavior problems. The findings suggested that children's aggressive behavior problems could be addressed by focusing on how children are taught to expect hostility in ambiguous situations and to respond with aggression. ([PMID 26170281](#)) [Jul 2015]

***Demographic Data Suggest Potential Strategies to Help Reduce Health Disparities:*** A higher lifespan variability -- the variability in the ages at which people die -- among blacks is usually explained by higher rates of certain causes of death, such as murder, which are more common among the young. However, when researchers analyzed data from death certificates by race, they found that taken all together, differences in causes of death account for only about 13 percent of the difference in lifespan variability between blacks and whites. This means that even if blacks and whites died of exactly the same causes, 87 percent of the difference in life expectancy between black and whites would persist. The results of this NICHD-funded study also indicated that efforts to reduce health disparities may be more effective if they target race as well as sex. For example, reducing the rates of HIV/AIDS among black men, while preventing heart disease and diabetes among black women, may help narrow the gap. ([PMID 25391224](#)) [Dec 2014]

### **Pregnancy and Perinatology**

***Outdated Standards May Misclassify Minority Fetuses as Growth-Restricted:*** Currently, many obstetricians and gynecologists rely on reference charts for determining if the fetus is growing at a healthy rate. These growth chart weights were derived from a study of predominantly white, middle-class women during the 1980s. NICHD researchers sought to compile standards that more accurately reflect optimal fetal growth during healthy pregnancies among the most common racial and ethnic groups in the United

States. The results showed that because of racial and ethnic differences in normal growth patterns, the current standards may lead to misclassification of up to 15 percent of fetuses of minority mothers as being too small. The inaccurate standards may lead to unnecessary tests and stress for these minority women, when their pregnancies actually are on track. ([PMID 26410205](#)) [Oct 2015]

***Rates of Survival Increasing for Extremely Preterm Infants:*** More than 450,000 premature babies are born each year in the United States. A generation ago, extremely preterm infants, those born before the 28th week of pregnancy, were very unlikely to survive. Thanks to medical advances, today these infants are surviving in greater numbers and escaping serious illness. NICHD-funded researchers reviewed the birth records of more than 35,000 premature infants born from 1993 to 2012 in 26 U.S. hospitals. They found that infants born at 23 and 24 weeks survived in greater numbers over the 20-year period. Of those born at 24 weeks, for example, only 52 percent survived in 1993 while 65 percent survived in 2012. A higher number of premature infants survived without major illnesses. For infants born at 27 weeks, for example, survival without major illness increased from 29 percent in 1993 to 47 percent in 2012. ([PMID 26348753](#)) [Sep 2015]

***Using Brain Scans to Identify Developmental Issues for Extremely Premature Babies:*** Babies born prematurely have a higher risk of problems with brain development. Since premature babies are at a higher risk of bleeding in the brain, doctors typically perform a brain ultrasound (scan) on these babies very soon after they are born. From these scans, they are also able to look at brain structure and check for any abnormalities that might be associated with developmental disabilities. In this study, NICHD-funded scientists compared the “early” scans (scans done soon after birth) of nearly 500 extremely premature babies (babies born at 24-27 weeks of pregnancy who were born 13-16 weeks prior to the due date) with brain scans that were conducted later, near the babies’ due dates. Researchers then assessed the babies’ development at between 18 and 22 months old. The scientists found that although the early scans were useful in detecting brain bleeds and other urgent medical issues, the scans that were done near the time of the babies’ due dates were more useful in predicting delays in development and disabilities. Being able to predict development delays is important so that early interventions can be targeted for children who are at greatest risk. Results of this study suggest that scans conducted near the due date are useful for physicians, parents and care providers to identify brain issues for premature babies. ([PMID 25554820](#)) [Jan 2015]

***Identifying Women at Risk for Spontaneous Preterm Birth:*** Preterm birth is the leading cause of health problems and death among newborns. However, scientists have not yet been able to pinpoint the causes of preterm birth. Because family history of spontaneous preterm birth may point to an inherited genetic factor, NICHD-funded researchers conducted genetic testing in women who had previously had a preterm birth and who also had a family history of spontaneous preterm birth. The researchers found 34 gene variants, all located in or near the insulin gene. This gene plays an important role in inflammation, and investigators have suspected it is that involved in spontaneous preterm birth. These researchers noted, however, that its exact role still needs to be determined. ([PMID 26070700](#)) [Sep 2015]

***Possible Proteomic Markers for Preterm Birth:*** Preterm births are the leading cause of infant morbidity and mortality, affecting approximately 12 percent of all births. The earlier the preterm birth, the greater the risk to the infant. Approximately 60 percent of all preterm births are spontaneous; in most of the remaining cases, a medical professional recommends delivering the baby early to protect the health of the mother or infant. If a woman has a history of spontaneous preterm birth (SPTB), she is considered at risk of another preterm birth. However, not all women with such a history will have a repeat SPTB, and there is no known way to gauge such risk in pregnant women with no history of SPTB. NICHD-funded scientists working to find early warning signs of SPTB and to understand its causes have found two proteins that are associated with early SPTB, and measured these proteins in the blood serum of pregnant women. The researchers used two complementary high-tech methods in a large group of pregnant women

with SPTB history. They found that the average level of one protein, called serpin B7, was higher in women that would subsequently deliver preterm prior to 34 weeks, compared to the levels in women that would deliver at term. If another protein, called calreticulin precursor, was also elevated, the combination of both of these proteins predicted 30 percent of the women who subsequently gave birth before 34 weeks, compared with 0 percent of those who carried their pregnancies to term. Although the findings are encouraging, the scientists cautioned that additional research should be done to see if the results can be repeated for other groups of women. They suggest, also, that techniques similar to theirs could be used to look for other possible protein markers of SPTB. ([PMID 24954659](#)) [Dec 2014]

***Change in Cervical Length over Time Does Not More Accurately Predict Preterm Birth:*** More than 450,000 babies were born preterm in the United States in 2012, and preterm birth cost the health care system more than \$26 billion. Infants who are born preterm are at increased risk of death and lifelong disabilities. Predicting who will have a preterm birth is difficult; preterm labor can start unexpectedly, and its cause is unknown. Previous studies have provided evidence that short cervical length, measured sonographically between weeks 18 and 24 of pregnancy, is one of the strongest predictors of preterm birth. NICHD researchers systematically reviewed pertinent studies to determine whether doctors could better predict preterm birth by using multiple measures that show cervical length shortening over time. The scientists found 14 studies that met their rigorous criteria, with a total of 3,374 single pregnancies and 1,024 twin pregnancies. Analyzing these data, they found that change in cervical length over time had only a low value for predicting preterm birth in single pregnancies and a low to moderate predictive value in twin pregnancies. The data also showed that change in cervical length over time did not offer better predictive value than a single measure of cervical length obtained between 18 and 28 weeks. The researchers concluded that for now, a single measure of cervical length is a better and more cost-effective test to predict preterm birth. ([PMID 26070703](#)) [Dec 2015]

***Retinopathy of Prematurity (ROP)*** is a sight-threatening disease in severely premature infants, in which abnormal growth of blood vessels injures the retina. The condition is treatable if discovered early. Some degree of ROP appears in more than half of all premature infants born at 30 weeks or younger, but only about 5 to 8 percent of cases become severe enough to require treatment. Additionally, many rural and underserved populations lack access to a point-of-care doctor who can make treatment decisions for ROP. A recent NEI clinical trial found that telemedicine is an effective diagnostic tool for ROP. Trained technicians, reviewing retinal images electronically sent to an off-site center, accurately identified patients in need of treatment in 98 percent of cases. This study legitimizes telemedicine as an effective diagnostic tool for ROP and holds promise for other diseases where access to specialists is limited. ([PMID 24970095](#)) [Oct 2014]

***U.S. Stillbirth Rates Unchanged after Move to Discourage Elective Deliveries before 39 Weeks:*** Research has shown that foregoing delivery before 39 weeks, unless there is a medical reason to deliver early, lowers the chances of newborn illness and death. However, a previous study in one hospital group linked a policy of avoiding such optional, or elective, deliveries before 39 weeks to an increase in stillbirths in its patients. To determine if concern about avoiding elective deliveries is warranted, NICHD-funded researchers analyzed national data from the U.S. fetal death and live birth data files of the Centers for Disease Control and Prevention. The researchers compared stillbirth rates and trends from 2006, before the recommendation to avoid elective deliveries, to those occurring in 2012, the most recent year after the recommendation that data were available. The analysis encompassed totals of roughly 50,000 stillbirths and 8.2 million live births, combined. The scientists concluded that efforts to prevent elective deliveries are not linked to an increase in stillbirth on a national level. ([PMID 26551188](#)) [Dec 2015]

***Stillbirth and Women’s Long Term Risk for Depression:*** Stillbirth is the death of a baby at or after the 20th week of pregnancy. It occurs in 1 out of 160 pregnancies in the United States. To assess how women recover from stillbirth, NICHD-funded researchers studied women at hospitals in Rhode Island, Massachusetts, Georgia, Texas, and Utah. From 2006 to 2008, the researchers enrolled 275 women who delivered a stillbirth and 522 women who delivered a healthy live birth after 37 weeks of pregnancy. In 2009, the researchers again contacted the women and asked them to complete a questionnaire, known as the Edinburgh Depression Scale, designed to gauge whether women are experiencing symptoms of depression. Physicians often use this scale to identify women for referral to a mental health professional for further testing. The researchers found that women who deliver a stillbirth were at a higher risk for long-lasting depression, even if they had no history of depression. The depression may last beyond the six months most people require to recover from a major loss, and persist for as long as 36 months. After accounting for other factors related to depression and stillbirth, the researchers found that women who had a stillbirth were twice as likely to have a high depression score compared to women who had a live birth. The results suggested that physicians may wish to consider screening women who have had a stillbirth for depression for at least 3 years after the stillbirth. ([PMID 25682858](#)) [Mar 2015]

***Women with Epilepsy at Higher Risk for Maternal Death, Preterm Labor, and Stillbirth:*** Epilepsy is a neurological condition that causes people to have recurring seizures. Thousands of women with epilepsy become pregnant every year, but little information has been available to determine the risks to the pregnant woman. NICHD-funded researchers reviewed medical records from over 20 million pregnant women from a nationally representative sample of hospitals, covering the years 2007-2011. The researchers found that women with epilepsy had a risk of death during delivery of 80 cases per 100,000 pregnancies, significantly higher than the 6 deaths per 100,000 pregnancies found among women without epilepsy. Women with epilepsy were also at higher risk for preeclampsia, cesarean delivery, preterm labor, and stillbirth. The results show that it is especially important to closely monitor pregnancy in women with epilepsy. ([PMID 26147878](#)) [Sep 2015]

***Study Suggests Most Women with Mild to Moderate Lupus Can Expect to Have Healthy Pregnancies:*** A large, long-term study among women with lupus has yielded important insights into how to predict who may develop pregnancy complications associated with the disease, and who is most likely to have a healthy pregnancy. Women with lupus have long been counseled to avoid pregnancy as pregnancy loss is more common in women with lupus than in women without the disease, especially when antiphospholipid antibody syndrome (APS)—a condition that frequently co-occurs with lupus—is present. APS causes clots inside the blood vessels (thrombosis). The NIAMS-supported Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus (PROMISSE) study enrolled more than 700 pregnant women with lupus, APS or no disease from sites in both the United States and Canada. The women joined the study in their first trimester, and were followed throughout their pregnancies. The researchers found that 81 percent of the pregnancies in women with lupus were free of serious complications. Five percent of the women experienced miscarriage, and 9 percent delivered prematurely. Ten percent of the babies were born with low birth weight. About 5 percent of the women developed lupus flares in the second or third trimesters. Most of the women who experienced complications had one or more risk factors during their first trimester, including the presence of a specific type of antiphospholipid antibody, treatment for high blood pressure, and a low platelet count, which can result in blood clotting problems. In addition, pregnancy complications were more frequent in African American and Hispanic women. 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](#)) [Aug 2015]

## **Structural Anomalies and Birth Defects**

***Large, Rare Deletions Increase the Risk of Down Syndrome–Associated Atrioventricular Septal Defects:*** Congenital heart defects, or heart defects that are present at birth, are very common in babies who are born with Down syndrome, a condition that causes lifelong intellectual disability. However, not all babies with Down syndrome have a heart defect, and many babies without Down syndrome have heart defects. To better understand a specific type of common heart defect called atrioventricular septal defects, (AVSDs), NICHD-supported scientists studied the genes in 452 infants with Down syndrome. Of these, 210 had AVSDs. They found that infants with AVSDs were more likely to have rare, large genetic information missing. This missing information is critical to embryonic development, suggesting that the missing genes can also negatively impact development of other organ systems. ([PMID 25341113](#)) [Jul 2015]

***Better Understanding of a New Mouse Model with a Complete Duplication of Human Chromosome 21:*** To study Down syndrome, NINDS-supported researchers created a "triple trisomic" mouse model and examined performance in these mice on locomotor activity, stereotypic and repetitive behavior, anxiety, working memory, long-term memory, and synaptic plasticity. Because the mice demonstrated a number of characteristics similar to Down syndrome, this model may help evaluate and validate findings in other, less complete, models of Down syndrome. ([PMID 26230397](#)) [Jul 2015]

***Proteins Overexpressed in Both Down Syndrome and Alzheimer's Disease May Contribute to Age-Dependent Memory Loss:*** Individuals with Down Syndrome acquire Alzheimer's Disease (AD) at a much higher rate than the general population, and they acquire it at earlier ages. This may likely be due to the fact that Down syndrome critical region 1 (DSCR1) and amyloid-precursor protein (APP) are both triplicated and up-regulated in Down syndrome, and up-regulated in AD. Calcineurin is an important protein in signal transduction, molecular pathways by which a cell responds to input. NINDS-supported researchers found that in flies up-regulation of an inhibitor of calcineurin called nebula, which is homologous to a gene in human DSCR1, rescued APP-induced memory deficits in young flies while enhancing memory loss in older flies. Nebula had differential effects across age: it corrected calcineurin signaling in young flies, but older flies have increased calcineurin activity, so nebula was chronically upregulated and led to mitochondrial dysfunction, oxidative stress, and subsequent memory loss. These results suggest that chronic upregulation of calcineurin inhibition may contribute to age-dependent memory loss in Down syndrome and Alzheimer's disease and suggests that correcting calcineurin signaling may improve memory during aging. ([PMID 26269644](#)) [Aug 2015]

***Craniosynostosis Linked to Stem Cell:*** Craniosynostosis is a birth defect in which the joints in a baby's skull fuse prematurely, leading to a misshapen head. The only current treatment for babies with craniosynostosis is to surgically remove the fused suture and reshape the bones of the skull to allow for brain expansion as the child grows. NIDCR-supported scientists have discovered that loss of a specific type of stem cell that resides within the sutures of skull is linked to craniosynostosis in a mouse model. These studies have the potential to inform precise manipulation of the local environment within the suture to support the stem cells required for normal skull development and thus prevent premature fusion of the skull bones in young children. ([PMID 25799059](#)) [April 2015]

***Successful Newborn Screening for SCID in the Navajo Nation:*** Severe combined immunodeficiency (SCID) is a rare group of genetic disorders of the immune system that occurs in about 1 in 50,000 births. However, a much higher rate has been reported in the Navajo Nation. A comprehensive newborn screening program was implemented in the Navajo Nation in 2012, based on NIH-supported research. When NICHD-supported scientists analyzed the results of this program, they confirmed that in the Navajo Nation, about 1 in 2,000 babies were born with one type of SCID, called SCID-A. This rate was nearly 30



times the rate of SCID-A found in the general U.S. population. Between February 2012 and July 2014, SCID-A was identified in several Navajo infants, and all of these babies were referred for critical early treatment. ([PMID 25762520](#)) [May 2015]

***Rare LRP6 Variants Identified in Spina Bifida Patients:*** Mutations in the gene for a protein called Lrp6 (low-density lipoprotein receptor-related protein 6) have been shown to cause neural tube defects (NTDs) in folate-sensitive mouse models. While recent research has implicated the association of Lrp6 mutations with neural tube defects in humans, relating these mouse models to specific genetic variants in the human population has been challenging. In an NINDS-funded study, investigators used in vitro model systems to evaluate the effect of patient DNA sequence mutations on the localization and function of Lrp6. The researchers identified specific human variants in the Lrp6 gene that function similarly to those demonstrated in the mouse models, and began to characterize the pathways by which these mutations may increase risk for neural tube defects. This research opens new avenues for investigation of the etiology and underlying mechanisms of spina bifida and other neural tube defects. ([PMID 25546815](#)) [Mar 2015]

***Nutrient Is Unlikely to Decrease the Risk of Neural Tube Defects:*** Neural tube defects (NTDs) are birth defects of the brain, spine, or spinal cord. They happen in the first month after conception, often before a woman even knows that she is pregnant. Getting enough folic acid, a type of B vitamin, before and during pregnancy can prevent many neural tube defects. Scientists have researched whether choline (another nutrient in the B vitamin group) could also decrease the risk of NTDs, but the results of these studies have been inconsistent. To help resolve this question, NICHD scientists took blood from pregnant women early in pregnancy and assessed their choline levels. Later, researchers compared the choline levels from women who had children with NTDs with choline levels from similar women who did not have children with NTDs. The results showed that choline levels in the mother were not related to NTD risk. Scientists concluded that adding choline supplements is unlikely to decrease the risk of NTDs. ([PMID 25240073](#)) [Oct 2014]

***Chromosome Region Linked to Gigantism:*** Gigantism results from a defect in the pituitary, a pea-sized gland at the base of the brain that makes growth hormones and controls the activity of other glands in the body. Some people with gigantism have a tumor in the pituitary that secretes extra hormone; others just have an oversized pituitary. Gigantism is often treated by removing the tumor, or even the entire pituitary, but can sometimes be treated with medication alone. Researchers supported by NICHD, NINDS, and NHGRI found a duplication of a short stretch of the X chromosome in some people with a rare disorder that causes excessive childhood growth. They believe that a single gene within the region likely has a large influence on how much children grow. In their study, the researchers used whole-genome analysis to find major changes in the DNA. Every person in the study who had gigantism as an infant or a toddler had the same defect, a duplication of a stretch of the X chromosome. Family members without gigantism did not have the duplication. ([NIH Press Release](#))

### **Pediatric Cancer**

***Evaluating a Possible Treatment for Diffuse Intrinsic Pontine Glioma:*** Diffuse intrinsic pontine glioma (DIPG) is a cancer that typically affects children aged 4-9 years and is usually fatal within a year even with radiation treatment. The tumor attacks the pons, a region connecting the brain with the spinal cord, and leads to progressive loss of muscle control. In this study, funded by NCI and NINDS, researchers collected tumor cells from 16 patients with DIPG and used high-throughput screening to identify drugs that slowed DIPG growth. They found that the most effective drugs affect histones, protein complexes that act like spools wound with genes on chromosomes, specifically by blocking histone deacetylases, a group of enzymes that regulate genes by removing chemical tags called acetyl groups. Panobinostat, a drug designed to block multiple types of histone deacetylases, inhibited DIPG cell growth in 12 of 16 cell

lines, both in culture and in mice. Plans are being developed to test the drug in clinical trials in children through NCI's Pediatric Brain Tumor Consortium. ([PMID 25939062](#), [NIH Press Release](#)) [Jun 2015]

***New Drug for Neuroblastoma:*** Prior to a groundbreaking discovery by scientists supported by the NCI, the majority of children diagnosed with advanced-stage neuroblastoma had a high risk of treatment failure and little hope of surviving, with less than 40 percent living five years after diagnosis. Now an immunotherapy 20 years in the making is providing new hope for children with this rare cancer. The FDA approved Unituxin in March 2015, based on the results of an NCI-supported Phase III Children's Oncology Group clinical trial. ([NCI Press Release](#), [Story from NCI Technology Transfer Center](#))

***Genetic Predisposition to Childhood Cancer:*** NCI-supported scientists completed the most comprehensive analysis to date of the role genes associated with cancer predisposition play in 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. ([PMID 26580448](#)). [Nov 2015]

***Genetic Analysis of Wilms Tumor:*** Wilms Tumor is the most common form of renal cancer in children. Researchers recently identified multiple novel mutated genes, including genes not previously reported as mutated in human cancers. This NCI-funded work identified mutations in genes involved with microRNA processing and kidney development ([PMID 25670082](#)), as well as a gene involved in transcriptional elongation ([PMID 26635203](#)). [Feb 2015]

***Trial Results Show High Remission Rate in Leukemia Following Immune Cell Therapy:*** Children and young adults with chemotherapy-resistant B-cell acute lymphoblastic leukemia (ALL) experienced high remission rates following treatment with an experimental immunotherapy. This finding, from an NCI-funded early-phase clinical trial, is important because children and young adults with chemotherapy-resistant leukemia who do not achieve remission have very poor outcomes. Estimates from 2014 have predicted that there will be over 6,000 cases of this type of cancer diagnosed in the United States, with more than half occurring in children and young adults (from age 1 to age 30). ([PMID 25319501](#); [NCI News](#)).

***Genome-Wide Association Study of Osteosarcoma:*** NCI researchers are leading genome-wide association studies to identify susceptibility loci for osteosarcoma, which is the most common primary malignant bone tumor in children and young adults, typically arising during the pubertal growth spurt. The *TP53* mutation is associated with LFS, a condition that predisposes people to a variety of cancers at a young age. In 2015, researchers identified an association between high *TP53* mutation prevalence in osteosarcoma in patients younger than 30 years of age and an association between a *TP53* rare variant and metastasis at diagnosis of osteosarcoma. These findings suggest that these mutations are important genetic susceptibility risk factors for young onset osteosarcoma ([Link to Journal Article](#)). In another 2015 study, investigators found a germline genetic variation that was significantly associated with risk of osteosarcoma metastasis ([PMID 26084801](#)).

***St. Jude Lifetime Cohort Study:*** NCI recently supported a childhood cancer survivorship cohort study that is complementary to the long-standing NCI Childhood Cancer Survivor Study (CCSS). The St. Jude Lifetime Cohort Study is designed to capture longitudinal, detailed in-person clinical assessment and functional performance information on children treated at St. Jude. Approximately 68 percent of St. Jude

Lifetime participants are also enrolled in CCSS. The addition of this valuable new resource will permit: 1) replication of findings from genome-wide association studies; 2) validation of prediction models; and 3) development of collaborative projects to refine risk-based follow-up guidelines and improve outcomes among childhood cancer survivors. ([Link to Description on St. Jude Children’s Research Hospital Website, NCT00760656](#))

### **Neurological Disorders**

***De Novo Mutations in Synaptic Transmission Genes in Epileptic Encephalopathies:*** Genetic studies are often too small to determine how individually rare mutations may contribute to complex diseases such as childhood onset epileptic encephalopathies. To address this challenge, epilepsy researchers supported by NINDS pooled their patient data samples with those from two other international cohorts and were able to both confirm a causal role for a previously implicated gene and demonstrate that *de novo* mutations occur significantly more often in epileptic encephalopathy patients than in the general population. By analyzing the functions of affected genes, the researchers also found that a majority of *de novo* mutations affect proteins that regulate synaptic transmission, or the communication between neurons, suggesting an important role for such pathways in severe childhood epilepsies. ([PMID 25262651](#)) [Oct 2014]

***Long-Term Outcomes of Generalized Tonic-Clonic Seizures in a Childhood Absence Epilepsy Trial:*** NINDS-funded researchers reported on a longitudinal assessment of generalized tonic-clonic seizures (GTCs) in a cohort of children with childhood absence epilepsy (CAE). This cohort of children was part of a randomized control trial of ethosuximide, valproate, or lamotrigine as treatment for CAE. While that trial identified ethosuximide as optimal initial therapy, ethosuximide is not considered effective against GTCs. The researchers sought to examine long-term outcomes of this cohort to determine the incidence and timing of GTCs as well as any effects of the three treatments on the risk of GTCs. Long-term follow-up (median of 7 years) showed a lower (12 percent) than previously reported occurrence of GTCs. Older age of onset of CAE was associated with a higher risk of GTCs. The researchers also found that the risk of developing GTCs did not appear to be a function of the initial treatment assignment, supporting the current clinical practice of ethosuximide as a first-line therapy for CAE. ([PMID 26311751](#)) [Sep 2015]

***Understanding the Effects of Pompe Disease:*** People with Pompe disease, a rare form of muscular dystrophy, lack an enzyme that cells depend on to break down a stored sugar, known as glycogen, into smaller glucose molecules that can be readily used for energy. Without enough of this enzyme, called acid alpha-glucosidase (GAA), glycogen can accumulate destructively in the liver, heart, and skeletal muscles, making it increasingly difficult to walk, eat, and even breathe. Looking for clues into how glycogen accumulation affects muscle weakness, NICHD-funded researchers examined muscle tissue from the legs and diaphragms of mice with Pompe disease. They found that the nerve-muscle, or neuromuscular, junctions looked strikingly different than those in normal mice. They were more fragmented and showed expansion of the area where nerves contact the muscle. Within the nerve cells themselves, scientists detected unusually low levels of certain key proteins that are essential for transmitting the signals that tell muscles to move. Likewise, a small study of humans with late-onset Pompe disease found evidence that their breathing and movement problems were likely rooted not only in muscle fibers, but also in the nerve cells that control those fibers. These findings provide a possible explanation for why the current therapy for Pompe disease—a biweekly infusion of the missing enzyme—slows, but fails to halt the disease process. While it is relatively easy to get replacement enzyme therapy into muscle cells, delivery to nerve cells poses a much tougher challenge. The results suggest that gene therapy, with the aim of delivering a healthy version of the GAA gene into motor neurons and other cells, could lead to improvements in heart, breathing, and muscle function for those with Pompe disease. Researchers are now looking to test this new approach. ([PMID 25217571](#)) [Feb 2015]



***Proteins in Cerebrospinal Fluid Hold Promise as Biomarkers of Post-Hemorrhagic Hydrocephalus:*** Intraventricular hemorrhage (IVH) is a type of intracranial bleeding common in premature infants. Post-hemorrhagic hydrocephalus (PHH) occurs in up to 50 percent of those with IVH. Previous research observed that key proteins are elevated in PHH. NINDS-supported researchers correlated levels of these proteins with ventricular size measured via ultrasound in preterm infants treated for PHH. Levels of all three molecules paralleled treatment-related changes in ventricular size. These results suggest that these proteins are potential biomarkers of PHH. ([PMID 25738507](#)) [Mar 2015]

***Mouse Model Reveals Gene Implicated in Hydrocephalus:*** Star-shaped brain cells called astrocytes produce p75NTR, a protein that helps these cells detect growth factors. Mice genetically engineered to have astrocytes that produce higher levels of a growth factor called TGF-beta are likely to develop hydrocephalus. Researchers found that eliminating the p75NTR gene (and thus, the ability to detect these growth factors) prevented hydrocephalus in these mice. It also prevented astrocytes from forming scars after injuries, which inhibit neural regeneration. This study was supported by NINDS, NIGMS, NCI, and NIA. ([PMID 26120963](#)) [Aug 2015]

***Genetic Causes of Cerebral Palsy:*** Cerebral palsy has multiple causes, but scientists believed that the genetic contribution to cerebral palsy was low (at about 2 percent). Whole-exome sequencing of 183 individuals with cerebral palsy revealed that 14 percent of cases, by strict criteria, had a potentially disease-causing gene variant. With support from NHGRI and NICHD, scientists found that the genetic contribution to cerebral palsy may be higher than previously believed. ([PMID 25666757](#)) [Feb 2015]

***Brain Connectivity a Potential Biomarker of Cord Blood Transfusion Efficacy:*** In an NINDS-funded longitudinal study of children with cerebral palsy, umbilical autologous cord blood transfusions (i.e., from the self) were paired with standard physical and occupational therapies. Neuroimaging and motor function were used to understand how these interventions affect brain development and to develop biomarkers to assess treatments. All children exhibited positive motor improvement, and researchers observed positive correlations between white matter connectivity (both whole-brain and sensorimotor) and improvements in motor function. Notably, neither of these factors related to the age of the child. These data suggest that increased brain connectivity reflects improved functional abilities, and that white matter connectivity may help scientists differentiate underlying mechanisms of functional improvement. ([PMID 25610796](#)) [Jan 2015]

***Identifying Pain in Nonverbal Children with Cerebral Palsy:*** Individuals with intellectual or neurodevelopmental disabilities, such as cerebral palsy, may be nonverbal or have difficulty letting caregivers and clinicians know when they are in pain. To investigate possible new methods of diagnosing pain, NICHD-supported researchers conducted a small, preliminary feasibility study to identify and compare a set of biomarkers in saliva from two small groups of children with cerebral palsy – one group with chronic pain, and another without chronic pain. This results of this noninvasive test showed that children with and without pain had generally different levels of several types of molecules in saliva. The findings were from only a small group of children, however, and more research on this approach is needed. ([PMID 25234580](#)) [Feb 2015]

## *Intellectual and Developmental Disabilities*

***Non-Verbal Children with Autism Spectrum Disorders (ASD):*** NIDCD supports research that focuses on language acquisition in children with ASD. Although there is no single explanation for the absence of fluent speech/language in children with ASD, technologies such as touch-screen computers and eye-tracking measures can help scientists assess how much these children understand language. Scientists found significant differences in how minimally verbal children process sounds and produce speech, which may underlie some of the language difficulties found. Moreover, auditory motor mapping training, a behavioral intervention that combines the use of singing and motor activities, appears to strengthen the language regions of the brain that may be abnormal in children with ASD. ([PMID 24839879](#), [PMID 24124067](#), [PMID 25808162](#), [PMID 25294649](#)) [2014, 2013, 2015, 2015]

***Improving Communication in Children with Autism:*** Many children with ASD have difficulty communicating. A frequently used treatment in many schools and clinics is applied behavior analysis (ABA). The ABA method, however, involves over 40 hours of instruction per week and can require many trials to learn a single word. An alternate intervention, called pivotal response treatment (PRT), is derived from ABA, but is play-based and child-initiated. In a comparative effectiveness study, NIDCD-supported scientists compared these two approaches. The PRT intervention improved verbal and pragmatic social communication in three months with only two hours of instruction per week. ([PMID 24840596](#)) [Nov 2014]

***Linking Preeclampsia and Autism:*** Preeclampsia is a complication during pregnancy in which a mother develops high blood pressure. NICHD and NIEHS recently funded a research project to explore whether there might be a connection between preeclampsia and ASD or developmental delay (DD). They collected information on over 700 children who had been diagnosed with ASD or DD and compared them with 350 children who did not have this diagnosis. They found that children with ASD were twice as likely to have had mothers with preeclampsia as children with typical development. ([PMID 25485869](#)) [Feb 2015]

***Diagnosing Autism with fMRI:*** Scientists are interested in developing more objective ways to diagnose autism. Functional MRI (fMRI) is a technique that is often used to measure brain activity. With support from NICHD and NIMH, researchers used fMRI to observe the brain activity of 17 adults diagnosed with autism and 17 adults who were not diagnosed with autism, asking these subjects to think about different types of social interactions. The scientists found striking differences between the two groups. The parts of the brain that usually see activity (“light up”) when someone is thinking about themselves did not light up for those with autism, but did light up for those without autism. Scientists believe that this is because the individuals with autism did not think about themselves when imagining the social interactions, while those without autism imagined themselves in the social situation, a difference that psychologists have observed when studying the behaviors of those with autism. The results of this study show promise for diagnosing autism and other psychological conditions through monitoring brain activity. ([PMID 25461818](#)) [Dec 2014]

***Immune Endophenotypes in Children with Autism Spectrum Disorder:*** NIEHS-supported researchers demonstrated that it is possible to characterize developmental/behavioral differences in children with autism based on immune profiles. The investigators found that when children were categorized into proinflammatory and noninflammatory groups based on the production of inflammatory-related cytokines, those with proinflammatory profiles showed more impaired developmental and behavioral scores, as well as increased problems with sleep and aggression. These children also displayed more impaired social affect and a trend toward increased severity of core autism symptoms. ([PMID 26493496](#)) [Sep 2015]

***Paternal Sperm DNA Methylation Associated with Early Signs of Autism Risk in an Autism-Enriched Cohort:*** Research supported by NIEHS revealed that epigenetic patterns in paternal sperm samples are predictive of early autism symptoms in the offspring. The investigators examined genome-wide DNA methylation (DNAm) in paternal semen biosamples obtained from an ASD enriched-risk pregnancy cohort, the Early Autism Risk Longitudinal Investigation (EARLI) cohort. Scientists identified 193 differentially methylated regions (DMRs) clustered near genes involved in neurogenesis and more general neuronal development. The results suggest that epigenetic differences in paternal sperm may contribute to autism risk in offspring. ([PMID 25878217](#)) [Aug 2015]

***Treating Irritability in Autism with Loxapine:*** Adolescents with severe autism spectrum disorders (ASD) can become irritable and aggressive. Current treatments for behavior problems in children and teens with ASD are costly and have adverse side effects. NICHD intramural scientists tested a drug called loxapine in a group of 16 ASD patients with high irritability. Starting with a low dosage, the researchers gradually increased loxapine dosage for 6 weeks while reducing dosages of other antipsychotic drugs. For the next 6 weeks, they held doses of all medications steady. The scientists measured teens' behavior and irritability on a standardized scale, and also tracked blood concentrations of a brain protein called BDNF to indicate loxapine's effects on the brain. Low BDNF levels are associated with several psychiatric and neurodegenerative disorders. The adolescents who completed the study had only minor side effects, and their behavior and irritability were much improved. BDNF levels rose significantly with loxapine treatment. Scientists concluded that loxapine shows promise as a potential treatment for irritability and aggressiveness in adolescents with ASD. ([PMID 25782098](#)) [Mar 2015]

***Over-Sensitivity to Stimulation in Children with Autism:*** A significant number of children with autism have very strong negative responses to noises, visual stimulation, and physical contact. This "sensory over-responsivity" can make it difficult for families to do errands and enjoy outings. To determine how best to treat this condition, scientists studied 19 high-functioning youths with autism spectrum disorders and 19 age- and IQ-matched typically developing youths, asking the children's parents to rate their children's sensory over-responsivity. Researchers used functional MRI scans to measure the children's brain activity as they were exposed to different kinds of stimulation: loud traffic noises, being rubbed on the arm with scratchy wool fabric, or both at the same time. All participants – those with autism without sensory over-responsivity, those with both autism and sensory over-responsivity, and typically developing children – responded to the stimulation in similar parts of their brains. Children with both autism and sensory over-responsivity had the strongest responses, especially when both the touch and noise were used at the same time. Moreover, these children took more time to get used to the stimulation and reduce their brain response, compared with both other groups. The researchers suggested that the children may benefit not only from reducing stimulation, but also from coping techniques to help them moderate their response to noise and touch. ([PMID 26061819](#)) [Aug 2015]

***Broccoli Sprout Extracts Administered to Young Men with ASD:*** A preliminary study found evidence of positive effects of an innovative therapeutic treatment for social behaviors in ASD. Researchers conducted a double blind, randomized, placebo-controlled trial of the phytochemical sulforaphane, a derivative of broccoli sprout extracts. Administered to young men (ages 13-27) with moderate-to-severe ASD, the results showed improvements in both parent/caregiver and physician ratings of social behavior and aberrant behaviors, when compared to placebo controls. ([PMID 25313065](#)) [Oct 2014]

***Long-Term Outcomes of Early Intervention in Six-Year-Olds with ASD:*** In a recent study co-funded by NICHD, NINDS, and NIDCD, scientists found that children with ASD who participated in the Early Start Denver Model treatment at 2-3 years of age continued to benefit two years later. The researchers found that children who had undergone this intervention showed improvements in core ASD symptoms and

behaviors compared with a similar group of children who received standard community-based care. ([PMID 26088663](#)) [Jul 2015]

***Size of Fragile X Mutations Correlates with Risk for Psychiatric Disorders:*** Fragile X syndrome and its associated conditions, Fragile X–associated primary ovarian insufficiency (FXPOI) and Fragile X–associated tremor/ataxia syndrome (FXTAS), are caused by mutations in the *FMR1* gene on the X chromosome. The size of the mutation (measured as the number of “repeats”) in the *FMR1* gene affects how serious the symptoms are. A normal *FMR1* gene has between 6 and 40 repeats. People with between 55 and 200 repeats have what is called a premutation that causes the *FMR1* gene to work improperly. People with a full mutation (200 or more repeats) usually have Fragile X syndrome, an inherited intellectual and developmental disability. Some women who carry the *FMR1* premutation are at risk for psychiatric problems, such as anxiety, depression, and obsessive-compulsive disorder. To assess the relationship between the size of the premutation and these problems, NICHD-funded researchers studied 299 adult women with 50 to 141 repeats in the *FMR1* gene. The women completed psychological assessments, and the researchers compared the results with the number of repeats in the women’s *FMR1* gene mutations. Scientists found a strong correlation between the number of repeats and the likelihood of psychological disorder. These findings could help identify women with premutations that may place them at greater risk of psychiatric problems, so doctors can ensure that they can receive appropriate support and treatment. ([PMID 24428240](#)) [Feb 2015]

***Possible Under-Diagnosis of Autism among Children with FXS:*** Past studies have indicated that 60-74 percent of males and 16-45 percent of females with FXS meet the criteria for autism spectrum disorder when they were assessed by trained researchers using state-of-the-art diagnosis methods. However, it is unclear how often children with FXS are accurately diagnosed with ASD in the community. NICHD-funded researchers tested 86 boys and girls with FXS to see if they also had ASD. They also asked the child’s parents whether or not the child has been previously diagnosed with ASD. Depending on the criteria and test used, 41-56 percent of the children were diagnosed with ASD by the researchers, but only 25 percent had previously received an ASD diagnosis. The difference in diagnosis rates was significantly higher for boys compared with girls. The results suggest that children with FXS, especially boys, may be under-diagnosed with ASD in the community. ([PMID 24528851](#)) [Oct 2014]

***Understanding How Fragile X Syndrome Affects Motor Nerve Cells:*** Using a mouse model of Fragile X, NICHD-funded researchers assessed how a lack of a key protein affects the dendritic spines of nerve cells. The dendritic spines help transmit electrical signals to the neuron’s cell body and may also serve to increase the number of possible contacts between neurons. In mice with normal protein levels, motor training increased the formulation of new dendritic spines and decreased the elimination of existing spines. In the Fragile X model mice who had less of the vital protein, there was less frequent turnover in the dendritic spines, and the new spines did not cluster together the way they did in normal mice. The spines that did form, however, stabilized their connections similarly to those in normal mice. The results suggest that the motor learning issues in individuals with Fragile X may be related to the formation of new dendritic spines in the nervous system, but not to a failure to maintain and stabilize connections among existing nerve cells. ([PMID 25950728](#)) [May 2015]

***Reversibility of Neuropathology and Motor Deficits in an Inducible Mouse Model for FXTAS:*** NINDS, NIA, and NIDCR supported development of a new transgenic mouse model for FXTAS. Researchers can induce expression of an expanded CGG repeat in the brain of these mice by exposing them to doxycycline (dox). After 8 weeks of dox exposure, mice developed intranuclear inclusions in brain tissue, replicating findings in patients with FXTAS. If expression of expanded CGG RNA was stopped at an early developmental age, the effect was reversible. This model allows for study of disease progression and the potential of disease reversibility, and suggests that early intervention might be beneficial for patients with FXTAS. ([PMID 26060190](#)) [Sep 2015]

***Movement Helps Improve Focus in Children with ADHD:*** About 11 percent of all children between the ages of 4 and 17 have attention-deficit/hyperactivity disorder (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 supported by NICHD and NIMH 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. ([PMID 26059476](#)) [epub Jun 2015]

***Phthalate Exposure Linked to Lower IQ:*** NIEHS-funded researchers found that 7-year-olds who experienced prenatal exposure to elevated levels of two phthalates had lower IQ scores than children exposed to lower levels. The new research adds to the group's earlier findings of associations between prenatal exposure to phthalates and problems with cognitive function and behavior at age 3. ([PMID 25493564](#)) [Dec 2014]

### **Mental Health**

***Predicting Progression to Psychosis from a Clinical High-Risk State.*** The North American Longitudinal Prodrome Study (NAPLS) is aimed at predicting which individuals who are showing mild symptoms of psychosis will become psychotic, and determining the brain mechanisms associated with psychosis onset. Although mild/attenuated symptoms of psychosis usually resolve with maturity, for a minority of individuals (approximately 20-30 percent), these symptoms herald full-blown psychosis. Because the typical age of onset for psychosis includes adolescence and early adulthood, participants in NAPLS range in age from 12 to 30 years when they enter this longitudinal study, and they are followed for two years with clinical and biological measures. Relative to individuals who do not progress to full psychosis, those who become psychotic show an acceleration of the normal developmental loss of cortical gray matter. As these changes are more pronounced in individuals with briefer durations of symptoms, this finding may play a more prominent role in acute (vs. slow, gradual) forms of psychosis onset. ([PMID 25034946](#)) [Jan 2015]

***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. The NIMH Division of Intramural Research Programs (IRP) has been conducting a longitudinal study of COS since 1990, recruiting patients with onset of schizophrenia before age 13.

- 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 and connection-specific developmental abnormalities in schizophrenia. ([PMID 26176706](#)) [Sept 2015]
- 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](#)) [Jan 2016]
- The researchers have found differences related to illness severity for gray and white matter volumes, rates of change, and connectivity among different areas of the brain. Clarifying the timing of disease-specific structural differences in brain development may help point to therapeutic targets in the future. ([PMID 25195638](#)) [Jan 2015]



***Antipsychotic Medications for Young People in the United States:*** A recent NIMH-supported study found that, between 2006 and 2010, rates of antipsychotic treatment of children (ages 1-12) declined somewhat, while rates among adolescents (ages 13-18) and young adults (ages 19-24) continued to rise. ([PMID 26132724](#)) While rates of both psychotherapy as well as psychotropic drug treatment rose among young people between 1996 and 2012, rates of any mental health treatment remained low relative to the prevalence of mental disorders ([PMID 25992747](#)). For instance, fewer than 15 percent of young people with a diagnosable mental disorder received any psychotropic medication in the previous year ([PMID 23403911](#)). At the same time, analyses of antipsychotic prescribing in 2008-2009 did suggest that many young people received those medications for off-label purposes (i.e., without an FDA-approved clinical indication), such as for management of impulsive and aggressive behaviors ([PMID 26132724](#)). [Sep 2015, May 2015, Sep 2015]

***How Schools and Neighborhoods Influence Adolescents' Risk for Depressive Symptoms:*** Studies estimate that 12 percent of young people have had symptoms of depression at some point in their life, and 29 percent of high school students report having felt sad or hopeless nearly every day in the past 2 weeks. Adolescent depression increases the risk for suicidal thoughts and behaviors, substance use, and recurring depression in adulthood. To better understand the causes of depression in adolescents, researchers analyzed data from approximately 16,000 adolescents in grades 7 to 12 in the 1994-1995 school years. The results showed that schools were notably more relevant than neighborhoods for adolescent depression, even after the researchers took race/ethnicity and socioeconomic status into account. The results suggest that intervention programs directed at schools may be especially helpful in addressing depression among young people. ([PMID 25713969](#)) [Apr 2015]

***Suicide Ideation and Suicidal Behavior among Adolescents:*** NIMH-funded researchers analyzed data from the National Comorbidity Survey Replication Adolescent Supplement (youth 13-18 years of age and their parents), and found that suicidal behaviors are common among U.S. adolescents, with rates approaching those of adults (estimated lifetime prevalence of suicide ideation, plans, and attempts were 12.1 percent, 4.0 percent, and 4.1 percent respectively). The majority of teens at risk for suicide had co-occurring mental disorders. ([PMID 23303463](#)) Although the overall suicide rate in school-aged children in the United States remained stable from 1993 to 2012, there was a significant increase in suicide incidence in Black children and a significant decrease in suicide incidence among White children. ([PMID 25984947](#)) [Jul 2015]

### **Substance Use**

***Brief Strategic Family Therapy (BSFT) Reduced Parental and Child Substance Use:*** BSFT is a family-centered approach involving 12-16 therapy sessions to modify family interactions associated with adolescent substance use and behavior problems. NIDA-funded researchers found that BSFT significantly decreased parental alcohol use compared to standard treatment, and this reduction was associated with improved family functioning. Adolescents in families that used BSFT had a significantly lower substance use than those in the comparison group if their parents used drugs at baseline. ([PMID 25462653](#)) [Mar 2015]

***Differences in Binge Drinking Vary with Age, Gender, and Ethnicity:*** NICHD-supported researchers analyzed data from the National Longitudinal Study of Adolescent Health. They found that racial and ethnic disparities varied over time for smoking, regular binge drinking, and marijuana use. All three behaviors were most prevalent among white teens, but the prevalence of smoking and binge drinking among Hispanic and black individuals continued to rise through their 20s. Understanding these

differences in substance use patterns may help in developing targeted interventions to help teens and young adults when they are most at risk. ([PMID 25452068](#)) [Feb 2015]

***In an Animal Model, Effects of Binge Drinking on the Brain Persist into Adulthood:*** Researchers supported by NIAAA used rodent models of adolescent binge drinking and adult alcohol dependence to gain insight into how alcohol affects white matter integrity in the frontal cortex of the brain. They found that adolescent binge drinking reduced the size of anterior branches of the corpus callosum, the band of nerve fibers joining the two hemispheres of the brain. The researchers also demonstrated that adolescent binge drinking was associated with damaged myelin, the insulating sheath that forms around the nerve cells that comprise white matter. Heavier drinking in adolescence also predicted worse performance on a working memory task in adulthood. These results suggest that adolescent binge drinking has significant effects on the brain and these changes may contribute to deficits in executive function in adulthood. ([PMID 25355229](#)) [Oct 2014]

***Heavy-Drinking during Adolescence Alters Brain Development:*** Human brain imaging studies have shown that over the course of adolescence, the volume of gray matter in the brain decreases, whereas the volume of white matter increases. Using magnetic resonance imaging, researchers supported by NIAAA and NIDA compared the volume of brain gray and white matter between adolescents before and after they started using alcohol. Adolescents who transitioned to heavy drinking during the study had smaller increases in white matter and an accelerated decline in gray matter in certain areas of the brain compared to non-drinking adolescents, providing further evidence that heavy drinking during adolescence alters brain development. ([PMID 25982660](#)) [Jun 2015]

***Dating Violence among Adolescents and Young Adults Who Misuse Alcohol:*** An NIAAA-supported study of 14-20 year olds seeking care in a single emergency department found that 22.5 percent of those who screened positive for alcohol misuse reported dating violence in the past year. Compared to alcohol-positive youth who did not experience dating violence, adolescents who did experience dating violence were more likely to be female, have a higher score on a test for alcohol misuse, be more prone to binge drinking, use illicit drugs or use prescription drugs for non-medical reasons, experience depression, and have a higher number of visits to the emergency department.. Starting to drink at an older age was associated with lower odds of dating violence. Dating violence interventions that consider these factors could potentially help to reduce alcohol misuse among youth seeking emergency department care. ([PMID 26088699](#)) [Aug 2015]

***Secondhand Tobacco Smoke Exposure and Neuromotor Function in Rural Children:*** An NIEHS-supported study found that secondhand tobacco smoke was associated with motor impairment in children, including diminished visuomotor coordination, fine motor integration, balance, and strength. ([PMID 25882879](#)) [Aug 2015]

***Four-Fold Increase in NICU for Neonatal Abstinence Syndrome (NAS):*** Incidence of NICU admissions for neonatal abstinence syndrome (NAS) rose from 7/1000 to 27/1000 over the period of 2004-2013. Rising rates of NAS have been associated with increases in the prescription of opioids for pain in pregnant women. ([PMID 25913111](#), [PMID 23889859](#), [PMID 25869370](#)) [May 2015, Aug 2013, May 2015]

## *Nutrition and Obesity in Pregnancy and Childhood*

***Understanding Breast Milk’s Protective Effects against Deadly GI Disease in Newborns:*** NIDDK-sponsored studies in newborn mice have uncovered how breast milk could protect against a sometimes lethal form of gastrointestinal disease in newborns called necrotizing enterocolitis or “NEC.” NEC is the most common and deadly form of GI disease affecting premature infants, causing destruction and permanent loss of entire portions of the intestine, which can lead to lifetime dependency on artificial nutritional support. These studies illuminate breast milk’s direct beneficial effects on the cells that line the inside of the intestine by guarding them against inappropriate inflammatory responses and cell death in the presence of gut bacteria. ([PMID 25899687](#)) [Sep 2015]

***Slowing Kidney Disease in Children:*** About 16 percent of the U.S. population has chronic kidney disease (CKD), a gradual loss of kidney function. Although most of the individuals with chronic kidney disease are adults, thousands of children in the U.S. are on dialysis or have received kidney transplants. Through the Chronic Kidney Disease in Children (CKiD) Cohort, researchers followed about 500 children with mild to moderate kidney disease over time to see if they could identify ways to predict the progression of CKD in children. The scientists found that by tracking worsening of certain biomarkers in the children, they could identify those patients whose CKD would worsen to the point that they needed dialysis or a kidney transplant. The results suggest that more aggressive treatment of high blood pressure in children with kidney disease might be helpful in slowing the disease. The CKiD study is funded primarily by NIDDK, with cofunding from NICHD and NHLBI. ([PMID 25799137](#)) [Jun 2015]

***Genetic Variations in Young Patients with Chronic Kidney Disease May Be Risk Factors:*** A fraction of children and adolescents enrolled in the Chronic Kidney Disease in Children Study (CKiD) have been found to have changes in their genetic material that may be important in the development of kidney disease and its complications. CKiD is a study of pediatric patients with mild to moderate kidney disease. For most children enrolled in CKiD, the cause of their kidney disease has been identified; however, in others it has not. Chromosomal microarrays showed that, of the 419 children in this group, 31 (7.4 percent) had copy number variants (CNVs). The CNVs involved changes in 10 genes previously shown to be associated with kidney disease and 12 others that are thought to be related to kidney disease based on their function. The identification of patients with these genomic changes may warrant more personalized clinical care and evaluation, because the genes in some of these regions are associated with a higher risk of certain complications, such as diabetes, heart disease, eye disease, or neurological problems. ([PMID 25893603](#)) [May 2015]

***Rapid Detection of Monogenic Causes of Childhood-Onset Steroid-Resistant Nephrotic Syndrome:*** Steroid-resistant nephrotic syndrome (SRNS) is frequently caused by genetic mutations. Researchers developed a genotyping approach that allows rapid mutation analysis of 21 genes that cause SRNS—perhaps obviating a course of high-dose steroids that would be ineffective. ([PMID 24742477](#)) A single gene cause has been detected in 29.5 percent of SRNS cases. ([PMID 25349199](#)) [Jun 2014, Jun 2015]

***Plant Toxins Linked to Biliary Atresia in Newborn Animals:*** Studies in cell and animal models by NIDDK-funded investigators have discovered a plant toxin that causes changes resembling biliary atresia, which is the most common form of severe liver disease in children and the leading cause for pediatric liver transplantation. These findings of a newly identified plant-derived chemical that is toxic specifically for bile duct cells, particularly in genetically susceptible animals, suggest that this or other similar chemicals in the environment might serve as a trigger for biliary atresia in young humans. These insights bring new light to our understanding of biliary atresia and point to directions for future research into means of preventing and treating this most important and fatal newborn liver disease. ([PMID 25947162](#)) [May 2015]



***Comparison of Overweight and Obese Military Dependent Adolescent Girls to Civilian Counterparts:*** NICHD-supported researchers found that adolescent girls from military families reported significantly more binge eating episodes per month, more concerns about weight and eating, and more severe depression compared to girls from civilian families. ([PMID 25955761](#)) [Sep 2015]

***Disparities in Weight and Weight Behaviors by Sexual Orientation in College Students:*** During the college years, many individuals experience changes in weight, dietary quality, physical activity, and other behaviors. This period is also often when many lesbian, gay, and bisexual (LGB) individuals declare their sexual identity. This NICHD-supported project used data from a representative sample of Midwestern college students to analyze weight and weight-related behaviors. The researchers found that many weight-related characteristics differ by sexual orientation, even after race/ethnicity, age and socio-economic status were controlled. The researchers also found that, for some individuals—described as “discordant”—self-described orientation did not match their self-reported behavior. Compared with heterosexual and “discordant” women, bisexual and lesbian women were more likely to be obese; bisexual women were also at higher risk for unhealthy behaviors related to weight, diet, physical activity, and weight control. Compared with heterosexual men, gay and bisexual men were less likely to be overweight, but they also reported exercising less, and had more unhealthy weight control behaviors. ([PMID 25393177](#)) [Jan 2015]

## **Diabetes**

***Bionic Pancreas Outperforms Insulin Pump in Adults, Youth:*** People with type 1 diabetes who used a bionic pancreas instead of manually monitoring glucose using fingerstick tests and delivering insulin using a pump were more likely to have blood glucose levels consistently within the normal range, with fewer dangerous lows or highs. ([PMID 24931572](#), [PMID 24757227](#)) [Jul 2014, May 2014]

***New Tools for Staging Presymptomatic Type 1 Diabetes (T1D):*** Using data from the Diabetes Prevention Trial-Type 1, researchers in the NIDDK-led Type 1 Diabetes TrialNet developed a measure of short-term glycemic progression that identified participants who did and did not progress to T1D. The new measure could allow shorter trials of preventive therapies for T1D ([PMID 25758770](#)). Concurrently, investigators in The Environmental Determinants of Diabetes in the Young (TEDDY) study determined that children who subsequently progressed to T1D usually expressed two or more autoantibodies ([PMID 25665818](#)). These and other findings from TrialNet and TEDDY led to a joint scientific statement about staging presymptomatic T1D from JDRF, the Endocrine Society, and the American Diabetes Association ([PMID 26404926](#)). [May 2015, May 2015, Oct 2015]

***Age at Gluten Introduction and Risk of Celiac Disease:*** The TEDDY study also includes efforts to investigate environmental triggers of celiac disease and recently found that age of exposure to gluten does not correlate with onset of celiac disease ([PMID 25601977](#)). [Feb 2015]

***Chronic High Blood Sugar May Be Detrimental to the Developing Brain of Young Children:*** Traditionally, pediatricians have allowed young children with type 1 diabetes to maintain above-normal blood sugar levels. Many physicians reasoned that it was safer to run high than low, since consistently low blood sugar levels could risk a child having a seizure. However, a recent NICHD-funded study shows that young children who have long-term high blood sugar levels are more likely to have slower brain growth. The results indicated that chronic high blood sugar levels may slow growth in the brain’s gray matter, which affects cells and signals, as well as in the brain’s white matter, which affects the brain’s wiring. However, researchers did not find significant cognitive differences between the healthy children and those with type 1 diabetes. A longer-term study of the same children is underway to address that

question. In the meantime, researchers recommend that physicians closely monitor blood sugar levels in children with type 1 diabetes. ([PMID 25488901](#)) [May 2015]

***Prenatal BPA Exposure Linked with Higher Levels of Oxidative Damage:*** NIEHS grantees report that exposure to the endocrine-disrupting chemical bisphenol A (BPA) during pregnancy can cause oxidative damage that may increase a child's risk of developing diabetes or heart disease later in life. The researchers tested multiple species of animals to replicate and strengthen human studies that showed BPA exposure during pregnancy can bring about a specific type of oxidative stress. ([PMID 25603046](#)). [Mar 2015]

### **Bone and Muscle Health**

***Estrogen Triggers the End of Long Bone Growth in Rabbits:*** In long bones, like those found in our arms and legs, growth occurs at the growth plates near the ends of the bones. As we reach adulthood, growth at the growth plates slows down and finally stops. To examine estrogen's role in this process, a team of researchers studied the effects of estrogen on growing rabbits. They found that estrogen accelerated the loss of special cells in the growth plate needed for continued growth and that this loss could explain the fact that estrogen speeds up aging of the growth plate, causing bone growth to stop. These findings can help scientists and health care practitioners better understand the biological processes that affect how our bodies grow and change. ([PMID 25574475](#)) [Dec 2014]

***Mouse Study Shows that a Potential Osteoporosis Therapy May Help Children who have Osteogenesis Imperfecta:*** Osteogenesis imperfecta (OI), also known as brittle bone disease, is a heritable rare bone disease. There is currently no effective therapy for OI patients, although bisphosphonates have been used in some OI patients with limited success. A recent NIAMS-supported study in mice demonstrated that a sclerostin antibody currently being tested in osteoporosis patients may be a good candidate for treating children who have OI type IV. Sclerostin antibody improved long bone mass defects seen with these OI mice and significantly increased long bone strength, without affecting the brittleness of the bone in these rapidly growing mice. Impressively, treatment with sclerostin antibody has improved bone strength of the long bone to levels comparable to the normal control mice without the OI mutation. ([PMID 25445450](#)) [Feb 2015]

***Understanding Caries Risk Factors through Genetics:*** NIDCR supports a number of studies investigating the interaction between genetics and environment to determine those at risk of developing dental decay so that effective prevention methods can be employed. ([PMID 25612913](#)) [2015] Other scientists have found that the protective effect of fluoride may obviate the contribution of genetic variants to caries susceptibility. ([PMID 25373699](#)) [Feb 2015]

***Sealants Can Prevent Further Tooth Decay:*** Although there is strong evidence for the effectiveness of dental sealants, one major barrier in sealant utilization is the concern of sealing over active caries lesions. NIDCR-supported scientists detected and monitored caries lesions through a clear sealant, finding that sealants were effective in preventing progression of decay in teeth with early caries lesions. ([PMID 25248613](#)) [Nov 2014]

### **Hearing**

***Potential Non-Antibiotic Treatment for Otitis Media (Ear Infections):*** Otitis media (OM) is an inflammation of the middle ear, usually caused by bacteria, that occurs when fluid builds up behind the eardrum. Five out of six children will have at least one ear infection by their third birthday. In fact, ear

infections are the most common reason parents bring their child to a doctor. NIDCD-supported scientists have repurposed a drug that has long been used to treat stroke as a novel treatment for OM. They found that topical administration of the drug, vinpocetine, suppressed inflammation and the overproduction of mucus caused by bacterial infection. This discovery may lead to a non-antibiotic agent to combat OM with minimum side effects. ([PMID 25972475](#)) [Jun 2015]

***A2ML1 Gene Mutation May Predispose Children to Otitis Media:*** In another NIDCD-supported study, an international group of scientists has identified a rare gene (A2ML1) mutation which may predispose some children to frequent, painful OM. Scientists will study how the normal form of the A2ML1 gene appears to provide protective function of the middle ear during OM. ([PMID 6121085](#)) [Aug 2015]

### **Childhood Diseases, Allergies, and Immunity**

***Five Modifier Loci of Lung Disease Severity in Cystic Fibrosis Identified:*** NHLBI funded researchers used genome-wide association analysis to identify five regions of the genome that modify lung disease severity in cystic fibrosis, which may provide potential new targets for modulating lung disease severity in cystic fibrosis. ([PMID 26417704](#)) [Sep 2015]

***Modest Benefit Seen from Treatment for Most Common Cystic Fibrosis Mutation:*** NHLBI scientists conducted two rigorous clinical trials to test whether a two-drug combination was more effective in patients with cystic fibrosis. The combination therapy yielded modest but significant improvements in breathing and resistance to infection in people with the most common CF-causing mutation. FDA has approved the combination for people 12 and over who have two copies of the  $\Delta F508$ -CFTR mutation. ([PMID 25981758](#)) [Jul 2015]

***Nanoparticles Can Deliver Triplex-Forming Peptide Nucleic Acid Molecules:*** Using a mouse model, NHLBI funded researchers demonstrated that nanoparticles can serve as an attractive delivery tool to deliver triplex-forming peptide nucleic acids that can induce DNA repair at targeted genomic sites. The method could be used for direct *in vivo* gene editing using other nucleic acid-based approaches, with possible application to cystic fibrosis. ([PMID 25914116](#)) [Apr 2015]

***Antibiotic Approved for Treating Infant Abdominal Infections:*** Among preterm infants, complicated intra-abdominal infections may be life threatening. During the last several years, physicians had begun prescribing meropenem for preterm infants with serious abdominal infections, because they lacked an effective alternative. However, meropenem had not been approved by the Food and Drug Administration (FDA) for treating these infections in young infants. Under the terms of Best Pharmaceuticals for Children Act, the NIH commissioned a study to determine whether meropenem was safe and effective in very young infants with complicated abdominal infectious. Researchers studied 200 infants, including premature infants. They found that treatment of infants with meropenem was safe and was not associated with increased risk for serious side effects. In addition, the scientists established dosing guidelines for infants of various ages, including premature infants. ([Link to Federal Register](#))

***Clinical Trial on Vaccine for Respiratory Syncytial Virus (RSV):*** NIAID supports research on respiratory syncytial virus (RSV), a leading cause of severe respiratory illness among young children, older adults, and those with compromised immune systems. In a Phase I trial, scientists demonstrated that an intranasal live, attenuated vaccine candidate produced neutralizing antibodies in young children who had never had RSV, suggesting that the vaccine candidate could provide protective immunity against RSV. ([NIAID News Release](#)) In addition, NIAID researchers are conducting a study at the NIH Clinical Center to better understand immune system responses to RSV and development of infection by exposing

healthy adult volunteers to RSV in a controlled setting. This study will assist researchers in the future development and testing of antivirals and vaccines to combat RSV. ([NIAID News Release](#)) [Aug 2015]

***Peanut Allergy Reduced When High-Risk Infants Consumed Peanuts from Infancy to Five Years of Age:*** NIAID-funded researchers demonstrated a profound, 81 percent reduction in peanut allergy when high-risk infants consumed peanuts from infancy to age 5. This groundbreaking study indicates that early peanut introduction is an effective approach to prevent peanut allergy and suggests that similar approaches for other food allergies should be tested. In June 2015, NIAID convened a meeting of experts to draft clinical practice guidelines for prevention of peanut allergy in light of this study's findings; NIAID anticipates that this addendum to the "2010 Guidelines for the Diagnosis and Management of Food Allergy" will be published in FY 2016. ([PMID 25705822](#); [NIAID News Release](#)) [Feb 2015]

***Genome-Wide Association Study Identifies Peanut Allergy Loci:*** NIAID-funded researchers conducted a large scale genome-wide association study of food allergy in a U.S. cohort and evaluated genetic and epigenetic factors. The results suggest changes in a small region of chromosome 6 are risk factors for peanut allergy in U.S. children of European descent. The genetic risk area is located among two tightly linked genes that regulate the presentation of allergens and microbial products to the immune system. This study is the first to use a genome-wide screening approach in patients with well-defined food allergy to identify risks for peanut allergy. ([PMID 25710614](#)) [Feb 2015]

***Antiretroviral Drug Exhibits Same Effects in Young Children and Adults:*** Scientists supported by NIAID and NICHD demonstrated that pediatric formulations of the antiretroviral drug raltegravir in HIV-positive children ages 4 weeks to 18 years exhibited pharmacokinetic effects consistent with those from prior studies in adults and older children. Raltegravir, the first of a class of drugs known as integrase inhibitors to receive FDA approval, was administered to children in the form of chewable tablets and oral granules as part of the open-label study, and results from this study provide helpful dosing information for use of raltegravir in pediatric populations. ([PMID 25753401](#)) [Jul 2015]

***Identifying a Superior Drug Regimen for Preventing Mother-to-Child HIV Transmission:*** The ongoing PROMISE (Promoting Maternal-Infant Survival Everywhere) study has found that one triple-drug regimen for preventing mother-to-child transmission may be safer than another for women and their babies. The PROMISE study, which began in 2010, aims to determine how best to safely reduce the risk of HIV transmission from infected pregnant women to their babies during pregnancy and after delivery. It also aims to learn how stopping versus continuing a triple-drug anti-HIV regimen after breastfeeding affects mothers who are in good immune health. The study has enrolled more than 3,500 HIV-infected pregnant or post-partum women in India, Malawi, South Africa, Tanzania, Uganda, Zambia and Zimbabwe, who did not meet national criteria for receiving anti-HIV treatment and more than 3,200 HIV-exposed infants of these women. This NIH-supported randomized-control trial compared two proven strategies for preventing mother-to-child HIV transmission before and during delivery, and found that one triple-drug regimen was significantly safer, supporting WHO recommendations. ([NIH News Release](#)) [Nov 2014]

***Genetic Ancestry Partially Explains Disparities in Asthma Risk among Latinos:*** Childhood asthma prevalence and morbidity varies among Latinos in the U.S. depending on country of origin/heritage. An NIMHD-funded study analyzed 5,493 Latinos using genome-wide data to determine proportion of African, European, and Native American ancestry. Results indicate that differences in the proportions of genetic ancestry can partially explain disparities in asthma susceptibility and lung function among Latinos. ([PMID 25301036](#)) [Jan 2015]

***Daycare Attendance, Breastfeeding, and Risk of Childhood Leukemia:*** Supported by NIEHS and NCI, researchers pooled data from several studies on daycare attendance and risk of illness. The findings

indicated that daycare center attendance in infancy and breastfeeding for at least six months are both associated with a decreased risk of acute lymphoblastic leukemia (ALL). The earlier the attendance began, the lower the risk. ALL accounts for 80 percent of childhood acute leukemia, which is the most common cancer for children under 15 years old. ([PMID 25731888](#)) [Apr 2015]

***Unique Germline Mutations Lead to Several Autoimmune Symptoms:*** NIAID intramural researchers identified a novel form of inherited autoimmunity. Researchers identified nine unique germline mutations in STAT3 as a cause of dysregulated cytokine signaling leading to symptoms such as lymphadenopathy, autoimmune cytopenias, multiorgan autoimmunity, and recurrent infections. ([PMID 25359994](#), [NCT00001350](#)) [Jan 2015]

***Identifying Biomarkers for Neonatal Lupus:*** Neonatal lupus is a rare autoimmune disorder that is present at birth. Many infants with neonatal lupus will have a condition that causes abnormal heart rhythm which may ultimately require a pacemaker. Neonatal lupus results from specific autoantibodies that travel from a pregnant woman to her developing fetus. With support from NICHD, NIAMS, and NCATS, researchers set out to identify biomarkers that may help physicians predict outcomes in babies with neonatal lupus. They tested infants and their mothers for biomarkers often used to identify risk for cardiovascular disease in adults. The researchers used data from a registry of mothers who had at least one child with neonatal lupus and had the specific antibodies associated with the disease. The scientists found that infants with higher levels of C-reactive protein in their umbilical cords (“cord CRP”) were more likely to have neonatal lupus. Moreover, the higher the level of cord CRP, the more severe the disease. However, there was no relationship between the level of CRP in the mother’s blood and whether or not the infant had neonatal lupus. Other biomarkers also showed higher levels in infants with neonatal lupus and were similarly related to severity of the condition. For researchers, these results support the idea that the developing immune system in the fetus is associated with neonatal lupus. For physicians, these biomarkers may help clinicians identify and monitor infants at highest risk for the disease. ([PMID 26293764](#)) [Aug 2015]

***NIAMS Researchers Identify Mechanisms Involved in Childhood-Onset Systemic Lupus Erythematosus:*** With an estimated prevalence of over 161 thousand people, systemic lupus erythematosus (SLE) is an autoimmune disease in which the immune system makes antibodies to cells in the body leading to widespread inflammation and tissue damage. SLE patients, both pediatric and adult, have a significantly enhanced risk of developing premature cardiovascular diseases. Childhood-onset SLE (cSLE) patients carry a longer burden of disease. NIAMS intramural researchers have identified an important role for type 1 interferons (IFNs) in the pathogenesis of childhood-onset and adult-onset SLE. The type 1 IFNs lead to significant impairment of endothelial progenitor cells (EPCs) and prevent their development into mature endothelial cells (ECs), leading to decreased vascular function. ([PMID 25891295](#)) [May 2015]

### **Childhood Injuries and Maltreatment**

***Time to Recovery from Concussion in Children.*** In a study of nearly 250 young concussion patients, NICHD-funded researchers found that these children and adolescents (five to 18 years old) took significantly longer to recover and return to school full-time than has been reported before. Previous studies estimated healing times after concussion ranging from 14 to 28 days in children, but in this study the median time to resolve patient symptoms was 64 days. Factors that seemed to explain the longer recovery times included loss of consciousness or dizziness at the time of concussion, abnormalities in initial vision assessments, history of prior concussion, and pre-injury anxiety and depression. ([PMID 25262302](#)) [Dec 2014]



***Hospitals Often Miss the Chance to Identify Child Maltreatment:*** For children under age two, a broken thigh bone or a head injury not received in a car crash may signal a pattern of earlier abuse. Follow up x-rays may reveal earlier, unreported bone breaks that have begun to heal and so can help confirm the suspicion of abuse. Long-standing guidelines from the American Academy of Pediatrics suggest that physicians order additional x-rays for children suspected of being victims of abuse. However, a recent NICHD-supported study found large differences across hospitals in whether they followed these guidelines. Researchers examined records from over 300 hospitals and almost 5,000 children, and found that only about half of small children with these injuries were screened for hidden fractures—many times, even when a child was known to have been abused previously. How frequently screening took place varied greatly from one hospital to another. Some hospitals screened every infant with a thigh bone fracture; a few others screened none at all. The results suggest that many U.S. hospitals may be missing the chance to find out if babies and toddlers have been physically abused. ([PMID 26169425](#)) [Aug 2015]

***Patterns of Child Maltreatment across Generations:*** Experts in child abuse and neglect have long accepted the idea that abused children may become abusive parents, but other factors in a person's life may mediate the effects of child abuse and neglect. To examine how abusive behavior may be passed on to the next generation, researchers funded by NIAAA, NIDA, NICHD, and NIMH studied three generations: parents in court-substantiated cases of abuse and neglect (generation 1); the offspring of these parents and a comparison group of children with no documented histories of childhood abuse or neglect from the same neighborhoods (generation 2); and the offspring of the generation 2 groups (generation 3). The researchers assessed physical abuse, sexual abuse, and neglect at multiple time points, interviewing generation 2 and generation 3 subjects several times over more than 20 years. They also collected child protection agency records. The researchers found that intergenerational transmission of abuse is complex. Generation 2 parents who had documented histories of childhood abuse or neglect, when compared to a matched group of parents, were more likely to be reported to child protective services because their child was maltreated. Their children were also more likely to report having been neglected or sexually abused. However, there was little evidence that physical abuse was passed down to the next generation. Parents with histories of any type of abuse or neglect were not necessarily more likely than the comparison parents to physically abuse their offspring. The scientists concluded that to develop effective interventions and preventive measures, it will be important to understand why neglect and sexual abuse are more likely to be transmitted. ([PMID 25814584](#)) [Mar 2015]

***FDA Approval for Neupogen:*** In March and November 2015, respectively, the FDA approved the use of Neupogen® and Neulasta® to treat adult and pediatric patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome). These FDA approvals were based on animal models and data from animal efficacy studies sponsored by the NIAID. Neupogen® (filgrastim) requires daily dosing, while Neulasta® (pegylated filgrastim) administration is once per week, providing improved administration in a radiation emergency.

### **Rare Pediatric Diseases**

***Atenolol versus Losartan in Children and Young Adults with Marfan Syndrome:*** This randomized clinical trial, conducted through the NHLBI's Pediatric Heart Network, compared two medications in children and young adults with Marfan syndrome. Aortic-root dissection, which is a risk when the aortic root enlarges, is the leading cause of death in Marfan syndrome. Patients with a dilated aortic root were treated with losartan versus atenolol over three years. Although the rate of change in the aortic root did not differ between treatment groups, the severity of aortic-root enlargement decreased over time in both groups, particularly in young subjects, suggesting that starting therapy at an earlier age and stage of the disease might be warranted. Both drugs were found to be well-tolerated and safe, resulting in more treatment options for patients with Marfan syndrome. ([PMID 25405392](#)) [Nov 2014]

***Menkes Disease***, an inherited disorder of copper transport, causes brain abnormalities and developmental delays beginning at 6-8 weeks of age. Patients commonly die by 3-years-old. NICHD-supported researchers treated two groups of infants with Menkes disease with copper histidine. Infants who received treatment before 1 month of age showed significantly higher levels of activity, movement, social skills, and language development compared with infants who received treatment at 1 month of age and older. ([PMID 25281031](#)) [Oct 2014]

***Angelman Syndrome: Possible Gene-Specific Treatment***: Angelman Syndrome affects 1 in 12,000 to 20,000 people, resulting in intellectual disability, delays in development, speech impairment, seizures, and problems with balance. Children with Angelman Syndrome receive a mutated gene from their mothers. This gene produces a long piece of RNA that blocks the functioning gene from their fathers. NICHD-funded researchers designed compounds called antisense oligonucleotides that stop this long piece of RNA from blocking the functional gene, which may be the first step in developing new treatments. ([PMID 25470045](#)) [Feb 2015]

***Identifying Mutations that Cause Severe Infantile Epileptic Encephalopathy***: The Common Fund's Undiagnosed Diseases Network supported a study that described pediatric patients with alanyl-tRNA synthetase (AARS) mutations that caused severe infantile epileptic encephalopathy with a central myelin defect and peripheral neuropathy. ([PMID 25817015](#)) [Apr 2015]

***Identifying Mutations that Differentiate Two Rare Diseases***: Researchers supported by The Common Fund's Undiagnosed Diseases Network identified a mutation that established the genetic basis of two rare diseases that are characterized by similar clinical features: Ablepharon Macrostomia and Barber-Say Syndromes. Patients affected by these ectodermal dysplasias exhibit abnormal development of the skin, hair, nails, teeth, or sweat glands. The researchers identified mutations in the TWIST2 protein in families affected by both AMS and BSS, which they tested in HeLa cells and zebrafish. ([PMID 26119818](#)) [Jul 2015]

***Understanding How Genetic Mutations Affect the Brain in Rett Syndrome***: Infants (almost always girls) who have Rett Syndrome seem normal at first, but they stop developing and even lose skills and abilities. Eventually, the syndrome leads to autistic symptoms and problems with thinking, communication, movement, the heart, digestion, sleeping, and breathing. Rett syndrome affects 1 out of every 10,000 to 15,000 girls born in the United States. Rett Syndrome is caused by abnormal forms (mutations) of a gene called MECP2. MECP2 makes proteins that influence the expression of many different genes, and this has made it challenging for scientists to understand exactly how the mutation on MECP2 causes the symptoms of Rett syndrome. In a recent study, scientists observed that many of the genes whose expression is increased by MECP2 are "long genes" – that is, they have a longer length than average. After confirming this finding using several methods, researchers funded by NICHD, NINDS, and NIGMS looked at this process further using a mouse model for Rett syndrome. They uncovered several clues that indicate that a widespread effect on "long genes" may help explain Rett syndrome. First, the Rett syndrome related symptoms were more severe in mice with greater mis-regulation of the "long genes". The timing of the gene expression corresponded with the timing of the symptoms of Rett syndrome. Finally, a similar process was observed in a mouse model for Fragile X syndrome, a similar disorder with a different genetic cause. The results of the study suggested that mis-regulation of "long genes" may be a common pathway whereby different genetic mutations can lead to developmental disorders with similar symptoms. ([PMID 25762136](#)) [Jun 2015]

***Scientists Identify Key Intermediary between Protein Synthesis and Day-Night Cycles***: Tuberous Sclerosis Complex (TSC) is a rare disorder resulting in numerous benign tumors in the brain and other organs, such as the kidneys, heart, eyes, lungs and skin, as well as autism and seizures. Many people with

TSC also have pronounced sleep disturbances. TSC results from mutations in either of two genes: TSC1 and TSC2. The genes control the mTOR pathway, a biological pathway that controls the process by which genetic sequences are translated into RNA, the molecular template from which proteins are made. Given the sleep disturbances seen in TSC patients, researchers decided to investigate how the mTOR pathway might be involved in circadian rhythms, the physiological changes that take place daily in tandem with the 24-hour cycle of day and night. The scientists identified a connection between the mTOR pathway and the control of circadian rhythms. When it's triggered by the mTOR pathway, S6K1 – an enzyme that adds a phosphate group to other molecules – modifies BMAL1, a protein central to the circadian clock. BMAL1 helps to ensure that the right protein is made at the appropriate time of day. If the timing of protein synthesis is thrown off, it might result in a shortage of some proteins at critical times, and an oversupply of others. Such aberrant protein production could potentially affect the structure and functioning of a variety of different kinds of cells, in the process contributing to developmental disorders, neurodegenerative diseases and cancers. This research was supported by NICHD, NCI, and NINDS. ([PMID 25981667](#)) [May 2015]

**Heterotaxy** is a disorder that results in certain organs forming in abnormal positions within the body. Babies with heterotaxy are usually first identified because they have structural problems with their hearts, livers, lungs, intestines, and/or spleens. Heterotaxy occurs in approximately 1 in 10,000 live births. The exact cause of heterotaxy is unknown, but researchers point to genetic factors because the disorder may run in families. NICHD-supported researchers identified 74 cases of classic heterotaxy from all live births in New York State during 1998–2005. The researchers extracted DNA from each infant's newborn dried blood spot, and genotyped the DNA to identify parts of chromosomes that were duplicated or deleted. They identified 20 rare genetic variants. Some genes identified by the study are important in determining left-right placement of the organs. These results will help scientists understand the genetics underlying heterotaxy and related disorders. ([PMID 25232849](#)). [May 2015]

**CHOPS Syndrome and Cornelia de Lange syndrome (CdLS):** Researchers have identified the cause of a new developmental syndrome, CHOPS, an acronym that refers to the symptoms seen in affected children: cognitive impairment, heart defects, obesity, pulmonary symptoms, and abnormal skeletal development. NICHD-funded researchers sequenced the genes of 3 CHOPS patients and found that all three had mutations in the *AFF4* gene. This gene produces a protein that is part of a cluster of proteins governing transcriptional elongation, which ensures that the right genes are expressed during the right time during development. Researchers compared transcription in cells from both CHOPS syndrome patients and CdLS patients, finding widespread changes in transcript elongation due to widespread changes in *AFF4* or cohesin binding, suggesting that the two syndromes share similar underlying mechanisms: disrupting transcriptional regulation. ([PMID 25730767](#)) [Apr 2015]

**New Experimental Model for Batten Disease:** Batten disease affects about one in 12,500 infants. The disease—actually a group of inherited neurodegenerative disorders—causes movement problems, slowing of thought processes, seizures, loss of vision, brain atrophy and early death. Mutations in 13 different genes (called *CLNs*) underlie various types of Batten disease. Currently, no effective treatment exists for any of the Batten disease types. Scientists are searching for new ways to learn about the disease and test experimental treatments. Researchers can sometimes use mice that are engineered to have disease mutations to study genetic diseases, but in many cases, the mice do not mimic the human condition, or their life spans are too short to conduct useful experiments. Recently, NICHD researchers used advanced molecular techniques to insert a version of the mutation (called nonsense mutation) into the *Cln1* gene in mice. Testing revealed that the mice carrying the nonsense mutations exhibited several key features of human INCL, confirming that the scientists had generated an animal model of INCL. This model will help researchers learn more about the mechanisms underlying this devastating disease and develop effective therapeutic strategies. ([PMID 25574475](#)) [Dec 2014]



***Gene Therapies for Lysosomal Storage Diseases Using Animal Models:*** Lysosomal storage diseases (LSDs) result from insufficiency of enzymes that normally degrade cellular compounds, leading to progressive damage throughout the body. Current therapies for LSDs involve stem-cell based approaches or weekly infusions of the enzyme that is deficient in the particular disorder. However, these therapies can themselves cause morbidity and mortality and can be relatively ineffective. Scientists have developed promising gene-therapy based approaches for treating LSDs in animal models, including canine mucopolysaccharidosis VII (Sly syndrome in humans) and feline mucopolysaccharidosis type I. The results of these studies suggest that effective treatments of LSDs in children are achievable using gene therapy. ([PMID 26022732](#), [PMID 25267637](#)) [Aug 2015, Oct 2014]

### **Global Pediatric Health**

***Screening for an Enzyme Deficiency in Newborns in Low income countries:*** Neonatal jaundice is a common condition, and most children with jaundice recover completely if they are screened and treated promptly. However, newborns with a condition called G6PD deficiency can develop sudden, rapidly progressing, dangerous cases of jaundice. If not treated very quickly, this can result in permanent damage. For this reason, the World Health Organization recommends screening for G6PD deficiency in newborns. However, screening for all newborns can be especially difficult in low- and middle-income countries, because current screening methods can be labor-intensive and costly. NICHD-supported researchers tested a digital microfluidics platform for G6PD screening, using blood samples from nearly 100 infants. The test was sensitive and accurate. Moreover, because the digital microfluidics test automates most of the process, it could be more practical to use in resource-limited settings. ([PMID 26459646](#)) [Nov 2015]

***Effect of HIV Treatment Choice on Malaria among Children:*** Results from a recent clinical trial showed that when certain anti-HIV drugs (protease inhibitors) are used for children, they can make certain anti-malaria drugs more effective. The protease inhibitors extended the time period in which the anti-malaria drugs prevented malaria from recurring. Researchers supported by NICHD and NIGMS used the data from this study to estimate the benefits of using protease inhibitors in place of other anti-HIV drugs in areas where new and existing cases of HIV and malaria ranged from low to high. The scientists found that in countries where malaria and HIV are both at high levels, using protease inhibitors could reduce the spread of malaria and save significant numbers of lives. ([PMID 25486414](#)) [Feb 2015]

***Identifying Infants with Developmental Delays in Low-income Countries:*** Infants born to families in low-income countries are at risk for developmental delays. Although early intervention is helpful, there are very few procedures in place in many of these countries to detect developmental delays in infants and very young children. Physicians and caregivers in these countries need inexpensive, objective, easy-to-use screening measures that can be administered in a variety of cultures. With support from NICHD, NIAID, and FIC, researchers translated and culturally adapted a smaller number of items from the Bayley Scales of Infant Development, a measure often used in high-income countries, for use as a screening tool for 12 month old infants in India, Pakistan, and Zambia. This screening tool was able to identify children suspected of having mental and motor delays. Compared with alternative screening tools, this test allowed clinicians to observe and interact with the child, and required only a limited amount of time because it had fewer items than other tests. ([PMID 25734979](#)) [Apr 2015]

***Harmful Gut Bacterial Effects Behind Persistent Childhood Undernutrition:*** An international research group has identified a group of bacteria that take hold in the gut during nutrient deficiency and damage the intestinal lining, thereby thwarting the body's ability to absorb available nutrients in the diet and to fend off disease. Scientists supported by NIDDK collected samples of fecal bacteria from severely undernourished infants and children living in Malawi and they tested the bacteria in mice. These findings may be used to identify individuals at risk for persistent childhood undernutrition and to design more

effective therapeutic and preventive strategies for ameliorating this global problem in the future. ([PMID 25717097](#)) [Feb 2015]

### **Technology and Tools**

***Databrary: Open Data Library for Sharing Media on Developmental Research:*** NICHD has supported the “Databrary,” a web-based, digital, open data library for developmental science, where researchers can deposit video, audio, and related metadata from developmental research projects around the world. The Databrary currently has over 14,600 files and over 3500 hours of recordings, and also offers free tools to manage and visualize data, identify patterns, and organize resources. Because these media are openly shared, other researchers can utilize the data to answer different questions, without having to collect their own costly videos. ([Link to Databrary](#); [PMID 26900512](#)) [Sep 2015]

***New Whole Genome Sequencing Method to Help Speed Diagnosis of Genetic Diseases:*** Genomic medicine uses an individual’s genome information to guide personalized strategies for preventing, diagnosing, or treating disease. Genomic medicine is a particularly powerful tool to help patients with very rare or newly discovered genetic diseases, where diagnosis is especially difficult. However, while the cost of whole genome sequencing has fallen dramatically, it remains too slow to be suitable for conditions where prompt emergency treatment is critical. NICHD-supported scientists recently tested a new whole genome sequencing system, made possible by improvements in software and sequencing techniques. They assessed the new method on 35 acutely ill infants with suspected genetic disorders. The results showed that the new method was accurate and faster, returning results in as little as 26 hours (compared to about 50 hours with previous methods). The whole genome sequencing was able to provide a diagnosis for over half the infants (20 of 35, or 57 percent); in nine of these infants, the condition ultimately diagnosed had not been considered at the time of the initial test. ([PMID 26419432](#)) [Sep 2015]

***A Rapid, High-Quality, Cost Effective, Comprehensive and Expandable Targeted Next-Generation Sequencing Assay for Inherited Heart Diseases:*** Thousands of genes can cause cardiomyopathies or coronary heart disease (CHD). Recently, molecular genetic determinants of cardiac disease are increasingly complementing traditional diagnostic methods. Researchers sought to develop a custom high throughput, clinical grade next-generation sequencing (NGS) assay for detecting cardiac disease gene mutations. The technology was found to be effective at detecting mutations in numerous cardiac genes. This provides a useful tool for DNA mutation detection and discovery. This method could also be used for genetic screening of at-risk family members. ([PMID 26264630](#)) [Aug 2015]

***Software Program Supports Community-Based Decision Making to Eliminate Disparities in Maternal and Child Health:*** Research funded by NIMHD has developed a Community Priority Index (CPI) and accompanying software program to facilitate prioritization of community health disparity issues. This instrument is the first of its kind that can be used to prioritize community health issues by combining subjective and objective data taken from community needs assessments into a single measure. ([PMID 25815045](#)) [2015]

***Developing a Screening Tool for Children with Chronic Pain:*** An estimated 1.7 million children in the United States have chronic pain. Unfortunately, it is often very difficult for physicians to know what treatments are most appropriate. In adults, screening questionnaires are sometimes used to identify patients at highest risk for poor outcomes, and to help determine which treatment approaches are needed. However, similar tools are not widely available for children. Researchers supported by NICHD and NINDS developed and tested a screening tool in over 300 children ages 8 to 18 years who sought treatment at a chronic pain clinic. The questions addressed the severity of pain, impact on the child’s life, sleep, fatigue, and psychosocial issues. The questionnaire was valid and was able to identify children with

the highest risk of poor outcomes, i.e., disability and emotional distress, and may be useful to inform treatment decisions. ([PMID 25906349](#)) [Aug 2015]

***Advanced Fetal Imaging:*** Overcoming ongoing movement is a challenge in imaging, especially if the patient is an infant or child. Researchers are developing a new MRI-based technology for high resolution anatomical and physiological neuroimaging that is not sensitive to motion. This approach will focus on developing state-of-the-art image acquisition tools for use during pregnancy. Improving fetal brain imaging using MRI as an additional tool to fetal ultrasound may be helpful for identifying fetal abnormalities with more consistency than current methods. ([PMID 26225129](#), [PMID 25601041](#), [PMID 25640187](#)) [Nov 2014, Apr 2015, Mar 2015]

***Data and Specimen Hub (DASH):*** NICHD recently developed the Data and Specimen Hub (DASH), a centralized resource for researchers to store and access de-identified data from completed studies supported by the NICHD. DASH can help investigators meet the NIH's data sharing requirements for their own studies and find study data from other investigators for secondary analyses. By supporting data sharing through DASH, NICHD aims to accelerate scientific findings and improve human health.

***Autism Brain Imaging Data Exchange (ABIDE):*** A group of researchers have pooled fMRI data sets, as well as structural MRIs and phenotypes, from over 500 individuals with ASD and over 500 age-matched controls. They have created an openly shared web-based resource called ABIDE. NIMH has provided funding to ABIDE to increase the sample size to over 2500 individuals with ASD and controls. This resource can now be used to explore brain connectivity and structural differences in ASD, and is expected to accelerate the pace of discovery. These data will also be made available via the National Database for Autism Research.

### **Clinical Care, Outreach, and Services**

***Addressing Health Disparities in the Mental Health of Refugee Children and Adolescents:*** This NIMHD-funded study used community-based participatory research methods to develop community needs assessments and identify local terms for child mental health problems among Somali Bantu and Bhutanese refugees in Massachusetts, between 2011 and 2014. Financial and language barriers impeded the abilities of families to assist youths who were struggling academically and socially. Participants identified resources both within and outside the refugee community to help with these problems. Both communities identified areas of distress corresponding to Western concepts of conduct disorders, depression, and anxiety. ([PMID 25905818](#)) [Jul 2015]

***Reducing Unnecessary Antibiotic Use in Pediatrics:*** Pediatricians may feel pressured by worried parents to prescribe antibiotics for acute childhood respiratory tract infections (ARTI), even when antibiotics would do no good. Using two similar surveys conducted in Massachusetts in 2000 and 2013, NICHD-supported researchers identified the most persistent, common misconceptions about antibiotics among parents. ([PMID 25964399](#)) [May 2015] Recognizing that parents, understandably, want physicians to help their sick children feel better, investigators in a different but related study tested a new strategy for advising parents about viral ARTIs. The strategy combined positive information for parents, i.e. actions they could take to relieve their children's symptoms, with negative information about the lack of antibiotic efficacy against viruses and the risk of contributing to antibiotic-resistant bacterial diseases. This approach appeared to reduce the risk of physicians unnecessarily prescribing an antibiotic for children with viral ARTIs while also yielding high parental ratings of physicians using this strategy. ([PMID 26195536](#))[Aug 2015]

***Parents' Knowledge of Antibiotic Use Improving, But Some Common Misconceptions Persist:*** Each year in the United States, at least 2 million people become infected with bacteria that are resistant to antibiotics and at least 23,000 people die each year as a direct result of these infections. Public health officials have tried to reduce unnecessary antibiotic use by educating health care providers and the general public. However, some parents mistakenly believe antibiotics are needed, particularly for respiratory tract infections, and providers may be responding to the parents' preferences. NICHD-supported researchers used two similar surveys conducted in Massachusetts in 2000 and 2013 to determine if parents' knowledge and attitudes about antibiotics changed over time and if they varied across certain groups. They found that, although a higher proportion of parents answered knowledge questions correctly in 2013 compared with 2000, a number of common misconceptions about the need for antibiotics persisted. Moreover, the results confirmed that younger parents, parents with Medicaid insurance, and parents with less education had less knowledge about appropriate antibiotic use. Specially targeted efforts may be needed to improve knowledge among these parents. ([PMID 26195539](#)) [Aug 2015]

***Implementation Fidelity in Family-Based Treatment for Anorexia Nervosa:*** NIMH-supported researchers recently developed a new psychometric tool to optimize treatment fidelity in Family-Based Treatment (FBT) for adolescent anorexia nervosa. Findings suggest that this new tool demonstrates good reliability and validity as a measure of treatment fidelity in the early phase of FBT. ([PMID 25142619](#)) [Mar 2016, Jan 2015]

***Health Education Program on Effective Asthma Self-Care Behaviors:*** Ineffective self-care behaviors can contribute to poor health outcomes for children with asthma. Recent findings from an NINR-supported study showed improvements in asthma episode management and prevention behaviors in medically underserved, primarily minority, lower socioeconomic, and inner-city school-age students who received a school and community based asthma health education and counseling program. ([PMID 25443867](#)) [Jan 2015]

***The Importance of Continued Parental Involvement in Predicting HIV Outcomes among Adolescents Living with HIV:*** More than 2.1 million adolescents are estimated to be living with HIV in low- and middle-income countries. NIMH-funded researchers are helping to identify factors that facilitate and hinder medication adherence among adolescents. One particular grant explored the role of parental attendance at clinical visits for HIV-positive adolescents ([K23MH095669](#)). Findings revealed that the absence of a parent from an adolescent's clinic visit was strongly associated with worse health outcomes. These results suggest that interventions to improve caregiver support and strengthen adolescent/parent relationships might be helpful. ([PMID 25822083](#)) [May 2015]

***Assessing Quality of Life in Children with Spina Bifida:*** Researchers and clinicians often use surveys to assess the health-related quality of life for children with spina bifida. Sometimes these surveys are completed by the child's parents, and sometimes by the children. NICHD-supported scientists were interested in how children's and parents' responses to similar surveys may differ, how the quality of life reports changed over time, and how quality of life for children with spina bifida compared with quality of life for children with other chronic health conditions. The scientists administered surveys to 134 families of children with spina bifida, 214 families of children with other chronic health conditions (including asthma, diabetes, or other conditions), and 684 families of children without health problems. The study showed that children with spina bifida had lower quality of life scores than children with other conditions or healthy children. Parents typically reported lower quality of life for the children compared with their children's own ratings. The majority of the quality of life ratings were stable over time, yet the children's social quality of life increased over time. The results show the importance of including the children's own perspectives in assessing quality of life for children with spina bifida. ([PMID 25434043](#)) [May 2015]

***Increasing Access to Improve Oral Health in Children:*** To improve the access to preventive oral health services, the US Preventive Services Task Force recommends regular visits to primary care clinicians along with the application of fluoride varnish to the teeth of all children under the age of five. An NIDCR-supported study of kindergarten students in North Carolina supports this recommendation, finding those with more than four preventative visits had overall improved oral health, although there are still potential improvements to be made in treating dental decay. ([PMID 26122805](#)) [Jul 2015]

***Full Day Preschool Program Improves School Readiness:*** Research has shown numerous benefits to enrolling disadvantaged children in preschool programs before they begin kindergarten, but less is known about whether full day programs provide the same benefit as half day programs. NICHD-supported researchers studied nearly 1000 children from low income, ethnic minority families who were enrolled in a public preschool program in Chicago. The program offered both half day and full day education for preschoolers, as well as many health and support services for families. Children who attended the full day program (7 hours) were compared to the children who attended the half day program (approximately 3 hours). Researchers looked at three measures to determine whether a part-day or full-day program was more helpful for young children: school readiness, attendance and parental involvement. The findings showed that children who attended the full-day program scored higher on 4 of 6 school readiness skills: language, math, socio-emotional development, and physical health. They also had higher attendance. There were no differences in parental involvement. In addition, children attending the full-day program tended to higher educational attainment, income, socioeconomic status (SES), and health insurance coverage, as well as lower rates of serious crime and incarceration, and substance abuse. ([PMID 25423219](#)) [Nov 2014]

### ***Pediatric Critical Care and Emergency Care***

***Safety and Efficacy of Blood Pressure Drug for Children Treated in Pediatric Intensive Care Units:*** Post-operative patients recovering from serious surgery, especially cardiac surgery, are often cared for in the pediatric intensive care unit. For all these seriously ill children, it is especially important to keep blood pressure at a safe level. Sodium nitroprusside (SNP) is a drug commonly used to control blood pressure in both adult and pediatric intensive care units. Although this drug has been used for many years, there is limited information on the safety and efficacy of SNP in children. NICHD-funded researchers conducted a very carefully controlled study to assess how well the drug works in critically ill children. In the first phase of the study, children were given SNP for 12-24 hours until their blood pressure was well controlled to a targeted level. (The target was determined by the child's physicians at the beginning of treatment.) In the second phase of the study, children were randomly assigned to continue receiving the drug or receive a placebo for 30 minutes, with their blood pressure being monitored every minute. The second phase ended after either 30 minutes, or when the blood pressure increased by a specific but safe amount compared with the target. The minute-by-minute blood pressure readings helped the researchers determine how well SNP controlled the blood pressure. Scientists tested the children's urine and blood to identify any problems associated with the drug and monitored the children carefully during and after the study. The researchers found that SNP was safe and effective. The odds of maintaining blood pressure control were 4 to 5 times higher in patients receiving SNP. Based on the results of this study, the U.S. Food and Drug Administration revised its labeling of SNP for use in children. ([PMID 25715047](#)) [Jun 2015]

***Two Treatments Yield Similar Results for Children with Cardiac Arrest:*** More than 6,000 children suffer out-of-hospital cardiac arrest in the United States each year, according to the American Heart Association's 2015 heart disease and stroke statistics. During cardiac arrest, the heart stops pumping effectively, and blood stops flowing to the brain and other vital organs. In many cases, the outcome is death or long-term disability. Therapeutic hypothermia, or whole body cooling, can improve survival and



health outcomes for adults after cardiac arrest and also for newborns with brain injury due to a lack of oxygen at birth. However, this treatment had not been previously studied in infants or children admitted to hospitals with cardiac arrest. Supported by NHLBI, researchers studied 295 children between 2 days and 18 years old who were admitted to children's hospitals for cardiac arrest, required chest compressions for at least two minutes and remained dependent on mechanical ventilation to breathe. After their parents or guardians provided consent, children were randomly assigned to one of the two treatment groups. One group received body cooling for two days followed by three days of normal temperature control. Another group received normal temperature control for five days. One year after treatment, researchers observed no difference in survival or cognitive function between groups. ([PMID 25913022](#)) [May 2015]

***Assessing and Reducing the Risk of Kidney Injury for Children Undergoing Heart Surgery:*** Children who are born with heart defects may need cardiopulmonary bypass (CPB) during the operation to repair the heart. However, surgery involving CPB can lead to complications such as acute kidney injury. Researchers set out to determine if hemolysis – a type of damage to red blood cells – increased the risk of kidney injury in children undergoing CPB. The scientists assessed the degree of hemolysis and kidney injury, and measured several kidney-related biomarkers, in children before and after CPB. The researchers found that CPB does lead to hemolysis, and that hemolysis was associated with acute kidney injury. Moreover, one of the urinary biomarkers (neutrophil gelatinase) was found to associate with both hemolysis and kidney injury. These findings could help surgeons identify new ways to reduce the risk of kidney injury in children undergoing heart surgery. ([PMID 24599483](#)) [Feb 2015]

***Mortality Rates Vary Among Hospitals Using Life-Saving ECMO Technology:*** Extracorporeal membrane oxygenation (ECMO) provides life support for patients recovering from lung failure, heart failure, or surgery. ECMO systems pump and oxygenate a patient's blood, allowing the heart and lungs to rest. More hospitals around the world are starting to use ECMO, but the complex technology requires an experienced and well-organized medical team. Also, ECMO is extremely costly compared with conventional care and may increase the risk of disability. NICHD-supported researchers analyzed an international registry with data from more than 56,000 patients who received ECMO at 290 medical centers between 1989 and 2013. Mortality rates at the ECMO centers varied widely: 18 percent to 50 percent for newborns, 25 percent to 66 percent for older children, and 33 percent to 92 percent for adults. Centers that handled more ECMO cases had lower mortality rates among newborns and adults (but not children) who received ECMO. This information may help decision makers weigh the advantages of expanding ECMO at existing centers or develop ECMO technology and teams at other hospitals. ([PMID 25695688](#)) [Apr 2015]

***Fluctuations in Sodium Levels Associated with Poorer Outcomes for Critically Ill Children with External Ventricular Drain (EVD):*** Children with traumatic brain injury often experience excess pressure and fluid buildup near the brain, which can be dangerous or fatal. To relieve this pressure, doctors may insert a plastic tube called an external ventricular drain (EVD), to drain fluid and monitor the pressure in the skull. Unfortunately, sometimes children treated with an EVD experience decreases or fluctuations in the sodium levels in their blood, and these changes in sodium levels may be associated with seizures. NICHD-supported researchers analyzed data from 380 children treated with an EVD to assess whether low sodium levels, fluctuating sodium levels, or both were associated with seizures or death. The scientists found that after controlling for other factors, low sodium levels were not associated with an increased risk of seizures or death. However, greater fluctuations in sodium levels were associated with increased risk of death in the hospital. The study was not designed to determine if the sodium fluctuations contributed to the risk by themselves, or whether the sodium varied more because the patient's underlying condition was more severe. For this reason, additional studies are needed to determine how to manage the care of children with an EVD to ensure the best possible outcome. ([PMID 25137551](#)) [Nov 2014]

***A Genomic-based Approach for Defining Infants at Risk for Sepsis.*** NIGMS-supported researchers have conducted a study that validates the use of genome wide expression profiling for infants with early sepsis (less than 3 days after birth) or late sepsis (3 – 30 days after birth). Distinct patterns of gene expression were observed for early and late stage sepsis and were distinct from the gene expression patterns of uninfected infants. Unique to neonates, the uninfected state and host response to sepsis is significantly affected by timing relative to birth. Future therapeutic approaches have the potential to be made more effective by considering the timing of the infectious event based on postnatal age. ([PMID 26052715](#)) [Jun 2015]

***Mitochondrial Dysfunction in Pediatric Septic Shock: Peripheral Blood Mononuclear Cells.***

Researchers have studied how sepsis affects the body at the cellular level, but these studies have been conducted mostly in adults, and it is not clear whether septic shock affects children in the same way. Scientists funded by NICHD and NCATS studied 13 children with septic shock to better understand how their mitochondria, the components of cells that are responsible for producing energy, were functioning in a specific type of cell called peripheral blood mononuclear cells (PBMC). They found that consistent with adults, the PBMCs of pediatric septic shock patients had dysfunctional mitochondria, which contributed to organ failure. Understanding what occurs at the cellular level during sepsis has the potential to lead to the development of more effective treatments for both adults and children. ([PMID 25251517](#)) [Jan 2015]

***Mitochondrial Dysfunction in Pediatric Septic Shock: Bioenergetic Function.*** Researchers supported by NIGMS, NICHD, and NHLBI conducted a study that supports the concept of mitochondrial bioenergetic function being an important determinant of outcomes in pediatric sepsis. A series of bioinformatics approaches were used to compare differentially expressed nuclear-encoded mitochondrial genes in children admitted to pediatric intensive critical care units. The greatest degree of repression of mitochondrial gene expression was observed in children with the most severe disease/highest mortality. The nuclear genome may be an important mechanism that contributes to alterations in mitochondrial bioenergetic function and outcomes in pediatric sepsis. ([PMID 25410281](#)) [Nov 2014]

## SELECTED NEW AND EXPANDED RESEARCH EFFORTS FOR FY 2015 IN PEDIATRICS

### Selected New Pediatric Research Efforts for FY 2015

NIH ICs launched a range of new research programs and efforts related to pediatrics in FY 2015. Selected highlights of new initiatives are given below. Several programs are focused on understanding risk factors for complex conditions in children. However, the majority of the programs are concerned with developing and delivering evidence-based treatments.

#### Child Development and Aging

##### ***Adolescent Brain Cognitive Development (ABCD) Study:*** ([NIDA News Release](#), [NIAAA News Release](#))

In September 2015, NIH launched the Adolescent Brain Cognitive Development (ABCD) Study to assess the short- and long-term impact of substance use on brain development. The ABCD Study will recruit approximately 10,000 children at age 9-10, before they initiate substance use. Researchers will follow these children over the next decade to examine the effects of alcohol, tobacco, and other substances of abuse, alone and in combination, on brain structure and function. Studies will track mental health, substance use patterns, academic achievement, IQ, cognitive skills, and many other outcomes. The study will also allow researchers to examine how pre-existing differences in brain structure and function during adolescence may contribute to substance misuse. The longitudinal design of the study will allow scientists to draw more meaningful conclusions and connections, at the individual level, between key genetic and biological factors and behavioral, social, and environmental influences during adolescence. The ABCD Study was 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.

#### Environmental, Family, and Community Influences

The NIH has awarded nearly \$144 million in new grants to develop new tools and measures in order to more effectively investigate environmental exposures from the womb to later years in a child's life. ([NIH News Release](#))

***ECHO:*** Understanding environmental influences on children's health and development remains a priority at NIH. The new Environmental influences on Child Health Outcomes (ECHO) program will continue to address the important goals of the National Children's Study. The overarching goal of the ECHO program is to explore environmental influences on children's health and development, and the impact of environmental exposures on pediatric health over time. By harmonizing the information gathered from existing cohorts of study participants, ECHO will create a new, larger cohort that will greatly increase scientists' ability to answer critical public health questions. The ECHO program will allow researchers to test new tools for environmental and pediatric monitoring, maximize the use of existing resources such as collections of biological tissues collected during pregnancy and delivery, leverage available data sets by funding additional analyses, and develop statistical models to predict disease development. Applications are currently pending review. ([ECHO Website](#))



***Pediatric Research using Integrated Sensor Monitoring Systems (PRISMS)*** ([PRISMS Website](#)) was launched in 2015 to develop sensor-based, integrated health monitoring systems for measuring environmental, physiological, and behavioral factors in pediatric epidemiological studies of asthma, and eventually other chronic diseases. The following three arms of the PRISMS Program will be closely aligned to ensure functionality of the overall program:

- *Sensor Development Projects for Asthma.* Researchers will develop wearable and non-wearable sensors that can monitor pediatric environmental exposures, physiological signals, activity, and/or behavior in a natural environment. ([RFA-EB-15-002](#))
- *Informatics Platform Technologies for Asthma.* Researchers will develop informatics platforms that will enable data acquisition from environmental, physiological, and behavior sensors. ([RFA-EB-15-003](#))
- *Data and Software Coordination and Integration Center.* Researchers will develop a center to coordinate and integrate outputs from the Informatics Technology Platform Centers. ([RFA-EB-15-004](#))

***Children's Health Exposure Analysis Resource (CHEAR):*** ([CHEAR Website](#)) This NIEHS initiative will create 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. The CHEAR infrastructure, comprising \$49.5 million in grants, will have three units. A six-member National Exposure Assessment Laboratory Network will provide access to state-of-the-art infrastructure for analysis of biological samples and responses associated with those exposures. A Data Repository, Analysis, and Science Center will provide support for data collection, statistical analysis and interpretation, and the development of community-based data standards, as well as new technologies and metadata standards. Finally, a coordinating center will provide administrative management, including interface with the research community and an index of additional exposure analysis tools outside of CHEAR. ([RFA-ES-15-009](#), [RFA-ES-15-010](#), [RFA-ES-15-011](#))

***Validation of Pediatric Patient-Reported Outcomes in Chronic Diseases (PEPR) Consortium:*** ([NIAMS News Release](#)) The Validation of Pediatric Patient-Reported Outcomes in Chronic Diseases (PEPR) Consortium will allow scientists to capitalize on recent advances in the science of patient-reported outcomes (PROs) to improve pediatric health and well-being by capturing the voice and experience of children and their families living with a variety of chronic diseases and conditions. The goal of the PEPR Consortium is 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. The research will also help to improve understanding of the effects of environmental stressors on symptoms and quality of life in children with a variety of chronic diseases or conditions.

***The Human Placenta Project*** ([NICHD News Release](#)), supported by the NICHD, NIBIB, and the NIH OD, is designed to support the initial stages of development of next-generation placental imaging and assessment technologies and methods. The focus of this research is on identifying specific technology gaps and developing new technologies or new applications of current technologies to explore the effects of environmental factors on placental structure and function throughout pregnancy.

**High Priority Behavioral and Social Research Networks:** (U24, [RFA-AG-14-007](#)) In September 2014, NIA (in collaboration with the UK Research Councils) launched a cooperative research network to explore the potential for midlife reversibility of biobehavioral or psychological risk associated with early life disadvantage (including childhood poverty, exposure to violence and abuse, and poor early life nutrition). Goals of the network are to stimulate research that will test causal hypotheses about the role of early adversity in determining health disparities in later life, address challenges associated with assessing early adversity retrospectively, and explore the potential of harnessing neuroplasticity to reverse or compensate for adverse outcomes associated with early deprivation and exposure to stress.

**Community Oral Health:** NIDCR awarded 10 research grants in FY 2015 as part of a new initiative focused on eliminating inequalities in access to care and improving the oral health of children. Children from certain racial and ethnic groups or from families with low levels of education and income are far more likely than other children to develop oral diseases, including tooth decay. Research projects include using text messaging in community health centers as part of a multi-level intervention to reduce early childhood caries, examining the influence of small financial incentives on improving oral health behaviors, and analyzing the relationship between community water fluoridation and dental caries in children.

**Early-life Factors and Cancer Development Later in Life:** ([PAR-15-126](#), [PA-15-125](#), [PA-15-124](#)) Supported by NCI, NICHD, and NIEHS, this program is intended to stimulate research focused on the role of early-life factors in cancer development later in life. Markers that predict malignancy or pre-malignant conditions would allow assessment of early-life exposures with relevant outcomes without having to wait 50 years for cancer development. Ultimately, a better mechanistic understanding of how early-life events and exposures contribute to the etiology of cancer later in life will allow for the development of effective interventions during pregnancy or early-life that may have a profound impact on cancer prevention.

### Pediatric Cancer

**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 several new inhibitors with potential to treat pediatric cancer are being studied for this purpose.

**DNA Sequencing to Identify Children Whose Tumors Have a Genetic Abnormality for Which Either an Approved or Investigational Targeted Therapy Exists:** The Pediatric Molecular Analysis for Therapy Choice (Pediatric MATCH) trial, part of the Precision Medicine Initiative for Oncology, will provide a tremendous opportunity to test a range of molecularly targeted therapies in children with advanced cancers who have few other treatment options. With the genomic data captured in the trial, it will also produce an invaluable resource for studying the genetic basis of why some pediatric cancers progress or recur while others do not. As in the adult NCI-MATCH trial, DNA sequencing will be used to identify children whose tumors have a genetic abnormality for which either an approved or investigational targeted therapy exists. Pediatric MATCH, which will be led by the NCI-funded Children's Oncology Group, is under development and is expected to launch in late 2016. Through the COG, NCI is also supporting nationwide clinical trials introducing new immunotherapy agents into evaluation for children with cancer and clinical trials evaluating precision medicine concepts in children with newly diagnosed lymphomas and leukemias. ([NCI Website](#))

Through the Children's Oncology Group (COG) and the **Pediatric Brain Tumor Consortium (PBTC)**, NCI is supporting nationwide clinical trials introducing new immunotherapy agents into evaluation for children with cancer. Ongoing clinical trials are evaluating blinatumomab for children with ALL at first

relapse, brentuximab vedotin for Hodgkin lymphoma and anaplastic large cell lymphoma, and nivolumab for children with relapsed solid tumors and lymphomas, pembrolizumab for children with relapsed high-grade gliomas, and dinutuximab and denosumab for osteosarcoma.

NCI-supported clinical trials through COG and PBTC are also evaluating precision medicine concepts, including clinical trials studying crizotinib for anaplastic large cell lymphoma (ALK-positive) sorafenib for FLT3-ITD AML, and selumetinib for pediatric low-grade gliomas (BRAF or NF1 mutated). On an ongoing basis, COG and PBTC researchers are evaluating targeted agents for their relevance for specific childhood cancers, and when appropriate are developing clinical trials to pursue these opportunities.

***The Common Fund's Gabriella Miller Kids First Pediatric Research Program*** ([Kids First Website](#)) is developing a data resource for the pediatric research community. The data resource will consist of well-curated clinical and genetic sequence data from childhood cancers and structural birth defects cohorts that researchers will be able to mine for insights into the complex role of genetics in these pediatric diseases. This is then expected to stimulate research toward more effective preventions and therapies for diverse conditions. In FY 2015 the Kids First program selected seven cohorts of children with childhood cancer or structural birth defects for whole genome sequencing. ([Kids First Funded Research](#)) Additional cohorts will be sequenced in FY 2016 and FY2017 and sequence and clinical data will be made available to the research community through the data resource.

#### Childhood Diseases, Allergies, and Immunity

***Primary Prevention of Asthma:*** In 2015, NHLBI issued two RFAs to enhance work on primary prevention of lung diseases including asthma ([RFA-HL-15-024](#), [RFA-HL-15-025](#)). NHLBI also released a Topic of Special Interest (HL-141; [Link to HL-141 Description](#)) to encourage the pulmonary clinical research community to submit appropriate, investigator-initiated, primary prevention trials.

***Natural History of Asthma with Longitudinal Environmental Sampling study (NHALES):*** In 2015, the NIEHS Clinical Research Unit began recruiting patients for NHALES. This study will help scientists understand how the environment affects asthma symptoms. In particular, NIEHS scientists will examine how bacteria living in and on humans and in their homes, known collectively as the microbiome, may be associated with asthma activity. ([NHALES Website](#))

***Cure Glomerulonephropathy (CureGN)*** is a multicenter five-year cohort study of 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. Enrollment for the CureGN study began on December 5th, 2014. ([CureGN Website](#))

#### Technology and Tools

***Bioengineering Research Partnership (BRP): Non- or Minimally-Invasive Methods to Measure Biochemical Substances during Neonatal and Perinatal Patient Care and Research:*** ([PAR-15-285](#), [RFA-HD-16-028](#)) This program will help bioengineering and biomedical scientists to collaborate in developing non- or minimally-invasive methods for measuring biochemical substances in connection with the care of perinatal patient populations. Lab-on-a-chip methods for rapid diagnostic or prognostic purposes are also encouraged.

***The Global Rare Diseases Patient Registry Data Repository*** is being developed as a web-based resource that aggregates, secures, and stores de-identified patient information from various rare disease registries.

The ultimate goal of the GRDR program is to provide a “one-stop shop” for rare disease data from registries across the world. Through the program, NCATS will give patients, health care professionals and researchers access to information about multiple rare diseases through one central resource. ([GRDR Website](#))

### **Selected Expanded Pediatric Research Efforts for FY 2015**

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

***NHGRI’s Electronic Medical Records and Genomics (eMERGE) Network*** ([eMERGE Network Website](#)) entered Phase III this year and continues to fund pediatric research. eMERGE investigators are linking existing biorepository samples from children to electronic medical records (EMRs) in order to explore variants associated with obesity, epilepsy, intellectual disability, and autism.

***The Autism Biomarkers Consortium for Clinical Trials (ABC-CT)***: A large, multisite project will receive a total of \$28 million over the next four years to evaluate 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. The effort is the latest addition to the prestigious list of projects supported by the NIH Biomarkers Consortium, a large public-private partnership that aims to accelerate biomedical research progress. Yale University investigators are overseeing the project ([U19MH108206](#)), with research sites at Duke University, the University of California, Los Angeles, the University of Washington, and Boston Children’s Hospital. Financial and in-kind support for the ABC-CT study is coordinated through the Foundation for the NIH. Funding is provided by NIMH, NINDS, NICHD, and the Simons Foundation Autism Research Initiative. All data generated in the project will be made available for other researchers to view and analyze through the NIH-funded [National Database for Autism Research](#). Blood samples from subjects and their parents will be collected for use in future genetic studies, and made available through the [NIMH Repository and Genomics Resource](#).

***Services Research for Autism Spectrum Disorders across the Lifespan (ServASD)***: NIMH awarded 12 grants in FY 2015 via the ServASD initiative to develop and test the effectiveness of systems-level interventions to improve functional and health outcomes of individuals with ASD during early childhood, the transition from youth to adulthood, and adulthood. In FY 2016, NIMH issued two new Funding Opportunity Announcements (FOAs) stemming from this initiative, targeting pilot research for services for transition-age youth ([RFA-MH-17-200](#)), and pilot studies of services strategies for adults with ASD ([RFA-MH-17-205](#)).

***Infant Brain and Behavioral Signatures of Later Emerging Risk for Mental Illness***: Technologies recently developed through the [Human Connectome Project](#) allow scientists to visualize how different brain regions connect to each other, providing unique insight into brain organization. NIMH-funded researchers are using these cutting-edge technologies to characterize the rapid and intensive brain development that occurs between 3 and 15 months of age ([R01MH104324](#)). The project will significantly advance our understanding of early brain development and behavioral associations in healthy infants, providing a foundation for understanding when and how brain development can go awry in neurodevelopmental disorders, such as autism.

***The NICHD's National Child and Maternal Health Education Program*** has launched a new effort to help providers and parents implement best practices in identifying and responding to postpartum depression and anxiety. MCHPEP continues to support its initiative, involving a variety of public-private partners, to prevent preterm birth, including elective preterm delivery. ([NICHD Spotlight](#)) The program includes a continuing medical education/continuing education (CME/CE) program on Medscape. The program aims to increase health care providers' knowledge about late preterm birth and inducing delivery for non-medical reasons before 39 weeks in the womb. ([NICHD Spotlight on CME Program](#))

***The Pediatric Eye Disease Investigator Group***, an NEI clinical trial network ([NCT02390531](#)), launched a new clinical trial in FY 15 to evaluate the anti-VEGF agent Avastin in infants with severe retinopathy of prematurity.

### ***Funding Opportunities in FY 2015 for Pediatric Research***

In FY 2015, the NIH issued 58 Funding Opportunity Announcements (FOAs) that specifically called for applications related to pediatric research. These FOAs are listed in Table 3 of the Appendix to this report. Much of the NIH's pediatric research portfolio comes from investigator-initiated research, and a large number of funded grants are associated with funding opportunities that do not have a pediatric focus. However, the FOAs listed in Table 3 provide information about the range of areas that NIH ICs have taken steps to address in pediatric research. In FY 2015, the NIH issued FOAs in research to advance vaccine safety, community-based participatory research, pediatric health disparities, health of sexual and gender minority (SGM) populations, end-of-life and palliative needs of adolescents and young adults, diabetes, underage drinking, substance abuse, asthma and pediatric drug formulations, 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 2015, approximately 113 NIH-supported center or network programs supported pediatric research, and many other additional programs support pediatric research outside of center/network grant mechanisms. Many, but not all, pediatric research programs were focused exclusively on child health. For example, the NICHD's Collaborative Pediatric Critical Care Research Network links pediatric intensive care units at hospitals across the country to conduct clinical studies to improve research practice in pediatric critical care. The center/network programs supporting pediatric research at the NIH include some that are targeted to a specific disease or condition—the Autism Centers of Excellence, for example—and others, like the pediatric component of the Clinical and Translational Science Awards, that are not specific to any one condition.

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 and Aging***

***Population Survey Data:*** Population surveys provide critical information for identifying risk factors and health disparities across a wide variety of conditions. The Fragile Families survey ([R01HD036916](#)), the National Longitudinal Survey of Youth ([AHD14002001](#)), the National Survey of Family Growth ([AHD12020001](#)), the National Longitudinal Study of Adolescent to Adult Health ([P01HD031921](#)), and the NEXT Generation Study ([275201200001I-0-27500010-1](#)) are among the population studies supported by the NICHD that continue to contribute to the scientific literature on pediatric research.

***National Longitudinal Study of Adolescent to Adult Health (Add Health):*** Supported by NICHD with other federal agencies, Add Health is a large, representative, longitudinal cohort study that has followed U.S. adolescents from 1994-1995, as they age into adulthood, to provide unique opportunities to understand how social environments and behaviors in adolescence are linked to health and achievement outcomes in young adults. The study combines longitudinal survey data on correspondents' social, economic, psychological and physical well-being with contextual data on family, neighborhood, community, school, friendships, peer groups, and romantic relationships. The most recent wave of interviews, when respondents were 33-34 years old, expanded the collection of biological data in Add Health to understand the social, behavioral, and biological linkages in health trajectories as the cohort ages through adulthood. The project makes its data available to researchers and the public. ([AddHealth Announcement](#))

***Leveraging a Recovery Act Resource to Accelerate Research on Neurodevelopment:*** ([RFA-MH-15-400](#))

In 2009, NIMH funded two large grants to characterize and collect data on cognitive function, emotion processing, stress reactivity, and other domains that are vulnerable to neurodevelopmental aberration from a large, representative cohort of already genotyped youth, and to build a resource of data and biomaterials for future studies. The Philadelphia Neurodevelopmental Cohort (PNC), the result of this collaborative effort, has collected data on approximately 10,000 youth (ages 8-21), including comprehensive neuroimaging on over 1,000 youth. In FY 2015, NIMH is funding efforts to develop techniques that use PNC data, either alone or in conjunction with other existing data, to advance our understanding of the multi-directional influences among genetics, brain maturation, neurocognitive function, and psychiatric symptoms across development. The initiative will stimulate broad use of the data resource, accelerate research on neurodevelopment and trajectories of risk for mental illness, advance methods for data

integration, enhance diversity of analytic approaches, foster collaborations, and support early stage investigators.

***Learning and Learning Disabilities:*** The NICHD supports research related to reading, writing, mathematics, and language learning and learning disabilities. Key areas for research include:

- Basic biobehavioral research designed to clarify the mechanisms underlying cognitive development and learning in typically developing children. We must understand how typical, healthy development and learning evolve, in order to fully comprehend what is developing differently, or not developing at all, when a child experiences a learning disability. Studies of specific interest include structural and functional neuroimaging of normal brain development from birth through early adulthood, gene and environment interactions influencing variations in brain development and learning, and neuroendocrine and molecular genetic mechanisms underlying brain-behavior associations throughout development. ([NICHD Child Development and Behavior Branch \(CDBB\) Cognitive Development, Behavioral Neuroscience, and Psychobiology Program](#))
- Improving understanding of both normal and atypical development of reading and written language skills, from preschool into adulthood; ([NICHD CDBB Reading, Writing, and Related Learning Disabilities Program](#))
- Determining the experiences that children need from birth to age 8 that prepare them to learn, read, and succeed in school; ([NICHD CDBB Early Learning and School Readiness Program](#))
- Understanding language development and learning, including:
  - Language development and psycholinguistics, from infancy through early adulthood;
  - Bilingualism and/or second-language acquisition; and
  - Reading in bilingual and/or English-language learning (ELL) children and youth. ([NICHD CDBB Language, Bilingualism, and Biliteracy Program](#))
- Basic and intervention research related to mathematical thinking and problem solving as well as to scientific reasoning, learning, and discovery from infancy into early adulthood. Studies examine factors that influence atypical development in mathematics and science learning, cognition, and reasoning in both humans and animal models. Factors of interest include genetic and neurobiological substrates, and cognitive, linguistic, sociocultural, and instructional influences. ([NICHD CDBB Mathematics and Science Cognition, Reasoning, and Learning: Development and Disorders Program](#))

The NICHD supports the ***Learning Disabilities Research Centers (LDRC) Consortium***, a program to develop knowledge on the causes, origins, and developmental course of learning disabilities. The LDRC Consortium addresses learning disabilities that affect reading and writing, including basic reading skills, reading fluency, reading comprehension, and written expression. Complementing the LDRC Consortium, the ***Learning Disabilities Innovation Hubs*** focus on understudied research topics and on projects that study people diagnosed with and at risk for learning disabilities. Projects also include mentorship of researchers who are in the early stages of their careers, with a particular focus on enhancing involvement of underrepresented groups in scientific careers. ([NICHD LDRC Consortium](#)); ([NICHD Learning Disabilities Innovation Hubs](#))

***Attention Deficit-Hyperactivity Disorder (ADHD) Heterogeneity, Mechanisms, and Risk Profile:*** The diversity of biological and behavioral factors at play in the current diagnostic framework for ADHD has long hampered traditional symptom-based classification methods. NIMH-funded researchers are addressing this problem through a longitudinal research project using dimensions of temperament and a graphical analytical measure called community detection to identify subgroups within a sample of over 430 children with and without ADHD ([R37MH059105](#), [R01MH086654](#)). The researchers have identified three novel subtypes of ADHD using this approach. Importantly, these novel subtypes were correlated

with peripheral physiological measures, central nervous system measures, and clinical outcomes assessed a year later. Such biologically based subtyping methods can better predict clinical course than symptom-based classifications, are stable over time, and are more informative regarding neurobiological mechanisms of pathology. This approach is consistent with the NIMH [Research Domain Criteria](#) (RDoC) project and demonstrates how RDoC may inform clinical practices for diagnosing and treating mental illness in the future. Related research efforts will incorporate genetic variation in the subtypes ([R01MH099064](#)). ([PMID 25006969](#)) [Sep 2014]

### **Environmental, Family, and Community Influences**

***NIEHS/EPA Centers for Children’s Environmental Health and Disease Prevention Research:*** ([NIEHS Centers](#)) Since 1998, the NIEHS/EPA 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. NIEHS and EPA have developed this cooperative program with multiple opportunities to enhance research focused on advancing scientific understanding of key determinants of children’s environmental health to meet each Agency’s mission by filling identified research gaps to promote healthy environments for children such as assessment of environmental exposures to flame retardants and other environmental chemicals in autism spectrum disorder, tobacco smoke exposure in ADHD and neurobehavioral dysfunction, and phthalates and high-fat diet in neurological development.

***Centers of Excellence on Environmental Health Disparities:*** NIEHS, NIMHD, and the US EPA fund five Centers that 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. One of the centers is examining the determinants of childhood and maternal obesity among Hispanic children and mothers, a population in California who have the greatest cumulative burden of harmful environmental exposures as well as elevated rates of obesity.

***Transgenerational Inheritance Following Environmental Exposure:*** This NIEHS-supported program was initiated to study, in mammals, the phenomenon of adverse outcomes in later generations removed from the original environmental insult. Some of the funded projects underway are looking at transgenerational inheritance of prenatal exposure to obesogenic chemicals; epigenetic effects of polychlorinated biphenyls; effects of phthalate exposure; and transgenerational susceptibility to asthma following air pollution exposure in earlier generations.

***NIEHS Intramural Research:*** NIEHS’s Developmental Neurobiology Group studies how genetic and environmental perturbations during development alter the fates and functions of specific sets of neurons and how these alterations lead to neurological disorders. Unraveling the genetic pathways that control final noradrenergic subtype identity is critical to the group’s understanding of related developmental and neurodegenerative diseases including autism, attention-deficit/hyperactivity disorder, depression and other cognitive disorders. The Synaptic & Developmental Plasticity Group conducts research aimed at bringing a better understanding of how environmental factors play a role in forming the circuitry of the brain so that the associated problems of brain disease caused by toxicant exposure can then begin to be addressed.

***Psychosocial Stressors, Air Pollution and Childhood Respiratory Health in Los Angeles Family and Neighborhood Survey (LAFANS):*** This NIEHS-supported study will use self-reported psychosocial stressors from children and their primary caregivers, many of whom are from a lower socioeconomic status, in data collected from LAFANS to evaluate the differential vulnerability to air pollution observed

by socioeconomic status. The goal of this work is to identify bio-social-behavioral risk factors that may contribute to childhood asthma ([Link to NIEHS Description](#)).

***Traffic-Related Air Pollutants and Respiratory Microbiome in Children:*** NIEHS is funding a project evaluating the impact of traffic-related air pollutants (TRAP) and the respiratory microbiome in children. This research aims to: (1) characterize bacterial community profiles of the lower respiratory tract microbiome in children ages 12-15; and (2) determine the association between childhood exposure to TRAP and the microflora in the lower respiratory tract of these children. A multidisciplinary team of researchers is involved. ([R21ES024807](#))

### **Pregnancy and Perinatology**

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

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

***The Norwegian Mother & Child Cohort (MoBa):*** MoBa is a prospective study of approximately 100,000 pregnant women enrolled at about week 18 of pregnancy with the goal of studying in utero and early life influences on childhood health through young adulthood. Women were followed through pregnancy with questionnaires and collection of biologic samples. A father's questionnaire and blood sample were also collected during pregnancy. Health outcomes include a broad range of rare and common health outcomes in children. In this pregnancy cohort, offspring are followed through childhood. The cohort is primarily funded by the Norwegian government, with additional support from NIEHS and others. NIEHS has funded the administration of the seven year questionnaire which includes outcome and exposure questions relevant to asthma and allergies (among other health conditions). Other NIEHS projects are looking at risk factors for cerebral palsy, neurodevelopmental outcomes, and childhood obesity. ([MoBa Website](#))

***Maternal-Fetal Medicines Unit (MFMU) Network:*** The MFMU Network is designed to conduct rigorous clinical trials in maternal-fetal medicine and obstetrics, particularly with respect to the continuing problem of preterm birth. The aims of the Network are to reduce maternal, fetal, and infant morbidity related to preterm birth, fetal growth abnormalities, and maternal complications, and to provide

the rationale for evidence-based, cost-effective obstetric practice. The network is primarily funded by the NICHD, with cofunding from other ICs for specific projects. Current projects include an observational study of hepatitis C in pregnancy, a clinical trial to determine whether administering hyperimmune globulin for congenital cytomegalovirus (CMV) can reduce mother-to-child transmission of CMV infection, and a study to determine whether thyroxine treatment of women with subclinical hypothyroidism or hypothyroxinemia diagnosed during the first half of pregnancy is associated with an intellectual improvement in their children at age five years. ([NICHD MFMU Network](#))

***Using Innovative Communication Technology to Improve Pre-Conception Health of Young African American Women:*** This NIMHD-funded study is testing an intervention to improve pre-conception health for African American women aged 18-25 through an internet-based health communication system that provides personalized health information through interaction with an animated avatar. The intervention includes sharing of personal stories from other women who have received the intervention, using an automated indexing algorithm that selects the stories most relevant to the woman's situation and stages of readiness to change her health behavior.

***Prenatal Alcohol and SIDS and Stillbirth (PASS) Network:*** The PASS Network is funded by the NICHD, the NIAAA, and the NIDCD. The Network is designed to conduct community-linked studies to investigate the role of prenatal exposure to alcohol in SIDS and adverse pregnancy outcomes, such as stillbirth and fetal alcohol spectrum disorders (FASDs). The Safe Passage Study ([NICHD PASS Network](#)) will enroll approximately 12,000 pregnant women from the United States and South Africa and will follow the development of their babies through pregnancy and the infants' first year of life. The long-term goals of the Safe Passage Study are to reduce fetal and infant mortality and improve child health in communities at high risk of prenatal maternal consumption of alcohol. Another substudy within the PASS Network is designed to address hearing loss in Native American populations. This study includes auditory tests of brainstem function, including auditory brainstem response (ABR) and otoacoustic emissions (OAE). The study will help develop better prevention and intervention strategies that can enhance the future health or lives of high-risk newborns in American Indian populations and increase knowledge about the importance of hearing screening and follow-through for underrepresented groups to ensure improved communication, occupational, and financial outcomes for these children. The PASS network has two primary clinical sites in the Northern Plains of North America (in North Dakota and South Dakota) and in the Western Cape of South Africa. The PASS Research Network study has just completed final enrollment and is now engaged in the process of data analysis and preparation of manuscripts to report findings.

***Safe to Sleep*** is a 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. ([NICHD Safe to Sleep](#))

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



flow. The NRN is funded primarily by the NICHD, with cofunding from other ICs for specific projects. ([NICHD Neonatal Research Network](#))

***The Infant Feeding and Early Development (IFED):*** IFED is a prospective birth cohort (with a few women sampled in the 3rd trimester of pregnancy). The study enrolled 283 newborns in the Philadelphia, PA area who were exclusively fed cow milk formula (n = 111), soy formula (n = 102) or breast milk (n = 70). Since soy is a rich source of plant based estrogen-like compounds, this study was conducted with the aims of i) characterizing early estrogen dependent development in the infant, and ii) studying the effects exclusive soy feeding (i.e., high dose exposure to a suspected endocrine disruptor) on estrogen-dependent outcomes. Specific health outcomes include sex hormone metabolism and breast and internal and external genital development in infancy.

***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](#)) This trial is supported by NINDS with supplemental funds by NIDDK to cover the cost of collecting renal function data and samples. ([U01NS077953](#))

***Transfusion of Prematures (TOP) Study:*** Though data are limited, it has been estimated that very low birth weight infants (<1500 g) in the U.S receive more than 250,000 total red cell transfusions/year. Despite the widespread use of transfusion in this population, there is no consensus regarding the optimal hemoglobin level at which such infants should be transfused. (Over transfusion could potentially endanger the neonate by impairing microvascular blood flow and tissue perfusion.) The NHLBI-funded Transfusion of Prematures (TOP) study is a definitive randomized clinical trial designed to resolve this issue. This trial, being performed by the NICHD Neonatal Research Network, is enrolling 1,824 extremely low birth weight (ELBW) infants who will be randomized to receive red blood cells using either a high hemoglobin (liberal) or lower hemoglobin (restrictive) threshold. The trial will compare the two groups for the incidence death or significant neurodevelopmental impairment in survivors at 18-22 months of corrected age.

***Natural History Studies:*** Often a comprehensive understanding of the natural history of many disorders relevant to newborn screening is unavailable. This gap in knowledge is a barrier to developing the most effective treatments for children with disorders identified by newborn screening, particularly as they age. Plus, many disorders are genetically and clinically variable, making it even more difficult to identify appropriate individual interventions and the proper ages at which to begin treatment. To address these concerns, NICHD is supporting two natural history studies related to newborn screening. The first is a multi-site project to define the natural history of inborn errors of metabolism. The second study follows children identified in a newborn screening pilot for spinal muscular atrophy.

***MOMs2 Study:*** The 2011 MOMs study (Management of Myelomeningocele) determined that fetal surgery greatly reduced complications of spina bifida. Efforts are underway involving NICHD, medical centers and professional societies to translate these findings into improved practice. NICHD, with additional support from NINDS, recently began the follow-up to the MOMs study, which is known as MOMs 2. This study is a follow-up of the MOMs children at school age to determine whether children who received the surgery before birth have better health and mental outcomes and live more independently and function more safely and appropriately in daily life than those who received the surgery after birth.

***The Hunter Kelly Newborn Screening Research Program*** was originally established as a provision under The Newborn Screening Saves Lives Act of 2007. Through the Program, NICHD 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.

### **Structural Abnormalities and Birth Defects**

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

***Genetic Susceptibility and Variability of Human Structural Brain Defects:*** (R01, [PA-14-056](#)): This program, supported by NICHD, NIAAA, NIDCR, NIDDK, NIEHS, and the NIH Office of Dietary Supplements, supports applications using animal models and translational/clinical approaches that take advantage of advances in genetics, biochemistry, molecular, and developmental biology to identify the specific genetic, epigenetic, environmental, or gene/environment interactions associated with the susceptibility to and variability of structural birth defects in human populations. Funded applicants will join the NICHD Birth Defects Working Group and participate in annual meetings that provide a forum to discuss research progress, exchange ideas, share resources, and foster collaborations supporting the goals of the NICHD Birth Defects Initiative.

***NICHD's Developmental Biology and Structural Variation Branch*** ([NICHD DBSVB](#)) supports basic, clinical, and translational research on normal and abnormal development relating to the causes and prevention of structural birth defects, as well as research training in relevant academic and medical areas. Among the Branch's high-priority research areas is basic research, primarily using a variety of animal models, on elucidating the biochemical, molecular biologic, genetic, and cellular mechanisms of embryonic development:

- ***Developmental Mechanisms of Human Structural Birth Defects:*** (P01, [RFA-HD-16-009](#)) These innovative, multidisciplinary, interactive, and synergistic program projects integrate basic, translational, and clinical approaches to understanding the developmental biology and genetic basis of significant congenital human malformations. At least one project will use basic research in an animal model system and at least one project will be clinical or translational in nature. The component research projects will share a common central theme, focus, or objective on a specific major developmental defect or malformation that is genotypically, mechanistically, biologically, or phenotypically analogous or homologous in both animal models and humans. [Reissue from original RFA in 2010, posted 2015, expired 2015]

- ***Systems Developmental Biology for Understanding Embryonic Development and the Ontogeny of Structural Birth Defects:*** (R01, [PAR-15-020](#)) This funding opportunity announcement (FOA) focuses on understanding how biological components work together, expanding molecular-level knowledge of genes, proteins, biochemical, biophysical and cellular processes into networks of interacting components that result in embryonic development. [Posted 2014, Expires 2016]

### **Pediatric Cancer**

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 ([PBTC Website](#)).
- The ***Childhood Cancer Survivor Study (CCSS)*** addresses the long-term effects of cancer and cancer therapy in approximately 35,000 survivors of childhood cancer diagnosed between 1970 and 1999 and approximately 8,000 siblings of survivors ([CCSS Website](#)).
- The ***Pediatric Preclinical Testing Consortium (PPTC)***, which identifies new, more effective agents for treating childhood cancers ([PPTC Website](#)).
- The ***Pediatric Oncology Branch (POB)*** in NCI's Center for Cancer Research, which conducts high-risk high-impact basic, translational and clinical studies ([POB Website](#)).
- The ***TARGET Initiative***, a public-private partnership harnessing genomics technology to identify molecular changes that drive childhood cancers ([TARGET Website](#)).
- A comprehensive program of ***Clinical Studies of Familial Cancer Syndromes***, several of which include children ([Hereditary Cancer Syndromes Website](#)).
- 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 ([COG Website](#)). 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. NCI is supporting a trial for children with relapsed low-grade glioma through the PBTC. This is a phase 2 clinical trial of an agent (selumetinib) that targets the pathway that is activated by the gene mutations that define this disease ([NCT01089101](#)).
- 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.

## Neurological Disorders

NINDS supports research related to pediatric critical care for acute neurological conditions, such as traumatic brain injury (TBI), pediatric stroke, and epilepsy, including status epilepticus. This research includes efforts to develop new and noninvasive procedures for monitoring brain activity and function in critical care settings that will lead to improvements in care delivery and in diagnosing and predicting adverse neurological outcomes. NINDS also supports clinical trials to assess the effectiveness or comparative effectiveness of treatments for critical neurological conditions affecting children. For example:

- ***The Approaches and Decisions in Acute Pediatric TBI Trial (ADAPT)*** is a five-year observational study to evaluate key aspects of pediatric TBI care for which evidence is lacking and practices vary across centers ([ADAPT Website](#)). This is an example of how NINDS-funded studies aim to improve outcomes for pediatric TBI by strengthening the evidence base for best treatment practices.
- The ***Established Status Epilepticus Treatment Trial (ESETT)*** will assess which of three antiseizure drugs is the most effective in terminating prolonged life-threatening seizures called status epilepticus in children and adults who fail to respond to first line benzodiazepine treatment. ESETT is being conducted within the Neurological Emergencies Treatment Trials (NETT) Network, which was established to conduct large, simple trials of rapid interventions for acute injuries and illnesses of the nervous system.

***Epilepsy Cohort Studies:*** Epilepsy is one of the most common neurological disorders affecting women of childbearing age, and poor pregnancy outcomes are more common in women with epilepsy and their children.

- The ***Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD)*** study, supported by the NINDS and the NICHD, follows over 300 women with epilepsy recruited during pregnancy to determine the effects of common epilepsy drugs (alone or in combination) on long-term neurodevelopment in children, as well as on maternal outcomes. Results from the initial funding period of this project—associating valproate exposure with adverse cognitive and other outcomes in children—are already informing clinical practice for managing epilepsy in women of childbearing age to optimize outcomes for both mother and child ([U01NS038455](#)).
- ***FEBSTAT:*** A longitudinal cohort study to clarify the relationship between prolonged febrile seizures (Febrile Status Epilepticus) in childhood and the development of chronic temporal lobe epilepsy and neuropsychological deficits

***Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (MDCRCs):*** Co-funded by the NICHD, NINDS, NIAMS, and NHLBI, the Paul Wellstone Muscular Dystrophy Research Centers are designed to foster the translation of new scientific findings and technological developments into novel treatments for muscular dystrophies (MDs). The Centers promote basic, translational, and clinical research and provide important resources that can be used by the national muscle biology and neuromuscular research communities. Each Center serves as a focal point for research collaborations in the field and provides training and advice about MDs for basic and clinical researchers. The Centers also engage patients and patient advocates in educational programs. Centers include one or more scientific research resource cores that support the specific projects and serve as a resource for the international research community. ([MDCRC Website](#))

***Updated Muscular Dystrophy Coordinating Committee's Action Plan Released:*** The Muscular Dystrophy Coordinating Committee's (MDCC) 2015 Action Plan for the Muscular Dystrophies, like the 2005 plan before it, outlines priority areas for improving treatments and reducing the personal and societal impacts of all types of muscular dystrophies, including childhood onset forms such as Duchenne.

It reflects the deliberations of basic, translational, and clinical researchers who were nominated by the federal and public members of the MDCC; feedback from patient advocacy groups and people affected by the muscular dystrophies; and participation by the federal agencies represented on the MDCC. Because the plan includes recommendations for the entire muscular dystrophy community, most objectives are relevant to multiple forms of muscular dystrophy. Communities with targeted interests are invited to use the MDCC 2015 Action Plan as a starting point for developing or updating their own strategic plans. ([MDCC Website](#))

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

### ***Intellectual and Developmental Disabilities***

***Predicting Risk and Outcomes of Cerebral Palsy (CP):*** This NINDS-funded study is prospectively following over 900 ELGANS from birth to age nine to identify early blood or placental biomarkers of neurodevelopmental disorders, including CP ([ELGAN Study Website](#)). Another study is using high-speed computer simulations to model the effects of perinatal injury on the longer term development and function of motor circuits in the brain and spinal cord, to aid in understanding and predicting the progression of motor deficits in CP and other disorders. In addition, scientists are taking advantage of data from the *NICHD Neonatal Research Network* to identify fetal genetic variation associated with higher risk of PTB-related outcomes, including CP, and to identify cytokines that explain these associations. ([R03HD079716](#)).

***Neuroprotective Interventions and Therapy Development for Cerebral Palsy (CP):*** NICHD is currently supporting a randomized control trial to determine if intraventricular hemorrhage, a major factor often leading to CP, can be prevented or ameliorated by delayed cord clamping, alone or in combination with one approved medical therapy (prophylactic indomethacin). ([R01HD070792](#)). Through NICHD's National Center for Medical Rehabilitation Research (NCMRR), NICHD supports research on therapies and rehabilitative approaches for CP. These efforts include using computer simulations to restore natural walking patterns in patients; characterizing posture and muscle movement of children and adults with CP, and identifying changes that take place as a child ages and develops; and research to identify predictors of successful therapies to improve hand movement and functioning, among others. ([R21HD077186](#); [R01HD069769](#); [R01HD076436](#)) NICHD is currently supporting a randomized control trial on constraint-induced movement therapy for infants with unilateral or asymmetrical CP, to determine the impact of 3 highly promising new therapies on neuromotor outcomes and brain development ([R01HD074574](#)). Another study is underway to determine the impact of an intense series of physiotherapies administered to children between the ages of 12-36 months ([R01HD079498](#)). These therapies have the potential to reprogram the brain by recruiting non-damaged neurons to compensate for damaged neurons. The NIH Clinical Center's Functional & Applied Biomechanics Section also conducts research on rehabilitative therapies and orthotic devices for people with CP. ([Clinical Center Functional and Applied Biomechanics Website](#)) NINDS and NICHD held a workshop, "State-of-the-Science and Treatment Decisions in Cerebral Palsy," on November 12-13, 2014. The goal of the workshop was to identify gaps and opportunities for research to inform the optimal management of cerebral palsy, given that evidence-based practice guidelines are not yet available and that tremendous variation exists in the types of interventions



prescribed and how they are administered. A publication of the workshop's proceedings was submitted for publication. NINDS and NICHD held a second, complementary workshop on March 24-25, 2016 focused on updating the state of the basic and translational cerebral palsy research and the evaluation of gaps and opportunities in these areas. A summary of the second workshop is in preparation. ([2014 Workshop Website](#), [2016 Workshop Website](#))

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

***Autism Centers of Excellence (ACEs):*** This trans-NIH initiative supports large-scale multidisciplinary studies on autism spectrum disorders (ASDs), with the goal of determining the disorders' causes and 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. This research was supported by NICHD, NIMH, NIDCD, NINDS, and NIEHS. ([ACE Website](#)) NIH created the ACE Program in 2007 with a series of five-year awards to launch an intense and coordinated research program into the causes of ASD and to find new treatments. The second iteration of the ACE program, launched in FY 12, comprises (a) three centers focused on possible causes of ASD, risk and resilience in ASD, and children with ASD who have limited speech and communication; and, (b) eight networks focusing on causes, preventive interventions, and improved treatment, as well as ASD among females, genetic variants associated with ASD among African Americans, and how genetic and environmental factors are associated with the development of ASD. For example:

- NINDS and NICHD support an ACE network to identify early biomarkers of ASD in infants with tuberous sclerosis, a rare genetic disease that causes tumors in the brain and other vital organs and that confers a high risk for ASD. Using advanced imaging technologies, the ACE researchers will track brain development in infants diagnosed with tuberous sclerosis complex, to gain insights into how ASD arises in this disorder and factors related to increased risk.
- NIMH supports an ACE network focused on understanding how genetics, brain function, and behavior impact girls with autism. The study will follow affected girls from childhood through adolescence. Data from the ACEs, along with all new NIH-funded ASD research involving human subjects will be submitted to the NIH National Database for Autism Research. NIH looks to the Interagency Autism Coordinating Committee (IACC) Strategic Plan for ASD Research developed with input from federal agencies and community stakeholders, as a guide for all research efforts on ASD. The IACC was reauthorized by the Autism Collaboration, Accountability, Research, Education, and Support Act of 2014 (or Autism Cares Act of 2014 - Public Law 113-157), which reauthorizes the committee to continue until September 30, 2019.

***National Database for Autism Research (NDAR):*** ([NDAR Website](#)) Most public and private funders of ASD research have made data sharing with the NDAR an integral part of funding new research projects, which will in turn make future data available to other researchers. The Autism Genetic Research Exchange, the Autism Tissue Program, the Interactive Autism Network, and the Simons Foundation Autism Research Initiative are now linked with NDAR. Collectively, this means that data from over

100,000 consenting de-identified research participants are available for secondary analysis by other qualified researchers. Data sharing requires a global universal identifier to track participants in different studies, and currently more than 100,000 research participants have been registered with such an identifier. 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. At NIH, more than 80 percent of newly awarded human-subject grants related to ASD are or will be contributing data to NDAR. Recent work has focused on establishing data analysis pipelines for certain types of data (imaging and genomics) that are available in NDAR. These pipelines are expected to help the research community discover correlations among the data available in NDAR.

***NIH Intramural Research Program on Autism:*** Continuing to accelerate the development and testing of innovative treatments for ASD, in addition to exploring how ASD symptoms manifest in diverse cohorts. Longitudinal data from a large natural history study are now providing insights with respect to brain development and immunological involvement in ASD. Researchers are conducting studies of specific symptoms (e.g., gastrointestinal problems) and specific genetic disorders related to ASD. The program has also continued to focus on treatment targets, particularly with respect to recently identified sleep pattern abnormalities, through a randomized controlled study of donepezil.

***Fragile X Syndrome Research Center (FXSRC) Program:*** NICHD, NINDS, and NIMH fund the FXSRC Program to support 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 ([FXSRC Website](#))

***Down Syndrome Registry:*** The CDC estimates that there are about 250,000 people living with Down syndrome in the United States. The NIH Down Syndrome Working Group has partnered with public and private organizations to create a centralized, secure national resource, DS-Connect™, for storing and sharing health information about Down syndrome. The registry allows people with Down syndrome and their family members, researchers, and parent and support groups to share information and health history in a safe, confidential, online database. Users can create and edit their customizable online profiles, share their profiles with Down syndrome investigators and biorepositories, and view information about medical research and Down syndrome-related events. DS-Connect™ also provides access to general information about Down syndrome, as well as aggregate, de-identified data based on user responses to survey questions. People with Down syndrome and their families create password-protected profiles after providing online informed consent to participate in the registry. If registered users give permission to be contacted about a research study, the registry coordinator may invite eligible users to contact the clinician or researcher directly to sign up for the study or trial. The registry complies with all regulations and laws governing privacy, personally identifiable information, and health data and has been created on a Federal Information Security Management Act (FISMA) moderate platform to ensure that the health and demographic information is protected. A professional portal to support investigators who request access to the de-identified data in the registry was launched in October 2014. In 2015, a Spanish-language version was launched. Discussions are ongoing about translation to other languages. ([DS-Connect Website](#))

## **Mental Health**

***Common Data Elements for Eating Disorders:*** One way to improve the yield and impact of research in any area of science is to provide investigators with a common set of tools and resources to facilitate sharing, comparing, and integration of data from multiple sources. NIMH has already made significant investments in data repositories such as the [National Database for Autism Research](#) (NDAR), the [National Database for Clinical Trials Related to Mental Illness](#) (NDCT), and the [Research Domain Criteria Database](#) (RDoCdb). These repositories allow data from multiple sources to be aggregated and easily accessed by the research community. Recently NIMH has made available a set of common data elements (CDEs) for use by researchers who are collecting data from human subjects related to eating disorders. The new collection of common data elements is available via the [PhenX Toolkit](#). NIMH grantees/applicants are strongly encouraged to incorporate these measures into research protocols and are discouraged from using alternative measures to collect similar data.

In line with the Institute's emphasis on the Research Domain Criteria Project ([RDoC](#)), in March 2013, NIMH released a funding opportunity announcement, ***Advancing Eating Disorders Research through Dimensional Studies of Biology and Behavior*** ([RFA-MH-14-030](#)) to solicit research that used dimensional constructs to integrate biology (e.g., brain circuits or physiological pathways) and behavior in the service of advancing the understanding of biological mechanisms and developmental trajectories of eating disorders. Five of the applications originally submitted in response to the RFA have been funded ([R01MH103436](#); [R01MH103419](#); [R01MH103402](#); [R01MH105452](#); [R01MH105662](#)).

***Developmental Trajectories of Bipolar Disorder in Children and Adolescents:*** NIMH currently supports three prospective, longitudinal studies that provide foundational knowledge about the pathways to and progression of bipolar spectrum disorders and the processes and mechanisms that underlie these pathways: the Course and Outcome of Bipolar Illness in Youth (COBY) study ([R01MH059929](#), [R01MH059691](#)), the Children of Bipolar Parents Study (BIOS) ([R01MH060952](#)), and the Longitudinal Assessment of Manic Symptoms (LAMS) study ([R01MH073967](#); [R01MH073801](#)). COBY tracks a cohort of youth with DSM-IV bipolar disorder to characterize the natural course and treatment of bipolar disorder in youth, focusing on progression through the stages of the disease. BIOS follows a cohort of youth at risk for bipolar disorder, with the goal of characterizing the pre-morbid and very early stages of mood pathology, and onset of bipolar disorder and related symptomatology in children at familial risk for bipolar disorder. LAMS follows a cohort ascertained for level of manic symptoms (representative of children seen at mental health clinics), to characterize the progression of early manic symptoms and the trajectory of mood and other mental disorders.

Because 51 percent of all U.S. suicide deaths involve a firearm, research efforts are needed to develop acceptable, effective ways to reduce the number of firearm suicide deaths. The [prioritized research agenda](#) of the ***National Action Alliance for Suicide Prevention*** continues to support community-based efforts that find common ground in gun safety.

***Harnessing Advanced Health Technologies to Drive Mental Health Improvement.*** (R01, [RFA-MH-13-060](#)). This NIMH-supported initiative is designed to solicit research to test the innovative use of existing technologies to significantly improve access to and quality of mental health care, and to propose the collection and use of actionable mental health information to improve outcomes of people with mental disorders. The initiative set aside funds specifically for pediatric research on this topic, including: using technology to improve eating disorders treatment; technology to enhance treatment for early conduct problems in low income families; mobile health solutions for behavioral skill implementation through homework; and expanding access to cognitive behavioral therapy for childhood anxiety disorders via smart phones.

## Substance Use

***Gene-Environment Interplay in Substance Use Disorders:*** (R01, [PA-15-110](#); R03, [PA-15-111](#); R21, [PA-15-112](#)) Supported by NIDA and NIAAA, this program seeks to stimulate and expand research on the interplay of genetic and environmental factors in the genesis, course, and outcomes of substance and alcohol use disorders (SUDs). Previous work in genetic epidemiology and molecular genetics has established that SUDs are highly heritable, developmental disorders with important genetic substrates. Building on these findings, new research using genetically informative approaches is helping to elucidate the complex interplay of genetic and environmental factors in developmental trajectories of SUDs and comorbid conditions, deepen and refine phenotypic definitions of SUDs, and meet the methodologic challenges of the field. Such studies hold great potential to promote understanding of the true contributions of both genetic and environmental factors to initiation, progression, comorbidity, adverse outcomes, and cessation of SUDs; to elucidate mechanisms of risk; and to enhance opportunities for translation to treatment, prevention, gene-finding and molecular studies.

The NIDA and the NIAAA continue to fund multiple programs addressing substance abuse specifically among adolescents.

***Screening, Brief Intervention, and Referral to Treatment (SBIRT):*** NIDA is currently supporting several new SBIRT studies utilizing various strategies to identify SUDs in various patient populations and within multiple medical settings, including SBIRT for adolescents in school-based health centers ([R01DA036604](#)).

***Translational Research on Interventions for Adolescents in the Legal System (JJ-TRIALS):*** (U01, [RFA-DA-13-009](#)) In 2013, NIDA funded 6 research centers and 1 coordinating center for this U01 cooperative focusing on the juvenile justice system. JJ-TRIALS is guided by the philosophy that all juvenile offenders can benefit from drug abuse and HIV-related prevention, screening, and treatment interventions. In 2015, the cooperative successfully fielded a national survey of juvenile justice agencies, juvenile court judges, and behavioral health agencies serving justice-involved youth regarding the delivery of evidence-based substance abuse and HIV prevention and treatment services for justice-involved youth; results will be released in 2016. In addition, in 2015, the cooperative launched a randomized controlled trial (RCT) comparing two different data-driven implementation interventions aimed at improving the uptake of evidence-based substance abuse screening, assessment, and treatment services in 39 juvenile justice agencies across the country. The study will yield insights into which strategies are most effective at helping juvenile justice organizations improve services that address youth substance use and HIV risk behaviors.

***Targeting Prescription Stimulant Misuse Among Youth:*** NIDA is interested in applications conducting either hypothesis-driven or hypothesis-generating controlled research to build an evidence base to address the problem of prescription stimulant medication (PSM) misuse in youth. For example, [RFA-DA-15-010](#) is a funding opportunity announcement seeking research applications that develop and test the efficacy of interventions to either prevent or reduce the misuse and diversion of PSMs among high school students and/or college students. (NIDA has also funded two studies aimed at generating evidence for the prevention and/or early intervention of prescription stimulant misuse among adolescents and college-attending youth ([U01DA040213](#)) and ([U01DA040219](#)).

***Sleep Disturbances and Substance Use Among Adolescents:*** Adolescent and adult users of alcohol and illicit drugs report more frequent sleep problems compared to nonusers. A longitudinal, prospective study of drug use (with a focus on marijuana - the most commonly used illicit drug in adolescence) will

investigate linkages, temporal dynamics, and mechanisms between sleep disturbances and drug use to determine if sleep disturbances can be integrated into future prevention efforts. ([R01DA034618](#))

***Drug Abuse Prevention Intervention Research:*** (R21, [PA-15-080](#); R03, [PA-15-081](#); R01, [PA-15-082](#)) NIDA supports research that will employ 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. Ideally, these grant applications will encompass investigations of 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.

***Using Social Media to Better Understand, Prevent, and Treat Substance Abuse:*** More than \$11 million over three years will be used to support research exploring the use of social media to advance prevention, as well as treatment of substance abuse and addiction. ([NIDA News Release](#))

***NIAAA College Alcohol Intervention Matrix (CollegeAIM):*** NIAAA will continue to promote its recently released [College Alcohol Intervention Matrix \(CollegeAIM\)](#). As part of the dissemination effort, CollegeAIM developers and NIAAA staff will present on the tool at meetings of higher education administrators and college health professionals. NIAAA, in collaboration with its College Presidents Working Group, will also be organizing regional workshops to present CollegeAIM to institutional officials and show them how use it. The interventions highlighted in CollegeAIM are rated on factors such as effectiveness, cost, and ease of implementation, allowing users to choose those interventions that best fit the needs of their campus. Sometimes, schools may decide to implement a strategy from the “lower effectiveness” or “too few studies to rate effectiveness” levels; however, if schools choose to implement such a strategy, NIAAA encourages them to incorporate an evaluation component to test the strategy’s viability and report the results of their evaluation.

***College Drinking Prevention Website:*** As part of its college drinking initiative, NIAAA continues to provide [www.CollegeDrinkingPrevention.gov](http://www.CollegeDrinkingPrevention.gov), a one-stop resource for comprehensive research-based information on issues related to alcohol misuse and binge drinking among college students that includes online tools for parents, students, and administrators

***Alcohol Screening and Brief Intervention for Youth:*** NIAAA continues to promote the use of Alcohol Screening and Brief Intervention for Youth: A Practitioner’s Guide, which was developed to help health care providers identify risk for alcohol use, alcohol use, and AUD in children and adolescents. The guide presents a two-question screening tool and an innovative youth alcohol risk estimator to help clinicians overcome time constraints and other common barriers to youth alcohol use screening. To date, more than 204,000 copies of the youth guide have been distributed. In 2013, NIAAA partnered with Medscape to develop an online training course to familiarize clinicians with use of the youth guide, and more than 35,500 health care providers have earned continuing medical education credit for completing the training. NIAAA is planning future outreach initiatives to further encourage participation in the course. ([LINK](#))

***Neurobiology of Adolescent Drinking in Adulthood (NADIA):*** In 2010, NIAAA launched the NADIA consortium, which 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. ([RFA-AA-10-006](#))



***Developing and Evaluating Underage Drinking Interventions in American Indian Communities:***

- NIAAA-supported researchers have partnered with the *Cherokee Nation Behavioral Health Services* to design, implement, and evaluate a new community-level intervention to prevent and reduce underage drinking and associated problems in American Indian and other youth in rural, high-risk, and underserved communities. The randomized controlled trial combines components of community environmental change and Screening, Brief Intervention, and Referral to Treatment (SBIRT) to create a community-based preventive intervention targeting high school students, parents, schools, merchants, and other segments of the community. The overall goals are to prevent access to alcohol and high-risk situations and to help adults recognize and intervene with teen drinking. ([R01AA020695](#))
- NIAAA-supported researchers, in partnership with the American Indian Higher Education Consortium and Tribal Colleges and Universities (TCUs), are developing and implementing a community-based intervention to prevent and reduce hazardous drinking and associated negative health, social, and academic outcomes among TCU students. Working with the tribal college community, the researchers will tailor an established screening and brief intervention for American Indian and Alaska Native students and implement and evaluate that intervention at participating TCUs. They will also develop and evaluate a community-level intervention that includes implementing harm reduction-focused alcohol use policies at TCUs, providing behavioral health resources to TCU students, and providing training and coaching to ensure the interventions are implemented as intended. ([R01AA022068](#))

***Alcohol Policy Information System (APIS):*** NIAAA is expanding this database, which currently tracks state and federal alcohol-related policies, to include policies related to the recreational use of marijuana. Designed as a tool for policy-makers, researchers, and the public, APIS facilitates research on the impact and effectiveness of these policies. Among the marijuana-specific policies under consideration for inclusion into APIS are those related to: underage use, driving under the influence, pricing and taxation, cultivation, sales and distribution, packaging, and permissible product types. ([APIS Website](#))

***The Collaborative Study on the Genetics of Alcoholism (COGA):*** Supported by NIAAA, this multi-site, multidisciplinary family study aims to identify and characterize the genes that contribute to risk for alcohol use disorder (AUD) and related phenotypes, as well as mechanisms by which these genes influence risk. ([NIAAA COGA Website](#))

***The Population Assessment of Tobacco and Health (PATH) Study:*** ([PATH Study Website](#)) is a large-scale NIH/FDA collaboration on a national longitudinal cohort study that will follow 46,000 U.S. 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. In 2015, the first empirical paper from the first wave was published in JAMA ([Link to Journal Article](#)), confirming the widespread appeal of flavored products among youth tobacco users.

***Smokefree.gov:*** NCI developed this online resource to disseminate evidence-based strategies to help people quit smoking tobacco. In FY 2015, an estimated 2.6 million individuals consulted the smoking cessation resources on NCI's [Smokefree.gov](#) website.

## *Nutrition and Obesity in Pregnancy and Childhood*

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

NICHD supports several programs on how research on nutrition can affect policies for school meals and infant feeding ([NICHD Obesity Topic](#)):

- NICHD investigators are analyzing implementation of the Institute of Medicine (IOM) school meal recommendations in three low and three middle income schools to assess meal participation rates, school food service costs, and student dietary intake at school. The results will identify what changes in student diets occur, identify any cost issues, and inform future policies.
- The federal Head Start program provides nutritional, health, and social services to more than 900,000 low income children and their families each year. NICHD-funded investigators are examining the questions of how and under what circumstances Head Start is more or less effective in promoting children's cognitive, social, and physical development to determine whether specific structure and quality of head Start centers, parenting behavior and other factors might enhance or curtail positive program impacts.
- Researchers are analyzing data on nearly 750,000 students in New York City schools since 2005. Data on height, weight, body mass index (BMI), and indicators of health-related fitness will be evaluated in the context of school district policies, neighborhood context, personnel interviews and school surveys. The project will provide considerable data on the impact of school food policies on childhood obesity and document evidence for which policies are successful and worth pursuing. Additional studies will evaluate the effect of the federally-mandated multi-state School Breakfast Program on childhood obesity rates as well as outcomes from food programs in Connecticut, Pennsylvania, Massachusetts, and Rhode Island.

***The Hyperglycemia and Adverse Pregnancy Outcome Follow-Up Study (HAPO-FUS)***, cosponsored by the NIDDK and the NICHD, is determining whether maternal glucose levels during pregnancy are associated with later obesity or adverse metabolic or cardiovascular status in offspring of mothers with well-characterized pregnancies, in addition to looking at maternal outcomes.

***Lifestyle Interventions for Expectant Moms (“LIFE-Moms”)***: Because maternal obesity and excessive weight gain during pregnancy is linked to adverse health consequences in mothers and offspring, the NIDDK, with other IC partners, started this set of studies of lifestyle interventions in overweight and obese pregnant women designed to control gestational weight gain and improve metabolic outcomes for the women and their offspring.

The four ***Childhood Obesity Prevention and Treatment Research (COPTR) Consortium*** trials are using multi-level interventions targeting preschoolers (2 to 5 years of age) and pre-adolescents or adolescents (7 to 16 years of age).

***Understanding Factors in Infancy and Early Childhood (Birth to 24 months) That Influence Obesity Development:*** NIDDK is interested in research that characterizes or identifies factors in early childhood (birth to 24 months) that may increase or mitigate risk for obesity and/or excessive weight gain. NIDDK is also interested in filling methodological research gaps relevant to the understanding of risk for development of obesity in children. These studies may also assess factors relevant to families and/or caregivers of children from birth to 24 months.

The ***Healthy Communities Study*** includes 130 communities and over 5,400 elementary and middle school aged children to identify characteristics of existing obesity-related community programs and policies that are associated with less childhood obesity and better eating and physical activity behaviors. Led by NHLBI, with support from other ICs.

The ***NEXT Generation Health Study*** includes students in the tenth grade at the start of the study, who are followed over seven years; a subsample of youth (NEXT Plus study), half of whom were overweight/obese at the start of the study, undergo multiple waves of objective measures of body size and function, physical activity and sedentary behavior, sleep and biomarkers for cardiovascular risk and dietary intake, in addition to the parent study's annual survey of health behaviors. Supported by NICHD.

Through the ***National Collaborative on Childhood Obesity Research*** (NCCOR) the NIH, CDC, Robert Wood Johnson Foundation, and USDA work to reach common goals, make the most of available resources, and share expertise to strengthen research. A special emphasis is put on populations and communities with the highest obesity rates. Led by NCI. ([NCCOR Website](#))

***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 (DSLID):** Launched in June 2013, the DSLID 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 DSLID 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. ([DSLID Website](#))
- **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. ([DSID Website](#))

***Office of Dietary Supplements (ODS) Iron Initiative:*** Iron status of pregnant women and young children is a current public health focus, and iron deficiency anemia in these vulnerable population groups is often a concern among health care providers in the U.S. ([ODS Fact Sheet](#)) Recently, the U.S. Preventive Services Task Force (USPSTF) determined that there was insufficient evidence to clarify the benefits and harms associated with screening pregnant women and infants (6-24 months) for iron deficiency as well as the routine iron supplementation for pregnant women. NIH has a role in helping to close the research gaps identified by USPSTF. ODS activities on iron relative to screening and supplementation focus on the convening of a conference to identify the specific research needs related to these topics, especially in

terms of appropriate screening measures and the benefits and harm associated with routine supplementation of replete pregnant women and infants.

***Teen Longitudinal Assessment of Bariatric Surgery (Teen-LABS)***: The NIDDK continues to support a multicenter observational study in teens, called the, to collect data on the longer-term risks and benefits of bariatric surgery in obese adolescents. In addition to investigating surgical outcomes, another broader goal of Teen-LABS is to understand better the etiology, pathophysiology, and behavioral aspects of severe obesity in youth and how this condition affects human beings over time. ([U01DK094830](#))

***Role of Environmental Chemical Exposures in the Development of Obesity, Type 2 Diabetes and Metabolic Syndrome***: Supported by NIEHS and NICHD, several studies focus on the role of environmental chemical exposures on certain long-term health outcomes, particularly during critical windows of development. Approximately 20 studies are being conducted in human birth cohorts examining environmental exposures including pesticides, traffic pollutants, metals, endocrine disruptors, and other factors. ([PA-12-185](#))

### **Diabetes**

NIDDK's ***SEARCH for Diabetes in Youth Cohort Study (UC4)*** provides population-based data on the incidence and prevalence of diabetes and its complications in U.S. youth. SEARCH is jointly led by the CDC and NIDDK.

The NIDDK-led type 1 diabetes ***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. ([TrialNet Website](#))

***Improving Management for Type 1 Diabetes***: NIDDK will continue to support research to improve the health of people with T1D and reduce patient burden. Recent data have indicated that maintaining blood glucose levels as close to normal as safely possible remains particularly challenging for adolescents and young adults ([PMID 25998289](#)), and NIDDK plans to continue support for research aiming to improve treatment adherence in young children, pre-teens, adolescents, and young adults ([RFA-DK-16-001](#), [RFA-DK-16-002](#), [RFA-DK-16-003](#)).

***Artificial Pancreas Technologies***: NIDDK continues to support research toward safe, portable artificial pancreas (AP) technologies linking a continuous blood glucose sensor and an insulin delivery system. NIDDK has funded research conducted by small businesses, academic investigators, and national research networks to test current systems, develop new AP technologies, and determine how these systems may be used to improve glucose control, quality of life, and health outcomes. Three projects were recently funded under [RFA-DK-14-024](#) to support advanced clinical trials testing the outpatient safety and efficacy of three different AP systems with the aim of improving glycemic control in children, adolescents, and/or adults with type 1 diabetes. A recently released RFA ([RFA-DK-16-008](#)) will be soliciting additional applications for FY16 funding in this area. These trials are expected to pave the way toward generating data to satisfy safety and efficacy requirements by regulatory agencies regarding AP device systems.

NIDDK leads several initiatives on diabetes research:

- ***The Environmental Determinants of Diabetes in the Young (TEDDY)***, supported by NIDDK, is a study to determine the infectious agents, dietary factors, or other environmental conditions that trigger type 1 diabetes in genetically susceptible individuals. This long-term study is currently following over 6,000 genetically susceptible newborns until age 15. Children enrolled in the study are developing autoimmunity and type 1 diabetes at the predicted rates. Pilot studies to address questions related to the etiology and pathogenesis of islet immunity and type 1 diabetes are under way in the following areas: microbiome and virome; gene expression markers; and metabolome and proteomics.
- ***Treatment Option for Type 2 Diabetes (T2D) in Adolescents and Youth (TODAY)*** is a cohort followed by NIDDK in order to track the progression of type 2 diabetes and related comorbidities and complications as the participants transition to young adulthood. This is a critical need to prevent a potential public health crisis, since the TODAY data suggest that individuals who develop type 2 diabetes during adolescence may be at risk for developing vascular complications, including cardiovascular disease, in the prime of their lives.
- ***Improving Diabetes Management in Young Children with Type 1 Diabetes (DP3)*** funded by NIDDK, seeks to develop, refine, and pilot test innovative strategies to improve diabetes management in young children with type 1 diabetes (5 years old and under). At the end of the funding period, there should be a well-developed and well-characterized intervention that has been demonstrated to be safe, feasible to implement, acceptable in the target population, and, if promising, ready to be tested in a larger efficacy trial.
- ***Advanced Clinical Trials to test Artificial Pancreas Device Systems in Type 1 Diabetes (UC4)***, supported by NIDDK, conducts advanced clinical trials designed to test the outpatient clinical safety and efficacy of artificial pancreas (AP) 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 AP device systems.

***Wireless Technology Assisted Weight Management in Pre-Diabetic Adolescents:*** This NIMHD-led study is comparing the effectiveness of a lifestyle change intervention delivered either via text messaging or using Lifestyle Group Visits, which include a personal health record and a web-based educational portal, in 18-24 year-old African Americans with a diagnosis of prediabetes

***Cooperative Study Group for Autoimmune Disease Prevention (CSGADP):*** Led by NIAID, this collaborative network of investigators has a focus on autoimmune disease prevention and a historical emphasis on T1D. The long-term goal of this program is to develop the knowledge base necessary to design interventions for the prevention of autoimmune disease that could be administered efficiently and safely to individuals at risk or to the general population, including infants and children. The *CSGADP* is supported by the *Special Diabetes Program* and regular NIAID appropriated funds.

### **Bone and Muscle Health**

***Orthotics in Pediatric Populations:*** The National Center for Medical Rehabilitation Research, housed at the NICHD, developed a new initiative to support small businesses that could design, build, and test novel orthotics that capitalize on the plasticity of the neuromuscular and skeletal systems in growing children. Specially designed orthotics could help improve function for children with disabilities such as cerebral palsy, spina bifida, and muscular dystrophy. Currently, children with disabilities use as few as half of prescribed medical devices because the child outgrows them, refuses to use them, or finds them unhelpful. This number may be partly reflective of the minimal innovation in the orthotics field. Many devices have changed little in the past 40 years; they are often aesthetically unpleasing, rigid plastic and metal devices



that limit clothing and shoe choices. However, innovations in plastics, sensors, and other materials show promise for improved orthotics that could benefit large numbers of children. ([RFA-HD-14-029](#))

NICHD supports studies on bone health as a way to understand healthy development and the origins of health and disease. This includes understanding cellular and molecular mechanisms governing longitudinal bone growth in childhood to enabling researchers to identify the effects of nutritional deficiency or excessive exercise on bone development.

- ***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 5 clinical centers in the United States, supported through the NICHD's Pediatric Growth and Nutrition Branch (PGNB). 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. ([NICHD BMDCS Website](#))
- ***Bone Mineral Accretion in Young Children:*** Supported by NICHD, the objectives of this longitudinal study are to develop regional and total body bone mineral content (BMC) and density (aBMD) reference data for children ages 1-5 y to aid identification of young children with bone deficits, and identify factors that influence bone accrual. The study will identify differences by sex and ancestry in normative data on bone mineral accretion. ([R01HD076321](#))

***Establishing Outcome Measures for Clinical Studies of Oral and Craniofacial Diseases and Conditions:*** (R01, [PAR-15-302](#)) Study outcomes or endpoints used in a clinical trial or study must provide reliable and valid signals to document the presence of disease, its severity, and its response to either experimental or conventional treatment. Both researchers and practicing clinicians recognize the need to validate and enhance existing methods or develop new technologies to diagnose and quantify the extent of several oral and craniofacial diseases and conditions, and to assess their responses to treatment(s). This continuing NIDCR program aims to address this problem by supporting research that will establish well-founded clinical outcome measures and methods to be used in oral and craniofacial research and ultimately patient care. The developed outcome assessment(s) may be used to diagnose or characterize a disease, its progression or severity, or it may serve as a clinical endpoint to measure treatment efficacy in future studies. This initiative also encourages development of clinician-reported, patient-reported or observer-reported (i.e., parent- or caregiver-reported) outcome measures to capture clinical differences that are meaningful to individuals affected by a disease or condition.

For more than 20 years, NIDCR's Intramural Research Program has supported research in pediatric diseases that affect bone health. For example:

- **Fibrous dysplasia/McCune-Albright syndrome (FD/MAS):** a disease of bone fragility that affects children and adults. Studies have led to four drug trials that aim to improve specific aspects of the disease and a public-private partnership with Amgen to perform preclinical and clinical studies. Researchers are working in collaboration with the FD/MAS community, including the MAGIC Foundation and the Fibrous Dysplasia Foundation.
- **Familial tumoral calcinosis (FTC):** a disease affecting mineral metabolism that results in the formation of calcium deposits in the soft tissues of the body. In a public-private partnership with Shire Pharmaceuticals a preclinical study of FTC is under way to better understand the mechanisms of disease with the goal of developing new therapies.
- **Caries research:** dental decay, tooth decay, or cavities due to bacterial activity. NIDCR researchers are studying the acquisition, stability, and interactions of harmful microbial species that live in the mouth.

NIDCR supports research to develop a more systematic model of craniofacial development. The benefits of this work include a more detailed picture of where the molecular glitches might arise in the system, for example, to cleft a lip, omit a tooth bud, or malform a bone. Problems with this developmental process result in birth defects such as:

- Cleft lip/cleft palate: the most common orofacial birth defect in the US, affecting one in 1,500 live births. NIDCR supports studies to determine the best time for surgical repair of defects in children to improve outcomes and research to identify the genes associated with cleft lip/cleft palate. Individuals with cleft lip and/or palate (CLP) have multiple special needs including speech and language problems, facial differences, atypical dental development, malocclusion, learning disabilities, chronic ear infections, and associated psychosocial sequelae. The goal of one NIDCR-supported study is to improve the understanding of quality of life (QoL) and related issues among youth with CLP who are between 8 and 18 years old and who are undergoing secondary corrective surgery. This study may provide insight into how effective cleft habilitation is at improving oral health-related QoL and overall QoL, and it may identify subgroups where targeted interventions are most needed. Another NIDCR study explores provider and family communication as they decide on treatment options for children with CLP. [R01DE018729](#)
- Craniosynostosis: a birth defect in which one or more of the sutures between the bones of a baby's skull close prematurely, before the brain is fully formed. The current treatment is to surgically remove the fused sutures and reshape the bones of the skull to allow for brain expansion as the child grows.
- Hereditary diseases like a rare inherited immune disorder called leukocyte adhesion deficiency Type I (LAD-I) that is associated with frequent microbial infections, including severe early-onset periodontal disease. Intramural NIDCR scientists and colleagues are studying children with LAD-I to understand the pathology and develop better treatments for children and adults with periodontitis.
- *The FaceBase Consortium* is designed to bring together investigators from across the spectrum of craniofacial development and dysmorphology research to collect, integrate, and disseminate a wide variety of data on the genomics, gene expression, and imaging of the face and skull. Using this critical information, researchers are identifying the underlying genetic causes of previously unexplained craniofacial birth defects and are developing tools to detect these types of developmental disorders. NIDCR has funded 10 research projects for this consortium.

## Hearing

**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. The NIDCD supports a wide variety of studies to develop new treatments for chronic and recurrent OM. These studies examine the bacterial pathogenesis and human immune responses following infection, how genetic risk factors make individuals more or less susceptible to OM, and whether environmental factors could reduce OM risks in children with genetic predisposition. The NIDCD also supports research on the delivery of drugs to the middle ear and studies that seek to develop vaccines against OM. ([NIDCD Info on Ear Infections](#))

**Longitudinal Studies of Children with Cochlear Implants:** NIDCD-supported scientists are studying large groups of children who were identified early with hearing loss and implanted with a cochlear implant. Knowledge from this research will shed light on the variables most related to improved speech and language acquisition as well as reading and higher academic performance in children with cochlear implants. Researchers are also evaluating the factors that may be responsible for the large individual differences seen in outcomes for these children. ([R01DC004797](#) and [R01DC010075](#))

***Clinical Trials on Hearing Aids and Cochlear Implants:*** NIDCD supports several clinical trials on hearing aids and cochlear implants. One trial is investigating the efficacy of telemedicine versus traditional face-to-face post-implant aural rehabilitation in children. ([U01DC013529](#)) Another trial is comparing the use of cochlear implant(s) versus hearing aids in developmentally delayed children. ([R01DC010075](#)) Another trial is examining robotic percutaneous cochlear implantation in children and adults. ([R01DC008408](#))

### **Childhood Diseases, Allergies, and Immunity**

***Oral Health Disparities Centers:*** Early childhood caries (ECC) is the most prevalent chronic childhood disease in the United States, particularly among economically disadvantaged, underserved children. Three centers, supported by the NIDCR, are conducting four large community-based randomized clinical trials to understand, prevent, and reduce oral health disparities, with a focus on preventing ECC. The studies are enrolling participants from American Indian communities, Hispanic communities in Southern California, and public housing projects in Boston. In FY 2015, NIDCR continued its investment to reduce disparities by awarding ten research grants aimed at identifying the best methods of eliminating inequities in access to care and improving the oral health of underserved children. These awards support a new NIDCR initiative, the [Multidisciplinary and Collaborative Research Consortium to Reduce Oral Health Disparities in Children](#). This work will help communities identify the best methods to reduce oral health disparities and inequities of underserved children by increasing access to care and providing innovative health promotion and disease prevention strategies. ([NIDCR Centers for Research to Reduce Disparities in Oral Health](#))

***Genetic, Social, and Behavioral causes of Early Childhood Caries (ECC):*** NIDCR-funded researchers are examining different populations to determine if certain genes are associated with dental caries of primary or permanent teeth. Two studies focus on the genetics of ECC: a longitudinal study of approximately 1,000 pregnant women in Appalachia to assess maternal and early childhood factors affecting development of ECC through age 2 years, and a cross-sectional study of approximately 6,000 3-5 year old children in Head Start programs to assess factors associated with ECC. NIDCR funded studies are also defining the social and behavioral factors most likely to cause ECC and developing interventions targeting these factors as a therapy for ECC.

***The Bench to Bassinet program*** is a pediatric cardiovascular translational research program supported by NHLBI. ([Bench to Bassinet Website](#))

- ***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.
- ***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.
- ***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. ([Pediatric Heart Network Website](#)) The PHN has enrolled approximately 3700 patients into observational studies.

***OPTIMIZE Trial:*** NHLBI continues to support the OPTIMIZE trial in children with cystic fibrosis ages 6 months to 18 years from 45 centers to evaluate chronic oral azithromycin as an adjunct therapy to inhaled tobramycin among children with early pseudomonas (Pa) infection to reduce pulmonary

exacerbation, reduce inflammation, and delay the transition to chronic Pa infection ([HL114623](#) and [HL114589](#)).

**NIDDK Studies on Cystic Fibrosis:** NIDDK is funding two observational studies to investigate the appropriate diet for infants with CF identified by newborn screening: the Baby Observational and Nutrition Study of CF (BONUS); and the Feeding Infants Right From the Start (FIRST) study which is specifically investigating the impact of breast versus formula feeding. ([R01DK095738](#), [R01DK072126](#))

**Primary Immune Deficiency Diseases:** Pediatric research in the NIAID intramural research program is primarily focused on investigations of congenital immune defects, development of vaccines for childhood diseases, and studies of infectious diseases with increased severity in children. The NIAID Primary Immune Deficiency (PID) Clinic is the focal point for studies of the genetics, pathophysiology, and treatment of chronic granulomatous disease, common variable immunodeficiency, hyperimmunoglobulin E syndrome, severe combined immunodeficiency, and many other PID diseases. The NIAID also conducts basic and clinical investigations of allergic diseases, pediatric-onset mastocytosis, and the immunology and pathogenesis of severe malaria in children. ([NIAID Primary Immune Deficiency Diseases Topic](#)) Pediatric research in the NIAID extramural program supports innovative studies to identify the clinical, molecular, immunological and genetic characteristics of primary immune deficiency diseases associated with defects in innate and adaptive immunity. Efforts are made toward development of novel diagnostic/newborn screening tools and biomarkers as well as therapeutic approaches, using cutting-edge approaches including highly innovative human cell and animal models. Novel therapeutic approaches that show promise during pre-clinical development are tested for safety and efficacy in clinical trials such as gene therapies for severe combined immunodeficiencies.

**Vaccine Development:** NIAID conducts and supports a robust research program in vaccine development, such as influenza vaccines.

- **NIAID's Vaccine and Treatment Evaluation Units (VTEUs)** work to develop new and improved vaccines and therapies against infectious diseases and have conducted hundreds of clinical trials, many of which have contributed to vaccine licensure. Currently, the VTEUs are conducting several studies involving pediatric subjects, including a Phase II study designed to assess the safety, reactogenicity, and immunogenicity of a H3N2v influenza vaccine candidate ([NCT02100436](#)), and a Phase II study to determine the safety and efficacy of mupirocin in eradicating colonization with *Staphylococcus aureus* and preventing the occurrence of invasive and other clinically significant *Staphylococcus aureus* infections among critically ill infants in the intensive care unit ([NCT01827358](#)).
- Researchers at the NIAID Vaccine Research Center are working to develop a vaccine against respiratory syncytial virus (RSV), a leading cause of illness and hospitalization among very young children worldwide. Building on their previous report describing the atomic structure of a metastable viral surface protein, NIAID scientists used the structural information to design stabilizing mutations and produce a vaccine antigen that elicited high levels of RSV-specific neutralizing antibodies when tested in animals. Early-stage human clinical trials of the candidate vaccine are planned in the next several years.
- The NIAID Division of Intramural Research (DIR) focuses on the development of vaccines against rotaviruses, herpesviruses, malaria, and major pediatric respiratory pathogens for which no vaccines currently exist (RSV, parainfluenza, influenza viruses). Recent phase I clinical trials include a completed trial on an intranasal RSV vaccine ([NCT01459198](#)) and a trial testing a live-attenuated human parainfluenza type 1 vaccine in adults and children ([NCT00641017](#)). Both vaccine strategies were developed by DIR investigators, and trials are being conducted in collaboration with colleagues at the Johns Hopkins Bloomberg School of Public Health and were part of a Cooperative Research and Development Agreement between NIAID and MedImmune, LLC.

NIAID supports the *Immunity in Neonates and Infants initiative* to improve the understanding of immune system development and immune defense mechanisms in neonates and infants.

Other NIAID initiatives support clinical research on immune-mediated diseases in pediatric cohorts:

- ***The Inner-City Asthma Consortium*** uses immune-based-therapies to reduce asthma severity and prevent disease.
- ***The Immune Tolerance Network*** (ITN) supported the “Learning Early About Peanut” (LEAP) study, which was the first randomized trial to prevent food allergy in a large cohort of high-risk infants. ITN is also conducting clinical trials of tolerance induction therapies/strategies to treat autoimmune diseases, prevent rejection of transplanted organs, and treat and prevent asthma and allergic diseases; 8 of 35 trials in development, ongoing, or completed during FY 2015 related to T1D. T1D clinical trials use a wide variety of treatment strategies including islet transplantation, immune cell depletion, antigen-specific intervention, or immune response modulators.
- ***The Consortium for Food Allergy Research*** (CoFAR; co-sponsor: NIDDK) develops treatment and prevention strategies to combat food allergies. CoFAR is conducting clinical trials to: investigate the safety and efficacy of baked egg compared to egg oral immunotherapy in patients who are allergic to egg but can consume baked egg products without an allergic reaction; assess the safety and efficacy of peanut immunotherapy applied via an adhesive patch placed on the skin in children and adults with peanut allergy; and elucidate the natural history of food allergy.
- ***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.

***Asthma:*** The NIAID supports the Inner-City Asthma Consortium to develop clinical trials that evaluate the safety and efficacy of immune-based therapies to reduce asthma severity and prevent disease among children living in inner-city environments. A longitudinal, prospective study of a birth cohort of 606 inner-city children (the Urban Environment and Childhood Asthma study) is examining the immunologic causes of recurrent wheezing and asthma. Another clinical trial compared short-term (4 to 5 months) use of Anti Immunoglobulin E (Anti-IgE) monoclonal antibody therapy versus short-term boost of inhaled steroids to protect against asthma fall seasonal exacerbations. The Asthma Phenotype in the Inner City (APIC) study, a year-long longitudinal study of over 700 children and adolescents with asthma, has collected information on response to treatment and clinical and immunology markers to identify different types of asthma. The NIAID also co-sponsors the Asthma and Allergic Diseases Cooperative Research Centers (AADCRCs) with the NIH Office of Research on Women’s Health (ORWH). Several AADCRC studies, as well as some NIAID sponsored Investigator-Initiated Clinical Trials, are examining the role of common respiratory infections in initiating asthma in young children. ([NIAID Asthma Topic](#))

***The Severe Asthma Research Program (SARP):*** Funded by NHLBI, SARP is the first NIH-coordinated effort to study the pathobiology of severe asthma and how it differs from mild to moderate asthma. The current program (SARP III) will utilize a multidisciplinary approach to achieve an integrated understanding of severe asthma at the molecular, cellular, and clinical levels over time.

***AsthmaNet:*** NHLBI's multi-center clinical trial network has multiple ongoing trials including the Best African American Response to Asthma Drugs (BARD) which addresses management of asthma in African Americans exclusively. Completed trials include trial of vitamin D for asthma in adults ([PMID 24838406](#)) [May 2014] and study of the use of antibiotics to reduce exacerbations in children. ([PMID 26575060](#)) [Nov 2015]



***Hepatitis B Research Network Clinical Centers Program***, including seven pediatric study sites supported by NIDDK, is promoting translational research on hepatitis B focusing upon elucidating the pathogenesis and natural history and developing means of treatment and control.

***Childhood Liver Disease Research Network (ChiLDReN)***: Their mission is 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.

***The Pediatric Acute Liver Failure Study Group*** is a collaborative study conducted across clinical centers in the United States and Canada aimed at identifying, characterizing, and developing management strategies for infants, children, and adolescents who present with acute liver failure.

***The Chronic Kidney Disease in Children (CKiD) study*** is a prospective cohort study of kidney disease in children and adolescents that seeks to identify risk factors for progression of disease, as well as the impact of chronic kidney disease on neurocognitive development, cardiovascular disease, and growth. The study has identified several risk factors for pediatric kidney disease as well as early manifestations of disease. An ancillary study to CKiD has been funded to investigate genetic factors associated with progression of kidney disease in the study population. CKiD has been renewed through 2018, and expanded to allow for the recruitment of additional patients. ([CKiD Website](#))

***Chronic Kidney Disease Biomarkers Consortium***: As part of this consortium, established in FY 2015 ([RFA-DK-14-011](#)), the NIDDK awarded a [U01 grant](#) to support a research team that will interrogate urine proteins from the Chronic Kidney Disease in Children (CKiD) cohort to identify biomarkers for progression and targets for treatment. CKiD is an ongoing study of nearly 900 children with chronic kidney disease enrolled at 1-16 years of age and followed annually.

***Adherence Studies in Adolescents with Chronic Kidney Disease or Diabetes*** supports research to improve adherence in adolescents with chronic disease. Specifically, on-going studies will 1) determine the efficacy of a structured, multi-component intervention in improving adherence to anti-rejection medications and graft outcomes, and to identify characteristics of healthcare systems that are independently associated with adherence, 2) test the impact of antihypertensive medication adherence in adolescents on blood pressure control and subsequent progression of chronic kidney disease and the influence of physician-adolescent communication on medication adherence over time, and 3) determine which daily self-regulatory skills are needed to maintain good adherence across the transition to young adulthood, the neurocognitive abilities that underlie these daily skills, and whether parental monitoring compensates for poor self-regulation.

***Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer***: As part of this consortium, established in FY 2015 ([RFA-DK-14-028](#)), the NIDDK awarded a U01 grant to support a pediatric pancreatitis consortium that will be part of this larger network. This work builds on a previous R21 award the NIDDK supported to form a pediatric pancreatitis interest group called “INSPPIRE” ([INSPPIRE Website](#)). The Consortium for the Study of Chronic Pancreatitis is a partnership with the National Cancer Institute that will undertake a major new effort to understand numerous research questions related to this devastating condition throughout the lifespan, including factors related to pancreatogenic diabetes and pancreatic cancer.

The NIDDK ***Inflammatory Bowel Disease (IBD) Genetics Consortium***: This is a major driver of the Institute's research program on the role of genetic factors in the development of Crohn's disease and ulcerative colitis. Currently, Consortium investigators are continuing to search for genetic factors that contribute to increased susceptibility for developing IBD and their role in disease processes and treatment

responses, focusing on factors unique to specific racial and ethnic groups, as well as adults and children. The Consortium is part of a 15-member international consortium, which has aided in increasing the power of analyses to enable discovery of additional risk variants for IBD. ([LINK](#))

***Predicting Response to Standardized Pediatric Colitis Therapy (PROTECT-UC):*** ([LINK](#)) NIDDK supports research on pediatric inflammatory bowel diseases through this clinical trial, looking at children newly diagnosed with ulcerative colitis and treated with standardized therapy designed to minimize exposure to more toxic drugs. Results from this trial will be integrated with an ongoing pediatric IBD study sponsored by the Crohn's and Colitis Foundation of America. The ***Methotrexate Response in Treatment of Ulcerative Colitis (MERIT-UC) trial*** ([MERIT-UC Website](#)) is investigating the therapeutic value of methotrexate (MTX), an inexpensive generic drug, in adult UC patients in whom established therapies have failed. Another continuing study, through the second phase of the ***Human Microbiome Project***, is a multi-institutional effort to understand how the human gut microbiome changes over time in adults and children with IBD. The overall goal of this study is to provide translationally actionable targets for IBD therapy or diagnosis. ([IBDMB Website](#))

***Juvenile Autoimmune Disease:*** NIEHS researchers are engaging in large natural history studies of children with orphan autoimmune muscle diseases called myositis to identify phenotypes in order to better understand their environmental and genetic risk factors. Another study, the Twin Sibling study protocol, has enrolled more than 200 twins and same-gender (close in age) sibling pairs discordant for systemic rheumatic diseases in recently-diagnosed patients with juvenile and adult myositis, rheumatoid arthritis, lupus and scleroderma to examine risk factors common to these systemic diseases. Environmental risk and severity factors, including ultraviolet light ([PMID 23658122](#)) and viral genes ([PMID 26556803](#)), have recently been identified for juvenile dermatomyositis and other pediatric systemic rheumatic diseases, including juvenile idiopathic arthritis and juvenile systemic lupus erythematosus. Genome wide association studies have revealed genetic risk factors for juvenile dermatomyositis. ([PMID 26291516](#))

***Environmental and Genetic Risk Factors for Juvenile Dermatomyositis and Other Pediatric Systemic Rheumatic Diseases:*** NIEHS intramural researchers are planning additional genetic studies, including detailed genetic sequencing studies of the HLA region in juvenile dermatomyositis and in autoantibody subgroups. In collaboration with investigators in NIAMS and NHGRI, they are in progress with whole genome and exome sequencing studies in multiplex families and certain autoantibody subgroups of juvenile dermatomyositis with severe disease and a young age of onset, with the goal of identifying additional genetic risk factors for these diseases. The researchers will analyze environmental exposure questionnaire data from the Twin Sibling and other studies to further examine ultraviolet light, infections, vaccines, hormone and pregnancy issues, and psychosocial stressors as potential environmental risk factors, and to examine the role of these exposures as modulators of outcomes in children with myositis. ([NIEHS Environmental Autoimmunity Group](#), [NIEHS Studies in the Natural History & Pathogenesis of Childhood-Onset and Adult-Onset Idiopathic Inflammatory Myopathies](#))

***Translational Autoinflammatory Disease Section of the NIAMS Intramural Research Program:*** Patients with autoinflammatory diseases often experience their first symptoms of disease early in life, even in the neonatal period. The Translational Autoinflammatory Disease Section of the NIAMS IRP evaluates patients with autoinflammatory diseases to understand the underlying immune dysregulation; identify the molecular and genetic cause (using next generation sequencing methods); translate the knowledge gained into better treatment approaches to improve patients' disease outcomes; and implement pilot studies with targeted treatments to safely evaluate their effects. The team's work has advanced how we care for children who have NOMID (Neonatal-onset Multisystem Inflammatory Disease), DIRA (Deficiency of the IL-1 Receptor Antagonist), CANDLE (Chronic Atypical Neutrophilic DermatosiS with Lipodystrophy and Elevated temperatures) and SAVI (STING-Associated Vasculopathy with onset in

Infancy). They are continuing to work with patients who have these conditions, as well as those who have undifferentiated inflammatory diseases for which diagnoses and treatments are lacking. ([NIAMS Translational Autoinflammatory Disease Section Website](#))

### **Childhood Injuries and Maltreatment**

**NICHD Consortium for Research on Pediatric Trauma and Injury Prevention:** ([PAR-14-324](#)) The NICHD Pediatric Trauma and Critical Illness Branch encourages multidisciplinary collaborations to target gaps in research on pediatric trauma and injury prevention. The branch has issued an FOA to encourage a team science approach to devise breakthrough ideas, concepts and approaches to therapies in pediatric trauma and injury prevention research.

**Traumatic Brain Injury:** Traumatic brain injury (TBI) is a leading cause of death and disability in children and young adults. Some studies supported by NIH include:

- **Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK TBI)** ([U01NS086090](#)) is an observational study at 11 sites of more than 3000 adults and children with TBI across the spectrum of injury severity. The project will establish more precise methods for TBI diagnosis and prognosis, improve outcome assessment, and compare the effectiveness and costs of tests, treatments, and services. The goal is to better characterize and stratify patients, allowing meaningful comparisons of treatments and outcomes, and thereby improve patient care and the next generation of clinical trials.
- **Approaches and Decisions in Acute Pediatric TBI (ADAPT) Trial** ([ADAPT Website](#)) is an observational study of 1000 children with severe TBI that will evaluate the association of 6 key aspects of pediatric care with outcomes. The results will provide compelling evidence to change clinical practice.
- **FNIH Sports and Health Program:** The FNIH Sports and Health Research Program, established by a \$30m donation from the NFL, is supporting cooperative agreements to define long-term changes in the brain years after mild TBI ([NINDS News Release](#)).

### **Rare Pediatric Diseases**

**Rare Diseases Clinical Research Network (RDCRN):** Led by the National Center for Advancing Translational Sciences (NCATS) and cofunded by eight other ICs, the Rare Diseases Clinical Research Network conducts collaborative clinical research in rare diseases, including longitudinal studies of individuals with rare diseases, clinical studies, and/or clinical trials. The RDCRN is comprised of 22 distinctive Rare Diseases Clinical Research Consortia (RDCRC) and a central Data Management and Coordinating Center that are working in concert to improve availability of rare disease information, treatment, clinical studies, and general awareness for both patients and the medical community. 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 Angelman, Rett, and Prader-Willi syndromes. ([RDCRN Website](#)). Some examples of consortia include:

- **Developmental Synaptopathies Consortium:** A group of ten medical centers are studying natural history, imaging biomarker discovery, and shared pathophysiology in 3 rare genetic disorders associated with intellectual and developmental disabilities: tuberous sclerosis complex (TSC), Phelan-McDermid Syndrome (*Shank3* mutations, also known as 22q13.3 deletion syndrome), and PTEN mutation patients. These data will be submitted to the National Database for Autism Research (NDAR). Supported by NINDS, NIMH, NICHD, and NCATS. ([DSC Website](#))

- ***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 FOXP1 mutations and have similar phenotypes to RTT. Supported by NICHD and NINDS. ([Rett Website](#))
- ***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 and NCATS. ([STAIR Website](#))
- ***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 and NCATS. ([UCDC Website](#))
- ***The Brittle Bone Disorders (BBD) Consortium of the Rare Diseases Clinical Research Network (RDCRN)***, initially funded in FY 2014, is a multi-center program that focuses on understanding and providing better treatment options for rare diseases characterized by bone fragility and fractures. It also demonstrates the potential of partnerships to translate scientific discoveries into improved oral health. 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. NIAMS, NIDCR, NIDCD and NCATS partnered with the Osteogenesis Imperfecta Foundation to fund this Consortium's efforts to better understand and treat osteogenesis imperfecta (OI), also known as brittle bone disease. Many individuals with OI have brittle teeth (dentinogenesis imperfecta) and may also have severe changes in jaw shape that impairs jaw function. ([BBD Website](#))

***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. ([TRND Website](#))

***Undiagnosed Diseases Network***: The Common Fund's [Undiagnosed Diseases Network](#) (UDN) has established clinical sites at academic centers across the country to aid in the diagnosis of rare and new diseases. The UDN builds upon the experience and expertise of the NIH intramural Undiagnosed Diseases Program, established in 2008, which has conducted state-of-the-art genetic and functional studies on almost 900 patients and provided diagnoses in approximately 25 percent of cases. Approximately 40 percent of patients seen in the Undiagnosed Disease Program are children, many of whom present with complex pediatric genetic disorders.

## *Global Pediatric Health*

***Global Network for Women’s and Children’s Health Research:*** The Global Network, funded by the NICHD, supports and conducts clinical trials in resource-limited countries by pairing foreign and U.S. investigators, with the goal of evaluating low-cost, sustainable interventions to improve maternal and child health and simultaneously building local research capacity and infrastructure. Today, the Global Network focuses on community-based common protocols, conducted at three or more sites, 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. ([NICHD Global Network Website](#))

NIAAA, NICHD, and ORWH support the ***Institute of Medicine Forum on Global Violence Prevention***, which promotes research on protective and risk factors for violence and encourages evidence-based violence prevention efforts.

- On June 18, 2015, the Forum released "Preventing Intimate Partner Violence in Uganda, Kenya, and Tanzania," a [summary](#) of a workshop convened jointly by the Institute of Medicine, National Research Council, and Ugandan National Academy of Science. The workshop brought together a variety of stakeholders to engage in a dialogue on promoting evidence-based intimate partner violence prevention interventions in the region.
- On September 17, 2015, the Forum released a brief [report](#) of its December 2014 activity, "Means of Violence—A Workshop," which focused on the means or methods used to commit violent acts that result in life-threatening events or death. Topics addressed during this workshop included: variations in the global characteristics, contexts, and social determinants of the lethal means of violence, including firearms; youth possession and acquisition of firearms; the relationship between alcohol and firearms violence; and approaches for reducing violence through firearms and other lethal means.
- On October 29-30, 2015, the Forum held a public workshop to explore the cultural and social norms that underlie the acceptance of violence, with a particular focus on violence against women across the lifespan, violence against children, and youth violence. The workshop panels also discussed the characteristics, variations, and determinants related to social and cultural norms in this context; what is known about the effectiveness of efforts to alter those norms in order to prevent and mitigate such violence; and the role of multiple sectors and stakeholders in its prevention.

***Malnutrition and Enteric Disease (MAL-ED) Network of Investigators:*** In 2015, the MAL-ED Network of Investigators, led by the Fogarty International Center and the Foundation for the National Institutes of Health implemented a new protocol to continue follow up of the study’s birth cohorts (originally followed to 24 months of age) located in eight field sites in Bangladesh, Brazil, India, Nepal, Pakistan, Peru, South Africa, and Tanzania. This new element of the study will assess cognitive development as well as health and nutrition status at 60-months of age and seek to evaluate the relationships between these measures and early life exposures (illness, enteric infection, nutrition, SES, etc.) measured in the initial protocol period. ([MAL-ED Website](#))



## **Technology and Tools**

***Newborn Screening Translational Research Network:*** Newborn screening programs across the United States currently screen more than four million infants per year. This public health program has saved countless lives through the early identification of infants who may appear healthy but who are at risk for serious disorders for which early interventions and treatments can be beneficial. After babies are born, they routinely receive a simple heel stick within the first 24 to 48 hours of life. A few drops of blood are collected on a filter paper card; using those dried blood spots, states routinely screen newborns for at least 30 congenital disorders. The NICHD's Newborn Screening Translational Research Network (NBSTRN) is a resource for investigators engaged in newborn screening related research. It enables biomedical investigators, with appropriate institutional review board (IRB) permission and privacy protections, to facilitate the development and assessment of new methods and technologies for newborn screening. ([NICHD NBSTRN Website](#)) Newborn screening research is challenging for a number of reasons: rules and regulations for newborn screening vary by state, and for rare disorders/conditions it may be difficult to recruit a sufficient number of research participants. To date, NBSTRN has developed three tools to facilitate newborn screening research:

- **Virtual Repository of Dried Blood Spots (VRDBS)** – A secure web-based tool that presents information from participating states and provides a centralized, deidentified view of DBS, allowing researchers to locate and request specimens from states.
- **Longitudinal Pediatric Disease Resource (LPDR)** – Made up of 684 common data elements that are applicable across any condition and additional condition-specific elements. Currently, the LPDR includes health information for 48 disorders such as metabolic disorders, spinal muscular atrophy, and lysosomal storage disorders. A data almanac that includes semantic definitions and codes to support electronic information exchange is under development. This data capture tool and management system was developed to leverage the existing [Research Electronic Data Capture \(REDCap\)](#) system to create user friendly clinical case report forms that incorporate national information standards to facilitate information sharing, data mining, and data aggregation.
- **Laboratory performance dataset** – A custom-designed and custom-coded application to collect and report analytical newborn screening and diagnosis data.

### ***The Innovative Therapies and Tools for Screenable Disorders in Newborns*** ([PAR-14-270](#)):

Technological innovations and improved knowledge of the genetic and molecular basis of various conditions have paved the way for screening an increasing number of disorders. Unfortunately, the pace of developing effective treatments lags behind. To address this challenge, NICHD, in collaboration with NINDS, NIDDK, and NIDCD, supported a program announcement to develop innovative therapies and tools for screenable disorders in newborns. Projects supported through this program include efforts to develop new therapies for individuals affected by phenylketonuria (PKU), identify biomarkers for mucopolysaccharidoses, and using N-carbamylglutamate to help treat hyperammonemia. NICHD also supports projects to develop novel technologies for newborn screening technology platforms that can detect rare conditions including lysosomal storage disorders, Friedreich ataxia, Wilson disease, and X-linked adrenoleukodystrophy. Other NICHD-supported researchers are looking to develop new screening tools for spinal muscular atrophy and Duchenne/Becker muscular dystrophy.

NLM has published a ***Newborn Screening Coding and Terminology Guide*** online. Using nationally-accepted vocabulary and electronic messaging standards will 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. ([Newborn Screening Coding and Terminology Guide](#))

***The BrainSpan Atlas of the Developing Brain:*** Technologies have come a long way in mapping the trajectory of mental illnesses. [The BrainSpan Atlas of the Developing Brain](#) – a partnership among the Allen Institute for Brain Science, Yale University, the University of Southern California, and NIMH – has created a comprehensive three-dimensional brain blueprint. The Atlas details not only the anatomy of the brain’s underlying structures, but also exactly where and when particular genes are turned on and off during mid-pregnancy – a time during fetal brain development when slight variations can have significant long-term consequences, including heightened risk for autism or schizophrenia. Knowledge of the location and time when a particular gene is turned on can help us understand how genes are disrupted in mental illnesses, providing important clues to future treatment targets and early interventions. Atlas resources are freely available to the public on the Allen Brain Atlas data portal. ([PMID 24695229](#); [PMID 24267886](#); [PMID 23911319](#))

***NIH NeuroBioBank:*** ([NeuroBioBank Website](#)) Formerly the NICHD Brain and Tissue Bank (BTB) for Developmental Disorders, is a network of brain and tissue banks that collect and distribute tissue from donors to the three NIH supporting institutes (NINDS, NIMH, NICHD). NICHD first established the BTB in 1991 at the University of Maryland School of Medicine. Since then, the research team at the bank has collected more than 84,000 specimens from individuals with >400 different disorders, including autism, Down syndrome, Fragile X syndrome, and muscular dystrophy. To expedite research on brain disorders, NIH is coordinating a Web-based resource for sharing post-mortem brain tissue. Under the NIH NeuroBioBank initiative, five brain banks will begin collaborating in a tissue sharing network for the neuroscience community. The goal is to increase the availability of, and access to, high quality specimens for research to understand the neurological basis of disease. Another goal is to increase tissue donation by increasing awareness of the value of these gifts for understanding brain disorders, via a concerted outreach effort to the disease advocacy community.

***OD/ORIP Supported National Primate Research Centers (NPRCs):*** ([NPRC Website](#)) The seven NPRCs provide facilities and expertise for comprehensive investigations related to fetal, neo-natal, 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.

***Development of Novel and Emerging Technologies to Support Zebrafish Models for Biomedical Research:*** With NICHD’s participation, DCM/ORIP/DPCPSI launched a new small business opportunity initiative aimed at improving all aspects of zebrafish model creation, preservation, and characterization ([PA-15-087](#) and [PA-15-086](#)). This initiative was based on recommendations from a 2013 multi-IC workshop organized by ORIP/DPCPSI and the Trans-NIH Zebrafish Coordinating Committee. Specific areas of research interest within this new initiative related to pediatrics include development of tools or techniques to elucidate the cellular, biochemical, molecular, and genetic mechanisms underlying normal and abnormal development as well as the study of general mechanisms of pattern formation and cell lineages, cell specification, differentiation, migration, and fate during early development and formation of organs/systems such as the fin, heart, nervous system, and neural crest.

***National Cooperative Reprogrammed Cell Research Groups (NCRCRG, [PAR-13-225](#)):*** FY 2015 marked NIMH’s second NCRCRG award, to support a consortium of academic and private industry partners who will compare the molecular and cellular characteristics of induced pluripotent stem cells generated from individuals with ASD, including individuals with FXS, compared with unaffected healthy controls ([U19MH107367](#)). This University of California, San Diego and Salk Institute-based NCRCRG also plans to generate a series of genomically-engineered lines bearing single, highly penetrant mutations, including mutations for the FMR1 gene in FXS. The group will systematically develop a series of assays that are robust and replicable in order to identify commonalities as well as differences between the

different monogenic ASDs. The ultimate goals are to describe causal mechanisms, to identify molecular targets for intervention, and to screen for novel therapeutic agents.

***Predictive Multiscale Models for Biomedical, Biological, Behavioral, Environmental and Clinical Research*** (U01, [PAR-15-085](#)) Through this interagency FOA, multiple agencies will support the development of multiscale models to accelerate biological, biomedical, behavioral, environmental and clinical research. The NIH, ARO, DOE, FDA, NASA, NSF, and ONR recognize that in order to efficiently and effectively address the challenges of understanding multiscale biological and behavioral systems, researchers will need predictive, computational models that encompass multiple biological and behavioral scales. These agencies are especially interested in the development of non-standard modeling methods and experimental approaches to facilitate multiscale modeling, and active participation in community-driven activities through the Multiscale Modeling (MSM) Consortium, [www.imagwiki.org](http://www.imagwiki.org) Supported by NIH, The U.S. Army Research Office (ARO), The Department of Energy (DOE), U.S. Food and Drug Administration (FDA), The National Aeronautics and Space Administration (NASA), The National Science Foundation (NSF), The Office of Naval Research (ONR).

The ***Human Oral Microbiome Database*** ([HOMD Website](#)) 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.

The ***Accelerating Medicines Partnership*** (AMP) Type 2 Diabetes program is taking the extensive available data on T2D genetics, broadening it, and making it more freely accessible and useful. NIDDK supports research to better understand metabolism and the mechanisms that lead to the development and progression of diabetes and to leverage past research investments in pursuit of better prevention and treatment approaches.

***Sudden Death in the Young (SDY) Registry***. NINDS and NHLBI continue to partner with the CDC to build on their Sudden Unexpected Infant Death (SUID) Case Registry to create a registry of Sudden Death in the Young (SDY), including both sudden unexplained death in epilepsy (SUDEP) and sudden cardiac death (SCD) in individuals up to age 19 in 10 states through 2018. By collecting comprehensive data, including biospecimens in a subset of cases, the registry will help define the scope of SUDEP in young people with epilepsy, develop standards for evaluating SUDEP cases, and establish a resource for research on SUDEP causes and risk factors. The Data Coordinating Center was awarded in 2013, and in September 2014, grants were awarded to 10 states for their participation in the registry. Case ascertainment started in January 2015 utilizing a standard autopsy protocol for all SUDEP and SCD; biospecimens are collected and stored at the Biorepository at the University of Michigan. ([LINK](#), [NIH News Release](#))

***The Genetic and Rare Diseases Information Center***, co-funded by NCATS and NHGRI, 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. ([GARD Website](#))

***NCATS Pharmaceutical Collection (NPC)***: NPC is a comprehensive, publicly accessible collection of approved and investigational molecular entities that provides a valuable resource for both validating new models of disease and better understanding the molecular basis of disease pathology and intervention. Investigators can access the NPC in two ways: as a free electronic resource that lists the drugs and their regulatory status and as a compound library used for collaborative high-throughput screening projects at the NCATS Chemical Genomics Center.

***Data Fusion: A Sustainable, Open Source Registry Advancing Pediatric Pulmonary Vascular Disease Research*** is a program awarded in 2014 in response to [RFA HL14-005](#). Clinical investigators will leverage electronic health records from multiple pediatric medical centers to understand the etiologies, clinical course and prognosis of pediatric pulmonary hypertension. Pulmonary Hypertension (PH) is a syndrome characterized by vasoconstriction and abnormal growth and function of pulmonary vessels, which leads to elevation of the pulmonary artery pressure. Left untreated, PH is often progressive and fatal and there is no cure. Investigators will gather information on how effective and safe PH medicines are in children.

***The Children and Clinical Studies Website:*** ([NHLBI Children and Clinical Studies Website](#)) From asthma and cancer treatments to vaccines, research in children saves lives and improves their health and well-being. This NHLBI resource helps parents and others learn more about how clinical studies are conducted in children, so they can make well-informed decisions about whether to enroll their child in a study. The site combines information about how pediatric clinical studies are conducted with award-winning video of children, parents, and healthcare providers discussing the rewards and challenges of participating in research to provide parents and health care providers an insider's guide to children's medical research.

### ***Clinical Care, Outreach, and Services***

***Pediatric Rheumatology Clinic:*** The NIH Pediatric Rheumatology Clinic, supported by the NIAMS, is a specialty-care medical facility dedicated to evaluating and treating children with pediatric rheumatic diseases who are enrolled in clinical trials. Since the causes of these diseases are unknown, the NIH also seeks 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. ([NIAMS NIH Pediatric Rheumatology Clinic Website](#))

***HIV/AIDS:*** NICHD, NIAID, and other ICs support and conduct domestic and international research related to HIV infection and its complications in pregnancy, infants, children, and adolescents. For example, NICHD, NIMH, and NIMHD support the ***Adolescent Medicine Trials Network*** for HIV/AIDS Interventions (ATN), the only national, multicenter research network devoted to the health and well-being of HIV-infected and at-risk adolescents and young adults. This network conducts research, often in collaboration with other networks, on how to prevent HIV transmission among at-risk adolescents, as well as how to treat HIV in this distinctive population. NICHD-supported researchers are also trying to understand the best ways to communicate with people about risky sexual behavior. Some of this research includes studying attitudes, perceptions, and knowledge of STIs and how to prevent them. As the HIV epidemic has evolved in the United States and globally, the NIH has ensured that research reflects these changes and addresses important research opportunities and gaps as they arise. NICHD and NIAID address research gaps related to many HIV-associated co-infections—such as tuberculosis, hepatitis, and malaria—in children and pregnant women. ([ATN Website](#)) NIAID and NICHD support the ***International Maternal Pediatric Adolescent AIDS Clinical Trial (IMPAACT) Network***. Their domestic research agenda includes a focus on evaluating pharmacokinetics, safety, optimal dosing, and long-term complications of new antiretroviral therapies (ART) for HIV/AIDS in pediatric and adolescent populations. IMPAACT's international research agenda includes a focus on the prevention of mother-to-child HIV transmissions and reduction of maternal and infant HIV/AIDS morbidity and mortality through studies such as PROMISE (see page 28). NIAID also supports the Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission study (IMPAACT P1115), a phase I/II study following

up on the observed sustained remission after early treatment of the “Mississippi toddler.” The IMPAACT P1115 trial is now enrolling and will evaluate whether ART initiated within 48 hours of birth can control viral replication in HIV-infected children and whether HIV viral suppression is sustained for at least 48 weeks in infants who stop ART ([NCT02140255](#); [NIAID News](#)). Future research in preventing perinatal transmission of HIV includes improving the safety and efficacy of antiretroviral prophylaxis for infants exposed to HIV during pregnancy and breastfeeding (e.g., improving maternal adherence to ART during breastfeeding, limiting the development of drug resistance, and preserving future treatment options if the infant becomes infected).

***Interventions to Eliminate Disparities in the HIV Treatment Cascade among Youth:*** This initiative will support research projects that implement and test comprehensive approaches to retain adolescents from health disparity populations in the HIV treatment cascade. Approaches are expected to include strategies to address a range of barriers that contribute to drop-off from the treatment cascade, including the absence of culturally or linguistically appropriate services; lack of awareness or information about existing services; logistic or attitudinal barriers to accessing services; absence of youth-friendly services; competing health, mental health, and psychosocial needs; stigma; and lack of peer, familial, and community support.

***Improving Shunt Development and Monitoring for Hydrocephalus:*** Due to shunt malfunction, obstruction, or infection, multiple shunt replacement surgeries remain common in the treatment of hydrocephalus. NINDS and NICHD support a SBIR/STTR initiative ([PA-12-189](#) and [PA-12-190](#)) to address this technological limitation. A Phase II SBIR is developing the first portable, non-invasive device for real time, continuous monitoring of changes in flow in CSF shunts ([NIH RePORTER Link to Phase II SBIR](#)). This device will result in improved clinical management of hydrocephalus by providing a non-invasive method for monitoring and researching shunt function.

***Patient Safety in the Context of Perinatal, Neonatal, and Pediatric Care*** ([PA-13-312](#), [PA-14-311](#), [PA-14-313](#)): Through these program announcements, NICHD encourages a wide range of collaborative research projects related to patient safety in the context of perinatal, neonatal and pediatric care both in routine hospital settings and in the intensive care units.

***Second Phase of Palliative Care: Conversations Matter® Initiative:*** When a child has a serious illness, it can be difficult and overwhelming for the whole family. Pediatric palliative care can help and can be a key part of care for a child with serious illness. Palliative care is available at any time during a serious illness and can be given at the same time as other treatments for a child’s illness. However, it can be difficult for children, families, and health care providers to have conversations about palliative care and oftentimes children and families are not aware that it can give them extra support in dealing with a serious illness. The NINR Palliative Care: Conversations Matter® initiative, which launched in FY 2014, is now in its second phase. The first phase was focused on providing materials and tools to assist health care providers in having sometimes difficult conversations with children and families about palliative care. The recently launched second phase is focused on children, parents, and families, and includes a new brochure, available in English and Spanish, to help them understand what palliative care is; how to identify when a child needs it; and the importance of such care for the whole family. ([NINR Palliative Care: Conversations Matter Website](#))



## **Pediatric Critical Care and Emergency Care**

Critical illness in childhood includes diseases and injuries that pose threats to life or limb or result from respiratory failure, cardiovascular collapse, severe infection, neurological emergencies, or multiple organ dysfunction syndrome—the abnormal or impaired function of several organs. Pediatric intensive care units (PICUs) treat children with the most critical and/or life-threatening conditions. NIH supports research on pediatric critical care through NICHD’s Pediatric Trauma and Critical Illness Branch, NINDS, NHLBI, NINR, and the NIH Clinical Center.

***The NICHD’s Pediatric Critical Care Program*** ([NICHD PTCIB Website](#)) focuses on developing research that links pediatric critical care medicine and science to the epidemiology, prevention, and treatment of childhood disabilities. It sponsors competitive investigator-initiated research on all aspects of pediatric critical care medicine—including critical analyses of outcomes for children who are survivors of trauma, congenital anomalies, neonatal asphyxia, infectious processes, septic shock, and many other less common but still devastating childhood processes. The program also supports research to develop new devices and instruments, and/or improve existing devices and instruments, to monitor and treat newborn infants and small children safely and effectively. ([PCCSDP Website](#)) In 2015, the NICHD’s Pediatric Trauma and Critical Illness Branch published its Strategic Plan ([Strategic Plan](#)) and Action Agenda ([Action Agenda](#)).

***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. For the 2014-2019 cycle, the CPCCRN includes seven clinical sites with large PICUs and a Data Coordinating Center ([RFA-HD-14-022](#), [RFA-HD-14-020](#)). 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. ([NICHD CCPRN Description](#); [CCPRN Website](#))

NICHD also supports other programs related to critical care in children, including Safe and Effective Instruments and Devices for Use in Neonatal and Pediatric Care Settings ([PAR-13-090](#), [PAR-13-091](#)), the NICHD Consortium for Research on Pediatric Trauma and Injury Prevention ([PAR-14-324](#)), Research on Emergency Medical Services for Children ([PA-12-141](#)), and Research on the Health Determinants and Consequences of Violence and its Prevention, Particularly Firearm Violence ([PA-13-363](#)).

***Pediatric Suicide Prevention in Emergency Departments*** ([RFA-MH-14-070](#)): In August 2014, NIMH supported researchers in conducting the Emergency Department Screen for Teens at Risk for Suicide (ED-STARS) study ([U01MH104311-01](#)). In 2009, there were approximately 9.8 million emergency room visits for youth ages 10-17; approximately 700,000 visits involved a psychiatric concern, and approximately 128,000 visits were for intentional self-harm ([Nationwide Emergency Department Sample](#)), making the emergency department a prime setting for suicide prevention efforts. Researchers are now developing and prospectively validating an instrument to screen for suicide risk, as well as refining algorithms capable of predicting which youth are most likely at risk for attempting suicide in the future. The capacity to classify youth as high, moderate, or low risk would be of tremendous benefit to emergency department clinicians, as it will enable efficient triaging of limited resources and identification of modifiable risk factors to target in treatment. The study is taking place in 13 hospital emergency departments affiliated with the Pediatric Emergency Care Applied Research Network, and the Whiteriver PHS Indian Hospital. These emergency departments serve geographically and socio-demographically

diverse groups of youth, including American Indian youth. More than 8,000 youth are being enrolled over the three-year project period. ([NIMH Science Update](#))

### **Pediatric Research at the NIH Clinical Center**

**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 FY2015, fourteen Institutes admitted 3,194 pediatric patients to the Clinical Center to 265 protocols that included children who were seen in 11,874 pediatric out-patient visits on 9,682 out-patient days and 618 inpatient admissions for 5,517 pediatric in-patient days. The proportion of Clinical Center activity that involved children was 12% of all Clinical Center inpatient activity and increased from 12% to 13 % of all Clinical Center outpatient visits. Overall, 12% of Clinical Center patients were under age 18 years.

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 1,611 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 FY2004. Now almost doubled in size, the family-centered residence can care for 65 families every night. In FY2015, 1,570 families stayed 14,314 nights at The Inn and The Woodmont House, a transitional home which was opened in FY2011 to accommodate up to 7 families requiring longer stays. This represents a 7.2% increase in nights accommodated. In FY2014, the Children's Inn opened 4 isolation rooms. The isolation rooms can accommodate residents on contact isolation for certain infections. In FY2015, The Inn had 24 residents stay for 288 nights in these isolation rooms. Since its opening in 1990, over 12,000 families have stayed at The Inn and The Woodmont House. Children and families have come from all 50 states and 86 countries.

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

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

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

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

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

The RPDP program is designed to establish predictive nonclinical models, including animal studies; cell-, tissue-, and organ-based systems; computational and systems modeling; and integration of signals and information from multiple systems to evaluate response- and age-specific toxicity, particularly neurologic and behavioral effects. The program performs nonclinical and clinical research to understand mechanisms of age- and developmentally related changes in metabolism and response to medicinal products, and it develops outcome and assessment measures that are age-appropriate to determine response or toxicity. The FDA is working closely with the NIH to maximize the success of this important program. ([BPCA Activities at NICHD](#), [NICHD RPDP Website](#))

***Clinical and Translational Science Awards:*** The NCATS Clinical and Translational Science Award (CTSA) program offers academic homes for translational sciences and supporting research resources needed by local and national research communities to improve the quality and efficiency of all phases of translational research, including clinical trials. CTSA centers also support the training of clinical and translational scientists and the development of all disciplines needed for a robust workforce for translational research. CTSA applicants are encouraged to summarize their vision for incorporation, where possible, of translational research integrated across the lifespan, with particular focus on pediatric and geriatric research. The CTSA program has supported a large number of pediatric studies, including scientific areas and conditions such as peanut allergy, newborn screening, Niemann-Pick type C1, fragile

X, rare muscle diseases, cystic fibrosis, and Charcot-Marie-Tooth disease (a rare neurological disorder with no known cure). ([CTSA Website](#))

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

***Child Health Research Career Development Awards (CHRC):*** The CHRC program was created to fill the gap in training for junior faculty who intend to devote their careers to academic pediatrics. The program provides funding for sustained mentoring and laboratory-based training and offers the vital foundation to compete for grant funding. During the past two decades, the NICHD has funded 780 pediatric investigators working in 15 different subspecialty areas of pediatrics in 38 pediatric departments throughout the United States. A majority of the scholars have remained in academic pediatrics and, through their independent research programs, they have trained countless undergraduate, graduate, and postdoctoral trainees who have contributed substantially to knowledge of childhood diseases. Many hold important leadership positions in their fields. ([CHRCDA Website](#)) ([RFA-HD-16-018](#))

***Pediatric Scientist Development Program (PSDP):*** The NICHD established the PSDP to provide scientific research experience (particularly in basic science areas) for pediatricians wishing to pursue careers in academic medicine. The PSDP has provided research training for more than 175 scholars across the country. Many PSDP scholars have gone on to strong research careers and have received subsequent NIH funding in pediatric research. ([PSDP Website](#))

***Pediatric Critical Care and Trauma Scientist Development Program:*** The NICHD Pediatric Critical Care and Trauma Scientist Development Program is a national faculty training program that develops successful pediatric critical care and pediatric trauma physician scientists. The goal of the program is to increase the number of highly trained, successfully funded, and sustainable pediatric critical care and pediatric trauma physician scientists who will conduct research to enhance the scientific understanding, clinical management, and long-term outcome of critical illness and trauma in children. ([PCCTSDP Website](#)) ([RFA-HD-14-019](#))

***Postdoctoral Research Training in Pediatric Clinical Pharmacology:*** ([RFA-HD-16-015](#)) NICHD has set aside specific funding to support training grants awarded to institutions or organizations that seek to develop clinician-scientists who will be leaders in the field of pediatric clinical pharmacology research, through training and experience in basic science and clinical research.

***Child Neurologist Career Development Program (CNCDP):*** Through a new FOA, NINDS supports a national training program to support the development of Child Neurologists as research scientists. ([RFA-NS-16-003](#))

***The NINDS Neurological Sciences Academic Development Award*** is designed to support the research career development of pediatric neurologists at educational institutions or professional organizations who have made a commitment to independent research careers. NINDS has supported this program since FY 2003. In FY 2015, NINDS funded awards to four institutions. ([PAR-13-362](#))

***Wellstone Center Training Core Expansion:*** In response to [RFA-AR-15-002](#), NIAMS funded a new training core at the UT Southwestern Medical Center Wellstone Muscular Dystrophy Cooperative Research Center. This Wellstone Center aims to improve treatment of DMD through the use of genomic editing to generate iPSCs. The new Training Core is seeking to “train a new generation of clinicians, physician-scientists, and basic scientists who will be able to apply these evolving technologies in the service of muscular dystrophy patients and their community.” All of the Wellstone Centers include training cores to provide support for stipends and research costs for trainees as well as support for

activities that enhance the institution's environment for training of students, fellows and early-stage investigators in muscular dystrophy research.

***NCI Pediatric Oncology Branch Training Opportunities:*** The NCI Pediatric Oncology Branch at the NIH Clinical Center supports a number of training and career development opportunities. The Pediatric Hematology/Oncology Fellowship is a joint program of the Pediatric Oncology Branch, NCI, NIH and Johns Hopkins University. Fellows receive combined clinical training during their first year at both Johns Hopkins Hospital and the NIH Clinical Center, with unparalleled exposure to clinical issues in pediatric hematology/oncology. Patients seen at both institutions are largely non-overlapping, giving trainees unique exposure to a wide range of diagnoses and management strategies. Fellows also have access to a variety of basic and translational research opportunities available at both campuses during subsequent years of the program. The NCI Pediatric Oncology Branch also provides graduate and postdoctoral research opportunities, medical student rotations, predoctoral fellowships, a psychology training program, and highly specialized 4-week resident elective rotations. ([Pediatric Oncology Branch Website](#))

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

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

***Office of Science Education (OSE):*** The OSE coordinated and sponsored the NIH Curriculum Supplements series that highlights NIH research for use by P-12 science teachers in their classrooms. The series continues to be available, for free, at <http://science.education.nih.gov>. The topics covered and the pedagogical approach used in the supplements matches the Common Core State Standards for mathematics and English language arts, as well as the Next Generation Science Standards.



## **APPENDIX**

Table 1: All NIH Pediatric Research, FY 2015

Table 2: Pediatric Research Initiative, FY 2015

Table 3: NIH Funding Opportunity Announcements That Solicited Applications for Pediatric Research, FY 2015

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 2015**

The totals below were derived from NIH’s Research, Condition, and Disease Categorization (RCDC) system, which uses sophisticated text data mining (categorizing and clustering using individual words and multiword phrases) in conjunction with NIH-wide definitions for matching extramural and intramural research grants and projects to categories. The RCDC use of data mining is designed to improve consistency and eliminate wide variability in defining the research categories reported. The reported levels represent the NIH’s best estimates based on the category definitions. The NIH does not expressly budget by category. The annual estimates reflect amounts that change as a result of science, actual research projects funded, and the NIH budget. A list of FY 2015 NIH-funded grants and projects in pediatric research is available at [LINK](#). The term “Common Fund” refers to research funded through the Office of Strategic Coordination, OD, NIH, to address key scientific issues that no one IC is positioned to address alone.

	Fiscal Year 2015
FIC	\$5,859,643
NCATS	\$12,591,379
NCCIH/NCCIH	\$3,740,798
NCI	\$353,522,528
NEI	\$82,948,271
NHGRI	\$42,353,753
NHLBI	\$327,644,311
NIA	\$15,731,591
NIAAA	\$109,057,927
NIAID	\$254,891,837
NIAMS	\$65,444,546
NIBIB	\$13,585,256
NICHD	\$693,075,851
NIDA	\$155,179,699
NIDCD	\$72,748,774
NIDCR	\$94,089,856
NIDDK	\$225,623,783
NIEHS	\$120,534,244
NIGMS	\$77,551,090
NIMH	\$371,472,879
NIMHD	\$39,493,756
NINDS	\$175,068,387
NINR	\$23,235,054
NLM	\$1,096,508
OD	\$172,108,951
Common Fund	\$29,097,602
Type 1 Diabetes	\$94,732,214
Grand Total	\$3,632,480,488

**Table 2: Pediatric Research Initiative, FY 2015**

*Definition of PRI Research:* Congress did not appropriate any funds to the NIH specifically for carrying out the PRI. For reporting purposes, PRI research is defined as new or significantly expanded pediatric research funded in the reporting year under FOAs for which ICs had set aside specified amounts of available funds. “Significant expansions” may include substantial increases in funding to expand an existing IC initiative beyond that for which funds were originally committed. For example, an expansion could add another grant or site to an existing initiative, expand or add a pediatric population to an existing intramural or extramural study, or launch a new pediatric clinical drug trial or other pediatric research within an established research infrastructure. This definition is consistent with congressional intent that the PRI be supported with dedicated, identifiable dollars that expand support for pediatric research. Table 2 below provides funding by NIH IC for research that meets this definition. A list of FY 2015 NIH-funded grants and projects for the PRI is available at [LINK](#).

	Fiscal Year 2015
FIC	\$30,000
NCATS	\$146,710
NCI	\$60,175,784
NEI	\$291,159
NHGRI	\$2,399,734
NHLBI	\$19,711,022
NIA	\$5,299,460
NIAAA	\$5,191,749
NIAID	\$52,282,561
NIAMS	\$320,002
NICHD	\$33,963,938
NIDA	\$36,642,734
NIDCD	\$814,561
NIDCR	\$30,872,853
NIDDK	\$5,487,432
NIEHS	\$19,831,250
NIMH	\$31,059,848
NIMHD	\$215,088
NINDS	\$6,166,157
OD	\$119,733,624
Common Fund	\$4,514,047
Type 1 Diabetes	\$76,463,890
Grand Total	\$511,613,603

**Table 3: NIH Funding Opportunity Announcements That Solicited Applications for Pediatric Research, FY 2015**

Announcement Number	Issuing Organization	Activity Code	Title
<a href="#">PA-15-124</a>	NCI	R03	Early-life Factors and Cancer Development Later in Life (R03)
<a href="#">PA-15-125</a>	NCI	R21	Early-life Factors and Cancer Development Later in Life (R21)
<a href="#">PA-15-126</a>	NCI	R01	Early-life Factors and Cancer Development Later in Life (R01)
<a href="#">PA-15-127</a>	NCI	R01	Advancing Translational and Clinical Probiotic/Prebiotic and Human Microbiome Research (R01)
<a href="#">RFA-CA-15-502</a>	NCI	U24	Limited Competition: Childhood Cancer Survivor Study (U24)
<a href="#">RFA-HL-15-027</a>	NHLBI	R43/R44	Human Cellular Models for Predicting Individual Responses to Cystic Fibrosis Transmembrane Conductance Regulator- Directed Therapeutics (R43/R44)
<a href="#">RFA-HL-17-001</a>	NHLBI	U01	Asthma Empowerment Collaborations to Reduce Childhood Asthma Disparities (U01)
<a href="#">PA-15-042</a>	NIA	R01	Family and Interpersonal Relationships in an Aging Context (R01)
<a href="#">PA-15-294</a>	NIAAA	R21	Screening and Brief Alcohol Interventions in Underage and Young Adult Populations (R21)
<a href="#">PA-15-295</a>	NIAAA	R01	Screening and Brief Alcohol Interventions in Underage and Young Adult Populations (R01)
<a href="#">PA-15-296</a>	NIAAA	R03	Screening and Brief Alcohol Interventions in Underage and Young Adult Populations (R03)
<a href="#">PA-15-299</a>	NIAAA	R01	Alcohol Use Disorders: Behavioral Treatment, Services and Recovery Research (R01)
<a href="#">PA-15-300</a>	NIAAA	R03	Alcohol Use Disorders: Behavioral Treatment, Services and Recovery Research (R03)
<a href="#">PA-15-301</a>	NIAAA	R21	Alcohol Use Disorders: Behavioral Treatment, Services and Recovery Research (R21)
<a href="#">PAR-15-274</a>	NIAID	R01	Ethical Issues in Research on HIV/AIDS and its Co-Morbidities (R01)
<a href="#">PAR-15-275</a>	NIAID	R21	Ethical Issues in Research on HIV/AIDS and its Co-Morbidities (R21)
<a href="#">PA-15-312</a>	NIAID	R01	Research to Advance Vaccine Safety (R01)
<a href="#">PA-15-313</a>	NIAID	R21	Research to Advance Vaccine Safety (R21)
<a href="#">PAR-15-327</a>	NIAID	R21	Ethical, Legal and Policy Issues in HIV Research with Key Populations (R21)
<a href="#">PAR-15-328</a>	NIAID	R01	Ethical, Legal and Policy Issues in HIV Research with Key Populations (R01)
<a href="#">PAR-15-085</a>	NIBIB	U01	Predictive Multiscale Models for Biomedical, Biological, Behavioral, Environmental and Clinical Research (U01)

<a href="#">RFA-AR-15-014</a>	NIAMS	U19	Validation of Pediatric Patient Reported Outcomes in Chronic Diseases (PEPR) Consortium (U19)
<a href="#">PAR-15-020</a>	NICHD	R01	Systems Developmental Biology for Understanding Embryonic Development and the Ontogeny of Structural Birth Defects (R01)
<a href="#">PAR-15-032</a>	NICHD	R13	Academic-Community Partnership Conference Series (R13)
<a href="#">PAR-15-072</a>	NICHD	R03	Limited Competition: Addressing Health Disparities in Maternal and Child Health through Community-Based Participatory Research (R03)
<a href="#">PA-15-198</a>	NICHD	R21	Studies at Perivable Gestation (R21)
<a href="#">PA-15-199</a>	NICHD	R03	Studies at Perivable Gestation (R03)
<a href="#">PA-15-200</a>	NICHD	R01	Studies at Perivable Gestation (R01)
<a href="#">PA-15-260</a>	NICHD	R15	The Health of Sexual and Gender Minority (SGM) Populations (R15)
<a href="#">PA-15-261</a>	NICHD	R01	The Health of Sexual and Gender Minority (SGM) Populations (R01)
<a href="#">PA-15-262</a>	NICHD	R03	The Health of Sexual and Gender Minority (SGM) Populations (R03)
<a href="#">PA-15-263</a>	NICHD	R21	The Health of Sexual and Gender Minority (SGM) Populations (R21)
<a href="#">PAR-15-285</a>	NICHD	R01	Bioengineering Research Partnership (BRP): Non- or Minimally-Invasive Methods to Measure Biochemical Substances during Neonatal and Perinatal Patient Care and Research (R01)
<a href="#">PAR-15-319</a>	NICHD	R15	Biomedical and Behavioral Research Innovations to Ensure Equity (BRITE) in Maternal and Child Health (R15)
<a href="#">RFA-HD-16-002</a>	NICHD	P50	CAPSTONE Centers for Multidisciplinary Research and Training in Child Abuse and Neglect (P50)
<a href="#">PA-15-035</a>	NIDA	R34	Research Aimed at Novel Behavioral Targets to Improve Adolescent Substance Abuse Treatment and Prevention Interventions (R34)
<a href="#">PA-15-036</a>	NIDA	R01	Research Aimed at Novel Behavioral Targets to Improve Adolescent Substance Abuse Treatment and Prevention Interventions (R01)
<a href="#">PA-15-080</a>	NIDA	R21	Drug Abuse Prevention Intervention Research (R21)
<a href="#">PA-15-081</a>	NIDA	R03	Drug Abuse Prevention Intervention Research (R03)
<a href="#">PA-15-082</a>	NIDA	R01	Drug Abuse Prevention Intervention Research (R01)
<a href="#">PA-15-110</a>	NIDA	R01	Gene-Environment Interplay in Substance Use Disorders (R01)
<a href="#">PA-15-111</a>	NIDA	R03	Gene-Environment Interplay in Substance Use Disorders (R03)
<a href="#">PA-15-112</a>	NIDA	R21	Gene-Environment Interplay in Substance Use Disorders (R21)



<a href="#">PA-15-141</a>	NIDA	R03	International Research Collaboration on Drug Abuse and Addiction Research (R03)
<a href="#">PA-15-142</a>	NIDA	R01	International Research Collaboration on Drug Abuse and Addiction Research (R01)
<a href="#">PA-15-143</a>	NIDA	R21	International Research Collaboration on Drug Abuse and Addiction Research (R21)
<a href="#">PAR-15-157</a>	NIDDK	R18	Pragmatic Research in Healthcare Settings to Improve Diabetes and Obesity Prevention and Care (R18)
<a href="#">PAR-15-302</a>	NIDCR	R01	Establishing Outcome Measures for Clinical Studies of Oral and Craniofacial Diseases and Conditions (R01)
<a href="#">PAR-15-158</a>	NIDDK	R34	Planning Grants for Pragmatic Research in Healthcare Settings to Improve Diabetes and Obesity Prevention and Care (R34)
<a href="#">PA-15-163</a>	NIDDK	R21	Exploratory/Developmental Clinical Research Grants in Obesity (R21)
<a href="#">PAR-15-346</a>	NIDDK	R01	Time-Sensitive Obesity Policy and Program Evaluation (R01)
<a href="#">PAR-15-146</a>	NINDS	U54	Countermeasures Against Chemical Threats (CounterACT) Research Centers of Excellence (U54)
<a href="#">PAR-15-315</a>	NINDS	R21	Countermeasures Against Chemical Threats (CounterACT) Exploratory/Developmental Projects in Translational Research (R21)
<a href="#">RFA-NS-16-003</a>	NINDS	K12	Child Neurologist Career Development Program (CNCDP) (K12)
<a href="#">PA-15-100</a>	NINR	R01	Maternal Nutrition and Pre-pregnancy Obesity: Effects on Mothers, Infants and Children (R01)
<a href="#">PA-15-324</a>	NINR	R01	End-of-Life and Palliative Needs of Adolescents and Young Adults (AYA) with Serious Illnesses (R01)
<a href="#">PA-15-325</a>	NINR	R21	End-of-Life and Palliative Needs of Adolescents and Young Adults (AYA) with Serious Illnesses (R21)
<a href="#">PAR-15-047</a>	OBSSR	R21	Systems Science and Health in the Behavioral and Social Sciences (R21)
<a href="#">PAR-15-048</a>	OBSSR	R01	Systems Science and Health in the Behavioral and Social Sciences (R01)

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

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